

Review

Beyond PD-1/PD-L1 Inhibition: What the Future Holds for Breast Cancer Immunotherapy

Sebastian Chrétien, Ioannis Zerdes, Jonas Bergh, Alexios Matikas and Theodoros Foukakis * 

Department of Oncology - Pathology, Karolinska Institutet, 171 76 Stockholm, Sweden; chretien.sebastian@gmail.com (S.C.); ioannis.zerdes@ki.se (I.Z.); Jonas.Bergh@ki.se (J.B.); alexios.matikas@ki.se (A.M.)

* Correspondence: theodoros.foukakis@ki.se; Tel.: +46851779953

Received: 8 April 2019; Accepted: 2 May 2019; Published: 5 May 2019



Abstract: Cancer immunotherapy has altered the management of human malignancies, improving outcomes in an expanding list of diseases. Breast cancer - presumably due to its perceived low immunogenicity - is a late addition to this list. Furthermore, most of the focus has been on the triple negative subtype because of its higher tumor mutational load and lymphocyte-enriched stroma, although emerging data show promise on the other breast cancer subtypes as well. To this point the clinical use of immunotherapy is limited to the inhibition of two immune checkpoints, Programmed Cell Death Protein 1 (PD-1) and Cytotoxic T-lymphocyte-associated Protein 4 (CTLA-4). Consistent with the complexity of the regulation of the tumor – host interactions and their lack of reliance on a single regulatory pathway, combinatory approaches have shown improved efficacy albeit at the cost of increased toxicity. Beyond those two checkpoints though, a large number of co-stimulatory or co-inhibitory molecules play major roles on tumor evasion from immunosurveillance. These molecules likely represent future targets of immunotherapy provided that the promise shown in early data is translated into improved patient survival in randomized trials. The biological role, prognostic and predictive implications regarding breast cancer and early clinical efforts on exploiting these immune-related therapeutic targets are herein reviewed.

Keywords: breast cancer; checkpoint inhibitors; co-stimulatory; immunotherapy; novel targets; PD-1; PD-L1

1. Introduction

The recognition of the importance of the tumor – host interactions in the prognosis of cancer patients significantly predates the current era of cancer immunotherapy. The gradual deciphering of these complex interactions is summarized in the conceptual framework laid out by Hanahan and Weinberg [1], where immunoediting is suggested as a driving force guiding tumor progression. Exploiting these advances only in part, cancer treatment by the inhibition of negative regulators has revolutionized the management of multiple human malignancies, culminating with the award of the 2018 Nobel Prize in Physiology or Medicine – the first ever bestowed upon research related to an anticancer therapy [2].

Beyond its utility as a treatment target, immune response to cancer has also been a subject of research concerning its role as both a prognostic and predictive biomarker. As an example, higher tumor-infiltrating lymphocyte (TIL) counts and expression of immune function genes have been shown to predict better outcomes in most breast cancer (BC) subtypes and increased rates of pathologic complete remission (pCR) following the administration of neoadjuvant chemotherapy (NACT) for early BC (EBC) [3,4]. In metastatic BC (MBC), TIL enumeration has not proven to be as successful [5], since TIL counts have been shown to be lower in metastatic sites compared to the primary tumor [6].

On the other hand, Programmed Cell Death Protein 1 (PD-1) and its ligand PD-L1, as well as cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), have been extensively evaluated as putative markers of response to immunotherapy with PD-1/PD-L1 and CTLA-4 blockade, respectively [7,8]. Although data stemming from randomized clinical trials in various human cancers are conflicting, in MBC only one phase 3 trial has been reported demonstrating increased benefit from the combination of atezolizumab and nab-paclitaxel compared to nab-paclitaxel alone in patients whose tumors expressed PD-L1 [9]. PD-1/PD-L1 and CTLA-4 checkpoint inhibitors are already the focus of advanced clinical trials (reviewed by Adams et al. [10]).

Despite the aforementioned exciting developments, it is clear that only a fraction of the potential immunologic therapeutic targets has been comprehensively characterized. Unfortunately, research on immunotherapy for BC has lagged behind due to its perceived lower immunogenicity [11]. Nevertheless, a growing body of literature focusing on a large number of co-stimulatory and inhibitory molecules suggests that the field of cancer immunotherapy in general, and BC in particular, is only in its early stages of development. Herein, we summarize available data on novel immunotherapy targets with a focus on BC (Figure 1).

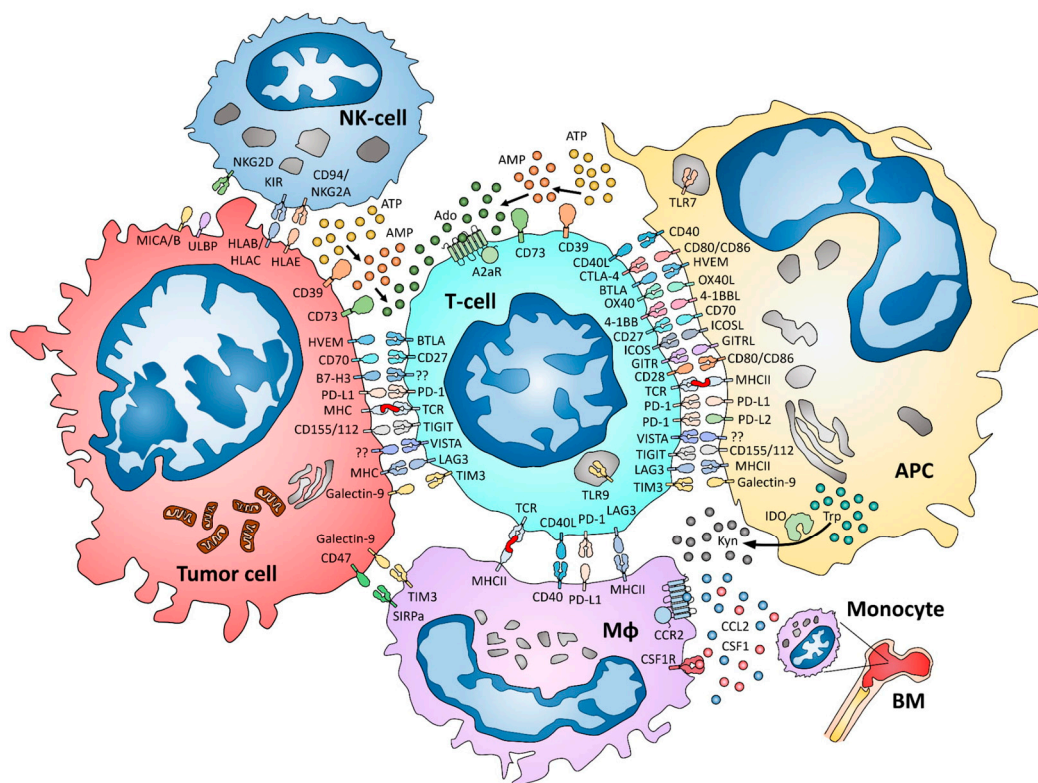


Figure 1. Interplay between tumor cells and immune system components in the tumor microenvironment. Abbreviations for represented cells and immune-related markers are explained in the main text.

2. Markers Predominantly Expressed on T-lymphocytes

2.1. LAG-3

Lymphocyte activation gene-3 (LAG-3) is a cluster of differentiation 4 (CD4) related negative regulator of immune response considered as a marker of T-cell exhaustion. It is expressed on both effector and regulatory T-cells, Natural Killer (NK)-cells, B-cells and dendritic cells (DC) [12–16]. Identified LAG-3 ligands are MHC (Major Histocompatibility Complex) class II molecules expressed on antigen presenting cells (APC), LSECTin and Galectin-3 [17,18]. LAG-3 is thought to inhibit the activity

and expansion of effector T-cells and enhances the suppressive activity of T-regulatory lymphocytes (Tregs) [19–22].

Published data on the role of LAG-3 in BC indicate that it is overexpressed in the tumor compared to the adjacent healthy breast tissue [23–25], while its overexpression has been associated with improved patient outcomes [26] (Table 1). Following promising pre-clinical results, LAG-3 inhibitors are currently being tested in early phase clinical trials including BC, as monotherapy or in combination with chemotherapy or anti-PD-1 therapy (Table 2). One phase I/II clinical trial testing IMP321 (Eftilagimod), a recombinant soluble LAG-3 Ig (Immunoglobulin) fusion protein, in combination with weekly paclitaxel as a first line treatment in 30 patients with MBC showed promising results, with a response rate of 50% [27].

Table 1. Expression and prognostic/predictive value of immune-related markers predominantly expressed on T-cells.

Marker	BC Subtype	Number of Patients	Method	Positive/ Overexpressing Cases	Prognostic/Predictive Value	Comments	Reference
LAG-3	All	8	RT-PCR	LAG-3 expression: 8/8 (100%)	NA	LAG-3 overexpression in BC compared to adjacent healthy tissue	[23]
	All	148 pre-NACT 114 post-NACT	IHC	LAG-3 positivity: Pre-NACT: 33/148 (22.3%) Post-NACT: 38/114 (33.3%)	LAG-3 expression: pedictive for pCR in UA but not MA	Positive case cut-off: expression \geq 5%	[28]
	TNBC	259 (training set) 104 (validation set)	IHC	LAG-3 positivity: 65/363 (18%)	LAG-3 positivity: trend to better RFS and OS in UA	Positive case cut-off: expression \geq 5%	[25]
	All	330 (training set) 3992 (validation set)	IHC	LAG-3 positivity: 327/2921 (11%)	LAG-3 positivity: better BCSS and RFS in MA but not when considering CD8, PD-1 and PD-L1	Positive case cut-off: \geq 1 TILs per TMA core 2921 evaluable in validation set	[26]
TIM-3	All	150	IHC	BC cases: TIM-3 + tumor cells 147/150 (98%) TIM-3+CD8+ T cells 135/150 (90%) Healthy controls: TIM-3+ epithelial cells 13/100 (13%) TIM-3+CD8+ T-cells 23/100 (23%)	NA		[29]
	All	20	FC	NA	NA	Peripheral blood: overexpression of TIM-3 in CD4+CXCR5+ICOS+ T cells compared to healthy controls TILs: overexpression of TIM-3 in CD4+CXCR5+ICOS+ T cells compared to peripheral blood of same patients	[30]
	All	8	RT-PCR	TIM-3 expression: 8/8 (100%)	NA	Overexpression in BC compared to healthy adjacent tissue	[23]

Table 1. Cont.

Marker	BC Subtype	Number of Patients	Method	Positive/ Overexpressing Cases	Prognostic/Predictive Value	Comments	Reference
	All	3169	Gene expression dataset	No overexpression	NA	Use of gene expression dataset <i>Genevestigator v3</i>	[31]
	All	3992 (3148 evaluable)	IHC	TIM-3+ iTILs: 332/3148 (11%) TIM-3+ sTILs: 630/3148	TIM-3+ iTILs: better BCSS TIM-3+ sTILs: statistically not significant better BCSS	TIM-3 iTILs cut-off: expression ≥ 1 iTIL TIM-3 sTILs cut-off: expression ≥ 2 sTILs TIM-3+ iTILs correlated to basal-like subtype	[32]
VISTA	NA	NA	NA	NA	NA	NA	NA
	All	3169	Gene expression dataset	TIGIT overexpression in 72%	NA	Use of gene expression dataset <i>Genevestigator v3</i>	[31]
TIGIT	TNBC	47	Gene expression dataset	NA	TIGIT overexpression: better RFS and OS	Use of gene expression dataset from GEO datasets (GDS2250 and GSE3744)	[33]
	All	8	RT-PCR	TIGIT expression: 8/8 (100%)	NA	No overexpression of TIGIT in BC compared to adjacent healthy tissue	[23]
	All	33	FC	NA	NA	PT Tregs: 80.5% expression of GITR Circulating Tregs: 28.9% expression of GITR	[34]
GITR	All	39	FC	NA	NA	PT CD4+h T cells: higher GITR expression than healthy control CD4+ T cells	[35]
	All	3169	Gene expression dataset	GITR overexpression in 42%	NA	Use of gene expression dataset <i>Genevestigator v3</i>	[31]
	Not specified	3	FC	NA	NA		[36]
	Not specified	17	FC	NA	NA	More T regs expressing GITR in BC patients than healthy donors ($n = 10$)	[37]

Table 1. Cont.

Marker	BC Subtype	Number of Patients	Method	Positive/ Overexpressing Cases	Prognostic/Predictive Value	Comments	Reference
B7-H3	All	221	IHC	B7-H3 high expression: Healthy controls: 14/85 (16.48%) BC: 178/221 (80.55%)	NA		[38]
	All	82	RT-PCR	B7-H3 overexpression: 32/82 (39%)	NA		[39]
	All	117	IHC	B7-H3 positivity: 106/117 (90.6%)	NA	Positive case cut-off: expression > 10%	[40]
	All	90	IHC	B7-H3 high: 83/90 (92%)	B7-H3 high: worse RFS but no association with OS		[41]
	All	74	IHC	B7-H3 IHC positivity: BC 42/74 (56.8%) healthy controls 32/74 (43.2%)	B7-H3 positivity: worse OS		[42]
	All	97	IHC	NA	NA	B7-H3 expression significantly higher in BC (<i>n</i> =97) compared to normal tissue (<i>n</i> = 53), benign, and precursor lesion (<i>n</i> = 182)	[43]
	All	208	IHC	B7-H3 positivity: BC: 154/208 (74%) Healthy controls: 3/7 (43%)	NA		[44]
	All	101	IHC	B7-H3 positivity: BC: 88/101 (88%) Healthy controls: 6/47 (12.8%)	NA		[45]
ICOS	All	120	IHC FC	NA	ICOS positivity: UA: worse PFS and OS MA: not significant	Positive case cut-off: expression ≥ 1.7 positive cells Tumoral Treg ICOS+: 69.9% BC circulating Treg ICOS+: 16.6% Healthy circulating Treg ICOS+: 21.3%	[46]

Table 1. Cont.

Marker	BC Subtype	Number of Patients	Method	Positive/ Overexpressing Cases	Prognostic/Predictive Value	Comments	Reference
4-1BB	All	3169	Gene expression dataset	4-1BB overexpression in 42%	NA	Use of gene expression dataset <i>Genevestigator v3</i>	[31]
	All	286	Gene expression dataset	NA	4-1BB expression: better DFMS		[47]
	Not specified	4	IHC	4-1BB positivity: 2/4 (50%)	NA	Positive case cut-off: expression > 10%	[48]
CD70	All	204	IHC	CD70 positivity: 5/204 (2.45%)	NA		[49]
	All	139 (110/139 with metastasis) 233 (stage I – III)	IHC	CD70 expression: 81/139 (58.3%)	CD70 expression: worse lung MFS		[50]
	All	16 (pre and post-NACT)	RT-PCR	NA	CD70 overexpression after NACT: better PFS		[51]
OX40 and OX40L	All	107 9 DCIS	IHC	Positivity in PT: OX40 91/107 (85%) OX40L 89/107 (83.2%) Positivity in DCIS: OX40 6/9 (66.7%) OX40L 7/9 (77.8%)	NA	Positive case cut-off: expression on > 10% tumor cells OX40 associated with advanced stage	[52]
	Not specified	19	IHC	OX40 positivity: 10/19 (52.6%)	NA	Positive case cut-off: expression on > 10% cells	[53]
	Not specified	Not specified	IHC FC	OX40+CD4+ TILs in 43% of the BC cases	NA	No OX40 expression on circulation CD4 T cells	[54]
	Not specified	45	IHC	OX40 positivity: 7/45 (15.55%)		OX40 expressed on TILs OX40 expression also found on positive LN	[55]
	Not specified	44	IHC	OX40 positivity: 7/18 (30%) of the CD4+ cases	NA		[56]

Table 1. Cont.

Marker	BC Subtype	Number of Patients	Method	Positive/ Overexpressing Cases	Prognostic/Predictive Value	Comments	Reference
BTLA	All	3080	Gene-expression dataset	BTLA overexpressed in TNBC compared to non-TNBC	BTLA overexpression in TNBC: better OS and DFS	Use of gene expression profiles of breast invasive carcinoma from TCGA and METABRIC	[57]
	All	660	IHC FC	BTLA positivity: 15/660 (2.3%)	NA	Positive case cut-off: ≥ 1 BTLA+ TIL All BTLA+ TILs also expressed PD-1 According to FC, CD4 and CD8+TILs don't express BTLA	[58]
TLR9	TNBC (Afro-American population)	51	IHC	TLR9 "low" expression: 27/51 (52.9%) TLR9 "high" expression: 22/51 (43.1%)	TLR9 high: no association with recurrence or BCSS	Variants of TLR9 gene associated with protection from breast cancer	[59]
	All and TNBC	84 of all subtypes 80 TNBC 350 of all subtypes	RT-PCR IHC	mRNA expression in cohort of 84 cases of all subtypes: overexpression in TNBC IHC expression in sub-group analyses of 38/84 cases of all subtypes: overexpression in 8/38 (21%) and 5/13 (38.5%) TNBC IHC expression in 80 TNBC cases: 32/80 (40%) mRNA expression in 350 cases of all subtypes: overexpression in 50/350 (14.3%) and 19/64 (29.7%) TNBC	High mRNA expression: trend to better MFS High protein expression in 80 TNBC: better MFS	TLR9 also expressed in pre-invasive lesions	[60]
	All	196	IHC	TLR9 high expression in TNBC: 51/99 (51.5%)	TLR9 high expression: <ul style="list-style-type: none"> All subtypes: no association found TNBC: high expression better BCSS 		[61]
	All	12	RT-PCR	TLR9 expression: 12/12 (100%)	NA		[62]

Table 1. Cont.

Marker	BC Subtype	Number of Patients	Method	Positive/ Overexpressing Cases	Prognostic/Predictive Value	Comments	Reference
	All	124	IHC	TLR9 positivity: 78/124 (63%)	<ul style="list-style-type: none"> TLR9 positivity: UA: worse PFS MA: not statistically significant 	Positive case cut-off: expression > 10% cells Expression significantly higher in tumors with positive axillary LN metastasis, ER- and advanced stage	[63]
	All	74	IHC	TLR9 expression: By tumor cells: 73/74 (98.6%) By fibroblasts 42/74 (58%)	TLR9 positive expression by fibroblasts: better DMFS		[64]
	All	124 116 post-menopausal	RT-PCR IHC	TLR9 mRNA: overexpression in ER- TLR9 IHC expression in 116 post-menopausal: 103/116 (88.8%)		IHC expression higher in ER and PR-	[65]
	All	141	IHC	TLR9 positivity: 136/141 (98%)	TLR9 positivity: worse DMFS	Higher expression in ER- and high grade tumors	[66]
A2aR	NA	NA	NA	NA	NA	NA	NA
	All	80	IHC	NA	CD73 expression in ER+ cases: no prognostic value CD73 expression in ER- cases: worse OS	CD73 expression associated with EGFR expression	[67]
CD73	All	136	IHC	CD73 positivity: 101/136 (74%)	CD73 positivity: UA: better DFS and OS MA: better DFS, trend to better OS		[68]
	All (Her2 status NA)	102	IHC	CD73 positivity: 9/102 (9%)	NA	Positive case cut-off: any expression by tumor cells	[69]
	Not specified	74	IHC	CD73 positivity: 60/74 (81%)	NA	Positive case cut-off: expression >5% cells	[70]

Table 1. Cont.

Marker	BC Subtype	Number of Patients	Method	Positive/ Overexpressing Cases	Prognostic/Predictive Value	Comments	Reference
	TNBC	122	IF	NA	<p>Tumor cells CD73 expression:</p> <ul style="list-style-type: none"> • UA: worse DFS and OS • MA: worse DFS, trend to worse OS <p>Stromal and immune CD73 expression: no prognostic value</p>		[71]
	All	119	IHC	CD73 positivity: 100/119 (84%)	NA		[72]
	All	202	Gene expression dataset	NA	<p>Gene-expression database of 1128 cases of all subtypes: worse DFS</p> <p>Gene-expression of 417 Her2+ cases: worse DFS</p> <p>Gene-expression of 784 ER+ and 211 TNBC cases: statistically NS trend to worse DFS</p> <p>METABRIC cohort of 1981 cases of all subtypes: worse DSS</p>		[73]
	All and TNBC	6209 all subtypes 59 TNBC	Gene expression dataset	NA	<p>6209 cases of all subtypes: worse OS for TNBC, no prognostic value for ER+ and Her2+ cases</p> <p>59 TNBC: worse response to NACT</p>		[74]

Table 1. Cont.

Marker	BC Subtype	Number of Patients	Method	Positive/ Overexpressing Cases	Prognostic/Predictive Value	Comments	Reference
CD39	Not specified	33	FC	PT CD39+CD8+ TILs mean frequency: 18.5% +/- 4.3% Circulating CD8+ T cells: no CD39 expression	NA		[75]
	All (Her2 NA)	11	FC	NA	NA	CD39+CD4+ TILs 28.7+/-5.8% vs 8.2+/-5.9% in normal adjacent tissue CD39+CD8+ TILs 9+/-3.5% vs 0.4+/-0.3% in normal adjacent tissue	[76]
	All	50	FC IF RT-PCR	NA	NA	CD39 +Th17 TILs 93.6% CD39 + TILs Tregs 50.9% CD39 overexpressed among IL-17 ^{Hi} tumors	[77]
	All	3169	Gene expression dataset	No CD39 overexpression	NA	Use of gene expression dataset <i>Genevestigator v3</i>	[31]
	Not specified	10	Gene expression dataset	CD39 overexpressed in BC compared to healthy tissue	NA	Micro-array dataset from <i>Turashvili et al. (BMC Cancer. 2007 Mar 27;7:55.)</i>	[78]

Abbreviations: LAG-3, lymphocyte-activation gene 3; TIM-3, T-cell immunoglobulin and mucin-domain containing-3; VISTA, V-domain Ig suppressor of T cell activation; TIGIT, T-cell immunoreceptor with Ig and ITIM domains; GITR, glucocorticoid-induced TNFR-related protein; B7-H3, B7 homolog 3; ICOS, Inducible T-cell costimulator; 4-1BB; CD70, cluster of differentiation 70; BTLA, B- and T-lymphocyte attenuator; TLR9, Toll-like receptor 9; A2aR, A2A adenosine receptor; CD73, cluster of differentiation 73; CD39, cluster of differentiation 39; BC, breast cancer; TNBC, triple-negative breast cancer; Her2, human epidermal growth factor receptor 2; NACT, neo-adjuvant chemotherapy; RT-PCR, reverse transcription polymerase chain reaction; IHC, immunohistochemistry; FC, flow-cytometry; IF, immunofluorescence; mRNA, messenger RNA; TILs, tumor-infiltrating lymphocytes; NA, not assessed; UA, univariate analysis; MA, multivariate analysis; pCR, pathological complete response; RFS, relapse-free survival; OS, overall survival; BCSS, breast cancer specific survival; PD-1, Programmed cell death 1; PD-L1, Programmed death-ligand 1; DFMS, distant-metastasis free survival; MFS, metastasis-free survival; PFS, progression-free survival; DFS, disease-free survival; ER, estrogen receptor; PR, progesterone receptor; NS, non significant; DSS, disease-specific survival; TMA, tissue microarray; Tregs, regulatory T cells; LN, lymph-node; TCGA, the cancer genome atlas; EGFR, epidermal growth factor receptor.

Table 2. Ongoing clinical trials potentially including breast cancer patients for targeting immune-related markers predominantly expressed on T-cells.

Target	Drug	Other Agent(s)	Phase	Disease	Line	NCT Identifier	Trial Status
LAG-3	IMP 321 (Eftilagimod)	+ Paclitaxel	I/II	Advanced BC	1st line	NCT00349934	Completed, published results [27]
		+ Paclitaxel	Ib	Hormone positive advanced BC	1st line	NCT02614833	Recruiting, safety results published [79]
		+ Paclitaxel	I	Advanced BC (chinese population)	1st line	NCT03600090	Not yet recruiting
		+ standard therapy	I	Advanced solid tumors	Any line	NCT03252938	Recruiting
	MK-4280	+/- Pembrolizumab (anti-PD1)	I	Advanced solid tumors	No standard therapy available	NCT02720068	Recruiting
	BMS-986016 (Relatlimab)	+/- Nivolumab (anti-PD1)	I	Advanced solid tumors	No standard therapy available	NCT02966548	Recruiting
		+ Nivolumab (anti-PD1) and BMS-986205 (IDO1 inhibitor) Or + Nivolumab (anti-PD1) and Ipilimumab (anti-CTLA4)	I/II	Advanced solid tumors	Any line	NCT03459222	Recruiting
	REGN3767	+/- REGN2810 (anti-PD1)	I	Advanced solid tumors	No standard therapy available	NCT03005782	Recruiting
	LAG525 (IMP701)	+/- PDR001 (anti-PD1)	I/II	Advanced solid tumors including TNBC	≥ 1 line	NCT02460224	Active, not recruiting Preliminary results published [80]
		+/- PDR001 (anti-PD1) +/- Carboplatin	II	Advanced TNBC	1 st or 2 nd line	NCT03499899	Suspended
		+ PDR001 (anti-PD1) + NIR178 (A2aR antagonist) or Capmantinib (C-MET inhibitor) or MCS110 (anti-M-CSF) or Canakinumab (anti-IL1)	I/Ib	TNBC	≤ 2 lines	NCT03742349	Recruiting
	TSR-033	+ anti-PD1	I	Advanced solid tumors	No standard therapy available	NCT03250832	Recruiting
	INCAGN02385	No	I	Advanced solid tumors including TNBC	No standard therapy available	NCT03538028	Not yet recruiting
	Sym022	No	I	Advanced solid tumors	No standard therapy available	NCT03489369	Recruiting
+ Sym021 (anti-PD1) or Sym023 (anti-TIM3)		I	Advanced solid tumors	No standard therapy available	NCT03311412	Recruiting	

Table 2. Cont.

Target	Drug	Other Agent(s)	Phase	Disease	Line	NCT Identifier	Trial Status
	MGD013 (Anti-LAG3 + Anti-PD1)	No	I	Advanced solid tumors	No standard therapy available	NCT03219268	Recruiting
	FS118 (Anti-LAG3 + Anti-PDL1)	No	I	Advanced solid tumors that progressed on anti-PD1/PDL-1 therapy	≥ 1 line	NCT03440437	Recruiting
	XmAb@22841 (Anti-LAG3 + Anti-CTLA4)	No	I	Advanced solid tumors including TNBC	No standard therapy available	NCT03849469	Not yet recruiting
	MBG453	+/- PDR001 (anti-PD1)	I-Ib/II	Advanced solid tumors (phase I)	No standard therapy available	NCT02608268	Recruiting
	TSR-022	No	I	Advanced solid tumors	No standard therapy available	NCT02817633	Recruiting
		+ Carboplatin + Nab-paclitaxel + TSR-042 (anti-PD1)	I	Advanced solid tumors	≤ 1 line (part B) ≤ 4 lines (part A)	NCT03307785	Recruiting
	LY3321367	+/- LY3300054 (anti-PDL1)	Ia/Ib	Advanced solid tumors	No standard therapy available	NCT03099109	Recruiting
	INCAGN02390	No	I	Advanced solid tumors including TNBC	No standard therapy available	NCT03652077	Recruiting
TIM-3	Sym023	No	I	Advanced solid tumors	No standard therapy available	NCT03489343	Recruiting
		+ Sym021 (anti-PD1) or Sym022 (anti-LAG3)	I	Advanced solid tumors	No standard therapy available	NCT03311412	Recruiting
	LY3321367	+/- LY3300054 (anti-PDL1)	I	Advanced solid tumors	Any line	NCT03099109	Recruiting
	BGB-A425	+/- Tislelizumab (anti-PD1) for phase II	I/II	Advanced solid tumors	No standard therapy available	NCT03744468	Recruiting
	LY3415244 (Anti-TIM3 + Anti-PDL1)	No	Ia/Ib	Advanced solid tumors	Any line (phase Ia) ≥ 1 line with anti-PD1 or anti-PDL1 therapy (phase Ib)	NCT03752177	Recruiting
	MBG453	+ PDR001 (anti-PD1)	I/II	Advanced solid tumors	No standard therapy available and no prior anti-PD1/PDL1 therapy	NCT02608268	Recruiting
VISTA	CA-170	No	I	Advanced solid tumors including TNBC	No standard therapy available	NCT02812875	Recruiting

Table 2. Cont.

Target	Drug	Other Agent(s)	Phase	Disease	Line	NCT Identifier	Trial Status
TIGIT	AB154	+/- AB122 (anti-PD1)	I	Advanced solid tumors	No standard therapy available	NCT03628677	Recruiting
	OMP-313M32 (Etigilimab)	+/- Nivolumab (anti-PD1)	Ia/Ib	Advanced solid tumors	No standard therapy available	NCT03119428	Active, not recruiting
	BMS-986207	+/- Nivolumab (anti-PD1)	I/II	Advanced solid tumors	No standard therapy available	NCT02913313	Recruiting
	MK-4166	+/- Pembrolizumab (anti-PD1)	I	Advanced solid tumors	No standard therapy available	NCT02132754	Active, not recruiting
	INCAGN01876	+/- Epacadostat (IDO1 inhibitor)	I/II	Advanced solid tumors (phase I)	No standard therapy available	NCT03277352	Active, not recruiting
		+/- Pembrolizumab (anti-PD1)					
		+/- Nivolumab (anti-PD1) +/- Ipilimumab (anti-CTLA4)	I/II	Advanced solid tumors (phase I)	No standard therapy available	NCT03126110	Recruiting
		No	I/II	Advanced solid tumors (phase I)	No standard therapy available	NCT02697591	Recruiting
	TRX518	+/- Gemcitabine +/- Pembrolizumab (anti-PD1) +/- Nivolumab (anti-PD1)	I	Advanced solid tumors (monotherapy and association with Gemcitabine)	No standard therapy available or indication for Gemcitabine	NCT02628574	Recruiting
GITR			No	I	Advanced solid tumors	No standard therapy available	NCT01239134
		+ Cyclophosphamide and/or Avelumab (anti-PDL1)	I/II	Advanced solid tumors including TNBC and hormone receptor positive refractory BC	TNBC: 2nd or 3rd line Hormone receptor positive BC: ≥ 1 line with aromatase inhibitor	NCT03861403	Not yet recruiting
	BMS-986156	+/- Nivolumab (anti-PD1)	I/IIa	Advanced solid tumors	No standard therapy available	NCT02598960	Active, not recruiting preliminary results [82]
		+/- Nivolumab (anti-PD1)	I	Advanced solid tumors	≥ 2 lines	NCT03335540	Recruiting
	GWN323	+/- PDR001 (anti-PD1)	I/Ib	Advanced solid tumors	Not specified	NCT02740270	Active, not recruiting
	MEDI1873	No	I	Advanced solid tumors	Not specified	NCT02583165	Completed, no published results
	OMP-336B11	No	Ia	Advanced solid tumors	No standard therapy available	NCT03295942	Active, not recruiting

Table 2. Cont.

Target	Drug	Other Agent(s)	Phase	Disease	Line	NCT Identifier	Trial Status
B7-H3	MGA271 (Enoblituzumab)	+/- Pembrolizumab (anti-PD1)	I	Advanced solid tumors including TNBC	No standard therapy available	NCT02475213	Active, not recruiting
		+ Ipilimumab (anti-CTLA4)	I	Advanced solid tumors including TNBC	No standard therapy available	NCT02381314	Active, not recruiting
	MGD009 (Orlotamab)	No	I	Advanced solid tumors including TNBC	≥ 1 prior line	NCT02628535	Recruiting
		MGA012 (anti-PD1)	I	Advanced solid tumors expressing B7-H3	No standard therapy available	NCT03406949	Recruiting
	MGC018	+/- MGA012 (anti-PD1)	I/II	Advanced solid tumors	No standard therapy available	NCT03729596	Recruiting
ICOS	JTX-2011	+/- Nivolumab (anti-PD1) +/- Ipilimumab (anti-CTLA4) +/- Pembrolizumab (anti-PD1)	I/II	Advanced solid tumors	No standard therapy available	NCT02904226	Recruiting, safety results published [83]
	BMS-986226	+/- Nivolumab (anti-PD1) or Ipilimumab (anti-CTLA4)	I/II	Advanced solid tumors	≥ 1 prior line	NCT03251924	Recruiting
4-1BB	PF-05082566 (Utolimumab)	+ Trastuzumab – Vinorelbine – Avelumab (anti-PDL1) + Trastuzumab – Avelumab (anti-PDL1)	II	Advanced Her2+ BC	≥ 1 prior line with progression under Trastuzumab - Pertuzumab	NCT03414658	Recruiting
		Cohort 1: + Trastuzumab – Emtansine Cohort 2: + Trastuzumab	IB	Advanced Her2+ BC	Cohort 1: ≥ 1 prior line with taxane and trastuzumab Cohort 2: ≥ 2 prior lines	NCT03364348	Recruiting
		+ Avelumab (anti-PDL1)	IB/II	Advanced solid tumors including TNBC	Any line	NCT02554812	Recruiting
		Arm A: + Avelumab (Anti-PD-L1) Arm C: + Avelumab (anti-PD-L1) and PF-04518600 (anti-OX40)	I/II	Advanced solid tumors	No standard therapy available	NCT03217747	Recruiting

Table 2. Cont.

Target	Drug	Other Agent(s)	Phase	Disease	Line	NCT Identifier	Trial Status
		+/- Nivolumab (anti-PD1)	I/II	Advanced solid tumors	Any line	NCT02253992	Active, not recruiting
		+ SBRT – Nivolumab (anti-PD1)	I	Advanced solid tumors	Any line	NCT03431948	Recruiting
	BMS-663513 (Urelumab)	No	I	Advanced solid tumors	No standard therapy available	NCT01471210	Completed, preliminary safety results published [84]
		+ Nivolumab (anti-PD1)	I	Advanced solid tumors	No standard therapy available	NCT02534506	Active, not recruiting
		+ Nivolumab (anti-PD1)	I/II	Advanced solid tumors	No standard therapy available	NCT03792724	Not yet recruiting
	PRS-343	+ Atezolizumab (anti-PDL1)	IB	Advanced solid tumors including Her2+ BC	≥ 2 nd line	NCT03650348	Recruiting
		No	I	Advanced solid tumors including Her2+ BC	No standard therapy available	NCT03330561	Recruiting
	ADG106	No	I	Advanced solid tumors	No standard therapy available	NCT03802955	Recruiting
		No	I	Advanced solid tumors	No standard therapy available	NCT03707093	Recruiting
	Anti-hCD70 CAR PBL	+ Aldesleukin (IL-2)	I/II	Advanced solid tumors expressing CD70	≥ 2 nd line	NCT02830724	Recruiting
CD27/CD70	ARGX-110 (Cusatuzumab)	No	I/II	Advanced solid tumors expressing CD70	No standard therapy available	NCT01813539	Active, not recruiting Safety results published [85]
	CDX-1127 (Varlilumab)	+ ONT-10 (Immunovaccine)	IB	Advanced BC	≥ 2 nd line	NCT02270372	Completed, no published results
	MOXR0916 (Vonlerolizumab)	No	I	Advanced solid tumors	No standard therapy available	NCT02219724	Active, not recruiting
OX40/OX40L		+ Atezolizumab (anti-PDL1)	IB	Advanced solid tumors	No standard therapy available	NCT02410512	Active, not recruiting Preliminary safety results published [86]
	PF-04518600	+ Avelumab (anti-PDL1) Or + Utolilumab (Anti-4-1BB) and Avelumab (anti-PDL1) +/- Radiation	I/II	Advanced solid tumors	No standard therapy available	NCT03217747	Recruiting

Table 2. Cont.

Target	Drug	Other Agent(s)	Phase	Disease	Line	NCT Identifier	Trial Status
	MEDI6383	+/- MEDI4736 (anti-PDL1)	I	Advanced solid tumors	No standard therapy available ≤ 5 prior lines	NCT02221960	Completed, no published results
	MEDI0562	+/- MEDI4736 (anti-PDL1) Or +/- Tremelimumab (anti-CTLA4)	I	Advanced solid tumors	No standard therapy available ≤ 3 prior lines	NCT02705482	Active, not recruiting
	INCAGN01949	No	I/II	Advanced solid tumors	No standard therapy available	NCT02923349	Active, not recruiting
		+/- Nivolumab (anti-PD1) +/- Ipilimumab (anti-CTLA4)	I/II	Advanced solid tumors (phase I)	No standard therapy available	NCT03241173	Active, not recruiting
	GSK3174998	+/- Pembrolizumab (anti-PD1)	I	Advanced solid tumors	No standard therapy available ≤ 5 prior lines	NCT02528357	Recruiting
		+ GSK1795091 (TLR4 agonist)	I	Advanced solid tumors including BC but not TNBC	No standard therapy available	NCT03447314	Recruiting
	MEDI6469	+ SBRT to liver or lung metastases	I/II	Advanced BC	≥ 1 prior line	NCT01862900	Completed, no published results
	mRNA 2416	No	I	Advanced solid tumors	No standard therapy available	NCT03323398	Recruiting
	BMS-986178	+ intra-tumoral SD-101 (TLR9 agonist)	I	Advanced solid tumors	≥ 1 prior line	NCT03831295	Recruiting
		+/- Nivolumab (anti-PD1) and/or Ipilimumab (anti-CTLA4)	I/IIa	Advanced solid tumors	≥ 1 prior line	NCT02737475	Recruiting
BTLA	NA	NA	NA	NA	NA	NA	NA
TLR9	IMO-2125 (Tilsotolomid) Intra-tumoral	No	Ib	Advanced solid tumors	Any line (previously treated with anti-PDL1 therapy if indicated)	NCT03052205	Active, not recruiting Preliminary safety results published [87]
	Agatolimod (CPG 7909; PF-3512676)	+ Trastuzumab	I/II	Advanced Her2+ BC	≤ 3 lines	NCT00043394	Completed, no published results
		+ Trastuzumab	I/II	Advanced Her2+ BC	Not specified	NCT00031278	Completed, no published results

Table 2. Cont.

Target	Drug	Other Agent(s)	Phase	Disease	Line	NCT Identifier	Trial Status
		+ Montanide@ISA-51 (immune modulator) + NY-ESO-1 protein (therapeutic vaccine)	I	Localised solid tumors	Neo-adjuvant or adjuvant chemotherapy authorised	NCT00299728	Completed, no published results
		+ Montanide ISA 720 (immune modulator) + Cyclophosphamide + NY-ESO-1-derived Peptides or Protein (therapeutic vaccine)	I	Advanced solid tumors expressing NY-ESO-1	≥ 2 nd line	NCT00819806	Completed, no results published
	MGN1703	+ Ipilimumab (anti-CTLA4)	I	Advanced solid tumors	No standard therapy available	NCT02668770	Recruiting
	SD-101	+ BMS 986178 (anti-OX40)	I	Advanced solid tumors	≥ 1 prior line	NCT03831295	Recruiting
		+ Pembrolizumab (anti-PD1)	II	Stage II or III BC	No prior treatment	NCT01042379	Recruiting
Adenosine pathway							
A2aR	NIR178	+/- NZV930 (anti-CD73) +/- PDR001 (anti-PD1)	I/IB	Advanced solid tumors including TNBC	No standard therapy available	NCT03549000	Recruiting
		+ PDR001 (anti-PD1) and LAG525 (anti-LAG3)	I	Advanced TNBC	≤ 2 prior lines	NCT03742349	Recruiting
	AZD4635	+/- Durvalumab (Anti-PDL1)	I	Advanced solid tumors	No standard therapy available	NCT02740985	Recruiting
	AB928	+ AB122 (anti-PD1)	I	Advanced solid tumors	No standard therapy available	NCT03629756	Recruiting
		+/- Pegylated liposomal doxorubicin	I/Ib	Advanced TNBC	No standard therapy available	NCT03719326	Recruiting
	CPI-444	+/- Atezolizumab (anti-PDL1)	I	Advanced solid tumors including TNBC	≥ 1 and ≤ 5 prior lines	NCT02655822	Recruiting
		+/- CPI-006 (anti-CD73)	I/IB	Advanced solid tumors including TNBC	≥ 1 and ≤ 5 prior lines	NCT03454451	Recruiting
	CD73	SRF373 (NZV930)	+/- PDR001 (anti-PD1) +/- NIR178 (A2aR antagonist)	I/IB	Advanced solid tumors including TNBC	No standard therapy available	NCT03549000
CPI-006		+/- CPI-444 (A2aR antagonist) +/- Pembrolizumab (anti-PD1)	I/IB	Advanced solid tumors including TNBC	≥ 1 and ≤ 5 prior lines	NCT03454451	Recruiting

Table 2. Cont.

Target	Drug	Other Agent(s)	Phase	Disease	Line	NCT Identifier	Trial Status
	BMS-986179	+/- Nivolumab (anti-PD1) +/- rHuPH20 (Recombinant human hyaluronidase)	I/IIA	Advanced solid tumors	Any line	NCT02754141	Recruiting, preliminary results published [88]
		+/- MEDI4736 (anti-PDL1)	I	Advanced solid tumors	Any line	NCT02503774	Recruiting
		+ Paclitaxel – Carboplatin – Durvalumab (anti-PDL1)	I/II	Advanced TNBC	1st line	NCT03616886	Recruiting
	MEDI9447 (Oleclumab)	No	I	Advanced solid tumors (Japanese population)	No standard therapy available	NCT03736473	Active, not recruiting
		+ NACT + pre-operative surgery + Durvalumab (anti-PDL1)	II	Luminal B BC (neo-adjuvant setting)	Neo-adjuvant setting	NCT03875573	Not yet recruiting
		+ Paclitaxel + Durvalumab (anti-PDL1)	I/II	Advanced TNBC	1st line	NCT03742102	Recruiting
CD39	NA	NA	NA	NA	NA	NA	NA

Abbreviations: LAG-3, lymphocyte-activation gene 3; TIM-3, T-cell immunoglobulin and mucin-domain containing-3; VISTA, V-domain Ig suppressor of T cell activation; TIGIT, T-cell immunoreceptor with Ig and ITIM domains; GITR, glucocorticoid-induced TNFR-related protein; B7-H3, B7 homolog 3; ICOS, Inducible T-cell costimulator; 4-1BB; CD27, cluster of differentiation 27; CD70, cluster of differentiation 70; BTLA, B- and T-lymphocyte attenuator; TLR9, Toll-like receptor 9; A2aR, A2A adenosine receptor; CD73, cluster of differentiation 73; CD39, cluster of differentiation 39; PD1, Programmed cell death 1; IDO1, Indoleamine 2, 3-dioxygenase 1; CTLA4, Cytotoxic T-Lymphocyte Associated Protein 4; PDL1, Programmed death-ligand 1, IL-2, Interleukine-2; SBRT, Stereotactic Body Radiation Therapy; NACT, neo-adjuvant chemotherapy; BC, breast cancer; TNBC, triple-negative breast cancer; Her2, human epidermal growth factor receptor 2.

2.2. TIM-3

T-cell immunoglobulin and mucin domain-containing protein 3 (TIM-3) is a negative regulator of adaptive and innate immune responses. It is expressed on CD8+ and CD4+ T helper 1 cells (Th1 cells), Tregs, NK cells, DC, monocytes and macrophages [89–92]. Known ligands to TIM-3 are Galectin-9, Ceacam1, HMGB1 (High Mobility Group Box 1) and phosphatidylserine, all expressed by a variety of cells including tumor cells [93–96]. TIM-3 induces an immunosuppressive environment by suppressing effector Th1 response [93], regulating CD8+ T cell exhaustion [97] and enhancing the regulating function of Tregs [90,98]. It also inhibits the stimulation of the innate immune response by competing with tumor-derived nucleic acids to bind HMGB1 and promoting the expansion of myeloid-derived suppressor cells (MDSC) [95,99].

TIM-3 seems to be upregulated both in BC samples compared to normal adjacent tissue and circulating lymphocytes, possibly through hypomethylation of its promoter [23,29] (Table 1). However, expression on immune cells has been reported to vary widely [29,100]. Burugu et al. evaluated TIM-3 IHC expression in 3992 BC samples of all subtypes and found that the TIM-3 intraepithelial TIL infiltration is associated with a better outcome [32]. TIM-3 polymorphisms might also play a role in the susceptibility to, and prognosis of BC [101–103].

Drugs targeting TIM-3 are currently being tested in early phase clinical trials including BC, alone or in combination with anti-PD1/PD-L1 check point inhibitors, with no published results yet (Table 2).

2.3. VISTA

V-domain Ig suppressor of T cell activation (VISTA) is a negative regulator of the T-cell immune activity functioning both as a ligand and receptor [104]. It has been shown to be expressed by CD4+ and CD8+ T-cells, Tregs, DC, NK-cells, monocytes, macrophages and granulocytes [105,106], as well as tumor cells [107–109]. VISTA exerts its immunosuppressive function by decreasing the T-cell production of effector cytokines, diminishing T-cell proliferation and increasing conversion to Tregs [106]. To our knowledge, VISTA's expression and prognostic impact in BC has never been assessed, although a phase 1 clinical trial which enrolls TNBC patients and tests an oral inhibitor of PD-L1, PD-L2 and VISTA is currently ongoing (Table 2).

2.4. TIGIT

T-cell immunoreceptor with Ig and ITIM domains (TIGIT) is a co-inhibitory molecule expressed on effector, memory and regulatory T-cells, follicular helper (Tfh) and NK-cells [110,111]. It competes with CD223 to bind its two identified ligands, CD155 and CD112, expressed on APC, fibroblasts, endothelial, epithelial cells and also on a variety of cancer cells, including BC [112]. TIGIT has different ways of exerting its immunosuppressive action: Direct inhibition of NK-cell function [113], direct inhibition of T-cell activation, proliferation and cytotoxicity by attenuating TCR-driven (T-cell receptor) activation signals [114] and indirect inhibition of T-cells by promoting the maturation of immunoregulatory DCs [111]. It also promotes the Tregs function by being a direct target to FoxP3 (Forkhead box P3) and inducing an enhanced suppressive function [115,116].

TIGIT expression in BC has only been assessed at the transcriptomic level, with most studies showing overexpression [23,31,33,117] (Table 1). In one study, overexpression was correlated with improved patient survival in TNBC [33], leading to the development of antibodies targeting TIGIT in combination with PD-1 blockade (Table 2).

2.5. GITR

Glucocorticoid-induced TNFR-related protein (GITR) is a co-stimulatory member of the tumor necrosis factor (TNF) receptor superfamily expressed constitutively on all T-cells [118,119]. It is also expressed on NK-cells, eosinophils, basophils, macrophages and B-cells [120]. Its activating ligand is the GITR ligand (GITRL), expressed on APC and endothelial cells [121,122]. Upon binding, GITR exerts an

immunostimulatory activity by directly enhancing T-cell proliferation and effector functions [123,124]. It also indirectly enhances the effector T-cell function by decreasing the intratumoral Treg numbers and suppressive function [125,126]. By avoiding activation-induced cell death, it also promotes an increase in memory T-cells [127].

Cari et al. assessed GITR mRNA expression in 3169 BC patients of all subtypes and found an overexpression in 42% of the cases [31]. Other studies demonstrated that expression is increased in both infiltrating [34] and circulating Tregs of BC patients [35,37]. Interestingly, GITR seems to also be overexpressed in CD4+ T-cells in BC-infiltrated lymph nodes [36] (Table 1).

BMS-986156, a GITR agonistic monoclonal antibody, in combination with nivolumab has demonstrated an acceptable safety profile and promising antitumor activity in advanced solid tumors [82]. Other agonist molecules targeting GITR are currently being tested in early phase clinical trials (Table 2).

2.6. B7-H3

B7 homolog 3 (B7-H3) is a member of the B7 family of immunomodulatory ligands. It is not spontaneously expressed in peripheral blood mononuclear cells but can be induced upon stimulation in APC, T-cells and NK-cells [128]. It is widely expressed in healthy solid organs and several malignancies, including BC [129]. Interestingly, it is also expressed by tumor-associated endothelial cells [45]. Although B7-H3 was initially seen as a co-stimulatory molecule, which increases CD4+ and CD8+ proliferation and enhances T cell cytotoxicity [129,130], the majority of recent studies highlight its co-inhibitory role. Indeed, it appears to downregulate T-cell proliferation and cytokine production [131], Th1 and Th2-mediated immune reactions [132] and inhibit NK cells activity [133]. Moreover, B7-H3 seems to influence cancer progression beyond its immunoregulatory role, by promoting migration, invasion and angiogenesis [134,135].

B7-H3 expression in BC has been extensively studied and demonstrated to confer worse prognosis [41,42] (Table 1). As a result, two antagonist drugs – a monoclonal antibody (enoblituzumab) and a dual-affinity re-targeting (DART[®]) protein (MGD009) – are currently under evaluation in early phase clinical trials including BC (Table 2).

2.7. ICOS

Inducible T cell co-stimulator (ICOS) is a specific T-cell molecule of the B7-binding CD28 family, expressed on activated T-cells after TCR engagement and enhanced by CD28 co-stimulation [136,137]. Its only ligand is ICOS-L, mainly expressed on APC [138–140] but also on endothelial and lung epithelial cells [141,142]. Although typically seen as an immune co-stimulatory pathway, notably through promoting cell proliferation/differentiation, enhancing Th1/Th2 function and facilitating T-dependent B-cell activation [136,137,143], ICOS/ICOS-L interaction might also have an immunosuppressive role through the accumulation of Tregs and secretion of IL-10 [46,144].

In a study by Faget et al., BC patients overexpressing ICOS had a significantly worse survival in the univariate but not multivariate analysis [46], while certain ICOS gene polymorphisms have also been associated with increased BC susceptibility in Chinese populations [145,146] (Table 1). Ongoing trials of agents targeting ICOS are shown in Table 2.

2.8. 4-1BB (CD137)

4-1BB (CD137) is a member of the TNF receptor superfamily, widely expressed on adaptive and innate immune cells like effector, helper and regulatory T-cells [147,148], B-cells [149], NK-cells [150,151], DCs [152], neutrophils, eosinophils, mast cells, monocytes and macrophages [153]. It is also expressed by a variety of other non-immunological cells, including endothelial and malignant hematological cells [154]. It exerts a co-stimulatory action upon ligation with its ligand 4-1BBL, resulting in enhanced T-cell and NK-cell proliferations, production of pro-inflammatory cytokines and cytotoxicity [150,155,156] and the inhibition of activation-induced cell-death in T-cells [157].

Two studies using gene-expression datasets demonstrated that 4-1BB is overexpressed in BC and is associated with better prognosis [31,47] (Table 1).

Monoclonal agonist antibodies are currently being tested in early phase clinical trials including BC (Table 2). Two early-phase studies (NCT00351325 and NCT00309023) raised concerns due to two hepatotoxicity-related deaths, though not replicated in a follow-up phase 1 study [158].

2.9. CD27 and CD70

CD27 and its only ligand CD70, are members of the TNF receptor and ligand superfamily that interact exclusively with each other. CD27 expression on T-cells is tightly regulated, with upregulation upon activation after the TCR stimulation followed by downregulation once the effector T-cell differentiation is acquired [159]. CD27 is also expressed on B-cells (germinal center and memory B-cells) and NK-cells [160–162]. CD70 expression on immune cells is also tightly regulated and is present on activated T-cells, stimulated B-cells, mature DC and NK-cells [163–166]. Interestingly, CD70 has also been found to be expressed in various hematological, sarcoma and carcinoma cells including BC [167]. The CD27-CD70 pathway exerts its co-stimulatory activity in great part through CD27 interaction with TNF receptor associated factors (TRAF), resulting in the activation of transcription factors of MAPK (Mitogen-activated Protein Kinase) and NFκB (Nuclear Factor kappa-light-chain-enhancer of activated B-cells) family. This leads to the expansion and survival of activated T cells [168–173]; differentiation to memory and effector T-cells [173–175]; activation of NK-cells [176,177]; and differentiation plus activation of B-cells [178–180].

CD70 protein expression in BC was assessed in two studies with contrasting results [49,50] (Table 1). Of interest, Liu et al. demonstrated that a high CD70 expression was correlated with worse lung metastasis-free survival, but not with other metastatic sites following relapse of EBC. In addition, gene expression studies showed that CD70 was overexpressed in basal-like compared to Luminal A cancers and that overexpression after NACT was associated with a better outcome [51,181].

Two antibodies, ARGX-110 targeting CD70 and CDX-1127 (Varlilumab) targeting CD27 are currently in early phase clinical trials. In addition, a trial is testing the safety and activity of administering peripheral blood lymphocytes transduced with a CD70-binding Chimeric Antigen Receptor (CAR) to patients with CD70-expressing cancers (Table 2).

2.10. OX40 and OX40L

OX40 (CD134) and OX40L are members of the TNF superfamily. OX40 is constitutively expressed on Tregs and transiently induced on activated CD4+ and CD8+ T-cells following TCR stimulation [182–184]. It has also been reported to be expressed by neutrophils, NK-cells and NKT-cells [185–187]. Its ligand, OX40L, is expressed on professional APC, NK-cells, Langerhans cells, vascular endothelial cells, monocytes, neutrophils and mast cells. Like OX40, it is upregulated upon activation [188–195]. OX40-OX40L interaction, like other TNF members, exerts a co-stimulatory effect through interacting with TRAF, which impacts CD4+ and CD8+ T cells by enhancing their proliferation and survival, generating memory cells, enhancing their effector function and promoting differentiation into Th1, Th2 and Th17 cells through various cytokines production [196–203].

Several studies have assessed OX40 expression in BC, showing an expression varying from 15.5% to 85% of cases (Table 1). Interestingly, Xie et al. reported expression on cancer cells while all the other studies reported expression on TILs [52]. Consequently, a number of agonistic monoclonal antibodies targeting OX40 and a mRNA encoding OX40L (injected intra-tumorally) are currently being tested in early phase clinical trials including BC, alone or in combination with other immunotherapies. (Table 2)

2.11. BTLA

BTLA (B and T Lymphocyte Attenuator) is an inhibitory Ig-domain-containing glycoprotein receptor of the CD28 superfamily expressed on activated T-cells, B-cells, Tfh cells, macrophages, DC, NKT-cells and NK-cells [204–208]. Its only proven ligand is HVEM (Herpes Virus Enter Mediator),

a member of the TNF receptor family, expressed on CD4+ and CD8+ T-cells (strongly on resting T cells, downregulated upon activation), naïve and memory but not activated B-cells, monocytes, DC, solid organs, tumor-associated endothelial cells or on various cancer cells including BC [209–212]. BTLA has also been described as a potential receptor for B7-H4 in BC [213]. BTLA exerts its T-cell inhibitory action upon binding HVEM, leading to a decreased T-cell proliferation and cytokine production with a predominant effect on CD4+ cells [214–219]. Data concerning its action on B-cell function is scarce but it appears to negatively regulate B-cell activation [220]. Interestingly, BTLA and PD-1 seem to be co-expressed on CD8+ T-cells.

Data concerning BTLA expression in BC is scarce (Table 1). Although it seems to be overexpressed at the transcriptomic level, especially in TNBC where it was also associated with improved survival [57], protein expression appeared to be limited in another study [58]. To our knowledge, no clinical trials for therapeutic targeting of BTLA are currently ongoing.

2.12. TLR9

Toll-like receptors (TLRs) are type I transmembrane glycoproteins of the pattern recognition receptors (PRR). They play a key role in immunity by allowing immune cells to recognize non-self or altered-self molecular patterns, activating the innate immune response and coordinating the innate and adaptive immune responses. The most studied member in BC is the intracellular receptor TLR9.

TLR9 is a DNA receptor that migrates from the endoplasmic reticulum to the endosomal/lysosomal compartment when DNA enters the cell [221,222]. When activated by DNA recognition, TLR9 initiates a signaling cascade [222,223], leading to the activation of various transcription factors like NF- κ B and AP-1 (Activator protein 1) [224], thus promoting the transcription of genes that are important for inflammatory and immune responses [225,226]. In addition, it promotes adaptive immunity by enhancing DC maturation and producing a favorable cytokine/chemokine milieu that results in the activation of Th1 and CD8 cytotoxic T lymphocytes as well as by promoting B-cell proliferation [227,228].

TLR9 expression and its prognostic role in BC has been reported by several studies with conflicting results [60,64] (Table 1). Nevertheless, it appears that TLR9 is expressed at higher levels in estrogen receptor (ER) negative and high-grade tumors. Regarding the prognostic significance of TLR9 expression, three studies associated high expression with a better outcome [60,61,64], while two other studies reported worse survival [63,66]. Of interest, Karki et al. demonstrated that BC patients have decreased serum levels of TLR9 compared to patients with benign lesions and healthy controls, proposing it as a potential diagnostic biomarker [229]. Moreover, several but not all studies have shown an association between TLR9 gene polymorphisms and BC susceptibility [230–233].

Therapeutic targeting of TLR9 has proven to be efficient in pre-clinical models of various cancers including BC and many drugs are currently being tested in several cancer types, some of them even reaching phase III (NCT03445533) (Table 2).

2.13. The Adenosine Pathway in Breast Cancer

The adenosine pathway is an important peripheral control mechanism for regulating the immune response in order to prevent over-activation and tissue damage. As with other immunoregulatory pathways, cancer cells are capable of hijacking it in order to promote tumor escape. Important components of this pathway are the adenosine receptor A2a (A2aR), through which the extracellular adenosine can activate its intracellular signaling pathway and the ectonucleotidases CD39 and CD73, which participate in extracellular adenosine production by dephosphorylating ATP.

A2aR is a G-protein-coupled receptor expressed on T and NKT-cells, B-cells, monocytes, macrophages, DC, NK-cells, mast cells, eosinophils and platelets [234]. CD73 is a cell-surface enzyme that can also be found as an enzymatically active soluble form. It is widely expressed on immune cells including B-cells, CD8+ and CD4+ T-cells, Tregs, neutrophils, MDSC, monocytes, macrophages, DC and NK-cells [235]. It is also expressed on a wide range of epithelial cells, endothelial cells and cancer cells including BC [235–237]. CD39, another cell-surface enzyme which produces

adenosine, is also expressed on a variety of immune cells [238–240]. It is also expressed on platelets, endothelial cells and cancer cells including lung, melanoma, pancreatic and lymphoma cells [241–243]. Like CD73, a soluble catalytically active form of CD39 exists [244]

The adenosine pathway exerts an immunosuppressive action by inhibiting effector T-cell activation [245], proliferation, cytokine production and cytotoxicity as well as promoting their immunosuppressive cytokine production [246,247]. In addition, it promotes Tregs formation [246], inhibits NK-cell antitumor activity [248], NKT-cell production of cytokines [249], macrophage proliferation [250] and DC maturation [251]. It has also been shown to increase the expression of other immune checkpoints [252].

CD73 expression on BC cells ranges from 9 to 84% of the cases and is generally associated with worse outcome, although one study reported contrasting results [68] (Table 1). In addition, CD39 is overexpressed both in TILs and circulating T cells of BC patients when compared to healthy controls, but its prognostic value has not been studied.

Numerous pre-clinical studies have demonstrated the efficacy of targeting the adenosine pathway in BC models, leading to the development of A2aR oral inhibitors and antibodies targeting CD73, currently in early phase clinical trials (Table 2). CD39 targeting therapies are currently under pre-clinical development but to our knowledge none have yet reached clinical trials.

3. Tumor-Associated Macrophages and Related Markers

Tumor-associated macrophages (TAMs) represent a major and heterogeneous distinct immune cell subpopulation in the tumor microenvironment (TME). In many tumor types, including BC, TAMs play a key role in tumor progression, angiogenesis, immune evasion and metastasis [253]. They also interact with other cell types through the secretion of various cytokines which in turn can modify the balance between tumor, stromal, endothelial and immune cells. According to the markers expressed on their cell surface as well as the factors they secrete, TAMs can be divided into two subtypes: a) the classically activated M1-like macrophages which have pro-inflammatory, anti-tumoral properties mainly through the secretion of TNF- α (Tissue Necrosis Factor alpha), IL-1, IL-2, IL-6, IL-12; and b) the selectively activated M2-like macrophages with anti-inflammatory, pro-tumoral phenotype mainly through TGF- β (Transforming growth factor beta), IL-4, IL-10 and IL-13 [254]. In terms of prognosis, TAMs were associated with worse overall survival in many solid tumors according to a large meta-analysis [255]. In BC in particular, a meta-analysis of sixteen studies revealed that a high TAM density was associated with worse overall survival (Hazard Ratio [HR]=1.50; 95% Confidence Intervals [CI] 1.20-1.88) and disease-free survival (HR=2.22; 95% CI 1.71-2.89) [256]. Overall, therapeutic strategies against TAMs are based on two major approaches: a) targeting TAM recruitment and activation, and b) reprogramming macrophage polarization towards an anti-tumoral phenotype. The first approach includes the elimination of TAM and monocyte accrual to the tumor site through the inhibition of mainly CSF-1/CSF-1R (Colony Stimulating Factor 1/ Colony Stimulating Factor 1 Receptor) and CCL2/CCR2 (C-C Motif Chemokine Ligand 2/ C-C Motif Chemokine Receptor 2) signaling axes. The second approach relies on the fact that TAMs are mostly of the M2-like phenotype and thus, stimulating the properties of the M1-like phenotype could be an effective treatment option to restore anti-tumoral activity. Such potential treatments for the macrophage polarization shift include CD40-agonists and/or TLR7 agonists. Whether the aforementioned therapeutic agents can be combined with other therapies which can target angiogenesis, increase phagocytic activity or enhance anti-tumor immunity is currently under investigation [257,258]. Moreover, recognition and targeting of other pro-tumoral chemokines and cytokines [259] or novel targets could broaden the therapeutic spectrum in cancer immunotherapy.

3.1. CSF-1/CSF-1R

TAM recruitment is highly controlled by the interaction of the glycoprotein CSF-1 with its receptor CSF-1R, a member of type III receptor tyrosine kinase family. Binding of CSF-1 to CSF-1R leads to

activation, recruitment and proliferation of TAMs [260]. CSF-1R is normally expressed in various cell types but its expression in BC cells has been correlated to worse prognosis [261–264] (Table 3). Therapeutic targeting of this axis is under active investigation (Table 4).

3.2. CCR2/CCL2

The recruitment of circulating monocytes from the bone marrow into the TME is also mediated by the expression of the chemokine ligand CCL2. The binding to its receptor CCR2 leads to the differentiation of monocytes into TAMs and to the subsequent promotion of their pro-tumoral activity, tumor cell proliferation, angiogenesis and metastatic dissemination [265,266]. Expression of these chemo-attractants has been linked to worse prognosis in BC patients [267–271] (Table 3). Targeting this axis using CCR2 antagonists and anti-CCL2 antibodies is currently being explored in advanced solid malignancies, including BC (Table 4).

Table 3. Expression and prognostic/predictive value of immune-related markers predominantly expressed by macrophages, NK and dendritic-cells in breast cancer (BC) patients.

Marker	BC Subtype	Number of Patients	Method	Positive/Overexpressing Cases	Prognostic/Predictive Value	Comments	Reference
Macrophage-related							
CSF-1/CSF-1R	All	581 (301 node-negative, 280 node-positive)	IHC	Positive cases: node-negative 114/301 (38.9%) node-positive 189/280 (67.5%)	Positivity in node negative: worse OS (not in node positive patients)		[264]
	All	196	IHC in situ RNA detection	74% CSF-1+ and 58% CSF-1R+ tumors	CSF-1+ tumor cells: poor survival	CSF-1+ tumor cells: more frequent metastases	[263]
	All	572	ELISA (circulating CSF1 levels)	NA	logCSF1: worse BCCS high CSF-1: worse outcome in post-menopausal patients	Cut-off: median serum CSF-1 expression	[262]
	All	68	IHC	NA	High CSF-1: worse DSS	High CSF-1R: marginally correlated to worse DSS	[261]
CCL2/CCR2	All	137	IHC	CCL2+ tumor cells: 30.7% in PTs vs 39.4% in paired recurrences CCL2+ stromal cells: 18.2% in PTs vs 22.6% in paired recurrences	No correlation	Significantly higher CCL2 expression in tumor cells of recurrences (especially the early ones) compared to PTs	[267]
	All	427	IHC	NA	Stromal but not epithelial CCL2 expression: worse RFS in basal-like subtype	Stromal CCL2 remained an independent factor of worse prognosis in basal-like subtype	[268]
	All	63	IHC	NA	CCR2 expression in tumor cells: worse DFS, MFS and OS	CCR2 expression in tumor cells associated with higher risk of metastasis. CCR2 expression in tumor cells remained an independent factor of worse MFS	[269]
	All	151 (135 evaluable)	IHC	CCL2 high: 65/135 (48.1%) CCL2 low: 70/135 (51.9%)	CCL2 high: worse RFS	High combined CCL2/VEGF expression was independently associated with worse RFS	[270]

Table 3. Cont.

Marker	BC Subtype	Number of Patients	Method	Positive/Overexpressing Cases	Prognostic/Predictive Value	Comments	Reference
	All	3554 (TCGA and kmpplot.com)	RNA-seq	NA	High mRNA CCL2 expression: better RFS in basal-like, HER2-enriched and luminal-B subtypes (median cutoff of mRNA expression)	No significant association between RFS and expression of CCL2 mRNA in the whole cohort and in luminal-A subtype	[271]
CD40	All	181	IHC	Cytoplasmic tumor cell expression: 53% Membrane tumor cell expression: 7.7% Nuclear tumor cell expression: 81%	CD40 cytoplasmic positivity: better OS	Positive association of CD40 cytoplasmic expression in HR+ breast tumors	[272]
NK cell-related							
CD94/NKG2A	All	28 (TDLN)	Flow cytometry	NA	NA	High expression of NKG2A in NK cells of tumor-draining lymph nodes described NKG2A+ NK cells correlated to locally advanced disease	[273]
NKG2D ligands (MICBAB, ULBP1-5)	All	677	IHC	Tumor cell expression: MIC-AB: 50% ULBP-1: 90% ULBP-2: 99% ULBP-3: 100% ULBP-4: 26% ULBP-5: 90%	High MIC-AB and ULBP-2 expression better RFS	Combined low expression of MIC-AB and ULBP-2 correlated to worse RFS	[274]
Dendritic cell-related							
	All (Pakistani population)	100	IHC	100% positive 24/100 low IDO (24%) 27/100 medium IDO (27%) 49/100 high IDO (49%)	Medium and high IDO: worse OS	IDO expression correlated to TNBC	[275]
IDO	All	203	IHC	100% positive 108/203 low IDO (53.2%) 95/203 intermediate and high IDO (46.8%)	General population: no difference in OS ER+ IDO intermediate/high: better OS Node-positive IDO intermediate/high: better DSS	IDO expression correlated to ER+	[276]

Table 3. Cont.

Marker	BC Subtype	Number of Patients	Method	Positive/Overexpressing Cases	Prognostic/Predictive Value	Comments	Reference
	All	26 primary tumor + TDLN 10 benign lesions	IHC	IDO positivity: PT: 12/26 (46.15%) TDLN: 19/26 (73.08%) Benign lesions: 1/10 (10%)	IDO expression: statistically not significant worse OS and TTP	IDO expression correlated to advanced stages, lymph-node metastasis and Treg infiltration No expression in healthy adjacent tissue	[277]
	All	155	IHC	Stromal positivity (>5%): 49/155 (31%) Epithelial positivity (>10%): 24/155 (15%)	IDO positivity: better OS	IDO positivity correlated to absence of lymph-node metastasis, ER- and TNBC	[278]
	All	242 primary tumor 20 TDLN 19 metastasis	IHC	IDO positivity: PT: 34/242 (14%) TDLN: 1/20 (5%) Metastasis: 0/19 (0%)	NA	IDO positivity correlated to high grade and TNBC Co-expression of IDO in 70% of PDL-1+ cases	[279]
	All	65	IHC	IDO positivity: 42/65 (64.6%)	IDO expression: worse OS and PFS in UA but not MA	IDO expression correlated to high grade, lymph-node metastasis	[280]
	All	54	IHC	IDO positivity: 27/54 (68.5%)	IDO expression: worse response to NACT and statistically not significant worse PFS and OS	IDO expression correlated to advanced stages, lymph-node metastasis	[281]
	All	129 PT 10 normal LN 17 metastatic LN	IHC	IDO expression: PT: NA Normal lymph-nodes 80% Metastatic lymph nodes 88.2%	NA	IDO expression correlated to lymph-node metastasis, ER-, TNBC and PD-1 expression	[282]
	All	54 PT 11 healthy controls	qRT-PCR	NA	NA	IDO expression reduced in tumor compared to healthy tissue IDO expression in tumor correlated to advanced stage	[283]
	All	46	IHC	IDO high: 26/46 (56.5%)	IDO high: worse response to NACT and worse PFS and OS	IDO high correlated to advanced stage and lymph-node metastasis	[284]
	HR+	362	IHC	IDO expression 276/362 (76.2%)	IDO expression: worse OS	IDO expression not correlated to clinico-pathological characteristics IDO expression negatively correlated to B-cell infiltration	[285]
	All	202	IHC	NA	IDO high (expression by CAFs): worse DSS and MFS		[286]

Table 3. Cont.

Marker	BC Subtype	Number of Patients	Method	Positive/Overexpressing Cases	Prognostic/Predictive Value	Comments	Reference
	All	91 PT 21 benign lesions 10 healthy controls	IHC	IDO expression: PT: 55/91 (60%) Benign lesions 9/21 (43%) Healthy controls 2/10 (20%)	NA	IDO expression correlated to advanced stage	[287]
	All	85	IHC	NA	NA	IDO expression correlated to Treg infiltration and lymph-node metastasis	[288]
	All	5	IHC	IDO expression 5/5 (100%)	NA		[289]

Abbreviations: CSF-1R, colony-stimulating factor 1 receptor; CSF-1, colony-stimulating factor 1; CCL2, C-C Motif Chemokine Ligand 2; CCR2, C-C Motif Chemokine Receptor 2; IDO, Indoleamine 2,3-dioxygenase; NK-cells, natural-killer cells; CD40, cluster of differentiation 40; CD94, cluster of differentiation 94; NKG2A, NK group member 2A; NKG2D, NK group member 2D; VEGF, vascular endothelial growth factor; IHC, immunohistochemistry; qRT-PCR, quantitative real-time polymerase chain reaction; T-reg, T-regulatory cells; OS, overall survival; PFS, progression-free survival; MFS, metastasis-free survival; RFS, relapse-free survival; TTP, time-to-progression; DSS, disease-specific survival; BCCS, breast cancer-specific survival; PT, primary tumor; NACT, neoadjuvant chemotherapy; PD-1, programmed death 1; TNBC, triple-negative breast cancer; ER, estrogen receptor; HR, hormone receptor; CAFs, cancer-associated fibroblasts; MICBA/B, MHC class I chain-related protein A and B; ULBP1-5, UL binding protein 1-5; LN, lymph node; TDLN, tumor-draining lymph node; NA, not available.

Table 4. Ongoing clinical trials potentially including breast cancer patients for targeting of immune-related markers predominantly expressed on macrophages, NK and dendritic cells.

Target	Drug	Other Agent(s)	Phase	Disease	Line	NCT Identifier	Trial Status
TAM-stimulatory markers							
<i>CSF-1/CSF-1R</i>							
CSF-1R/CSF-1 inhibitors	PLX 3397 (Pexidartinib)	+ Eribulin	Ib/II	Metastatic breast cancer	≥ 1 prior line	NCT01596751	Active, not recruiting
		No	I	Advanced solid tumors	No standard therapy available	NCT01004861	Active, not recruiting
		+/- Paclitaxel	Ib	Advanced solid tumors	Not specified	NCT01525602	Completed, no published results
	ARRY-382	+/- Pembrolizumab (anti-PD1)	Ib/II	Advanced solid tumors including TNBC (phase Ib)	No standard therapy available	NCT02880371	Recruiting
		No	I	Advanced or metastatic solid tumors	No standard therapy available	NCT01316822	Completed, no published results
	BLZ945	+/- PDR001 (anti-PD1)	I	Advanced solid tumors including TNBC	Not specified	NCT02829723	Recruiting
Anti CSF-1R antibodies	LY3022855 (IMC-CS4)	No	I	Advanced BC	≥ 1 prior line	NCT02265536	Completed, no published results
		+ Durvalumab (anti-PDL1) or Tremelimumab (anti-CTLA4)	I	Advanced solid tumors	Not specified	NCT02718911	Completed, no published results
		No	I	Advanced solid tumors	No standard therapy available	NCT01346358	Completed, safety results published [290]
	RO5509554 (Emactuzumab)	+ Atezolizumab (anti-PDL1)	I	Advanced solid tumors including TNBC	Not specified	NCT02323191	Recruiting
		+/- Paclitaxel	I	Advanced solid tumors	No standard therapy available	NCT01494688	Completed, preliminary safety and activity results published [291]
		+ RO7009789 (CD40 agonist)	Ib	Advanced solid tumors including TNBC	No standard therapy available	NCT02760797	Completed, no published results
	AMG820	No	I	Advanced solid tumors	Not specified	NCT01444404	Completed, no published results

Table 4. Cont.

Target	Drug	Other Agent(s)	Phase	Disease	Line	NCT Identifier	Trial Status
	SNDX-6352	Phase Ia: SNDX-6352 monotherapy Phase Ib: + Durvalumab (anti-PDL1)	I	Advanced solid tumors	≥ 1 prior line and no standard therapy available	NCT03238027	Recruiting
	Cabiralizumab (BMS-986227, FPA008)	+/- Nivolumab (anti-PD1)	I	Advanced malignancies	No standard therapy available	NCT03158272	Recruiting
		+ Nivolumab (anti-PD1) and SBRT	I	Advanced malignancies	No standard therapy available	NCT03431948	Recruiting
	PD 0360324 (M-CSF mAb)	+ Avelumab (anti-PDL1)	Ib/II	Advanced solid tumors including TNBC	No standard therapy available	NCT02554812	Recruiting
CCL2/CCR2							
CCR2 antagonist	PF-04136309	+ Avelumab (anti-PDL1) +Utomilumab (anti-4-1BB)	Ib/II	Advanced solid tumors including TNBC	No standard therapy available	NCT02554812	Recruiting
CD47 – SIRPα							
Anti-CD47 antibodies	Hu5F9-G4	+ Cetuximab (anti-EGFR)	Ib/II	Advanced solid tumors including BC (phase Ib)	≥ 1 prior line	NCT02953782	Recruiting
		+Avelumab (anti-PDL1)	Ib	Advanced solid tumors	Not specified	NCT03558139	Recruiting
	CC-90002	No	I	Advanced solid tumors	No standard therapy available	NCT02367196	Recruiting
	IBI188	No	Ia	Advanced solid tumors	No standard therapy available	NCT03763149	Recruiting
		No	I	Advanced solid tumors	No standard therapy available	NCT03717103	Recruiting
	AO-176	No	I	Advanced solid tumors	No standard therapy available	NCT03834948	Recruiting
	SRF231	No	I/Ib	Advanced solid tumors	No standard therapy available	NCT03512340	Recruiting
SIRPα-IgG1-Fc	TTI-621 (intra-tumoral injection)	+/- PD1/PDL1 Inhibitor	I	Advanced solid tumors with percutaneously accessible lesions	No standard therapy available	NCT02890368	Recruiting
	ALX148	+/- Trastuzumab or Pembrolizumab (anti-PD1) or Rituximab (anti-CD20)	I	Advanced solid tumors	No standard therapy available	NCT03013218	Recruiting, preliminary safety results published [292]

Table 4. Cont.

Target	Drug	Other Agent(s)	Phase	Disease	Line	NCT Identifier	Trial Status
TAM-inhibitory markers							
CD40 (agonists)	CP-870,893	No	I	Advanced solid tumors	No standard therapy available	NCT02225002	Completed, no published results
		No	I	Advanced solid tumors	Patients who had clinical benefit following a single infusion of CP-870,893	NCT02157831	Completed
	RO7009789 Selicrelumab	+ Atezolizumab (anti PDL1)	Ib	Advanced solid tumors	No standard therapy available	NCT02304393	Recruiting
		+ Emactuzumab (anti-CSF-1R)	I	Advanced solid tumors including TNBC	No standard therapy available	NCT02760797	Completed, no published results
		+ Vanucizumab (anti-VEGF-A and angiopoietin-2)	I	Metastatic solid tumors	Not specified	NCT02665416	Recruiting
	ADC-1013 (intra-tumoral or intra-venous injection)	No	I	Advanced solid tumors	Not specified	NCT02379741	Completed, no published results
	JNJ-64457107	No	I	Advanced solid tumors	Not specified	NCT0282909	Recruiting
TLR7 (agonists)	Imiquimod	+ Cyclophosphamide and Radiotherapy	I/II	Advanced BC with skin metastases	Any line	NCT01421017	Completed, no published results
NK cell-inhibitory markers							
CD94/ NKG2A	IPH2201	+ Durvalumab (anti-PDL1)	I/II	Advanced solid tumors	Any line	NCT02671435	Recruiting
KIR family	Lirilumab (anti-KIR2DL1,2,3 antibody)	+Nivolumab (anti-PD1) Or + Nivolumab (anti-PD1) and Ipilimumab (anti-CTLA4)	I	Advanced and/or metastatic solid tumors	Not specified	NCT03203876	Active, not recruiting
		+Nivolumab (anti-PD1)	I/II	Advanced solid tumors	≥ 1 and ≤ 5 prior lines	NCT01714739	Active, not recruiting

Table 4. Cont.

Target	Drug	Other Agent(s)	Phase	Disease	Line	NCT Identifier	Trial Status
IDO	Small-molecule inhibitor of IDO-1	+ INCB01158 (arginase inhibitor) +/- Pembrolizumab (anti-PD1)	I/II	Advanced solid tumors	No standard therapy available	NCT03361228	Active, not recruiting
		+ Pembrolizumab (anti-PD1)	I/II	Advanced or metastatic solid tumors including TNBC (phase I)	≥ 1 prior line	NCT02178722	Active, not recruiting Preliminary safety and efficacy results published [293]
		+ Sirolimus (mTOR inhibitor)	I	Advanced solid tumors	≥ 1 prior line and no standard therapy available	NCT03217669	Recruiting
		+Nivolumab (anti-PD1) and Ipilimumab (anti-CTLA4) (group A) + Nivolumab (anti-PD1) + lirilumab (anti-KIR) (group B)	I/II	Advanced solid tumors	No standard therapy available (phase I) ≥ 1 prior line (phase II)	NCT03347123	Active, not recruiting
		+ Durvalumab (anti-PDL1)	I/II	Advanced solid tumors	≥ 1 prior line	NCT02318277	Active, not recruiting
		+ Pembrolizumab (anti-PD1) And mFOLFOX6 Or (anti-PD1) Gemcitabine and Nab-Paclitaxel Or Carboplatin and Paclitaxel Or Pemetrexed, and Platinum agent Or Cyclophosphamide Or Gemcitabine and Platinum agent Or Platinum agent and 5-Fu	I/II	Advanced solid tumors	Not specified	NCT03085914	Active, not recruiting
		+/- Pembrolizumab (anti-PD1) Or +/-Pembrolizumab (anti-PD1) and Carboplatin or Cisplatin and Paclitaxel Or +/- Pembrolizumab (anti-PD1) and Carboplatin and Paclitaxel	I	Advanced solid tumors (Japanese population)	No standard therapy available	NCT02862457	Active, not recruiting Preliminary safety and efficacy results published [294]
		Epacadostat (INCB024360)					

Table 4. Cont.

Target	Drug	Other Agent(s)	Phase	Disease	Line	NCT Identifier	Trial Status
		+ Pembrolizumab (anti-PD1) and Azacitidine (DNA methyl transferase inhibitor) Or + INCB057643 (BET inhibitor) + Pembrolizumab (anti-PD1) Or + INCB059872 (LSD1 inhibitor) and Pembrolizumab (anti-PD1)	I/II	Advanced solid tumors	No standard therapy available	NCT02959437	Active, not recruiting
		No	I	Advanced solid tumors	No standard therapy available	NCT01195311	Completed, safety results published [295]
		+ Pembrolizumab (anti-PD1) and INCAGN01876 (anti-GITR)	I/II	Advanced solid tumors	No standard therapy available	NCT03277352	Active, not recruiting
		+ Itacitinib (JAK inhibitor)	I	Advanced solid tumors including TNBC	No standard therapy available	NCT02559492	Active, not recruiting
		No	Ib	Resectable metastatic solid tumors	Eligible for surgical resection and no standard therapy available	NCT03471286	Recruiting
	GDC-0919 (navoximod)	+ Atezolizumab (anti-PD-1)	Ib	Advanced solid tumors	≥ 1 prior line	NCT02471846	Active, not recruiting
	NLG802	No	I	Advanced solid tumors	Not specified	NCT03164603	Recruiting

Abbreviations: TAM, tumor-associated macrophages; CSF-1R, colony-stimulating factor 1 receptor; CSF-1, colony-stimulating factor 1; PD-1, programmed death 1; PD-L1, programmed death ligand 1; SBRT, stereotactic body radiation therapy; CCL2, C-C Motif Chemokine Ligand 2; CCR2, C-C Motif Chemokine Receptor 2; CD47, cluster of differentiation 47; SIRP α , signal regulatory protein alpha; IDO, Indoleamine 2,3-dioxygenase; TLR7, toll-like receptor 7; NK-cells, natural-killer cells; CD40, cluster of differentiation 40; CD94, cluster of differentiation 94; KIR, Killer Immunoglobulin Receptors; NKG2A, NK group member 2A; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; KIR2DL1, Killer cell immunoglobulin-like receptor 2DL1; JAK, janus kinase; mTOR, mammalian target of rapamycin; BC, breast cancer; TNBC, triple-negative breast cancer; LSD1, lysine specific demethylase 1; BET, Bromodomain and Extra-Terminal motif; EGFR, epidermal growth factor receptor; VEGF-A, vascular endothelial growth factor A.

3.3. CD47 and SIRP α

Interaction between the two cell-surface immunoglobulin family members, CD47 and signal regulatory protein alpha (SIRP α), is crucial for the regulation of phagocytosis. CD47 is expressed on cancer cells while SIRP α is expressed on macrophages. Upon interaction, the anti-tumor immunity is diminished as CD47 represents a 'don't eat me' signal, thus impairing phagocytosis [296,297]. Through targeting this checkpoint axis using anti-CD47 antibodies, CD47-Fc and/or SIRP α -Fc fusion proteins, the macrophage phagocytic capacity can be restored (antibody-dependent cellular phagocytosis, ADCP) towards an effective immune response. The first reported efficacy results of the Hu5F9-G4 inhibitor combined with rituximab in non-Hodgkin's lymphoma are promising [298]. Possible synergistic effects of such treatments with anti-HER2 or anti-PD-L1/PD-1 antibodies are being tested in clinical trials (Table 4).

3.4. TLR7

TLR7 represents an intracellular receptor, member of the toll-like receptors transmembrane glycoprotein family. Its expression can enhance the DC function and can re-programme macrophages towards an anti-tumoral M1 phenotype [299,300]. Therefore, its activation using TLR7 agonists could provide effective anti-tumor responses. Indeed, the use of the topical TLR7-agonist imiquimod in combination with nab-paclitaxel led to the short-term regression of BC cutaneous metastases in early phase trials [301,302] (Table 4).

3.5. CD40

CD40 represents a co-stimulatory protein, member of the TNF receptor family and is an emerging target in cancer immunotherapy. CD40 is mostly expressed by APC and macrophages and binding of its ligand (CD40L) on T-cells results in T-cell activation [303]. Preclinical data of the CD40-agonist efficacy have been reported in BC and other tumor types, demonstrating the promotion of T-cell responses [304,305]. CD40 activation using agonistic monoclonal antibodies can also lead to the enhancement of macrophage tumoricidal and pro-inflammatory properties mainly through MHC-II upregulation [303]. Preliminary results indicate activity and durable immune responses [306] (Table 4).

4. Natural-Killer Cells and Related Markers

4.1. Killer Immunoglobulin Receptors (KIR)

NK-cells represent an immune cell subpopulation with an active role in effective antitumor immunity [307]. MHC class I specific Killer Immunoglobulin Receptor (KIR) family members are mostly expressed on the surface of NK-cells. Some KIR - upon binding to their ligands HLA-B or HLA-C - can hinder NK cell activation [308], while others are associated with NK stimulatory properties and better prognosis for cancer patients [309,310]. Ongoing clinical trials are underway, testing antibodies against NK-inhibiting KIR family members in combination with other immune checkpoint inhibitors (Table 4).

4.2. CD94/NKG2A

NK group member 2A (NKG2A) represents a novel inhibitory receptor, which forms heterodimers with CD94, both belonging to the C-type lectin-like family and expressed mainly on the surface of NK-cells and also on CD8+ T-cells. Upon binding of the complex to its MHC class I (HLA-E) ligand, the anti-tumoral capacity of NK-cells can be hindered and an immunosuppressive phenotype through T-cell inactivation is established [308,311]. Recently, two preclinical studies in colorectal and head and neck carcinoma demonstrated that blockade of this receptor may be a new appealing immunotherapeutic target [312,313]. Expression of NKG2A has been described in BC patients [273], however no studies on therapeutic targeting are ongoing (Table 3).

4.3. NK-Cell Activating Receptors

NK-cells are activated through various receptors such as the natural cytotoxicity receptor (NCR) family (NCR1 or NKp46, NCR2 or NKp44, NCR3 or NKp30) and NK group member 2D (NKG2D). The latter recognizes several ligands including MHC class I polypeptide-related sequence (MICA/MICB) and UL16-binding proteins (ULBP1-6) and their interaction leads to enhanced cytotoxicity [314,315]. Expression of NKG2D ligands has been associated with improved survival in BC [274,316,317] (Table 3).

5. IDO

Indoleamine 2,3 dioxygenase-1 (IDO1) is an enzyme mostly found in DC and an appealing target for cancer immunotherapy [318]. It plays an important role in metabolism-mediated immune regulation by catalyzing the conversion of amino acid tryptophan to kynurenine and thus impairing T-cell activation and promoting Treg expansion [319,320]. IDO expression in BC patients has been extensively studied, with varying positivity, from 14 to 100% of the cases [276,279]. Most of the studies describe a predominant expression by tumor cells with limited expression by stromal dendritic-like cells and occasional expression by myoepithelial cells. Although conflicting results have been reported, the majority of the studies show that the IDO expression is correlated to an advanced stage at diagnosis, high grade, ER negativity and worse outcome [277,278]. Recent findings from a phase I trial, indicate the activity and safety of targeting IDO in combination with anti-PD-L1 monoclonal antibody atezolizumab in various advanced solid tumors including BC [321].

6. Myeloid-Derived Suppressor Cells

MDSCs represent a heterogeneous population of immature myeloid cells including progenitor cells, immature DCs, macrophages and granulocytes. In humans, MDSCs are defined by the positive expression of CD33 and CD11b and negative or reduced expression of HLA-DR. MDSCs are further classified as monocytic or granulocytic MDSCs when CD14 or CD15 is expressed, respectively.

MDSCs play a major role in promoting an immunosuppressive microenvironment through various mechanisms: Production of reactive oxygen and nitrogen species depleting TILs [322,323], impairment of lymphocyte-homing [324], promotion of other immunosuppressive cells such as Tregs and M2-macrophages [325,326], depletion of metabolites involved in the T cell function such as L-arginine and cysteine [327,328] PD-L1 expression [329] and adenosine production by upregulating the expression of ectonucleosidases CD39 and CD73 [330]. In addition to their immunosuppressive effect, MDSCs also promote tumor dissemination and metastasis by affecting epithelial-mesenchymal transition [331], degradation of extra-cellular matrix [332], stem cell formation [333], angiogenesis and formation of premetastatic niches [334,335].

Presence of MDSCs in BC patients has been studied both in peripheral blood and primary tumors. Patients with BC have elevated levels of circulating MDSCs compared to healthy donors or patients with benign lesions and the levels of MDSCs increase with tumor burden (i.e. clinical stage), making it a potential tool for BC diagnosis [336,337]. MDSCs are also present in the BC tumor microenvironment at significantly higher levels than the adjacent healthy breast tissue and one study found that TNBC seems to be more infiltrated than other BC subtypes [338–340]. Moreover, MDSCs represent a potential biomarker for predicting both survival and response to NACT, with higher levels of circulating of infiltrating MDSCs being associated with worse survival and pCR rates [340–343].

As a result, targeting MDSCs is a putative therapeutic tool for BC patients and different strategies have shown promising results in pre-clinical studies [344–347]. Briefly, current treatment strategies aim to modulate myelopoiesis by forcing differentiation into mature cells or inhibiting maturation from precursor cells, block MDSC accumulation in tumor sites and block MDSC immunosuppressive functions [348]. To our knowledge, only pre-clinical data of MDSC targeting in BC have been published but three early-phase clinical trials are currently ongoing (NCT03145012; NCT02922764; NCT02499328).

7. Implementing Combination Immunotherapy in the Clinic

Blockade of the PD-1/PD-L1 axis through the use of monoclonal antibodies as monotherapies has met with considerable success during the past decade. The central concept of immunotherapy with the inhibition of negative regulators of the immune response is the restoration of activity of exhausted cytotoxic T-lymphocytes. As evidenced by the observation of responses among patients lacking a local immune response (no PD-1/PD-L1 expression at the protein level, absence of TIL), a pre-existing immune response is not an absolute prerequisite needed for the elicitation of responses to treatment. Nevertheless, response rates and response duration following treatment with a monotherapy seem to be lower among those patients [349].

Intriguingly, the combined immune checkpoint blockade confers superior results compared to PD-1 blockade alone in this patient group. Data derived from the phase 3 CheckMate 067 trial indicate that double PD-1 and CTLA-4 blockade with nivolumab and ipilimumab improved both progression-free (HR=0.67; 95% CI were not reported) and overall survival (HR = 0.70) compared with nivolumab alone in patients with metastatic melanoma and PD-L1 expression lower than 1% [350]. Although this analysis is exploratory and the trial was not designed to perform this comparison, it provides support for immunotherapy combinations. The theoretical background seems intuitive. Mechanistically the two checkpoints function on different sites of immune activation: CTLA-4 carries out its function at the sites of priming whereas PD-1 is responsible for maintaining tolerance by dampening the activation of T-lymphocytes in the periphery [351]. It is unclear however whether the combinatory approach is successful thanks to an additive effect of the two inhibitors or if it results from the suppression of escape mechanisms. Similarly, it is conceivable that the inhibition of other negative regulators or agonistic activation of co-stimulatory molecules in combination with each other or with established immunotherapies can lead to further improvements in terms of patient outcomes. It is clear however that a mechanistic understanding of the biology of the candidate therapeutic targets and of the cross-talk that is activated upon inhibition is of paramount importance. Further underscoring the need for a deep understanding of the underlying biologic processes and the rational design of novel agents is the failure of the combination of the once promising IDO1 inhibitor epacadostat to improve outcomes in combination with pembrolizumab versus pembrolizumab alone in patients with metastatic melanoma [352].

While increased efficacy is the main goal, two barriers need to be overcome for successful integration of novel immunotherapies: Toxicity and financial cost. The clinical use of the checkpoint inhibition is associated with a risk for serious, potentially fatal immune-related adverse events (irAEs). Following this paradigm, the ability to inhibit multiple targets simultaneously may be limited by the adverse event profile of such combinations. It is important to note that while it is unclear whether the same molecular mechanisms that drive tumor rejection are to blame for the induction of irAEs, both retrospective [353] and limited prospective data [354] show a correlation between irAEs and better outcomes. This correlation has not been adequately studied if it also concerns combinatorial immunotherapy, which is associated with a higher risk for severe irAEs according to the aforementioned CheckMate 067 trial [350].

On the other hand, the revolution of cancer immunotherapy has brought to the limelight the associated financial costs. Published data indicate that the combination of nivolumab and ipilimumab, despite its efficacy, is not a cost-effective option [355]. How quickly and widely the combination will be adopted in light of the positive results from randomized trials on malignancies that can be readily treated with other options [356,357], remains to be seen. It is reasonable to assume that future combinations with novel agents will not differ in that respect. In addition, the evaluation of novel combinations will likely be plagued by the same problems that have affected PD-1/PD-L1 inhibitors: Inconclusive predictive biomarkers lacking analytical validity and clinical validity/utility, variety of companion diagnostics using different antibodies and cut-offs, trials reporting different results from different antibodies in the same clinical setting and overabundance of available options with no hints

on their differential efficacy [7]. It is therefore imperative that future phase 3 trials will be based on robust preclinical and early clinical data.

8. Conclusions

A large number of co-stimulatory or co-inhibitory molecules regulating tumor evasion from immunosurveillance have been studied in BC (Table 5). As reviewed here, there are solid pre-clinical data on the function of these factors and emerging data on their regulation and their role in the clinical setting. These molecules likely represent future targets of immunotherapy provided that the promise shown in early data is translated into improved patient survival in randomized trials.

Table 5. Overview of immune-related markers' characteristics including origin of expression and their role in anti-tumor immunity.

Marker	Types of Cells Expressed	Function on Anti-tumor Immunity
LAG-3	Effector T-cells, Tregs, NK-cells, B-cells, dendritic cells (DC)	Co-inhibitory
TIM-3	CD8+, CD4+ T helper 1 cells (Th1 cells), Tregs, NK cells, DC, monocytes, macrophages	Co-inhibitory
VISTA	CD8+, CD4+ T-cells, Tregs, NK cells, DC, monocytes, macrophages, granulocytes	Co-inhibitory
TIGIT	Effector, memory, follicular helper (Tfh) T-cells, Tregs, NK-cells	Co-inhibitory
GITR	T-cells	Co-stimulatory
B7-H3	T-cells, antigen-presenting cells (APC), NK-cells	Co-stimulatory Co-inhibitory
ICOS	T-cells	Co-stimulatory Co-inhibitory
4-1BB	Effector, helper T-cells, Tregs, B-cells, NK-cells, DC, neutrophils, eosinophils, mast cells, monocytes, macrophages	Co-stimulatory
CD27	T-cells, B-cells, NK-cells	Co-stimulatory
OX40	Tregs, neutrophils, NK-cells and NKT-cells, CD4+ and CD8+ T-cells (upon TCR stimulation)	Co-stimulatory
BTLA	T-cells, B-cells, Tfh cells, macrophages, DC, NKT-cells, NK-cells	Co-inhibitory
A2aR	T-cells, NKT-cells, B-cells, monocytes, macrophages, DC, NK-cells, mast cells, eosinophils, platelets	Co-inhibitory
CD73	B-cells, CD8+, CD4+ T-cells, Tregs, neutrophils, MDSC, monocytes, macrophages, DC, NK-cells, endothelial cells, cancer cells	Co-inhibitory
CD39	Platelets, endothelial cells, cancer cells	Co-inhibitory
CCR2	Monocytes, macrophages	Co-inhibitory
CD47	Cancer cells	Co-inhibitory
CD40	APC, macrophages	Co-stimulatory
CD94/NKG2A	NK-cells, CD8+ T-cells	Co-inhibitory
NKG2D	NK-cells	Co-stimulatory
IDO	Cancer cells, stromal dendritic-like cells, myoepithelial cells	Co-inhibitory

While it seems counterintuitive that the development of the next generation of immunotherapy agents precedes the optimization of the currently available ones, early recognition of the most promising agents can hasten their implementation in clinical practice. As we previously characterized the emergence of the PD-1/PD-L1 inhibition as the “end of the beginning” of cancer immunotherapy [7],

the exciting advances that are described in this review could very well represent the “beginning of the end” of non-selective cytotoxic chemotherapy.

Author Contributions: Conceptualization, I.Z., A.M. and T.F.; Literature review, S.C. and I.Z.; Writing—initial draft preparation, S.C. and I.Z.; Writing—review and editing, J.B., A.M. and T.F. All authors have read and approved the submitted version of the manuscript.

Funding: This research was funded by Swedish Cancer Society (grant number CAN 2018/846).

Acknowledgments: Alexios Matikas was supported by the Stockholm County Council (clinical postdoctoral appointment). Theodoros Foukakis is recipient of the Senior Clinical Investigator Award from the Swedish Cancer Society (grant number CAN 2017/1043). We thank Ioannis Mantas for his help with the illustrative work.

Conflicts of Interest: Sebastian Chrétien, Ioannis Zerdes and Alexios Matikas have no conflicts of interest to disclose. Theodoros Foukakis: Institutional grants from Roche and Pfizer and personal fees from Novartis, Pfizer, Roche and UpToDate; Jonas Bergh receives research fundings from Merck paid to Karolinska Institutet and from Amgen, Bayer, Pfizer, Roche and Sanofi-Aventis paid to Karolinska University Hospital. No personal payments. Payment from UpToDate for a chapter in breast cancer prediction paid to Asklepios Medicine HB.

References

- Hanahan, D.; Weinberg, R.A. Hallmarks of cancer: the next generation. *Cell* **2011**, *144*, 646–674. [CrossRef]
- Nobelprizemedicine.org. Available online: http://www.nobelprizemedicine.org/wp-content/uploads/2018/10/Adv_info_2018.pdf (accessed on 24 March 2019).
- Denkert, C.; von Minckwitz, G.; Darb-Esfahani, S.; Lederer, B.; Heppner, B.I.; Weber, K.E.; Budczies, J.; Huober, J.; Klauschen, F.; Furlanetto, J.; et al. Tumour-infiltrating lymphocytes and prognosis in different subtypes of breast cancer: a pooled analysis of 3771 patients treated with neoadjuvant therapy. *Lancet Oncol.* **2018**, *19*, 40–50. [CrossRef]
- Matikas, A.; Lövrot, J.; Ramberg, A.; Eriksson, M.; Lindsten, T.; Lekberg, T.; Hedenfalk, I.; Loman, N.; Bergh, J.; Hatschek, T.; et al. Dynamic evaluation of the immune infiltrate and immune function genes as predictive markers for neoadjuvant chemotherapy in hormone receptor positive, HER2 negative breast cancer. *Oncoimmunology* **2018**, *7*, e1466017. [CrossRef] [PubMed]
- Foukakis, T.; Lövrot, J.; Matikas, A.; Zerdes, I.; Lorent, J.; Tobin, N.; Suzuki, C.; Brage, S.E.; Carlsson, L.; Einbeigi, Z.; et al. Immune gene expression and response to chemotherapy in advanced breast cancer. *Br. J. Cancer* **2018**, *118*, 480–488. [CrossRef]
- Ogiya, R.; Niihara, N.; Kumaki, N.; Bianchini, G.; Kitano, S.; Iwamoto, T.; Hayashi, N.; Yokoyama, K.; Oshitanai, R.; Terao, M.; et al. Comparison of tumor-infiltrating lymphocytes between primary and metastatic tumors in breast cancer patients. *Cancer Sci* **2016**, *107*, 1730–1735. [CrossRef]
- Zerdes, I.; Matikas, A.; Bergh, J.; Rassidakis, G.Z.; Foukakis, T. Genetic, transcriptional and post-translational regulation of the programmed death protein ligand 1 in cancer: biology and clinical correlations. *Oncogene* **2018**, *37*, 4639–4661. [CrossRef]
- Kassardjian, A.; Shintaku, P.I.; Moatamed, N.A. Expression of immune checkpoint regulators, cytotoxic T lymphocyte antigen 4 (CTLA-4) and programmed death-ligand 1 (PD-L1), in female breast carcinomas. *PLoS ONE* **2018**, *13*, e0195958. [CrossRef]
- Schmid, P.; Adams, S.; Rugo, H.S.; Schneeweiss, A.; Barrios, C.H.; Iwata, H.; Diéras, V.; Hegg, R.; Im, S.-A.; Shaw Wright, G.; et al. Atezolizumab and Nab-Paclitaxel in Advanced Triple-Negative Breast Cancer. *N. Engl. J. Med.* **2018**, *379*, 2108–2121. [CrossRef]
- Adams, S.; Gatti-Mays, M.E.; Kalinsky, K.; Korde, L.A.; Sharon, E.; Amiri-Kordestani, L.; Bear, H.; McArthur, H.L.; Frank, E.; Perlmutter, J.; et al. Current Landscape of Immunotherapy in Breast Cancer: A Review. *JAMA Oncol.* **2019**. [CrossRef]
- Yarchoan, M.; Hopkins, A.; Jaffee, E.M. Tumor Mutational Burden and Response Rate to PD-1 Inhibition. *N. Engl. J. Med.* **2017**, *377*, 2500–2501. [CrossRef]
- Huang, C.-T.; Workman, C.J.; Flies, D.; Pan, X.; Marson, A.L.; Zhou, G.; Hipkiss, E.L.; Ravi, S.; Kowalski, J.; Levitsky, H.I.; et al. Role of LAG-3 in regulatory T cells. *Immunity* **2004**, *21*, 503–513. [CrossRef] [PubMed]
- Triebel, F.; Jitsukawa, S.; Baixeras, E.; Roman-Roman, S.; Genevee, C.; Viegas-Pequignot, E.; Hercend, T. LAG-3, a novel lymphocyte activation gene closely related to CD4. *J. Exp. Med.* **1990**, *171*, 1393–1405. [CrossRef] [PubMed]

14. Huard, B.; Tournier, M.; Triebel, F. LAG-3 does not define a specific mode of natural killing in human. *Immunol. Lett.* **1998**, *61*, 109–112. [[CrossRef](#)]
15. Kisielow, M.; Kisielow, J.; Capoferri-Sollami, G.; Karjalainen, K. Expression of lymphocyte activation gene 3 (LAG-3) on B cells is induced by T cells. *Eur. J. Immunol.* **2005**, *35*, 2081–2088. [[CrossRef](#)] [[PubMed](#)]
16. Buisson, S.; Triebel, F. LAG-3 (CD223) reduces macrophage and dendritic cell differentiation from monocyte precursors. *Immunology* **2005**, *114*, 369–374. [[CrossRef](#)]
17. Xu, F.; Liu, J.; Liu, D.; Liu, B.; Wang, M.; Hu, Z.; Du, X.; Tang, L.; He, F. LSECtin expressed on melanoma cells promotes tumor progression by inhibiting antitumor T-cell responses. *Cancer Res.* **2014**, *74*, 3418–3428. [[CrossRef](#)]
18. Kouo, T.; Huang, L.; Pucsek, A.B.; Cao, M.; Solt, S.; Armstrong, T.; Jaffee, E. Galectin-3 Shapes Antitumor Immune Responses by Suppressing CD8+ T Cells via LAG-3 and Inhibiting Expansion of Plasmacytoid Dendritic Cells. *Cancer Immunol. Res.* **2015**, *3*, 412–423. [[CrossRef](#)]
19. Maçon-Lemaître, L.; Triebel, F. The negative regulatory function of the lymphocyte-activation gene-3 co-receptor (CD223) on human T cells. *Immunology* **2005**, *115*, 170–178. [[CrossRef](#)]
20. Workman, C.J.; Dugger, K.J.; Vignali, D.A.A. Cutting edge: molecular analysis of the negative regulatory function of lymphocyte activation gene-3. *J. Immunol.* **2002**, *169*, 5392–5395. [[CrossRef](#)]
21. Workman, C.J.; Vignali, D.A.A. Negative regulation of T cell homeostasis by lymphocyte activation gene-3 (CD223). *J. Immunol.* **2005**, *174*, 688–695. [[CrossRef](#)] [[PubMed](#)]
22. Gandhi, M.K.; Lambley, E.; Duraiswamy, J.; Dua, U.; Smith, C.; Elliott, S.; Gill, D.; Marlton, P.; Seymour, J.; Khanna, R. Expression of LAG-3 by tumor-infiltrating lymphocytes is coincident with the suppression of latent membrane antigen-specific CD8+ T-cell function in Hodgkin lymphoma patients. *Blood* **2006**, *108*, 2280–2289. [[CrossRef](#)]
23. Sasidharan Nair, V.; El Salhat, H.; Taha, R.Z.; John, A.; Ali, B.R.; Elkord, E. DNA methylation and repressive H3K9 and H3K27 trimethylation in the promoter regions of PD-1, CTLA-4, TIM-3, LAG-3, TIGIT, and PD-L1 genes in human primary breast cancer. *Clin. Epigenetics* **2018**, *10*, 78. [[CrossRef](#)]
24. Kok, M. LAG-3: Another brake to release in breast cancer? *Ann. Oncol.* **2017**, *28*, 2907–2908. [[CrossRef](#)] [[PubMed](#)]
25. Bottai, G.; Raschioni, C.; Losurdo, A.; Di Tommaso, L.; Tinterri, C.; Torrisi, R.; Reis-Filho, J.S.; Roncalli, M.; Sotiriou, C.; Santoro, A.; et al. An immune stratification reveals a subset of PD-1/LAG-3 double-positive triple-negative breast cancers. *Breast Cancer Res.* **2016**, *18*. [[CrossRef](#)]
26. Burugu, S.; Gao, D.; Leung, S.; Chia, S.K.; Nielsen, T.O. LAG-3+ tumor infiltrating lymphocytes in breast cancer: clinical correlates and association with PD-1/PD-L1+ tumors. *Ann. Oncol.* **2017**, *28*, 2977–2984. [[CrossRef](#)]
27. Brignone, C.; Gutierrez, M.; Mefti, F.; Brain, E.; Jarcau, R.; Cvitkovic, F.; Bousetta, N.; Medioni, J.; Gligorov, J.; Grygar, C.; et al. First-line chemoimmunotherapy in metastatic breast carcinoma: combination of paclitaxel and IMP321 (LAG-3Ig) enhances immune responses and antitumor activity. *J. Transl. Med.* **2010**, *8*, 71. [[CrossRef](#)]
28. Wang, Y.; Dong, T.; Xuan, Q.; Zhao, H.; Qin, L.; Zhang, Q. Lymphocyte-Activation Gene-3 Expression and Prognostic Value in Neoadjuvant-Treated Triple-Negative Breast Cancer. *J. Breast Cancer* **2018**, *21*, 124–133. [[CrossRef](#)] [[PubMed](#)]
29. Zhang, H.; Xiang, R.; Wu, B.; Li, J.; Luo, G. T-cell immunoglobulin mucin-3 expression in invasive ductal breast carcinoma: Clinicopathological correlations and association with tumor infiltration by cytotoxic lymphocytes. *Mol. Clin. Oncol.* **2017**, *7*, 557–563. [[CrossRef](#)]
30. Zhu, S.; Lin, J.; Qiao, G.; Wang, X.; Xu, Y. Tim-3 identifies exhausted follicular helper T cells in breast cancer patients. *Immunobiology* **2016**, *221*, 986–993. [[CrossRef](#)]
31. Cari, L.; Nocentini, G.; Migliorati, G.; Riccardi, C. Potential effect of tumor-specific Treg-targeted antibodies in the treatment of human cancers: A bioinformatics analysis. *Oncoimmunology* **2018**, *7*, e1387705. [[CrossRef](#)] [[PubMed](#)]
32. Burugu, S.; Gao, D.; Leung, S.; Chia, S.K.; Nielsen, T.O. TIM-3 expression in breast cancer. *Oncoimmunology* **2018**, *7*. [[CrossRef](#)] [[PubMed](#)]
33. Martínez-Canales, S.; Cifuentes, F.; Gregorio, M.L.D.R.; Serrano-Oviedo, L.; Galán-Moya, E.M.; Amir, E.; Pandiella, A.; Györfy, B.; Ocaña, A. Transcriptomic immunologic signature associated with favorable clinical outcome in basal-like breast tumors. *PLoS ONE* **2017**, *12*, e0175128. [[CrossRef](#)]

34. Li, C.-H.; Kuo, W.-H.; Chang, W.-C.; Huang, S.-C.; Chang, K.-J.; Sheu, B.-C. Activation of regulatory T cells instigates functional down-regulation of cytotoxic T lymphocytes in human breast cancer. *Immunol. Res.* **2011**, *51*, 71–79. [[CrossRef](#)]
35. Benevides, L.; Cardoso, C.R.B.; Tiezzi, D.G.; Marana, H.R.C.; Andrade, J.M.; Silva, J.S. Enrichment of regulatory T cells in invasive breast tumor correlates with the upregulation of IL-17A expression and invasiveness of the tumor. *Eur. J. Immunol.* **2013**, *43*, 1518–1528. [[CrossRef](#)] [[PubMed](#)]
36. Krausz, L.T.; Fischer-Fodor, E.; Major, Z.Z.; Fetica, B. GITR-expressing regulatory T-cell subsets are increased in tumor-positive lymph nodes from advanced breast cancer patients as compared to tumor-negative lymph nodes. *Int. J. Immunopathol. Pharmacol.* **2012**, *25*, 59–66. [[CrossRef](#)] [[PubMed](#)]
37. Ostapchuk, Y.O.; Perfilyeva, Y.V.; Kustova, E.A.; Urazalieva, N.T.; Omarbaeva, N.A.; Talaeva, S.G.; Belyaev, N.N. Functional heterogeneity of circulating T regulatory cell subsets in breast cancer patients. *Breast Cancer* **2018**. [[CrossRef](#)]
38. Sun, J.; Guo, Y.-D.; Li, X.-N.; Zhang, Y.-Q.; Gu, L.; Wu, P.-P.; Bai, G.-H.; Xiao, Y. B7-H3 expression in breast cancer and upregulation of VEGF through gene silence. *Oncol. Targets Ther.* **2014**, *7*, 1979–1986. [[CrossRef](#)] [[PubMed](#)]
39. Arigami, T.; Narita, N.; Mizuno, R.; Nguyen, L.; Ye, X.; Chung, A.; Giuliano, A.E.; Hoon, D.S.B. B7-h3 ligand expression by primary breast cancer and associated with regional nodal metastasis. *Ann. Surg.* **2010**, *252*, 1044–1051. [[CrossRef](#)] [[PubMed](#)]
40. Liu, C.; Liu, J.; Wang, J.; Liu, Y.; Zhang, F.; Lin, W.; Gao, A.; Sun, M.; Wang, Y.; Sun, Y. B7-H3 expression in ductal and lobular breast cancer and its association with IL-10. *Mol. Med. Rep.* **2013**, *7*, 134–138. [[CrossRef](#)] [[PubMed](#)]
41. Maeda, N.; Yoshimura, K.; Yamamoto, S.; Kuramasu, A.; Inoue, M.; Suzuki, N.; Watanabe, Y.; Maeda, Y.; Kamei, R.; Tsunedomi, R.; et al. Expression of B7-H3, a Potential Factor of Tumor Immune Evasion in Combination with the Number of Regulatory T Cells, Affects Against Recurrence-Free Survival in Breast Cancer Patients. *Ann. Surg. Oncol.* **2014**, *21*, 546–554. [[CrossRef](#)]
42. Cong, F.; Yu, H.; Gao, X. Expression of CD24 and B7-H3 in breast cancer and the clinical significance. *Oncol. Lett.* **2017**, *14*, 7185–7190. [[CrossRef](#)]
43. Wilson, K.E.; Bachawal, S.V.; Abou-Elkacem, L.; Jensen, K.; Machtaler, S.; Tian, L.; Willmann, J.K. Spectroscopic Photoacoustic Molecular Imaging of Breast Cancer using a B7-H3-targeted ICG Contrast Agent. *Theranostics* **2017**, *7*, 1463–1476. [[CrossRef](#)]
44. Seaman, S.; Zhu, Z.; Saha, S.; Zhang, X.M.; Yang, M.Y.; Hilton, M.B.; Morris, K.; Szot, C.; Morris, H.; Swing, D.A.; et al. Eradication of Tumors through Simultaneous Ablation of CD276/B7-H3-Positive Tumor Cells and Tumor Vasculature. *Cancer Cell* **2017**, *31*, 501–515. [[CrossRef](#)] [[PubMed](#)]
45. Bachawal, S.V.; Jensen, K.C.; Wilson, K.E.; Tian, L.; Lutz, A.M.; Willmann, J.K. Breast Cancer Detection by B7-H3 Targeted Ultrasound Molecular Imaging. *Cancer Res.* **2015**, *75*, 2501–2509. [[CrossRef](#)] [[PubMed](#)]
46. Faget, J.; Bendriss-Vermare, N.; Gobert, M.; Durand, I.; Olive, D.; Biota, C.; Bachelot, T.; Treilleux, I.; Goddard-Leon, S.; Lavergne, E.; et al. ICOS-ligand expression on plasmacytoid dendritic cells supports breast cancer progression by promoting the accumulation of immunosuppressive CD4+ T cells. *Cancer Res.* **2012**, *72*, 6130–6141. [[CrossRef](#)]
47. Alizadeh, A.A.; Gentles, A.J.; Alencar, A.J.; Liu, C.L.; Kohrt, H.E.; Houot, R.; Goldstein, M.J.; Zhao, S.; Natkunam, Y.; Advani, R.H.; et al. Prediction of survival in diffuse large B-cell lymphoma based on the expression of 2 genes reflecting tumor and microenvironment. *Blood* **2011**, *118*, 1350–1358. [[CrossRef](#)]
48. Wang, Q.; Zhang, P.; Zhang, Q.; Wang, X.; Li, J.; Ma, C.; Sun, W.; Zhang, L. Analysis of CD137 and CD137L Expression in Human Primary Tumor Tissues. *Croat Med. J.* **2008**, *49*, 192–200. [[CrossRef](#)] [[PubMed](#)]
49. Ryan, M.C.; Kostner, H.; Gordon, K.A.; Duniho, S.; Sutherland, M.K.; Yu, C.; Kim, K.M.; Nesterova, A.; Anderson, M.; McEarchern, J.A.; et al. Targeting pancreatic and ovarian carcinomas using the auristatin-based anti-CD70 antibody–drug conjugate SGN-75. *Br. J. Cancer* **2010**, *103*, 676–684. [[CrossRef](#)] [[PubMed](#)]
50. Liu, L.; Yin, B.; Yi, Z.; Liu, X.; Hu, Z.; Gao, W.; Yu, H.; Li, Q. Breast cancer stem cells characterized by CD70 expression preferentially metastasize to the lungs. *Breast Cancer* **2018**. [[CrossRef](#)]
51. Tvrdík, D.; Skálová, H.; Dundr, P.; Povýšil, C.; Velenská, Z.; Berková, A.; Staněk, L.; Petruželka, L. Apoptosis—Associated genes and their role in predicting responses to neoadjuvant breast cancer treatment. *Med. Sci. Monit.* **2012**, *18*, BR60–BR67. [[CrossRef](#)]

52. Xie, F.; Wang, Q.; Chen, Y.; Gu, Y.; Mao, H.; Zeng, W.; Zhang, X. Costimulatory molecule OX40/OX40L expression in ductal carcinoma in situ and invasive ductal carcinoma of breast: An immunohistochemistry-based pilot study. *Pathol. Res. Pract.* **2010**, *206*, 735–739. [[CrossRef](#)] [[PubMed](#)]
53. Xie, F.; Wang, Q.; Chen, Y.; Gu, Y.; Shi, Q.; Ge, Y.; Yu, G.; Wu, H.; Mao, Y.; Wang, X.; et al. Characterization and application of two novel monoclonal antibodies against human OX40: costimulation of T cells and expression on tumor as well as normal gland tissues. *Tissue Antigens* **2006**, *67*, 307–317. [[CrossRef](#)]
54. Morris, A.; Vetto, J.T.; Ramstad, T.; Funatake, C.J.; Choolun, E.; Entwisle, C.; Weinberg, A.D. Induction of anti-mammary cancer immunity by engaging the OX-40 receptor in vivo. *Breast Cancer Res. Treat.* **2001**, *67*, 71–80. [[CrossRef](#)] [[PubMed](#)]
55. Ramstad, T.; Lawnicki, L.; Vetto, J.; Weinberg, A. Immunohistochemical analysis of primary breast tumors and tumor-draining lymph nodes by means of the T-cell costimulatory molecule OX-40. *Am. J. Surg.* **2000**, *179*, 400–406. [[CrossRef](#)]
56. Weinberg, A.D.; Rivera, M.M.; Prell, R.; Morris, A.; Ramstad, T.; Vetto, J.T.; Urba, W.J.; Alvord, G.; Bunce, C.; Shields, J. Engagement of the OX-40 receptor in vivo enhances antitumor immunity. *J. Immunol.* **2000**, *164*, 2160–2169. [[CrossRef](#)]
57. Liu, Z.; Li, M.; Jiang, Z.; Wang, X. A Comprehensive Immunologic Portrait of Triple-Negative Breast Cancer. *Transl. Oncol.* **2018**, *11*, 311–329. [[CrossRef](#)] [[PubMed](#)]
58. Muenst, S.; Soysal, S.D.; Gao, F.; Obermann, E.C.; Oertli, D.; EGillanders, W. The presence of programmed death 1 (PD-1)-positive tumor-infiltrating lymphocytes is associated with poor prognosis in human breast cancer. *Breast Cancer Res. Treat.* **2013**, *139*. [[CrossRef](#)]
59. Chandler, M.R.; Keene, K.S.; Tuomela, J.M.; Forero-Torres, A.; Desmond, R.; Vuopala, K.S.; Harris, K.W.; Merner, N.D.; Selander, K.S. Lower frequency of TLR9 variant associated with protection from breast cancer among African Americans. *PLoS ONE* **2017**, *12*, e0183832. [[CrossRef](#)]
60. Meseure, D.; Vacher, S.; Drak Alsibai, K.; Trassard, M.; Nicolas, A.; Leclere, R.; Lerebours, F.; Guinebretiere, J.M.; Marangoni, E.; Lidereau, R.; et al. Biopathological Significance of TLR9 Expression in Cancer Cells and Tumor Microenvironment Across Invasive Breast Carcinomas Subtypes. *Cancer Microenviron* **2016**, *9*, 107–118. [[CrossRef](#)]
61. Tuomela, J.; Sandholm, J.; Karihtala, P.; Ilvesaro, J.; Vuopala, K.S.; Kauppila, J.H.; Kauppila, S.; Chen, D.; Pressey, C.; Härkönen, P.; et al. Low TLR9 expression defines an aggressive subtype of triple-negative breast cancer. *Breast Cancer Res. Treat.* **2012**, *135*, 481–493. [[CrossRef](#)]
62. Sandholm, J.; Kauppila, J.H.; Pressey, C.; Tuomela, J.; Jukkola-Vuorinen, A.; Vaarala, M.; Johnson, M.R.; Harris, K.W.; Selander, K.S. Estrogen receptor- α and sex steroid hormones regulate Toll-like receptor-9 expression and invasive function in human breast cancer cells. *Breast Cancer Res. Treat.* **2012**, *132*, 411–419. [[CrossRef](#)]
63. Qiu, J.; Shao, S.; Yang, G.; Shen, Z.; Zhang, Y. Association of Toll like receptor 9 expression with lymph node metastasis in human breast cancer. *Neoplasma* **2011**, *58*, 251–255. [[CrossRef](#)]
64. González-Reyes, S.; Marín, L.; González, L.; González, L.O.; del Casar, J.M.; Lamelas, M.L.; González-Quintana, J.M.; Vizoso, F.J. Study of TLR3, TLR4 and TLR9 in breast carcinomas and their association with metastasis. *BMC Cancer* **2010**, *10*, 665. [[CrossRef](#)] [[PubMed](#)]
65. Berger, R.; Fiegl, H.; Goebel, G.; Obexer, P.; Ausserlechner, M.; Doppler, W.; Hauser-Kronberger, C.; Reitsamer, R.; Egle, D.; Reimer, D.; et al. Toll-Like Receptor 9 expression in breast and ovarian cancer is associated with poorly differentiated tumors. *Cancer Sci.* **2010**, *101*, 1059–1066. [[CrossRef](#)]
66. Jukkola-Vuorinen, A.; Rahko, E.; Vuopala, K.S.; Desmond, R.; Lehenkari, P.P.; Harris, K.W.; Selander, K.S. Toll-like receptor-9 expression is inversely correlated with estrogen receptor status in breast cancer. *J. Innate Immun.* **2009**, *1*, 59–68. [[CrossRef](#)] [[PubMed](#)]
67. Zhi, X.; Wang, Y.; Yu, J.; Yu, J.; Zhang, L.; Yin, L.; Zhou, P. Potential prognostic biomarker CD73 regulates epidermal growth factor receptor expression in human breast cancer. *IUBMB Life* **2012**, *64*, 911–920. [[CrossRef](#)]
68. Supernat, A.; Markiewicz, A.; Welnicka-Jaskiewicz, M.; Seroczynska, B.; Skokowski, J.; Sejda, A.; Szade, J.; Czapiewski, P.; Biernat, W.; Zaczek, A. CD73 expression as a potential marker of good prognosis in breast carcinoma. *Appl. Immunohistochem. Mol. Morphol.* **2012**, *20*, 103–107. [[CrossRef](#)]
69. Krüger, K.H.; Thompson, L.F.; Kaufmann, M.; Möller, P. Expression of ecto-5'-nucleotidase (CD73) in normal mammary gland and in breast carcinoma. *Br. J. Cancer* **1991**, *63*, 114–118. [[CrossRef](#)]

70. Samanta, D.; Park, Y.; Ni, X.; Li, H.; Zahnow, C.A.; Gabrielson, E.; Pan, F.; Semenza, G.L. Chemotherapy induces enrichment of CD47+/CD73+/PDL1+ immune evasive triple-negative breast cancer cells. *Proc. Natl. Acad. Sci. USA* **2018**, *115*, E1239–E1248. [[CrossRef](#)]
71. Buisseret, L.; Pommey, S.; Allard, B.; Garaud, S.; Bergeron, M.; Cousineau, I.; Ameye, L.; Bareche, Y.; Paesmans, M.; Crown, J.P.A.; et al. Clinical significance of CD73 in triple-negative breast cancer: multiplex analysis of a phase III clinical trial. *Ann. Oncol.* **2018**, *29*, 1056–1062. [[CrossRef](#)]
72. Yu, J.; Wang, X.; Lu, Q.; Wang, J.; Li, L.; Liao, X.; Zhu, W.; Lv, L.; Zhi, X.; Yu, J.; et al. Extracellular 5'-nucleotidase (CD73) promotes human breast cancer cells growth through AKT/GSK-3 β / β -catenin/cyclinD1 signaling pathway. *Int. J. Cancer* **2018**, *142*, 959–967. [[CrossRef](#)] [[PubMed](#)]
73. Turcotte, M.; Allard, D.; Mittal, D.; Bareche, Y.; Buisseret, L.; José, V.; Pommey, S.; Delisle, V.; Loi, S.; Joensuu, H.; et al. CD73 Promotes Resistance to HER2/ErbB2 Antibody Therapy. *Cancer Res.* **2017**, *77*, 5652–5663. [[CrossRef](#)] [[PubMed](#)]
74. Loi, S.; Pommey, S.; Haibe-Kains, B.; Beavis, P.A.; Darcy, P.K.; Smyth, M.J.; Stagg, J. CD73 promotes anthracycline resistance and poor prognosis in triple negative breast cancer. *Proc. Natl. Acad. Sci. USA* **2013**, *110*, 11091–11096. [[CrossRef](#)]
75. Canale, F.P.; Ramello, M.C.; Núñez, N.; Araujo Furlan, C.L.; Bossio, S.N.; Gorosito Serrán, M.; Tosello Boari, J.; Del Castillo, A.; Ledesma, M.; Sedlik, C.; et al. CD39 Expression Defines Cell Exhaustion in Tumor-Infiltrating CD8+ T Cells. *Cancer Res.* **2018**, *78*, 115–128. [[CrossRef](#)] [[PubMed](#)]
76. Syed Khaja, A.S.; Toor, S.M.; El Salhat, H.; Faour, I.; Ul Haq, N.; Ali, B.R.; Elkord, E. Preferential accumulation of regulatory T cells with highly immunosuppressive characteristics in breast tumor microenvironment. *Oncotarget* **2017**, *8*, 33159–33171.
77. Thibaudin, M.; Chaix, M.; Boidot, R.; Végran, F.; Derangère, V.; Limagne, E.; Berger, H.; Ladoire, S.; Apetoh, L.; Ghiringhelli, F. Human ectonucleotidase-expressing CD25^{high} Th17 cells accumulate in breast cancer tumors and exert immunosuppressive functions. *Oncoimmunology* **2016**, *5*, e1055444. [[CrossRef](#)] [[PubMed](#)]
78. Bastid, J.; Cottalorda-Regairaz, A.; Alberici, G.; Bonnefoy, N.; Eliaou, J.-F.; Bensussan, A. ENTPD1/CD39 is a promising therapeutic target in oncology. *Oncogene* **2013**, *32*, 1743–1751. [[CrossRef](#)] [[PubMed](#)]
79. Duhoux, F.P.; Jager, A.; Dirix, L.Y.; Huizing, M.T.; Jerusalem, G.H.M.; Vuylsteke, P.; De Cuyper, E.; Breiner, D.; Mueller, C.; Brignone, C.; et al. Combination of paclitaxel and a LAG-3 fusion protein (eftilagimod alpha), as a first-line chemoimmunotherapy in patients with metastatic breast carcinoma (MBC): Final results from the run-in phase of a placebo-controlled randomized phase II. *JCO* **2018**, *36*, 1050. [[CrossRef](#)]
80. Hong, D.S.; Schoffski, P.; Calvo, A.; Sarantopoulos, J.; Ochoa De Olza, M.; Carvajal, R.D.; Prawira, A.; Kyi, C.; Esaki, T.; Akerley, W.L.; et al. Phase I/II study of LAG525 \pm spartalizumab (PDR001) in patients (pts) with advanced malignancies. *JCO* **2018**, *36*, 3012. [[CrossRef](#)]
81. Koon, H.B.; Shepard, D.R.; Merghoub, T.; Schaer, D.A.; Sirard, C.A.; Wolchok, J.D. First-in-human phase 1 single-dose study of TRX-518, an anti-human glucocorticoid-induced tumor necrosis factor receptor (GITR) monoclonal antibody in adults with advanced solid tumors. *JCO* **2016**, *34*, 3017. [[CrossRef](#)]
82. Siu, L.L.; Steeghs, N.; Meniawy, T.; Joerger, M.; Spratlin, J.L.; Rottey, S.; Nagrial, A.; Cooper, A.; Meier, R.; Guan, X.; et al. Preliminary results of a phase I/IIa study of BMS-986156 (glucocorticoid-induced tumor necrosis factor receptor–related gene [GITR] agonist), alone and in combination with nivolumab in pts with advanced solid tumors. *JCO* **2017**, *35*, 104. [[CrossRef](#)]
83. Burris, H.A.; Callahan, M.K.; Tolcher, A.W.; Kummar, S.; Falchook, G.S.; Pachynski, R.K.; Tykodi, S.S.; Gibney, G.T.; Seiwert, T.Y.; Gainor, J.F.; et al. Phase 1 safety of ICOS agonist antibody JTX-2011 alone and with nivolumab (nivo) in advanced solid tumors; predicted vs observed pharmacokinetics (PK) in ICONIC. *JCO* **2017**, *35*, 3033. [[CrossRef](#)]
84. Segal, N.H.; Logan, T.F.; Hodi, F.S.; McDermott, D.; Melero, I.; Hamid, O.; Schmidt, H.; Robert, C.; Chiarion-Sileni, V.; Ascierto, P.A.; et al. Results from an Integrated Safety Analysis of Urelumab, an Agonist Anti-CD137 Monoclonal Antibody. *Clin. Cancer Res.* **2017**, *23*, 1929–1936. [[CrossRef](#)] [[PubMed](#)]
85. Awada, A.; Rolfo, C.D.; Rottey, S.; Ysebrant de Lendonck, L.; Schroyens, W.A.; Offner, F.; Silence, K.; Dreier, T.; Moshir, M.; de Haard, H.; et al. A phase I, first-in-human study of ARGX-110, a monoclonal antibody targeting CD70, a receptor involved in immune escape and tumor growth in patients with solid and hematologic malignancies. *JCO* **2014**, *32*, 3023. [[CrossRef](#)]

86. Infante, J.R.; Hansen, A.R.; Pishvaian, M.J.; Chow, L.Q.M.; McArthur, G.A.; Bauer, T.M.; Liu, S.V.; Sandhu, S.K.; Tsai, F.Y.-C.; Kim, J.; et al. A phase Ib dose escalation study of the OX40 agonist MOXR0916 and the PD-L1 inhibitor atezolizumab in patients with advanced solid tumors. *JCO* **2016**, *34*, 101. [[CrossRef](#)]
87. Babiker, H.M.; Borazanci, E.H.; Subbiah, V.; Diab, A.; Woodhead, G.; Hennemeyer, C.; Shah, A.H.; Hultsch, R.; Murthy, R.; Miller, C.; et al. Preliminary safety of deep/visceral (D/V) image guided (IG) intratumoral injection (ITI) of IMO-2125. *JCO* **2018**, *36*, e15150. [[CrossRef](#)]
88. Siu, L.L.; Burris, H.; Le, D.T.; Hollebecque, A.; Steeghs, N.; Delord, J.-P.; Hilton, J.; Barnhart, B.; Segal, E.; Sanghavi, K.; et al. Abstract CT180: Preliminary phase 1 profile of BMS-986179, an anti-CD73 antibody, in combination with nivolumab in patients with advanced solid tumors. *Cancer Res.* **2018**, *78*, CT180. [[CrossRef](#)]
89. Monney, L.; Sabatos, C.A.; Gaglia, J.L.; Ryu, A.; Waldner, H.; Chernova, T.; Manning, S.; Greenfield, E.A.; Coyle, A.J.; Sobel, R.A.; et al. Th1-specific cell surface protein Tim-3 regulates macrophage activation and severity of an autoimmune disease. *Nature* **2002**, *415*, 536–541. [[CrossRef](#)]
90. Gao, X.; Zhu, Y.; Li, G.; Huang, H.; Zhang, G.; Wang, F.; Sun, J.; Yang, Q.; Zhang, X.; Lu, B. TIM-3 Expression Characterizes Regulatory T Cells in Tumor Tissues and Is Associated with Lung Cancer Progression. *PLoS ONE* **2012**, *7*. [[CrossRef](#)] [[PubMed](#)]
91. Anderson, A.C.; Anderson, D.E.; Bregoli, L.; Hastings, W.D.; Kassam, N.; Lei, C.; Chandwaskar, R.; Karman, J.; Su, E.W.; Hirashima, M.; et al. Promotion of tissue inflammation by the immune receptor Tim-3 expressed on innate immune cells. *Science* **2007**, *318*, 1141–1143. [[CrossRef](#)] [[PubMed](#)]
92. Gleason, M.K.; Lenvik, T.R.; McCullar, V.; Felices, M.; O'Brien, M.S.; Cooley, S.A.; Verneris, M.R.; Cichocki, F.; Holman, C.J.; Panoskaltis-Mortari, A.; et al. Tim-3 is an inducible human natural killer cell receptor that enhances interferon gamma production in response to galectin-9. *Blood* **2012**, *119*, 3064–3072. [[CrossRef](#)] [[PubMed](#)]
93. Zhu, C.; Anderson, A.C.; Schubart, A.; Xiong, H.; Imitola, J.; Khoury, S.J.; Zheng, X.X.; Strom, T.B.; Kuchroo, V.K. The Tim-3 ligand galectin-9 negatively regulates T helper type 1 immunity. *Nat. Immunol.* **2005**, *6*, 1245–1252. [[CrossRef](#)]
94. Huang, Y.-H.; Zhu, C.; Kondo, Y.; Anderson, A.C.; Gandhi, A.; Russell, A.; Dougan, S.K.; Petersen, B.-S.; Melum, E.; Pertel, T.; et al. CEACAM1 regulates TIM-3-mediated tolerance and exhaustion. *Nature* **2015**, *517*, 386–390. [[CrossRef](#)]
95. Chiba, S.; Baghdadi, M.; Akiba, H.; Yoshiyama, H.; Kinoshita, I.; Dosaka-Akita, H.; Fujioka, Y.; Ohba, Y.; Gorman, J.V.; Colgan, J.D.; et al. Tumor-infiltrating DCs suppress nucleic acid-mediated innate immune responses through interactions between the receptor TIM-3 and the alarmin HMGB1. *Nat. Immunol.* **2012**, *13*, 832–842. [[CrossRef](#)]
96. DeKruyff, R.H.; Bu, X.; Ballesteros, A.; Santiago, C.; Chim, Y.-L.E.; Lee, H.-H.; Karisola, P.; Pichavant, M.; Kaplan, G.G.; Umetsu, D.T.; et al. T cell/transmembrane, Ig, and mucin-3 allelic variants differentially recognize phosphatidylserine and mediate phagocytosis of apoptotic cells. *J. Immunol.* **2010**, *184*, 1918–1930. [[CrossRef](#)]
97. Fourcade, J.; Sun, Z.; Benallaoua, M.; Guillaume, P.; Luescher, I.F.; Sander, C.; Kirkwood, J.M.; Kuchroo, V.; Zarour, H.M. Upregulation of Tim-3 and PD-1 expression is associated with tumor antigen-specific CD8+ T cell dysfunction in melanoma patients. *J. Exp. Med.* **2010**, *207*, 2175–2186. [[CrossRef](#)]
98. Sehrawat, S.; Suryawanshi, A.; Hirashima, M.; Rouse, B.T. Role of Tim-3/Galectin-9 Inhibitory Interaction In Viral Induced Immunopathology: Shifting The Balance Towards Regulators. *J. Immunol.* **2009**, *182*, 3191–3201. [[CrossRef](#)] [[PubMed](#)]
99. Dardalhon, V.; Anderson, A.C.; Karman, J.; Apetoh, L.; Chandwaskar, R.; Lee, D.H.; Cornejo, M.; Nishi, N.; Yamauchi, A.; Quintana, F.J.; et al. Tim-3/galectin-9 pathway: regulation of Th1 immunity through promotion of CD11b+Ly-6G+ myeloid cells. *J. Immunol.* **2010**, *185*, 1383–1392. [[CrossRef](#)] [[PubMed](#)]
100. De Mingo Pulido, Á.; Gardner, A.; Hiebler, S.; Soliman, H.; Rugo, H.S.; Krummel, M.F.; Coussens, L.M.; Ruffell, B. TIM-3 Regulates CD103+ Dendritic Cell Function and Response to Chemotherapy in Breast Cancer. *Cancer Cell* **2018**, *33*, 60–74. [[CrossRef](#)] [[PubMed](#)]
101. Cheng, S.; Ju, Y.; Han, F.; Wang, Y.; Xu, Y.; Qu, T.; Lu, Z. T Cell Immunoglobulin- and Mucin-Domain-Containing Molecule 3 Gene Polymorphisms and Susceptibility to Invasive Breast Cancer. *Ann. Clin. Lab. Sci.* **2017**, *47*, 668–675. [[PubMed](#)]
102. Gao, X.; Yang, J.; He, Y.; Zhang, J. Quantitative assessment of TIM-3 polymorphisms and cancer risk in Chinese Han population. *Oncotarget* **2016**, *7*, 35768–35775. [[CrossRef](#)]

103. Wang, Z.; Liu, X.; Wang, X.; Chong, T.; Lin, S.; Wang, M.; Ma, X.; Liu, K.; Xu, P.; Feng, Y.; et al. Polymorphisms in TIM-3 and breast cancer susceptibility in Chinese women: A case-control study. *Oncotarget* **2016**, *7*, 43703–43712. [[CrossRef](#)]
104. Nowak, E.C.; Lines, J.L.; Varn, F.S.; Deng, J.; Sarde, A.; Mabaera, R.; Kuta, A.; Le Mercier, I.; Cheng, C.; Noelle, R.J. Immunoregulatory functions of VISTA. *Immunol. Rev.* **2017**, *276*, 66–79. [[CrossRef](#)] [[PubMed](#)]
105. Wang, L.; Rubinstein, R.; Lines, J.L.; Wasiuk, A.; Ahonen, C.; Guo, Y.; Lu, L.-F.; Gondek, D.; Wang, Y.; Fava, R.A.; et al. VISTA, a novel mouse Ig superfamily ligand that negatively regulates T cell responses. *J. Exp. Med.* **2011**, *208*, 577–592. [[CrossRef](#)]
106. Lines, J.L.; Sempere, L.F.; Wang, L.; Pantazi, E.; Mak, J.; O’Connell, S.; Ceeraz, S.; Suriawinata, A.A.; Yan, S.; Ernstoff, M.S.; et al. VISTA is an immune checkpoint molecule for human T cells. *Cancer Res.* **2014**, *74*, 1924–1932. [[CrossRef](#)] [[PubMed](#)]
107. Böger, C.; Behrens, H.-M.; Krüger, S.; Röcken, C. The novel negative checkpoint regulator VISTA is expressed in gastric carcinoma and associated with PD-L1/PD-1: A future perspective for a combined gastric cancer therapy? *Oncoimmunology* **2017**, *6*. [[CrossRef](#)]
108. Loos, M.; Hedderich, D.M.; Ottenhausen, M.; Giese, N.A.; Laschinger, M.; Esposito, I.; Kleeff, J.; Friess, H. Expression of the costimulatory molecule B7-H3 is associated with prolonged survival in human pancreatic cancer. *BMC Cancer* **2009**, *9*, 463. [[CrossRef](#)]
109. Sakr, M.A.; Takino, T.; Domoto, T.; Nakano, H.; Wong, R.W.; Sasaki, M.; Nakanuma, Y.; Sato, H. GI24 enhances tumor invasiveness by regulating cell surface membrane-type 1 matrix metalloproteinase. *Cancer Sci.* **2010**, *101*, 2368–2374. [[CrossRef](#)]
110. Boles, K.S.; Vermi, W.; Facchetti, F.; Fuchs, A.; Wilson, T.J.; Diacovo, T.; Cella, M.; Colonna, M. A novel molecular interaction for the adhesion of follicular CD4 T cells to follicular dendritic cells. *Eur. J. Immunol.* **2009**, *39*, 695–703. [[CrossRef](#)]
111. Yu, X.; Harden, K.; Gonzalez, L.C.; Francesco, M.; Chiang, E.; Irving, B.; Tom, I.; Ivelja, S.; Refino, C.J.; Clark, H.; et al. The surface protein TIGIT suppresses T cell activation by promoting the generation of mature immunoregulatory dendritic cells. *Nat. Immunol.* **2009**, *10*, 48–57. [[CrossRef](#)] [[PubMed](#)]
112. Blockade of CD112R and TIGIT signaling sensitizes human natural killer cell functions. Available online: <https://www.ncbi.nlm.nih.gov/doc-distant.univ-lille2.fr/pubmed/28623459> (accessed on 2 September 2018).
113. Stanietsky, N.; Simic, H.; Arapovic, J.; Toporik, A.; Levy, O.; Novik, A.; Levine, Z.; Beiman, M.; Dassa, L.; Achdout, H.; et al. The interaction of TIGIT with PVR and PVRL2 inhibits human NK cell cytotoxicity. *Proc. Natl. Acad. Sci. USA* **2009**, *106*, 17858–17863. [[CrossRef](#)]
114. Joller, N.; Hafler, J.P.; Brynedal, B.; Kassam, N.; Spoerl, S.; Levin, S.D.; Sharpe, A.H.; Kuchroo, V.K. TIGIT has T cell intrinsic inhibitory functions. *J. Immunol.* **2011**, *186*, 1338–1342. [[CrossRef](#)]
115. Zhang, Y.; Maksimovic, J.; Naselli, G.; Qian, J.; Chopin, M.; Blewitt, M.E.; Oshlack, A.; Harrison, L.C. Genome-wide DNA methylation analysis identifies hypomethylated genes regulated by FOXP3 in human regulatory T cells. *Blood* **2013**, *122*, 2823–2836. [[CrossRef](#)]
116. Joller, N.; Lozano, E.; Burkett, P.R.; Patel, B.; Xiao, S.; Zhu, C.; Xia, J.; Tan, T.G.; Sefik, E.; Yajnik, V.; et al. Treg cells expressing the coinhibitory molecule TIGIT selectively inhibit proinflammatory Th1 and Th17 cell responses. *Immunity* **2014**, *40*, 569–581. [[CrossRef](#)] [[PubMed](#)]
117. Johnston, R.J.; Comps-Agrar, L.; Hackney, J.; Yu, X.; Huseni, M.; Yang, Y.; Park, S.; Javinal, V.; Chiu, H.; Irving, B.; et al. The immunoreceptor TIGIT regulates antitumor and antiviral CD8(+) T cell effector function. *Cancer Cell* **2014**, *26*, 923–937. [[CrossRef](#)]
118. Shimizu, J.; Yamazaki, S.; Takahashi, T.; Ishida, Y.; Sakaguchi, S. Stimulation of CD25(+)CD4(+) regulatory T cells through GITR breaks immunological self-tolerance. *Nat. Immunol.* **2002**, *3*, 135–142. [[CrossRef](#)]
119. McHugh, R.S.; Whitters, M.J.; Piccirillo, C.A.; Young, D.A.; Shevach, E.M.; Collins, M.; Byrne, M.C. CD4(+)CD25(+) immunoregulatory T cells: gene expression analysis reveals a functional role for the glucocorticoid-induced TNF receptor. *Immunity* **2002**, *16*, 311–323. [[CrossRef](#)]
120. Hanabuchi, S.; Watanabe, N.; Wang, Y.-H.; Wang, Y.-H.; Ito, T.; Shaw, J.; Cao, W.; Qin, F.X.-F.; Liu, Y.-J. Human plasmacytoid dendritic cells activate NK cells through glucocorticoid-induced tumor necrosis factor receptor-ligand (GITRL). *Blood* **2006**, *107*, 3617–3623. [[CrossRef](#)]
121. Tone, M.; Tone, Y.; Adams, E.; Yates, S.F.; Frewin, M.R.; Cobbold, S.P.; Waldmann, H. Mouse glucocorticoid-induced tumor necrosis factor receptor ligand is costimulatory for T cells. *Proc. Natl. Acad. Sci. USA* **2003**, *100*, 15059–15064. [[CrossRef](#)]

122. Kim, J.D.; Choi, B.K.; Bae, J.S.; Lee, U.H.; Han, I.S.; Lee, H.W.; Youn, B.S.; Vinay, D.S.; Kwon, B.S. Cloning and characterization of GITR ligand. *Genes Immun.* **2003**, *4*, 564–569. [[CrossRef](#)]
123. Ronchetti, S.; Zollo, O.; Bruscoli, S.; Agostini, M.; Bianchini, R.; Nocentini, G.; Ayroldi, E.; Riccardi, C. GITR, a member of the TNF receptor superfamily, is costimulatory to mouse T lymphocyte subpopulations. *Eur. J. Immunol.* **2004**, *34*, 613–622. [[CrossRef](#)]
124. Kanamaru, F.; Youngnak, P.; Hashiguchi, M.; Nishioka, T.; Takahashi, T.; Sakaguchi, S.; Ishikawa, I.; Azuma, M. Costimulation via Glucocorticoid-Induced TNF Receptor in Both Conventional and CD25+ Regulatory CD4+ T Cells. *J. Immunol.* **2004**, *172*, 7306–7314. [[CrossRef](#)] [[PubMed](#)]
125. Ji, H.; Liao, G.; Faubion, W.A.; Abadía-Molina, A.C.; Cozzo, C.; Laroux, F.S.; Caton, A.; Terhorst, C. Cutting edge: the natural ligand for glucocorticoid-induced TNF receptor-related protein abrogates regulatory T cell suppression. *J. Immunol.* **2004**, *172*, 5823–5827. [[CrossRef](#)]
126. Coe, D.; Begom, S.; Addey, C.; White, M.; Dyson, J.; Chai, J.-G. Depletion of regulatory T cells by anti-GITR mAb as a novel mechanism for cancer immunotherapy. *Cancer Immunol. Immunother.* **2010**, *59*, 1367–1377. [[CrossRef](#)]
127. Nocentini, G.; Giunchi, L.; Ronchetti, S.; Krausz, L.T.; Bartoli, A.; Moraca, R.; Migliorati, G.; Riccardi, C. A new member of the tumor necrosis factor/nerve growth factor receptor family inhibits T cell receptor-induced apoptosis. *Proc. Natl. Acad. Sci. USA* **1997**, *94*, 6216–6221. [[CrossRef](#)]
128. Steinberger, P.; Majdic, O.; Derdak, S.V.; Pfistershammer, K.; Kirchberger, S.; Klausner, C.; Zlabinger, G.; Pickl, W.F.; Stöckl, J.; Knapp, W. Molecular Characterization of Human 4Ig-B7-H3, a Member of the B7 Family with Four Ig-Like Domains. *J. Immunol.* **2004**, *172*, 2352–2359. [[CrossRef](#)]
129. Chapoval, A.I.; Ni, J.; Lau, J.S.; Wilcox, R.A.; Flies, D.B.; Liu, D.; Dong, H.; Sica, G.L.; Zhu, G.; Tamada, K.; et al. B7-H3: a costimulatory molecule for T cell activation and IFN-gamma production. *Nat. Immunol.* **2001**, *2*, 269–274. [[CrossRef](#)]
130. Luo, L.; Chapoval, A.I.; Flies, D.B.; Zhu, G.; Hirano, F.; Wang, S.; Lau, J.S.; Dong, H.; Tamada, K.; Flies, A.S.; et al. B7-H3 Enhances Tumor Immunity In Vivo by Costimulating Rapid Clonal Expansion of Antigen-Specific CD8+ Cytolytic T Cells. *J. Immunol.* **2004**, *173*, 5445–5450. [[CrossRef](#)] [[PubMed](#)]
131. Suh, W.-K.; Gajewska, B.U.; Okada, H.; Gronski, M.A.; Bertram, E.M.; Dawicki, W.; Duncan, G.S.; Bukczynski, J.; Plyte, S.; Elia, A.; et al. The B7 family member B7-H3 preferentially down-regulates T helper type 1-mediated immune responses. *Nat. Immunol.* **2003**, *4*, 899–906. [[CrossRef](#)] [[PubMed](#)]
132. Fukushima, A.; Sumi, T.; Fukuda, K.; Kumagai, N.; Nishida, T.; Yamazaki, T.; Akiba, H.; Okumura, K.; Yagita, H.; Ueno, H. B7-H3 regulates the development of experimental allergic conjunctivitis in mice. *Immunol. Lett.* **2007**, *113*, 52–57. [[CrossRef](#)]
133. Castriconi, R.; Dondero, A.; Augugliaro, R.; Cantoni, C.; Carnemolla, B.; Sementa, A.R.; Negri, F.; Conte, R.; Corrias, M.V.; Moretta, L.; et al. Identification of 4Ig-B7-H3 as a neuroblastoma-associated molecule that exerts a protective role from an NK cell-mediated lysis. *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 12640–12645. [[CrossRef](#)] [[PubMed](#)]
134. Chen, Y.-W.; Tekle, C.; Fodstad, O. The immunoregulatory protein human B7H3 is a tumor-associated antigen that regulates tumor cell migration and invasion. *Curr. Cancer Drug Targets* **2008**, *8*, 404–413. [[CrossRef](#)]
135. Xie, C.; Liu, D.; Chen, Q.; Yang, C.; Wang, B.; Wu, H. Soluble B7-H3 promotes the invasion and metastasis of pancreatic carcinoma cells through the TLR4/NF-κB pathway. *Sci. Rep.* **2016**, *6*, 27528. [[CrossRef](#)] [[PubMed](#)]
136. Hutloff, A.; Dittrich, A.M.; Beier, K.C.; Eljaschewitsch, B.; Kraft, R.; Anagnostopoulos, I.; Kroczeck, R.A. ICOS is an inducible T-cell co-stimulator structurally and functionally related to CD28. *Nature* **1999**, *397*, 263–266. [[CrossRef](#)] [[PubMed](#)]
137. McAdam, A.J.; Chang, T.T.; Lumelsky, A.E.; Greenfield, E.A.; Boussiotis, V.A.; Duke-Cohan, J.S.; Chernova, T.; Malenkovich, N.; Jabs, C.; Kuchroo, V.K.; et al. Mouse Inducible Costimulatory Molecule (ICOS) Expression Is Enhanced by CD28 Costimulation and Regulates Differentiation of CD4+ T Cells. *J. Immunol.* **2000**, *165*, 5035–5040. [[CrossRef](#)] [[PubMed](#)]
138. Swallow, M.M.; Wallin, J.J.; Sha, W.C. B7h, a novel costimulatory homolog of B7.1 and B7.2, is induced by TNFalpha. *Immunity* **1999**, *11*, 423–432. [[CrossRef](#)]
139. Yoshinaga, S.K.; Whoriskey, J.S.; Khare, S.D.; Sarmiento, U.; Guo, J.; Horan, T.; Shih, G.; Zhang, M.; Coccia, M.A.; Kohno, T.; et al. T-cell co-stimulation through B7RP-1 and ICOS. *Nature* **1999**, *402*, 827–832. [[CrossRef](#)] [[PubMed](#)]

140. Aicher, A.; Hayden-Ledbetter, M.; Brady, W.A.; Pezzutto, A.; Richter, G.; Magaletti, D.; Buckwalter, S.; Ledbetter, J.A.; Clark, E.A. Characterization of Human Inducible Costimulator Ligand Expression and Function. *J. Immunol.* **2000**, *164*, 4689–4696. [[CrossRef](#)]
141. Qian, X.; Agematsu, K.; Freeman, G.J.; Tagawa, Y.; Sugane, K.; Hayashi, T. The ICOS-ligand B7-H2, expressed on human type II alveolar epithelial cells, plays a role in the pulmonary host defense system. *Eur. J. Immunol.* **2006**, *36*, 906–918. [[CrossRef](#)]
142. Khayyamian, S.; Hutloff, A.; Büchner, K.; Gräfe, M.; Henn, V.; Kroczeck, R.A.; Mages, H.W. ICOS-ligand, expressed on human endothelial cells, costimulates Th1 and Th2 cytokine secretion by memory CD4+ T cells. *Proc. Natl. Acad. Sci. USA* **2002**, *99*, 6198–6203. [[CrossRef](#)]
143. Gigoux, M.; Lovato, A.; Leconte, J.; Leung, J.; Sonenberg, N.; Suh, W.-K. Inducible costimulator facilitates T-dependent B cell activation by augmenting IL-4 translation. *Mol. Immunol.* **2014**, *59*, 46–54. [[CrossRef](#)]
144. Van Berkel, M.E.A.T.; Oosterwegel, M.A. CD28 and ICOS: similar or separate costimulators of T cells? *Immunol. Lett.* **2006**, *105*, 115–122. [[CrossRef](#)] [[PubMed](#)]
145. Zhifu, Y.; Mingli, J.; Shuang, C.; Fan, W.; Zhenkun, F.; Wangyang, C.; Lin, Z.; Guangxiao, L.; Yashuang, Z.; Dianjun, L. SNP-SNP interactions of immunity related genes involved in the CD28/B7 pathway with susceptibility to invasive ductal carcinoma of the breast. *Gene* **2015**, *566*, 217–222. [[CrossRef](#)]
146. Xu, F.; Li, D.; Zhang, Q.; Fu, Z.; Zhang, J.; Yuan, W.; Chen, S.; Pang, D.; Li, D. ICOS gene polymorphisms are associated with sporadic breast cancer: a case-control study. *BMC Cancer* **2011**, *11*, 392. [[CrossRef](#)]
147. Schoenbrunn, A.; Frensch, M.; Kohler, S.; Keye, J.; Dooms, H.; Moewes, B.; Dong, J.; Loddenkemper, C.; Sieper, J.; Wu, P.; et al. A converse 4-1BB and CD40 ligand expression pattern delineates activated regulatory T cells (Treg) and conventional T cells enabling direct isolation of alloantigen-reactive natural Foxp3+ Treg. *J. Immunol.* **2012**, *189*, 5985–5994. [[CrossRef](#)]
148. Kwon, B.S.; Weissman, S.M. cDNA sequences of two inducible T-cell genes. *Proc. Natl. Acad. Sci. USA* **1989**, *86*, 1963–1967. [[CrossRef](#)] [[PubMed](#)]
149. Vinay, D.S.; Lee, S.J.; Kim, C.H.; Oh, H.S.; Kwon, B.S. Exposure of a Distinct PDCA-1+ (CD317) B Cell Population to Agonistic Anti-4-1BB (CD137) Inhibits T and B Cell Responses Both In Vitro and In Vivo. *PLoS ONE* **2012**, *7*. [[CrossRef](#)]
150. Melero, I.; Johnston, J.V.; Shufford, W.W.; Mittler, R.S.; Chen, L. NK1.1 cells express 4-1BB (CDw137) costimulatory molecule and are required for tumor immunity elicited by anti-4-1BB monoclonal antibodies. *Cell. Immunol.* **1998**, *190*, 167–172. [[CrossRef](#)]
151. Kim, D.-H.; Chang, W.-S.; Lee, Y.-S.; Lee, K.-A.; Kim, Y.-K.; Kwon, B.S.; Kang, C.-Y. 4-1BB engagement costimulates NKT cell activation and exacerbates NKT cell ligand-induced airway hyperresponsiveness and inflammation. *J. Immunol.* **2008**, *180*, 2062–2068. [[CrossRef](#)]
152. Pauly, S.; Broll, K.; Wittmann, M.; Giegerich, G.; Schwarz, H. CD137 is expressed by follicular dendritic cells and costimulates B lymphocyte activation in germinal centers. *J. Leukoc. Biol.* **2002**, *72*, 35–42.
153. Lee, S.-W.; Park, Y.; So, T.; Kwon, B.S.; Cheroutre, H.; Mittler, R.S.; Croft, M. Identification of regulatory functions for 4-1BB and 4-1BBL in myelopoiesis and the development of dendritic cells. *Nat. Immunol.* **2008**, *9*, 917–926. [[CrossRef](#)]
154. Bartkowiak, T.; Curran, M.A. 4-1BB Agonists: Multi-Potent Potentiators of Tumor Immunity. *Front. Oncol.* **2015**, *5*. [[CrossRef](#)]
155. Lee, H.-W.; Park, S.-J.; Choi, B.K.; Kim, H.H.; Nam, K.-O.; Kwon, B.S. 4-1BB promotes the survival of CD8+ T lymphocytes by increasing expression of Bcl-xL and Bfl-1. *J. Immunol.* **2002**, *169*, 4882–4888. [[CrossRef](#)]
156. Shuford, W.W.; Klussman, K.; Tritchler, D.D.; Loo, D.T.; Chalupny, J.; Siadak, A.W.; Brown, T.J.; Emswiler, J.; Raecho, H.; Larsen, C.P.; et al. 4-1BB costimulatory signals preferentially induce CD8+ T cell proliferation and lead to the amplification in vivo of cytotoxic T cell responses. *J. Exp. Med.* **1997**, *186*, 47–55. [[CrossRef](#)]
157. Hurtado, J.C.; Kim, Y.J.; Kwon, B.S. Signals through 4-1BB are costimulatory to previously activated splenic T cells and inhibit activation-induced cell death. *J. Immunol.* **1997**, *158*, 2600–2609. [[PubMed](#)]
158. Melero, I.; Gangadhar, T.C.; Kohrt, H.E.; Segal, N.H.; Logan, T.; Urba, W.J.; Hodi, F.S.; Ott, P.A.; Perez-Gracia, J.L.; Wolchok, J.D.; et al. A phase I study of the safety, tolerability, pharmacokinetics, and immunoregulatory activity of urelumab (BMS-663513) in subjects with advanced and/or metastatic solid tumors and relapsed/refractory B-cell non-Hodgkin's lymphoma (B-NHL). *JCO* **2013**, *31*, TPS3107.
159. Hintzen, R.Q.; Lens, S.M.; Beckmann, M.P.; Goodwin, R.G.; Lynch, D.; Lier, R.A. van Characterization of the human CD27 ligand, a novel member of the TNF gene family. *J. Immunol.* **1994**, *152*, 1762–1773. [[PubMed](#)]

160. Agematsu, K. Memory B cells and CD27. *Histol. Histopathol.* **2000**, *15*, 573–576. [[PubMed](#)]
161. Jung, J.; Choe, J.; Li, L.; Choi, Y.S. Regulation of CD27 expression in the course of germinal center B cell differentiation: the pivotal role of IL-10. *Eur. J. Immunol.* **2000**, *30*, 2437–2443. [[CrossRef](#)]
162. Hayakawa, Y.; Smyth, M.J. CD27 Dissects Mature NK Cells into Two Subsets with Distinct Responsiveness and Migratory Capacity. *J. Immunol.* **2006**, *176*, 1517–1524. [[CrossRef](#)] [[PubMed](#)]
163. Bowman, M.R.; Crimmins, M.A.; Yetz-Aldape, J.; Kriz, R.; Kelleher, K.; Herrmann, S. The cloning of CD70 and its identification as the ligand for CD27. *J. Immunol.* **1994**, *152*, 1756–1761. [[PubMed](#)]
164. Lens, S.M.; de Jong, R.; Hooibrink, B.; Koopman, G.; Pals, S.T.; van Oers, M.H.; van Lier, R.A. Phenotype and function of human B cells expressing CD70 (CD27 ligand). *Eur. J. Immunol.* **1996**, *26*, 2964–2971. [[CrossRef](#)] [[PubMed](#)]
165. Hashimoto-Okada, M.; Kitawaki, T.; Kadowaki, N.; Iwata, S.; Morimoto, C.; Hori, T.; Uchiyama, T. The CD70–CD27 interaction during the stimulation with dendritic cells promotes naive CD4+ T cells to develop into T cells producing a broad array of immunostimulatory cytokines in humans. *Int Immunol* **2009**, *21*, 891–904. [[CrossRef](#)] [[PubMed](#)]
166. Titanji, K.; Sammiceli, S.; De Milito, A.; Mantegani, P.; Fortis, C.; Berg, L.; Kärre, K.; Travi, G.; Tassandin, C.; Lopalco, L.; et al. Altered distribution of natural killer cell subsets identified by CD56, CD27 and CD70 in primary and chronic human immunodeficiency virus-1 infection. *Immunology* **2008**, *123*, 164–170. [[CrossRef](#)]
167. Wajant, H. Therapeutic targeting of CD70 and CD27. *Expert Opin. Ther. Targets* **2016**, *20*, 959–973. [[CrossRef](#)]
168. Van Oosterwijk, M.F.; Juwana, H.; Arens, R.; Tesselaar, K.; van Oers, M.H.J.; Eldering, E.; van Lier, R.A.W. CD27-CD70 interactions sensitise naive CD4+ T cells for IL-12-induced Th1 cell development. *Int. Immunol.* **2007**, *19*, 713–718. [[CrossRef](#)] [[PubMed](#)]
169. Peperzak, V.; Veraar, E.A.M.; Keller, A.M.; Xiao, Y.; Borst, J. The Pim kinase pathway contributes to survival signaling in primed CD8+ T cells upon CD27 costimulation. *J. Immunol.* **2010**, *185*, 6670–6678. [[CrossRef](#)] [[PubMed](#)]
170. Hendriks, J.; Xiao, Y.; Borst, J. CD27 Promotes Survival of Activated T Cells and Complements CD28 in Generation and Establishment of the Effector T Cell Pool. *J. Exp. Med.* **2003**, *198*, 1369–1380. [[CrossRef](#)]
171. Dolfi, D.V.; Boesteanu, A.C.; Petrovas, C.; Xia, D.; Butz, E.A.; Katsikis, P.D. Late signals from CD27 prevent Fas dependent apoptosis of primary CD8+ T cells. *J. Immunol.* **2008**, *180*, 2912–2921. [[CrossRef](#)] [[PubMed](#)]
172. Carr, J.M.; Carrasco, M.J.; Thaventhiran, J.E.D.; Bambrough, P.J.; Kraman, M.; Edwards, A.D.; Al-Shamkhani, A.; Fearon, D.T. CD27 mediates interleukin-2-independent clonal expansion of the CD8+ T cell without effector differentiation. *Proc. Natl. Acad. Sci. USA* **2006**, *103*, 19454–19459. [[CrossRef](#)]
173. Xiao, Y.; Peperzak, V.; Keller, A.M.; Borst, J. CD27 instructs CD4+ T cells to provide help for the memory CD8+ T cell response after protein immunization. *J. Immunol.* **2008**, *181*, 1071–1082. [[CrossRef](#)]
174. Hendriks, J.; Gravestien, L.A.; Tesselaar, K.; van Lier, R.A.; Schumacher, T.N.; Borst, J. CD27 is required for generation and long-term maintenance of T cell immunity. *Nat. Immunol.* **2000**, *1*, 433–440. [[CrossRef](#)]
175. Peperzak, V.; Veraar, E.A.M.; Xiao, Y.; Babala, N.; Thiadens, K.; Brugmans, M.; Borst, J. CD8+ T cells produce the chemokine CXCL10 in response to CD27/CD70 costimulation to promote generation of the CD8+ effector T cell pool. *J. Immunol.* **2013**, *191*, 3025–3036. [[CrossRef](#)] [[PubMed](#)]
176. Kelly, J.M.; Darcy, P.K.; Markby, J.L.; Godfrey, D.I.; Takeda, K.; Yagita, H.; Smyth, M.J. Induction of tumor-specific T cell memory by NK cell-mediated tumor rejection. *Nat. Immunol.* **2002**, *3*, 83–90. [[CrossRef](#)] [[PubMed](#)]
177. Takeda, K.; Oshima, H.; Hayakawa, Y.; Akiba, H.; Atsuta, M.; Kobata, T.; Kobayashi, K.; Ito, M.; Yagita, H.; Okumura, K. CD27-mediated activation of murine NK cells. *J. Immunol.* **2000**, *164*, 1741–1745. [[CrossRef](#)]
178. Agematsu, K.; Kobata, T.; Yang, F.C.; Nakazawa, T.; Fukushima, K.; Kitahara, M.; Mori, T.; Sugita, K.; Morimoto, C.; Komiyama, A. CD27/CD70 interaction directly drives B cell IgG and IgM synthesis. *Eur. J. Immunol.* **1995**, *25*, 2825–2829. [[CrossRef](#)]
179. Agematsu, K.; Nagumo, H.; Oguchi, Y.; Nakazawa, T.; Fukushima, K.; Yasui, K.; Ito, S.; Kobata, T.; Morimoto, C.; Komiyama, A. Generation of plasma cells from peripheral blood memory B cells: synergistic effect of interleukin-10 and CD27/CD70 interaction. *Blood* **1998**, *91*, 173–180.
180. Kobata, T.; Jacquot, S.; Kozlowski, S.; Agematsu, K.; Schlossman, S.F.; Morimoto, C. CD27-CD70 interactions regulate B-cell activation by T cells. *Proc. Natl. Acad. Sci. USA* **1995**, *92*, 11249–11253. [[CrossRef](#)] [[PubMed](#)]
181. Petrau, C.; Cornic, M.; Bertrand, P.; Maingonnat, C.; Marchand, V.; Picquenot, J.-M.; Jardin, F.; Clatot, F. CD70: A Potential Target in Breast Cancer? *J. Cancer* **2014**, *5*, 761–764. [[CrossRef](#)] [[PubMed](#)]

182. Fujita, T.; Ukyo, N.; Hori, T.; Uchiyama, T. Functional characterization of OX40 expressed on human CD8+ T cells. *Immunol. Lett.* **2006**, *106*, 27–33. [[CrossRef](#)] [[PubMed](#)]
183. Montler, R.; Bell, R.B.; Thalhoffer, C.; Leidner, R.; Feng, Z.; Fox, B.A.; Cheng, A.C.; Bui, T.G.; Tucker, C.; Hoen, H.; et al. OX40, PD-1 and CTLA-4 are selectively expressed on tumor-infiltrating T cells in head and neck cancer. *Clin. Transl. Immunol.* **2016**, *5*, e70. [[CrossRef](#)] [[PubMed](#)]
184. Lai, C.; August, S.; Albibas, A.; Behar, R.; Cho, S.-Y.; Polak, M.E.; Theaker, J.; MacLeod, A.S.; French, R.R.; Glennie, M.J.; et al. OX40+ Regulatory T Cells in Cutaneous Squamous Cell Carcinoma Suppress Effector T-Cell Responses and Associate with Metastatic Potential. *Clin. Cancer Res.* **2016**, *22*, 4236–4248. [[CrossRef](#)] [[PubMed](#)]
185. Baumann, R.; Yousefi, S.; Simon, D.; Russmann, S.; Mueller, C.; Simon, H.-U. Functional expression of CD134 by neutrophils. *Eur. J. Immunol.* **2004**, *34*, 2268–2275. [[CrossRef](#)] [[PubMed](#)]
186. Liu, C.; Lou, Y.; Lizée, G.; Qin, H.; Liu, S.; Rabinovich, B.; Kim, G.J.; Wang, Y.-H.; Ye, Y.; Sikora, A.G.; et al. Plasmacytoid dendritic cells induce NK cell-dependent, tumor antigen-specific T cell cross-priming and tumor regression in mice. *J. Clin. Invest* **2008**, *118*, 1165–1175. [[CrossRef](#)]
187. Zaini, J.; Andarini, S.; Tahara, M.; Saijo, Y.; Ishii, N.; Kawakami, K.; Taniguchi, M.; Sugamura, K.; Nukiwa, T.; Kikuchi, T. OX40 ligand expressed by DCs costimulates NKT and CD4+ Th cell antitumor immunity in mice. *J. Clin. Invest* **2007**, *117*, 3330–3338. [[CrossRef](#)] [[PubMed](#)]
188. Ohshima, Y.; Tanaka, Y.; Tozawa, H.; Takahashi, Y.; Maliszewski, C.; Delespesse, G. Expression and function of OX40 ligand on human dendritic cells. *J. Immunol.* **1997**, *159*, 3838–3848. [[PubMed](#)]
189. Karulf, M.; Kelly, A.; Weinberg, A.D.; Gold, J.A. OX40 ligand regulates inflammation and mortality in the innate immune response to sepsis. *J. Immunol.* **2010**, *185*, 4856–4862. [[CrossRef](#)] [[PubMed](#)]
190. Wang, Q.; Chen, Y.; Ge, Y.; Sun, J.; Shi, Q.; Ju, S.; Dai, J.; Yu, G.; Zhang, X. Characterization and functional study of five novel monoclonal antibodies against human OX40L highlight reverse signalling: enhancement of IgG production of B cells and promotion of maturation of DCs. *Tissue Antigens* **2004**, *64*, 566–574. [[CrossRef](#)]
191. Fujita, T.; Kambe, N.; Uchiyama, T.; Hori, T. Type I interferons attenuate T cell activating functions of human mast cells by decreasing TNF-alpha production and OX40 ligand expression while increasing IL-10 production. *J. Clin. Immunol.* **2006**, *26*, 512–518. [[CrossRef](#)]
192. Souza, H.; Elia, C.; Spencer, J.; MacDonald, T. Expression of lymphocyte-endothelial receptor-ligand pairs, $\alpha 4\beta 7$ /MAdCAM-1 and OX40/OX40 ligand in the colon and jejunum of patients with inflammatory bowel disease. *Gut* **1999**, *45*, 856–863. [[CrossRef](#)]
193. Sato, T.; Ishii, N.; Murata, K.; Kikuchi, K.; Nakagawa, S.; Ndhlovu, L.C.; Sugamura, K. Consequences of OX40-OX40 ligand interactions in langerhans cell function: enhanced contact hypersensitivity responses in OX40L-transgenic mice. *Eur. J. Immunol.* **2002**, *32*, 3326–3335. [[CrossRef](#)]
194. Weinberg, A.D.; Wegmann, K.W.; Funatake, C.; Whitham, R.H. Blocking OX-40/OX-40 ligand interaction in vitro and in vivo leads to decreased T cell function and amelioration of experimental allergic encephalomyelitis. *J. Immunol.* **1999**, *162*, 1818–1826.
195. Zingoni, A.; Sornasse, T.; Cocks, B.G.; Tanaka, Y.; Santoni, A.; Lanier, L.L. Cross-talk between activated human NK cells and CD4+ T cells via OX40-OX40 ligand interactions. *J. Immunol.* **2004**, *173*, 3716–3724. [[CrossRef](#)]
196. Maxwell, J.R.; Weinberg, A.; Prell, R.A.; Vella, A.T. Danger and OX40 Receptor Signaling Synergize to Enhance Memory T Cell Survival by Inhibiting Peripheral Deletion. *J. Immunol.* **2000**, *164*, 107–112. [[CrossRef](#)] [[PubMed](#)]
197. Gramaglia, I.; Jember, A.; Pippig, S.D.; Weinberg, A.D.; Killeen, N.; Croft, M. The OX40 costimulatory receptor determines the development of CD4 memory by regulating primary clonal expansion. *J. Immunol.* **2000**, *165*, 3043–3050. [[CrossRef](#)]
198. Gramaglia, I.; Weinberg, A.D.; Lemon, M.; Croft, M. Ox-40 Ligand: A Potent Costimulatory Molecule for Sustaining Primary CD4 T Cell Responses. *J. Immunol.* **1998**, *161*, 6510–6517.
199. Ito, T.; Wang, Y.-H.; Duramad, O.; Hori, T.; Delespesse, G.J.; Watanabe, N.; Qin, F.X.-F.; Yao, Z.; Cao, W.; Liu, Y.-J. TSLP-activated dendritic cells induce an inflammatory T helper type 2 cell response through OX40 ligand. *J. Exp. Med.* **2005**, *202*, 1213–1223. [[CrossRef](#)]
200. Zhang, Z.; Zhong, W.; Hinrichs, D.; Wu, X.; Weinberg, A.; Hall, M.; Spencer, D.; Wegmann, K.; Rosenbaum, J.T. Activation of OX40 Augments Th17 Cytokine Expression and Antigen-Specific Uveitis. *Am. J. Pathol.* **2010**, *177*, 2912–2920. [[CrossRef](#)] [[PubMed](#)]

201. Baum, P.R.; Gayle, R.B.; Ramsdell, F.; Srinivasan, S.; Sorensen, R.A.; Watson, M.L.; Seldin, M.F.; Baker, E.; Sutherland, G.R.; Clifford, K.N. Molecular characterization of murine and human OX40/OX40 ligand systems: identification of a human OX40 ligand as the HTLV-1-regulated protein gp34. *EMBO J.* **1994**, *13*, 3992–4001. [[CrossRef](#)]
202. Bansal-Pakala, P.; Halteman, B.S.; Cheng, M.H.-Y.; Croft, M. Costimulation of CD8 T cell responses by OX40. *J. Immunol.* **2004**, *172*, 4821–4825. [[CrossRef](#)]
203. Lee, S.-W.; Park, Y.; Song, A.; Cheroutre, H.; Kwon, B.S.; Croft, M. Functional dichotomy between OX40 and 4-1BB in modulating effector CD8 T cell responses. *J. Immunol.* **2006**, *177*, 4464–4472. [[CrossRef](#)] [[PubMed](#)]
204. Han, P.; Goularte, O.D.; Rufner, K.; Wilkinson, B.; Kaye, J. An Inhibitory Ig Superfamily Protein Expressed by Lymphocytes and APCs Is Also an Early Marker of Thymocyte Positive Selection. *J. Immunol.* **2004**, *172*, 5931–5939. [[CrossRef](#)]
205. Iwata, A.; Watanabe, N.; Oya, Y.; Owada, T.; Ikeda, K.; Suto, A.; Kagami, S.; Hirose, K.; Kanari, H.; Kawashima, S.; et al. Protective roles of B and T lymphocyte attenuator in NKT cell-mediated experimental hepatitis. *J. Immunol.* **2010**, *184*, 127–133. [[CrossRef](#)]
206. Šedý, J.R.; Bjordahl, R.L.; Bekiaris, V.; Macauley, M.G.; Ware, B.C.; Norris, P.S.; Lurain, N.S.; Benedict, C.A.; Ware, C.F. CD160 activation by herpesvirus entry mediator augments inflammatory cytokine production and cytolytic function by NK cells. *J. Immunol.* **2013**, *191*, 828–836. [[CrossRef](#)]
207. Del Rio, M.-L.; Kaye, J.; Rodriguez-Barbosa, J.-I. Detection of protein on BTLA^{low} cells and in vivo antibody-mediated down-modulation of BTLA on lymphoid and myeloid cells of C57BL/6 and BALB/c BTLA allelic variants. *Immunobiology* **2010**, *215*, 570–578. [[CrossRef](#)] [[PubMed](#)]
208. M’Hidi, H.; Thibault, M.-L.; Chetaille, B.; Rey, F.; Bouadallah, R.; Nicollas, R.; Olive, D.; Xerri, L. High expression of the inhibitory receptor BTLA in T-follicular helper cells and in B-cell small lymphocytic lymphoma/chronic lymphocytic leukemia. *Am. J. Clin. Pathol.* **2009**, *132*, 589–596. [[CrossRef](#)] [[PubMed](#)]
209. Kwon, B.S.; Tan, K.B.; Ni, J.; Kwi-Ok-Oh, Z.H.L.; Kim, K.K.; Kim, Y.-J.; Wang, S.; Gentz, R.; Yu, G.-L.; Harrop, J.; et al. A Newly Identified Member of the Tumor Necrosis Factor Receptor Superfamily with a Wide Tissue Distribution and Involvement in Lymphocyte Activation. *J. Biol. Chem.* **1997**, *272*, 14272–14276. [[CrossRef](#)] [[PubMed](#)]
210. Duhon, T.; Pasero, C.; Mallet, F.; Barbarat, B.; Olive, D.; Costello, R.T. LIGHT costimulates CD40 triggering and induces immunoglobulin secretion; a novel key partner in T cell-dependent B cell terminal differentiation. *Eur. J. Immunol.* **2004**, *34*, 3534–3541. [[CrossRef](#)]
211. Morel, Y.; Truneh, A.; Sweet, R.W.; Olive, D.; Costello, R.T. The TNF superfamily members LIGHT and CD154 (CD40 ligand) costimulate induction of dendritic cell maturation and elicit specific CTL activity. *J. Immunol.* **2001**, *167*, 2479–2486. [[CrossRef](#)]
212. Zhai, Y.; Guo, R.; Hsu, T.L.; Yu, G.L.; Ni, J.; Kwon, B.S.; Jiang, G.W.; Lu, J.; Tan, J.; Ugustus, M.; et al. LIGHT, a novel ligand for lymphotoxin beta receptor and TR2/HVEM induces apoptosis and suppresses in vivo tumor formation via gene transfer. *J. Clin. Invest* **1998**, *102*, 1142–1151. [[CrossRef](#)]
213. Xu, Z.; Shen, J.; Wang, M.H.; Yi, T.; Yu, Y.; Zhu, Y.; Chen, B.; Chen, J.; Li, L.; Li, M.; et al. Comprehensive molecular profiling of the B7 family of immune-regulatory ligands in breast cancer. *Oncoimmunology* **2016**, *5*. [[CrossRef](#)] [[PubMed](#)]
214. Chemnitz, J.M.; Lanfranco, A.R.; Braunstein, I.; Riley, J.L. B and T Lymphocyte Attenuator-Mediated Signal Transduction Provides a Potent Inhibitory Signal to Primary Human CD4 T Cells That Can Be Initiated by Multiple Phosphotyrosine Motifs. *J. Immunol.* **2006**, *176*, 6603–6614. [[CrossRef](#)] [[PubMed](#)]
215. Krieg, C.; Han, P.; Stone, R.; Goularte, O.D.; Kaye, J. Functional analysis of B and T lymphocyte attenuator engagement on CD4⁺ and CD8⁺ T cells. *J. Immunol.* **2005**, *175*, 6420–6427. [[CrossRef](#)]
216. Otsuki, N.; Kamimura, Y.; Hashiguchi, M.; Azuma, M. Expression and function of the B and T lymphocyte attenuator (BTLA/CD272) on human T cells. *Biochem. Biophys. Res. Commun.* **2006**, *344*, 1121–1127. [[CrossRef](#)] [[PubMed](#)]
217. Murphy, T.L.; Murphy, K.M. Slow down and survive: Enigmatic immunoregulation by BTLA and HVEM. *Annu. Rev. Immunol.* **2010**, *28*, 389–411. [[CrossRef](#)] [[PubMed](#)]
218. Derré, L.; Rivals, J.-P.; Jandus, C.; Pastor, S.; Rimoldi, D.; Romero, P.; Michielin, O.; Olive, D.; Speiser, D.E. BTLA mediates inhibition of human tumor-specific CD8⁺ T cells that can be partially reversed by vaccination. *J. Clin. Invest.* **2010**, *120*, 157–167. [[CrossRef](#)]

219. Watanabe, N.; Gavrieli, M.; Sedy, J.R.; Yang, J.; Fallarino, F.; Loftin, S.K.; Hurchla, M.A.; Zimmerman, N.; Sim, J.; Zang, X.; et al. BTLA is a lymphocyte inhibitory receptor with similarities to CTLA-4 and PD-1. *Nat. Immunol.* **2003**, *4*, 670–679. [[CrossRef](#)]
220. Vendel, A.C.; Calemine-Fenaux, J.; Izrael-Tomasevic, A.; Chauhan, V.; Arnott, D.; Eaton, D.L. B and T Lymphocyte Attenuator Regulates B Cell Receptor Signaling by Targeting Syk and BLNK. *J. Immunol.* **2009**, *182*, 1509–1517. [[CrossRef](#)]
221. Leifer, C.A.; Kennedy, M.N.; Mazzoni, A.; Lee, C.; Kruhlak, M.J.; Segal, D.M. TLR9 is localized in the endoplasmic reticulum prior to stimulation. *J. Immunol.* **2004**, *173*, 1179–1183. [[CrossRef](#)]
222. Latz, E.; Schoenemeyer, A.; Visintin, A.; Fitzgerald, K.A.; Monks, B.G.; Knetter, C.F.; Lien, E.; Nilsen, N.J.; Espevik, T.; Golenbock, D.T. TLR9 signals after translocating from the ER to CpG DNA in the lysosome. *Nat. Immunol.* **2004**, *5*, 190–198. [[CrossRef](#)]
223. Kawagoe, T.; Sato, S.; Jung, A.; Yamamoto, M.; Matsui, K.; Kato, H.; Uematsu, S.; Takeuchi, O.; Akira, S. Essential role of IRAK-4 protein and its kinase activity in Toll-like receptor-mediated immune responses but not in TCR signaling. *J. Exp. Med.* **2007**, *204*, 1013–1024. [[CrossRef](#)] [[PubMed](#)]
224. Sato, S.; Sanjo, H.; Takeda, K.; Ninomiya-Tsuji, J.; Yamamoto, M.; Kawai, T.; Matsumoto, K.; Takeuchi, O.; Akira, S. Essential function for the kinase TAK1 in innate and adaptive immune responses. *Nat. Immunol.* **2005**, *6*, 1087–1095. [[CrossRef](#)]
225. Adachi, O.; Kawai, T.; Takeda, K.; Matsumoto, M.; Tsutsui, H.; Sakagami, M.; Nakanishi, K.; Akira, S. Targeted disruption of the MyD88 gene results in loss of IL-1- and IL-18-mediated function. *Immunity* **1998**, *9*, 143–150. [[CrossRef](#)]
226. Kawai, T.; Sato, S.; Ishii, K.J.; Coban, C.; Hemmi, H.; Yamamoto, M.; Terai, K.; Matsuda, M.; Inoue, J.; Uematsu, S.; et al. Interferon-alpha induction through Toll-like receptors involves a direct interaction of IRF7 with MyD88 and TRAF6. *Nat. Immunol.* **2004**, *5*, 1061–1068. [[CrossRef](#)]
227. Hemmi, H.; Takeuchi, O.; Kawai, T.; Kaisho, T.; Sato, S.; Sanjo, H.; Matsumoto, M.; Hoshino, K.; Wagner, H.; Takeda, K.; et al. A Toll-like receptor recognizes bacterial DNA. *Nature* **2000**, *408*, 740–745. [[CrossRef](#)]
228. Lipford, G.B.; Sparwasser, T.; Zimmermann, S.; Heeg, K.; Wagner, H. CpG-DNA-mediated transient lymphadenopathy is associated with a state of Th1 predisposition to antigen-driven responses. *J. Immunol.* **2000**, *165*, 1228–1235. [[CrossRef](#)] [[PubMed](#)]
229. Karki, K.; Pande, D.; Negi, R.; Khanna, S.; Khanna, R.S.; Khanna, H.D. Correlation of serum toll like receptor 9 and trace elements with lipid peroxidation in the patients of breast diseases. *J. Trace Elem. Med. Biol.* **2015**, *30*, 11–16. [[CrossRef](#)] [[PubMed](#)]
230. AL-HARRAS, M.F.; HOUSSEN, M.E.; SHAKER, M.E.; FARAG, K.; FAROUK, O.; MONIR, R.; EL-MAHDY, R.; ABO-HASHEM, E.M. Polymorphisms of glutathione S-transferase π 1 and toll-like receptors 2 and 9: Association with breast cancer susceptibility. *Oncol. Lett.* **2016**, *11*, 2182–2188. [[CrossRef](#)]
231. Wan, G.-X.; Cao, Y.-W.; Li, W.-Q.; Li, Y.-C.; Zhang, W.-J.; Li, F. Associations between TLR9 polymorphisms and cancer risk: evidence from an updated meta-analysis of 25,685 subjects. *Asian Pac. J. Cancer Prev.* **2014**, *15*, 8279–8285. [[CrossRef](#)]
232. Resler, A.J.; Malone, K.E.; Johnson, L.G.; Malkki, M.; Petersdorf, E.W.; McKnight, B.; Madeleine, M.M. Genetic variation in TLR or NFkappaB pathways and the risk of breast cancer: a case-control study. *BMC Cancer* **2013**, *13*, 219. [[CrossRef](#)]
233. Etokebe, G.E.; Knezević, J.; Petricević, B.; Pavelić, J.; Vrbanec, D.; Dembić, Z. Single-nucleotide polymorphisms in genes encoding toll-like receptor -2, -3, -4, and -9 in case-control study with breast cancer. *Genet. Test Mol. Biomarkers* **2009**, *13*, 729–734. [[CrossRef](#)]
234. Cekic, C.; Linden, J. Purinergic regulation of the immune system. *Nat. Rev. Immunol.* **2016**, *16*, 177–192. [[CrossRef](#)]
235. Allard, B.; Longhi, M.S.; Robson, S.C.; Stagg, J. The ectonucleotidases CD39 and CD73: novel checkpoint inhibitor targets. *Immunol. Rev.* **2017**, *276*, 121–144. [[CrossRef](#)] [[PubMed](#)]
236. Antonioli, L.; Pacher, P.; Vizi, E.S.; Haskó, G. CD39 and CD73 in immunity and inflammation. *Trends Mol. Med.* **2013**, *19*, 355–367. [[CrossRef](#)]
237. Resta, R.; Yamashita, Y.; Thompson, L.F. Ecto-enzyme and signaling functions of lymphocyte CD73. *Immunol. Rev.* **1998**, *161*, 95–109. [[CrossRef](#)] [[PubMed](#)]
238. Kansas, G.S.; Wood, G.S.; Tedder, T.F. Expression, distribution, and biochemistry of human CD39. Role in activation-associated homotypic adhesion of lymphocytes. *J. Immunol.* **1991**, *146*, 2235–2244. [[PubMed](#)]

239. Koziak, K.; Sévigny, J.; Robson, S.C.; Siegel, J.B.; Kaczmarek, E. Analysis of CD39/ATP diphosphohydrolase (ATPDase) expression in endothelial cells, platelets and leukocytes. *Thromb. Haemost.* **1999**, *82*, 1538–1544. [[CrossRef](#)] [[PubMed](#)]
240. Borsellino, G.; Kleinewietfeld, M.; Di Mitri, D.; Sternjak, A.; Diamantini, A.; Giometto, R.; Höpner, S.; Centonze, D.; Bernardi, G.; Dell'Acqua, M.L.; et al. Expression of ectonucleotidase CD39 by Foxp3+ Treg cells: hydrolysis of extracellular ATP and immune suppression. *Blood* **2007**, *110*, 1225–1232. [[CrossRef](#)] [[PubMed](#)]
241. Kas-Deelen, A.M.; Bakker, W.W.; Olinga, P.; Visser, J.; de Maar, E.F.; van Son, W.J.; The, T.H.; Harmsen, M.C. Cytomegalovirus infection increases the expression and activity of ecto-ATPase (CD39) and ecto-5' nucleotidase (CD73) on endothelial cells. *FEBS Lett.* **2001**, *491*, 21–25. [[CrossRef](#)]
242. Do Carmo Araújo, M.; Rocha, J.B.T.; Morsch, A.; Zanin, R.; Bauchspiess, R.; Morsch, V.M.; Schetinger, M.R.C. Enzymes that hydrolyze adenine nucleotides in platelets from breast cancer patients. *Biochim. Biophys. Acta* **2005**, *1740*, 421–426. [[CrossRef](#)] [[PubMed](#)]
243. Leone, R.D.; Emens, L.A. Targeting adenosine for cancer immunotherapy. *J Immunother Cancer* **2018**, *6*. [[CrossRef](#)] [[PubMed](#)]
244. Yegutkin, G.G.; Wieringa, B.; Robson, S.C.; Jalkanen, S. Metabolism of circulating ADP in the bloodstream is mediated via integrated actions of soluble adenylylate kinase-1 and NTPDase1/CD39 activities. *FASEB J.* **2012**, *26*, 3875–3883. [[CrossRef](#)]
245. MacKenzie, W.M.; Hoskin, D.W.; Blay, J. Adenosine suppresses alpha(4)beta(7) integrin-mediated adhesion of T lymphocytes to colon adenocarcinoma cells. *Exp. Cell Res.* **2002**, *276*, 90–100. [[CrossRef](#)]
246. Zarek, P.E.; Huang, C.-T.; Lutz, E.R.; Kowalski, J.; Horton, M.R.; Linden, J.; Drake, C.G.; Powell, J.D. A2A receptor signaling promotes peripheral tolerance by inducing T-cell anergy and the generation of adaptive regulatory T cells. *Blood* **2008**, *111*, 251–259. [[CrossRef](#)] [[PubMed](#)]
247. Raskovalova, T.; Lokshin, A.; Huang, X.; Su, Y.; Mandic, M.; Zarour, H.M.; Jackson, E.K.; Gorelik, E. Inhibition of cytokine production and cytotoxic activity of human antimelanoma specific CD8+ and CD4+ T lymphocytes by adenosine-protein kinase A type I signaling. *Cancer Res.* **2007**, *67*, 5949–5956. [[CrossRef](#)]
248. Williams, B.A.; Manzer, A.; Blay, J.; Hoskin, D.W. Adenosine acts through a novel extracellular receptor to inhibit granule exocytosis by natural killer cells. *Biochem. Biophys. Res. Commun.* **1997**, *231*, 264–269. [[CrossRef](#)]
249. Nowak, M.; Lynch, L.; Yue, S.; Ohta, A.; Sitkovsky, M.; Balk, S.P.; Exley, M.A. The A2aR adenosine receptor controls cytokine production in iNKT cells. *Eur. J. Immunol.* **2010**, *40*, 682–687. [[CrossRef](#)]
250. Xaus, J.; Valledor, A.F.; Cardó, M.; Marquès, L.; Beleta, J.; Palacios, J.M.; Celada, A. Adenosine inhibits macrophage colony-stimulating factor-dependent proliferation of macrophages through the induction of p27kip-1 expression. *J. Immunol.* **1999**, *163*, 4140–4149. [[PubMed](#)]
251. Wilson, J.M.; Ross, W.G.; Agbai, O.N.; Frazier, R.; Figler, R.A.; Rieger, J.; Linden, J.; Ernst, P.B. The A2B Adenosine Receptor Impairs the Maturation and Immunogenicity of Dendritic Cells. *J. Immunol.* **2009**, *182*, 4616–4623. [[CrossRef](#)]
252. Sevigny, C.P.; Li, L.; Awad, A.S.; Huang, L.; McDuffie, M.; Linden, J.; Lobo, P.I.; Okusa, M.D. Activation of Adenosine 2A Receptors Attenuates Allograft Rejection and Alloantigen Recognition. *J. Immunol.* **2007**, *178*, 4240–4249. [[CrossRef](#)]
253. Williams, C.B.; Yeh, E.S.; Soloff, A.C. Tumor-associated macrophages: unwitting accomplices in breast cancer malignancy. *NPJ Breast Cancer* **2016**, *2*. [[CrossRef](#)]
254. Aras, S.; Zaidi, M.R. TAMEless traitors: macrophages in cancer progression and metastasis. *Br. J. Cancer* **2017**, *117*, 1583–1591. [[CrossRef](#)]
255. Zhang, Q.; Liu, L.; Gong, C.; Shi, H.; Zeng, Y.; Wang, X.; Zhao, Y.; Wei, Y. Prognostic significance of tumor-associated macrophages in solid tumor: a meta-analysis of the literature. *PLoS ONE* **2012**, *7*, e50946. [[CrossRef](#)]
256. Zhao, X.; Qu, J.; Sun, Y.; Wang, J.; Liu, X.; Wang, F.; Zhang, H.; Wang, W.; Ma, X.; Gao, X.; et al. Prognostic significance of tumor-associated macrophages in breast cancer: a meta-analysis of the literature. *Oncotarget* **2017**, *8*, 30576–30586. [[CrossRef](#)] [[PubMed](#)]
257. Mantovani, A.; Marchesi, F.; Malesci, A.; Laghi, L.; Allavena, P. Tumour-associated macrophages as treatment targets in oncology. *Nat. Rev. Clin. Oncol.* **2017**, *14*, 399–416. [[CrossRef](#)] [[PubMed](#)]

258. DeNardo, D.G.; Ruffell, B. Macrophages as regulators of tumour immunity and immunotherapy. *Nat. Rev. Immunol.* **2019**. [[CrossRef](#)] [[PubMed](#)]
259. Thomas, J.K.; Mir, H.; Kapur, N.; Bae, S.; Singh, S. CC chemokines are differentially expressed in Breast Cancer and are associated with disparity in overall survival. *Sci. Rep.* **2019**, *9*, 4014. [[CrossRef](#)]
260. Achkova, D.; Maher, J. Role of the colony-stimulating factor (CSF)/CSF-1 receptor axis in cancer. *Biochem. Soc. Trans.* **2016**, *44*, 333–341. [[CrossRef](#)] [[PubMed](#)]
261. Richardsen, E.; Uglehus, R.D.; Johnsen, S.H.; Busund, L.-T. Macrophage-colony stimulating factor (CSF1) predicts breast cancer progression and mortality. *Anticancer Res.* **2015**, *35*, 865–874.
262. Aharinejad, S.; Salama, M.; Paulus, P.; Zins, K.; Berger, A.; Singer, C.F. Elevated CSF1 serum concentration predicts poor overall survival in women with early breast cancer. *Endocr. Relat. Cancer* **2013**, *20*, 777–783. [[CrossRef](#)] [[PubMed](#)]
263. Scholl, S.M.; Pallud, C.; Beuvon, F.; Hacene, K.; Stanley, E.R.; Rohrschneider, L.; Tang, R.; Pouillart, P.; Lidereau, R. Anti-colony-stimulating factor-1 antibody staining in primary breast adenocarcinomas correlates with marked inflammatory cell infiltrates and prognosis. *J. Natl. Cancer Inst.* **1994**, *86*, 120–126. [[CrossRef](#)]
264. Kluger, H.M.; Dolled-Filhart, M.; Rodov, S.; Kacinski, B.M.; Camp, R.L.; Rimm, D.L. Macrophage colony-stimulating factor-1 receptor expression is associated with poor outcome in breast cancer by large cohort tissue microarray analysis. *Clin. Cancer Res.* **2004**, *10*, 173–177. [[CrossRef](#)]
265. Bonapace, L.; Coissieux, M.-M.; Wyckoff, J.; Mertz, K.D.; Varga, Z.; Junt, T.; Bentires-Alj, M. Cessation of CCL2 inhibition accelerates breast cancer metastasis by promoting angiogenesis. *Nature* **2014**, *515*, 130–133. [[CrossRef](#)] [[PubMed](#)]
266. Qian, B.-Z.; Li, J.; Zhang, H.; Kitamura, T.; Zhang, J.; Campion, L.R.; Kaiser, E.A.; Snyder, L.A.; Pollard, J.W. CCL2 recruits inflammatory monocytes to facilitate breast-tumour metastasis. *Nature* **2011**, *475*, 222–225. [[CrossRef](#)]
267. Heiskala, M.; Leidenius, M.; Joensuu, K.; Heikkilä, P. High expression of CCL2 in tumor cells and abundant infiltration with CD14 positive macrophages predict early relapse in breast cancer. *Virchows Arch.* **2019**, *474*, 3–12. [[CrossRef](#)] [[PubMed](#)]
268. Yao, M.; Yu, E.; Staggs, V.; Fan, F.; Cheng, N. Elevated expression of chemokine C-C ligand 2 in stroma is associated with recurrent basal-like breast cancers. *Mod. Pathol.* **2016**, *29*, 810–823. [[CrossRef](#)]
269. Labovsky, V.; Martinez, L.M.; Davies, K.M.; de Luján Calcagno, M.; García-Rivello, H.; Wernicke, A.; Feldman, L.; Matas, A.; Giorello, M.B.; Borzone, F.R.; et al. Prognostic significance of TRAIL-R3 and CCR-2 expression in tumor epithelial cells of patients with early breast cancer. *BMC Cancer* **2017**, *17*, 280. [[CrossRef](#)]
270. Ueno, T.; Toi, M.; Saji, H.; Muta, M.; Bando, H.; Kuroi, K.; Koike, M.; Inadera, H.; Matsushima, K. Significance of macrophage chemoattractant protein-1 in macrophage recruitment, angiogenesis, and survival in human breast cancer. *Clin. Cancer Res.* **2000**, *6*, 3282–3289. [[PubMed](#)]
271. Lavender, N.; Yang, J.; Chen, S.-C.; Sai, J.; Johnson, C.A.; Owens, P.; Ayers, G.D.; Richmond, A. The Yin/Yan of CCL2: a minor role in neutrophil anti-tumor activity in vitro but a major role on the outgrowth of metastatic breast cancer lesions in the lung in vivo. *BMC Cancer* **2017**, *17*, 88. [[CrossRef](#)]
272. Slobodova, Z.; Ehrmann, J.; Krejci, V.; Zapletalova, J.; Melichar, B. Analysis of CD40 expression in breast cancer and its relation to clinicopathological characteristics. *Neoplasma* **2011**, *58*, 189–197. [[CrossRef](#)] [[PubMed](#)]
273. Frazao, A.; Messaoudene, M.; Nunez, N.; Dulphy, N.; Roussin, F.; Sedlik, C.; Zitvogel, L.; Piaggio, E.; Toubert, A.; Caignard, A. CD16+NKG2Ahigh Natural Killer Cells Infiltrate Breast Cancer-Draining Lymph Nodes. *Cancer Immunol. Res.* **2019**, *7*, 208–218. [[CrossRef](#)]
274. De Kruijff, E.M.; Sajet, A.; van Nes, J.G.H.; Putter, H.; Smit, V.T.H.B.M.; Eagle, R.A.; Jafferji, I.; Trowsdale, J.; Liefers, G.J.; van de Velde, C.J.H.; et al. NKG2D ligand tumor expression and association with clinical outcome in early breast cancer patients: an observational study. *BMC Cancer* **2012**, *12*, 24. [[CrossRef](#)] [[PubMed](#)]
275. Asghar, K.; Loya, A.; Rana, I.A.; Tahseen, M.; Ishaq, M.; Farooq, A.; Bakar, M.A.; Masood, I. Indoleamine 2,3-dioxygenase expression and overall survival in patients diagnosed with breast cancer in Pakistan. *Cancer Manag. Res.* **2019**, *11*, 475–481. [[CrossRef](#)] [[PubMed](#)]
276. Soliman, H.; Rawal, B.; Fulp, J.; Lee, J.-H.; Lopez, A.; Bui, M.M.; Khalil, F.; Antonia, S.; Yfantis, H.G.; Lee, D.H.; et al. Analysis of indoleamine 2-3 dioxygenase (IDO1) expression in breast cancer tissue by immunohistochemistry. *Cancer Immunol. Immunother.* **2013**, *62*, 829–837. [[CrossRef](#)] [[PubMed](#)]

277. Yu, J.; Sun, J.; Wang, S.E.; Li, H.; Cao, S.; Cong, Y.; Liu, J.; Ren, X. Upregulated expression of indoleamine 2,3-dioxygenase in primary breast cancer correlates with increase of infiltrated regulatory T cells in situ and lymph node metastasis. *Clin. Dev. Immunol.* **2011**, *2011*, 469135. [[CrossRef](#)] [[PubMed](#)]
278. Jacquemier, J.; Bertucci, F.; Finetti, P.; Esterni, B.; Charafe-Jauffret, E.; Thibult, M.-L.; Houvenaeghel, G.; Van den Eynde, B.; Birnbaum, D.; Olive, D.; et al. High expression of indoleamine 2,3-dioxygenase in the tumour is associated with medullary features and favourable outcome in basal-like breast carcinoma. *Int. J. Cancer* **2012**, *130*, 96–104. [[CrossRef](#)]
279. Dill, E.A.; Dillon, P.M.; Bullock, T.N.; Mills, A.M. IDO expression in breast cancer: an assessment of 281 primary and metastatic cases with comparison to PD-L1. *Mod. Pathol.* **2018**, *31*, 1513–1522. [[CrossRef](#)] [[PubMed](#)]
280. Wei, L.; Zhu, S.; Li, M.; Li, F.; Wei, F.; Liu, J.; Ren, X. High Indoleamine 2,3-Dioxygenase Is Correlated With Microvessel Density and Worse Prognosis in Breast Cancer. *Front. Immunol.* **2018**, *9*. [[CrossRef](#)]
281. Li, F.; Zhao, Y.; Wei, L.; Li, S.; Liu, J. Tumor-infiltrating Treg, MDSC, and IDO expression associated with outcomes of neoadjuvant chemotherapy of breast cancer. *Cancer Biol. Ther.* **2018**, *19*, 695–705. [[CrossRef](#)] [[PubMed](#)]
282. Ye, Q.; Wang, C.; Xian, J.; Zhang, M.; Cao, Y.; Cao, Y. Expression of programmed cell death protein 1 (PD-1) and indoleamine 2,3-dioxygenase (IDO) in the tumor microenvironment and in tumor-draining lymph nodes of breast cancer. *Hum. Pathol.* **2018**, *75*, 81–90. [[CrossRef](#)]
283. Eftekhari, R.; Esmaeili, R.; Mirzaei, R.; Bidad, K.; de Lima, S.; Ajami, M.; Shirzad, H.; Hadjati, J.; Majidzadeh-A, K. Study of the tumor microenvironment during breast cancer progression. *Cancer Cell Int.* **2017**, *17*, 123. [[CrossRef](#)] [[PubMed](#)]
284. Li, F.; Wei, L.; Li, S.; Liu, J. Indoleamine-2,3-dioxygenase and Interleukin-6 associated with tumor response to neoadjuvant chemotherapy in breast cancer. *Oncotarget* **2017**, *8*, 107844–107858. [[CrossRef](#)] [[PubMed](#)]
285. Carvajal-Hausdorf, D.E.; Mani, N.; Velcheti, V.; Schalper, K.A.; Rimm, D.L. Objective measurement and clinical significance of IDO1 protein in hormone receptor-positive breast cancer. *J. Immunother. Cancer* **2017**, *5*, 81. [[CrossRef](#)]
286. Chen, J.-Y.; Li, C.-F.; Kuo, C.-C.; Tsai, K.K.; Hou, M.-F.; Hung, W.-C. Cancer/stroma interplay via cyclooxygenase-2 and indoleamine 2,3-dioxygenase promotes breast cancer progression. *Breast Cancer Res.* **2014**, *16*, 410. [[CrossRef](#)] [[PubMed](#)]
287. Isla Larrain, M.T.; Rabassa, M.E.; Lacunza, E.; Barbera, A.; Cretón, A.; Segal-Eiras, A.; Croce, M.V. IDO is highly expressed in breast cancer and breast cancer-derived circulating microvesicles and associated to aggressive types of tumors by in silico analysis. *Tumour Biol.* **2014**, *35*, 6511–6519. [[CrossRef](#)]
288. Yu, J.; Du, W.; Yan, F.; Wang, Y.; Li, H.; Cao, S.; Yu, W.; Shen, C.; Liu, J.; Ren, X. Myeloid-derived suppressor cells suppress antitumor immune responses through IDO expression and correlate with lymph node metastasis in patients with breast cancer. *J. Immunol.* **2013**, *190*, 3783–3797. [[CrossRef](#)]
289. Juhász, C.; Nahleh, Z.; Zitron, I.; Chugani, D.C.; Janabi, M.Z.; Bandyopadhyay, S.; Ali-Fehmi, R.; Mangner, T.J.; Chakraborty, P.K.; Mittal, S.; et al. Tryptophan metabolism in breast cancers: molecular imaging and immunohistochemistry studies. *Nucl. Med. Biol.* **2012**, *39*, 926–932. [[CrossRef](#)] [[PubMed](#)]
290. Dowlati, A.; Rugo, H.S.; Harvey, R.D.; Kudchadkar, R.R.; Carvajal, R.D.; Manji, G.A.; Hamid, O.; Klempner, S.J.; Tang, S.; Yu, D.; et al. A phase I study of LY3022855, a colony-stimulating factor-1 receptor (CSF-1R) inhibitor, in patients (pts) with advanced solid tumors. *JCO* **2017**, *35*, 2523. [[CrossRef](#)]
291. Gomez-Roca, C.A.; Cassier, P.A.; Italiano, A.; Cannarile, M.; Ries, C.; Brillouet, A.; Mueller, C.; Jegg, A.-M.; Meneses-Lorente, G.; Baehner, M.; et al. Phase I study of RG7155, a novel anti-CSF1R antibody, in patients with advanced/metastatic solid tumors. *JCO* **2015**, *33*, 3005. [[CrossRef](#)]
292. Lakhani, N.J.; LoRusso, P.; Hafez, N.; Krishnamurthy, A.; O'Rourke, T.J.; Kamdar, M.K.; Fanning, P.; Zhao, Y.; Jin, F.; Wan, H.; et al. A phase 1 study of ALX148, a CD47 blocker, alone and in combination with established anticancer antibodies in patients with advanced malignancy and non-Hodgkin lymphoma. *JCO* **2018**, *36*, 3068. [[CrossRef](#)]
293. Gangadhar, T.C.; Hamid, O.; Smith, D.C.; Bauer, T.M.; Wasser, J.S.; Luke, J.J.; Balmanoukian, A.S.; Kaufman, D.R.; Zhao, Y.; Maleski, J.; et al. Preliminary results from a Phase I/II study of epacadostat (incb024360) in combination with pembrolizumab in patients with selected advanced cancers. *J. Immunother. Cancer* **2015**, *3*, O7. [[CrossRef](#)]

294. Fujiwara, Y.; Shitara, K.; Shimizu, T.; Yonemori, K.; Matsubara, N.; Ohno, I.; Kogawa, T.; Naito, Y.; Leopold, L.; Sasahara, K.; et al. Abstract A204: INCB024360 (Epacadostat) monotherapy and in combination with pembrolizumab in patients with advanced solid tumors: primary results from first-in-Japanese phase I study (KEYNOTE-434). *Mol. Cancer Ther.* **2018**, *17*, A204.
295. Beatty, G.L.; O'Dwyer, P.J.; Clark, J.; Shi, J.G.; Bowman, K.J.; Scherle, P.A.; Newton, R.C.; Schaub, R.; Maleski, J.; Leopold, L.; et al. First-in-Human Phase I Study of the Oral Inhibitor of Indoleamine 2,3-Dioxygenase-1 Epacadostat (INCB024360) in Patients with Advanced Solid Malignancies. *Clin. Cancer Res.* **2017**. [[CrossRef](#)] [[PubMed](#)]
296. Brown, E.J.; Frazier, W.A. Integrin-associated protein (CD47) and its ligands. *Trends Cell Biol.* **2001**, *11*, 130–135. [[CrossRef](#)]
297. Willingham, S.B.; Volkmer, J.-P.; Gentles, A.J.; Sahoo, D.; Dalerba, P.; Mitra, S.S.; Wang, J.; Contreras-Trujillo, H.; Martin, R.; Cohen, J.D.; et al. The CD47-signal regulatory protein alpha (SIRPα) interaction is a therapeutic target for human solid tumors. *Proc. Natl. Acad. Sci. USA* **2012**, *109*, 6662–6667. [[CrossRef](#)] [[PubMed](#)]
298. Advani, R.; Flinn, I.; Popplewell, L.; Forero, A.; Bartlett, N.L.; Ghosh, N.; Kline, J.; Roschewski, M.; LaCasce, A.; Collins, G.P.; et al. CD47 Blockade by Hu5F9-G4 and Rituximab in Non-Hodgkin's Lymphoma. *N. Engl. J. Med.* **2018**, *379*, 1711–1721. [[CrossRef](#)] [[PubMed](#)]
299. Le Mercier, I.; Poujol, D.; Sanlaville, A.; Sisirak, V.; Gobert, M.; Durand, I.; Dubois, B.; Treilleux, I.; Marvel, J.; Vlach, J.; et al. Tumor promotion by intratumoral plasmacytoid dendritic cells is reversed by TLR7 ligand treatment. *Cancer Res.* **2013**, *73*, 4629–4640. [[CrossRef](#)] [[PubMed](#)]
300. Yusuf, N. Toll-like receptor mediated regulation of breast cancer: a case of mixed blessings. *Front. Immunol.* **2014**, *5*, 224. [[PubMed](#)]
301. Salazar, L.G.; Lu, H.; Reichow, J.L.; Childs, J.S.; Coveler, A.L.; Higgins, D.M.; Waisman, J.; Allison, K.H.; Dang, Y.; Disis, M.L. Topical Imiquimod Plus Nab-paclitaxel for Breast Cancer Cutaneous Metastases: A Phase 2 Clinical Trial. *JAMA Oncol.* **2017**, *3*, 969–973. [[CrossRef](#)] [[PubMed](#)]
302. Adams, S.; Kozhaya, L.; Martiniuk, F.; Meng, T.-C.; Chiriboga, L.; Liebes, L.; Hochman, T.; Shuman, N.; Axelrod, D.; Speyer, J.; et al. Topical TLR7 agonist imiquimod can induce immune-mediated rejection of skin metastases in patients with breast cancer. *Clin. Cancer Res.* **2012**, *18*, 6748–6757. [[CrossRef](#)]
303. Vonderheide, R.H.; Glennie, M.J. Agonistic CD40 antibodies and cancer therapy. *Clin. Cancer Res.* **2013**, *19*, 1035–1043. [[CrossRef](#)] [[PubMed](#)]
304. Ma, H.S.; Poudel, B.; Torres, E.R.; Sidhom, J.-W.; Robinson, T.M.; Christmas, B.; Scott, B.; Cruz, K.; Woolman, S.; Wall, V.Z.; et al. A CD40 Agonist and PD-1 Antagonist Antibody Reprogram the Microenvironment of Nonimmunogenic Tumors to Allow T-cell-Mediated Anticancer Activity. *Cancer Immunol. Res.* **2019**, *7*, 428–442. [[CrossRef](#)] [[PubMed](#)]
305. Winograd, R.; Byrne, K.T.; Evans, R.A.; Odorizzi, P.M.; Meyer, A.R.L.; Bajor, D.L.; Clendenin, C.; Stanger, B.Z.; Furth, E.E.; Wherry, E.J.; et al. Induction of T-cell Immunity Overcomes Complete Resistance to PD-1 and CTLA-4 Blockade and Improves Survival in Pancreatic Carcinoma. *Cancer Immunol. Res.* **2015**, *3*, 399–411. [[CrossRef](#)] [[PubMed](#)]
306. Vonderheide, R.H.; Flaherty, K.T.; Khalil, M.; Stumacher, M.S.; Bajor, D.L.; Hutnick, N.A.; Sullivan, P.; Mahany, J.J.; Gallagher, M.; Kramer, A.; et al. Clinical activity and immune modulation in cancer patients treated with CP-870,893, a novel CD40 agonist monoclonal antibody. *J. Clin. Oncol.* **2007**, *25*, 876–883. [[CrossRef](#)] [[PubMed](#)]
307. Guillerey, C.; Smyth, M.J. NK Cells and Cancer Immunoediting. *Curr. Top. Microbiol. Immunol.* **2016**, *395*, 115–145. [[PubMed](#)]
308. Muntasell, A.; Ochoa, M.C.; Cordeiro, L.; Berraondo, P.; López-Díaz de Cerio, A.; Cabo, M.; López-Botet, M.; Melero, I. Targeting NK-cell checkpoints for cancer immunotherapy. *Curr. Opin. Immunol.* **2017**, *45*, 73–81. [[CrossRef](#)]
309. Jobim, M.R.; Jobim, M.; Salim, P.H.; Portela, P.; Jobim, L.F.; Leistner-Segal, S.; Bittelbrunn, A.C.; Menke, C.H.; Biazús, J.V.; Roesler, R.; et al. Analysis of KIR gene frequencies and HLA class I genotypes in breast cancer and control group. *Hum. Immunol.* **2013**, *74*, 1130–1133. [[CrossRef](#)] [[PubMed](#)]
310. Beksac, K.; Beksac, M.; Dalva, K.; Karaagaoglu, E.; Tirnaksiz, M.B. Impact of “Killer Immunoglobulin-Like Receptor /Ligand” Genotypes on Outcome following Surgery among Patients with Colorectal Cancer: Activating KIRs Are Associated with Long-Term Disease Free Survival. *PLoS ONE* **2015**, *10*, e0132526. [[CrossRef](#)] [[PubMed](#)]

311. Braud, V.M.; Allan, D.S.; O’Callaghan, C.A.; Söderström, K.; D’Andrea, A.; Ogg, G.S.; Lazetic, S.; Young, N.T.; Bell, J.I.; Phillips, J.H.; et al. HLA-E binds to natural killer cell receptors CD94/NKG2A, B and C. *Nature* **1998**, *391*, 795–799. [[CrossRef](#)]
312. André, P.; Denis, C.; Soulas, C.; Bourbon-Caillet, C.; Lopez, J.; Arnoux, T.; Bléry, M.; Bonnafous, C.; Gauthier, L.; Morel, A.; et al. Anti-NKG2A mAb Is a Checkpoint Inhibitor that Promotes Anti-tumor Immunity by Unleashing Both T and NK Cells. *Cell* **2018**, *175*, 1731–1743. [[CrossRef](#)]
313. Van Montfoort, N.; Borst, L.; Korner, M.J.; Sluijter, M.; Marijt, K.A.; Santegoets, S.J.; van Ham, V.J.; Ehsan, I.; Charoentong, P.; André, P.; et al. NKG2A Blockade Potentiates CD8 T Cell Immunity Induced by Cancer Vaccines. *Cell* **2018**, *175*, 1744–1755. [[CrossRef](#)]
314. Raulet, D.H. Roles of the NKG2D immunoreceptor and its ligands. *Nat. Rev. Immunol.* **2003**, *3*, 781–790. [[CrossRef](#)]
315. Moretta, A.; Bottino, C.; Vitale, M.; Pende, D.; Cantoni, C.; Mingari, M.C.; Biassoni, R.; Moretta, L. Activating receptors and coreceptors involved in human natural killer cell-mediated cytotoxicity. *Annu. Rev. Immunol.* **2001**, *19*, 197–223. [[CrossRef](#)] [[PubMed](#)]
316. Ascierto, M.L.; Idowu, M.O.; Zhao, Y.; Khalak, H.; Payne, K.K.; Wang, X.-Y.; Dumur, C.I.; Bedognetti, D.; Tomei, S.; Ascierto, P.A.; et al. Molecular signatures mostly associated with NK cells are predictive of relapse free survival in breast cancer patients. *J. Transl. Med.* **2013**, *11*, 145. [[CrossRef](#)] [[PubMed](#)]
317. Abouelghar, A.; Hasnah, R.; Taouk, G.; Saad, M.; Karam, M. Prognostic values of the mRNA expression of natural killer receptor ligands and their association with clinicopathological features in breast cancer patients. *Oncotarget* **2018**, *9*, 27171–27196. [[CrossRef](#)]
318. Brochez, L.; Chevolet, I.; Kruse, V. The rationale of indoleamine 2,3-dioxygenase inhibition for cancer therapy. *Eur. J. Cancer* **2017**, *76*, 167–182. [[CrossRef](#)] [[PubMed](#)]
319. Théate, I.; van Baren, N.; Pilotte, L.; Moulin, P.; Larrieu, P.; Renaud, J.-C.; Hervé, C.; Gutierrez-Roelens, I.; Marbaix, E.; Sempoux, C.; et al. Extensive profiling of the expression of the indoleamine 2,3-dioxygenase 1 protein in normal and tumoral human tissues. *Cancer Immunol. Res.* **2015**, *3*, 161–172. [[CrossRef](#)]
320. Mellor, A.L.; Keskin, D.B.; Johnson, T.; Chandler, P.; Munn, D.H. Cells expressing indoleamine 2,3-dioxygenase inhibit T cell responses. *J. Immunol.* **2002**, *168*, 3771–3776. [[CrossRef](#)]
321. Jung, K.H.; LoRusso, P.M.; Burris, H.A.; Gordon, M.S.; Bang, Y.-J.; Hellmann, M.D.; Cervantes, A.; Ochoa de Olza, M.; Marabelle, A.; Hodi, F.S.; et al. Phase I Study of the Indoleamine 2,3-Dioxygenase 1 (IDO1) Inhibitor Navoximod (GDC-0919) Administered with PD-L1 Inhibitor (Atezolizumab) in Advanced Solid Tumors. *Clin. Cancer Res.* **2019**. [[CrossRef](#)]
322. Corzo, C.A.; Cotter, M.J.; Cheng, P.; Cheng, F.; Kusmartsev, S.; Sotomayor, E.; Padhya, T.; McCaffrey, T.V.; McCaffrey, J.C.; Gavrillovich, D.I. Mechanism regulating reactive oxygen species in tumor-induced myeloid-derived suppressor cells. *J. Immunol.* **2009**, *182*, 5693–5701. [[CrossRef](#)]
323. Raber, P.L.; Thevenot, P.; Sierra, R.; Wyczechowska, D.; Halle, D.; Ramirez, M.E.; Ochoa, A.C.; Fletcher, M.; Velasco, C.; Wilk, A.; et al. Subpopulations of myeloid-derived suppressor cells impair T cell responses through independent nitric oxide-related pathways. *Int. J. Cancer* **2014**, *134*, 2853–2864. [[CrossRef](#)] [[PubMed](#)]
324. Ku, A.W.; Muhitch, J.B.; Powers, C.A.; Diehl, M.; Kim, M.; Fisher, D.T.; Sharda, A.P.; Clements, V.K.; O’Loughlin, K.; Minderman, H.; et al. Tumor-induced MDSC act via remote control to inhibit L-selectin-dependent adaptive immunity in lymph nodes. *Elife* **2016**, *5*. [[CrossRef](#)] [[PubMed](#)]
325. Huang, B.; Pan, P.-Y.; Li, Q.; Sato, A.I.; Levy, D.E.; Bromberg, J.; Divino, C.M.; Chen, S.-H. Gr-1+CD115+ immature myeloid suppressor cells mediate the development of tumor-induced T regulatory cells and T-cell anergy in tumor-bearing host. *Cancer Res.* **2006**, *66*, 1123–1131. [[CrossRef](#)]
326. Beury, D.W.; Parker, K.H.; Nyandjo, M.; Sinha, P.; Carter, K.A.; Ostrand-Rosenberg, S. Cross-talk among myeloid-derived suppressor cells, macrophages, and tumor cells impacts the inflammatory milieu of solid tumors. *J. Leukoc. Biol.* **2014**, *96*, 1109–1118. [[CrossRef](#)]
327. Rodriguez, P.C.; Quiceno, D.G.; Zabaleta, J.; Ortiz, B.; Zea, A.H.; Piazuelo, M.B.; Delgado, A.; Correa, P.; Brayer, J.; Sotomayor, E.M.; et al. Arginase I production in the tumor microenvironment by mature myeloid cells inhibits T-cell receptor expression and antigen-specific T-cell responses. *Cancer Res.* **2004**, *64*, 5839–5849. [[CrossRef](#)]
328. Srivastava, M.K.; Sinha, P.; Clements, V.K.; Rodriguez, P.; Ostrand-Rosenberg, S. Myeloid-derived suppressor cells inhibit T-cell activation by depleting cystine and cysteine. *Cancer Res.* **2010**, *70*, 68–77. [[CrossRef](#)]

329. Lu, C.; Redd, P.S.; Lee, J.R.; Savage, N.; Liu, K. The expression profiles and regulation of PD-L1 in tumor-induced myeloid-derived suppressor cells. *Oncoimmunology* **2016**, *5*, e1247135. [[CrossRef](#)]
330. Li, J.; Wang, L.; Chen, X.; Li, L.; Li, Y.; Ping, Y.; Huang, L.; Yue, D.; Zhang, Z.; Wang, F.; et al. CD39/CD73 upregulation on myeloid-derived suppressor cells via TGF- β -mTOR-HIF-1 signaling in patients with non-small cell lung cancer. *Oncoimmunology* **2017**, *6*, e1320011. [[CrossRef](#)]
331. Toh, B.; Wang, X.; Keeble, J.; Sim, W.J.; Khoo, K.; Wong, W.-C.; Kato, M.; Prevost-Blondel, A.; Thiery, J.-P.; Abastado, J.-P. Mesenchymal transition and dissemination of cancer cells is driven by myeloid-derived suppressor cells infiltrating the primary tumor. *PLoS Biol.* **2011**, *9*, e1001162. [[CrossRef](#)] [[PubMed](#)]
332. Yang, L.; Huang, J.; Ren, X.; Gorska, A.E.; Chytil, A.; Aakre, M.; Carbone, D.P.; Matrisian, L.M.; Richmond, A.; Lin, P.C.; et al. Abrogation of TGF beta signaling in mammary carcinomas recruits Gr-1+CD11b+ myeloid cells that promote metastasis. *Cancer Cell* **2008**, *13*, 23–35. [[CrossRef](#)] [[PubMed](#)]
333. Cui, T.X.; Kryczek, I.; Zhao, L.; Zhao, E.; Kuick, R.; Roh, M.H.; Vatan, L.; Szeliga, W.; Mao, Y.; Thomas, D.G.; et al. Myeloid-derived suppressor cells enhance stemness of cancer cells by inducing microRNA101 and suppressing the corepressor CtBP2. *Immunity* **2013**, *39*, 611–621. [[CrossRef](#)] [[PubMed](#)]
334. Yang, L.; DeBusk, L.M.; Fukuda, K.; Fingleton, B.; Green-Jarvis, B.; Shyr, Y.; Matrisian, L.M.; Carbone, D.P.; Lin, P.C. Expansion of myeloid immune suppressor Gr+CD11b+ cells in tumor-bearing host directly promotes tumor angiogenesis. *Cancer Cell* **2004**, *6*, 409–421. [[CrossRef](#)] [[PubMed](#)]
335. Yan, H.H.; Pickup, M.; Pang, Y.; Gorska, A.E.; Li, Z.; Chytil, A.; Geng, Y.; Gray, J.W.; Moses, H.L.; Yang, L. Gr-1+CD11b+ myeloid cells tip the balance of immune protection to tumor promotion in the premetastatic lung. *Cancer Res.* **2010**, *70*, 6139–6149. [[CrossRef](#)] [[PubMed](#)]
336. Jin, G.; Zhang, Y.; Chang, X.; Zhang, Y.; Xu, J.; Wei, M.; Zeng, X. Increased Percentage of mo-MDSCs in Human Peripheral Blood May Be a Potential Indicator in the Diagnosis of Breast Cancer. *Oncol. Res. Treat.* **2017**, *40*, 603–608. [[CrossRef](#)]
337. Diaz-Montero, C.M.; Salem, M.L.; Nishimura, M.I.; Garrett-Mayer, E.; Cole, D.J.; Montero, A.J. Increased circulating myeloid-derived suppressor cells correlate with clinical cancer stage, metastatic tumor burden, and doxorubicin-cyclophosphamide chemotherapy. *Cancer Immunol. Immunother.* **2009**, *58*, 49–59. [[CrossRef](#)]
338. Toor, S.M.; Syed Khaja, A.S.; El Salhat, H.; Faour, I.; Kanbar, J.; Quadri, A.A.; Albashir, M.; Elkord, E. Myeloid cells in circulation and tumor microenvironment of breast cancer patients. *Cancer Immunol. Immunother.* **2017**, *66*, 753–764. [[CrossRef](#)]
339. Kumar, S.; Wilkes, D.W.; Samuel, N.; Blanco, M.A.; Nayak, A.; Alicea-Torres, K.; Gluck, C.; Sinha, S.; Gabrilovich, D.; Chakrabarti, R. Δ Np63-driven recruitment of myeloid-derived suppressor cells promotes metastasis in triple-negative breast cancer. *J. Clin. Invest.* **2018**, *128*, 5095–5109. [[CrossRef](#)]
340. Peng, D.; Tanikawa, T.; Li, W.; Zhao, L.; Vatan, L.; Szeliga, W.; Wan, S.; Wei, S.; Wang, Y.; Liu, Y.; et al. Myeloid-derived suppressor cells endow stem-like qualities to breast cancer cells through IL-6/STAT3 and NO/NOTCH cross-talk signaling. *Cancer Res.* **2016**, *76*, 3156–3165. [[CrossRef](#)]
341. Gonda, K.; Shibata, M.; Ohtake, T.; Matsumoto, Y.; Tachibana, K.; Abe, N.; Ohto, H.; Sakurai, K.; Takenoshita, S. Myeloid-derived suppressor cells are increased and correlated with type 2 immune responses, malnutrition, inflammation, and poor prognosis in patients with breast cancer. *Oncol. Lett.* **2017**, *14*, 1766–1774. [[CrossRef](#)]
342. Wesolowski, R.; Duggan, M.C.; Stiff, A.; Markowitz, J.; Trikha, P.; Levine, K.M.; Schoenfield, L.; Abdel-Rasoul, M.; Layman, R.; Ramaswamy, B.; et al. Circulating myeloid derived suppressor cells increase in patients undergoing neo-adjuvant chemotherapy for breast cancer. *Cancer Immunol. Immunother.* **2017**, *66*, 1437–1447. [[CrossRef](#)] [[PubMed](#)]
343. Montero, A.J.; Diaz-Montero, C.M.; Deutsch, Y.E.; Hurley, J.; Koniaris, L.G.; Rumboldt, T.; Yasir, S.; Jorda, M.; Garret-Mayer, E.; Avisar, E.; et al. Phase 2 study of neoadjuvant treatment with NOV-002 in combination with doxorubicin and cyclophosphamide followed by docetaxel in patients with HER-2 negative clinical stage II-IIIc breast cancer. *Breast Cancer Res. Treat.* **2012**, *132*, 215–223. [[CrossRef](#)]
344. Su, Z.; Ni, P.; She, P.; Liu, Y.; Richard, S.A.; Xu, W.; Zhu, H.; Wang, J. Bio-HMGB1 from breast cancer contributes to M-MDSC differentiation from bone marrow progenitor cells and facilitates conversion of monocytes into MDSC-like cells. *Cancer Immunol. Immunother.* **2017**, *66*, 391–401. [[CrossRef](#)]
345. Hong, H.-J.; Lim, H.X.; Song, J.H.; Lee, A.; Kim, E.; Cho, D.; Cohen, E.P.; Kim, T.S. Aminoacyl-tRNA synthetase-interacting multifunctional protein 1 suppresses tumor growth in breast cancer-bearing mice by negatively regulating myeloid-derived suppressor cell functions. *Cancer Immunol. Immunother.* **2016**, *65*, 61–72. [[CrossRef](#)]

346. Qian, X.; Zhang, Q.; Shao, N.; Shan, Z.; Cheang, T.; Zhang, Z.; Su, Q.; Wang, S.; Lin, Y. Respiratory hyperoxia reverses immunosuppression by regulating myeloid-derived suppressor cells and PD-L1 expression in a triple-negative breast cancer mouse model. *Am. J. Cancer Res.* **2019**, *9*, 529–545.
347. Yin, T.; Zhao, Z.-B.; Guo, J.; Wang, T.; Yang, J.-B.; Wang, C.; Long, J.; Ma, S.; Huang, Q.; Zhang, K.; et al. Aurora-A inhibition eliminates myeloid cell-mediated immunosuppression and enhances the efficacy of anti-PD-L1 therapy in breast cancer. *Cancer Res.* **2019**. [[CrossRef](#)]
348. Ugel, S.; Delpozzo, F.; Desantis, G.; Papalini, F.; Simonato, F.; Sonda, N.; Zilio, S.; Bronte, V. Therapeutic targeting of myeloid-derived suppressor cells. *Curr. Opin. Pharmacol.* **2009**, *9*, 470–481. [[CrossRef](#)] [[PubMed](#)]
349. Shen, X.; Zhao, B. Efficacy of PD-1 or PD-L1 inhibitors and PD-L1 expression status in cancer: meta-analysis. *BMJ* **2018**, *362*, k3529. [[CrossRef](#)] [[PubMed](#)]
350. Wolchok, J.D.; Chiarion-Sileni, V.; Gonzalez, R.; Rutkowski, P.; Grob, J.-J.; Cowey, C.L.; Lao, C.D.; Wagstaff, J.; Schadendorf, D.; Ferrucci, P.F.; et al. Overall Survival with Combined Nivolumab and Ipilimumab in Advanced Melanoma. *N. Engl. J. Med.* **2017**, *377*, 1345–1356. [[CrossRef](#)]
351. Wei, S.C.; Duffy, C.R.; Allison, J.P. Fundamental Mechanisms of Immune Checkpoint Blockade Therapy. *Cancer Discov.* **2018**, *8*, 1069–1086. [[CrossRef](#)]
352. Epacadostat Combined with Pembrolizumab in Patients with Unresectable or Metastatic Melanoma - The ASCO Post. Available online: <http://www.ascopost.com/News/58726> (accessed on 17 March 2019).
353. Freeman-Keller, M.; Kim, Y.; Cronin, H.; Richards, A.; Gibney, G.; Weber, J.S. Nivolumab in Resected and Unresectable Metastatic Melanoma: Characteristics of Immune-Related Adverse Events and Association with Outcomes. *Clin. Cancer Res.* **2016**, *22*, 886–894. [[CrossRef](#)]
354. Teraoka, S.; Fujimoto, D.; Morimoto, T.; Kawachi, H.; Ito, M.; Sato, Y.; Nagata, K.; Nakagawa, A.; Otsuka, K.; Uehara, K.; et al. Early Immune-Related Adverse Events and Association with Outcome in Advanced Non-Small Cell Lung Cancer Patients Treated with Nivolumab: A Prospective Cohort Study. *J. Thorac. Oncol.* **2017**, *12*, 1798–1805. [[CrossRef](#)] [[PubMed](#)]
355. Oh, A.; Tran, D.M.; McDowell, L.C.; Keyvani, D.; Barcelon, J.A.; Merino, O.; Wilson, L. Cost-Effectiveness of Nivolumab-Ipilimumab Combination Therapy Compared with Monotherapy for First-Line Treatment of Metastatic Melanoma in the United States. *J. Manag. Care Spec. Pharm.* **2017**, *23*, 653–664. [[CrossRef](#)] [[PubMed](#)]
356. Hellmann, M.D.; Ciuleanu, T.-E.; Pluzanski, A.; Lee, J.S.; Otterson, G.A.; Audigier-Valette, C.; Minenza, E.; Linardou, H.; Burgers, S.; Salman, P.; et al. Nivolumab plus Ipilimumab in Lung Cancer with a High Tumor Mutational Burden. *N. Engl. J. Med.* **2018**, *378*, 2093–2104. [[CrossRef](#)] [[PubMed](#)]
357. Motzer, R.J.; Tannir, N.M.; McDermott, D.F.; Arén Frontera, O.; Melichar, B.; Choueiri, T.K.; Plimack, E.R.; Barthélémy, P.; Porta, C.; George, S.; et al. Nivolumab plus Ipilimumab versus Sunitinib in Advanced Renal-Cell Carcinoma. *N. Engl. J. Med.* **2018**, *378*, 1277–1290. [[CrossRef](#)] [[PubMed](#)]

