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Next-generation CTLA-4 targeting molecules and combination therapy: promising strategies for improving cancer immunotherapy

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ABSTRACT

Radiation therapy and anti-CTLA-4 combination therapy can induce meaningful responses in some patients. Adding CD40 may provide additional benefit. Next-generation anti-CTLA-4 antibodies, such as botensilimab, are showing promise in clinical trials. Combining botensilimab with RT and/or CD40 agonist may offer additional benefits for challenging tumor types.

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Main Text

CTLA-4 blockade with ipilimumab launched the immune checkpoint blockade (ICB) era and revolutionized cancer immunotherapy. However, ipilimumab monotherapy provides durable responses to only a minority of patients, even within responsive tumor types. This underscores a critical need for more rational combinations and next-generation anti-CTLA-4 antibodies that address the challenges of resistance and improve outcomes for a broader patient population.

In addition to a highly immunosuppressive microenvironment, a major challenge in treating 'cold' and ICB refractory tumors is immune recognition and generating effective T cell responses against the cancer. Radiation therapy (RT) can help induce responses to CTLA-4 ICB by releasing tumor antigen and subsequent activation and priming for tumor-specific T cells.[1] Consistently, clinical benefit from the combination (RT+aCTLA-4) has been associated with peripheral expansion of novel and preexisting anti-tumor T cell clones.[2] Still, most patients do not respond to RT+aCTLA-4, and complete and durable responses are rare.[2,3]

Recently, researchers conducted an analysis of the tumor microenvironment (TME) in ICB-refractory triple-negative breast cancer (TNBC) mouse models to identify avenues for enhancing treatment outcomes.[4] The studies revealed that RT +aCTLA-4 increased T cell clonality, and the frequency of Th1-like CD4 T cells and early activated and effector memory CD8 T cells in the TME. However, meaningful responses occurred in a minority of treated mice. The authors analyzed their data for additional combinatorial targets and demonstrated that adding an agonistic CD40 antibody significantly improved response rates. Mechanistically, the response was associated with activation of cross-presenting dendritic cells and increased priming and recruitment of tumor antigen-specific CD8 T cells to the tumor microenvironment (TME).

Next-generation anti-CTLA-4 antibodies are being developed to improve response rates. Compared to first generation CTLA-4 molecules, they have been modified to overcome dose-limiting toxicity, improve T cell activation, and/or promote intratumoral T regulatory cells (Treg) depletion (Table 1). Some molecules use an enzyme-cleavable mask to avoid toxicity due to on-target off-tumor activity, making the molecule active only in the presence of proteases that are more prevalent in the TME. Although this strategy could reduce toxicity and enable higher CTLA-4 blocking doses, it is uncertain if it will improve response rates. Early clinical trials have not yet shown a clear advantage in terms of avoiding toxicity while maintaining efficacy. In contrast, to enhance the efficacy of CTLA-4 blockade, researchers are engineering next-generation anti-CTLA-4 antibodies to bind more strongly to activating Fc-gamma receptors (FcγRs). This depletes immune-suppressive Tregs by antibody-dependent cellular cytotoxicity/phagocytosis (ADCC/P) mechanisms and enhances T cell priming by improving the quality of the immune synapse between T cells and FcyR-expressing antigen-presenting cells[5,6]. In preclinical models, Fc-enhancement provided a more favorable environment for anti-tumor T cells to eliminate cancer cells.[7]

Botensilimab, Agenus' Fc-enhanced anti-CTLA-4 antibody, is one of the most advanced next-generation molecules in the class currently in clinical trials (Table 1). Remarkedly, botensilimab ± balstilimab (Agenus' anti-PD-1 antibody) demonstrated an 23% response rate in patients with microsatellite stable colorectal cancer (MSS-CRC; response rate reported for patients without active liver metastasis), an indication for which ipilimumab/nivolumab and tremelimumab/durvalumab are ineffective.[8,9] Botensilimab's

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Table 1. Reported clinical data on next generation mono-specific anti-CTLA-4 molecules.

Asset (Company)[a] and attributes	Indication, N (Treatment)[b]	ORR[c] (%)	DCR[d] (%)	Grade 3+ TRAE[e] % (n/N)	Conference/year
Botensilimab (Agenus)	MSS-CRC 3 L+, no active liver mets, $N = 69$ (+ balstilimab)	23%	80%	39% (39/101)[f]	ESMO-GI/2023
• IgG1	Pt refractory/resistant ovarian cancer, $N = 24$ (+ balstilimab)	33%	67%	41% (10/24)	SGO/2023
• Fc engineered	Sarcoma 2 L+, $N = 13$ (+ balstilimab)	46%	69%	23% (3/13)	CTOS/2022
	PD-1 r/r NSCLC, $N = 8$ (+ balstilimab)	50%	88%	N/A	SITC/2022
	Solid tumors, $N = 27$ (monotx)	15%	48%	27% (12/44)	SITC/2021
ONC-392 (OncoC4/BioNTech)	PD-1 r/r NSCLC, $N = 27$ (monotx)	22%	70%	43% (15/33)	ASCO/2023
• IgG1	Pt-resistant ovarian cancer, $N = 26$ (monotx)	15%	73%	34% (11/32)	SITC/2022
• pH sensitive	Solid tumors, $N = 13$ (+ pembrolizumab)	23%	62%	39% (5/13)	SITC/2022
• Fc engineered					
ADG116 (Adagene)	Solid tumors, $N = 36$ (monotx)	3%	33%	6% (3/50)	SITC/2022
• IgG1	Solid tumors, $N = 5$ (+ toripalimab)	20%	100%	66% (6/9)	SITC/2022
• Reduced blocking activity	Solid tumors, $N = 5$ (+ pembrolizumab)	0%	40%	33% (2/6)	SITC/2022
ADG126 (Adagene)	Solid tumors, $N = 27$ (monotx)	0%	37%	0%	AACR/2023
• IgG1	Solid tumors, $N = 18$ (+ toripalimab)	11%	56%	25% (5/20	AACR/2023
• Partial ligand blocking	Solid tumors, $N = 11$ (+ pembrolizumab)	9%	36%	18% (2/11)	AACR/2023
• SAFEBody™					
• Masked peptide, tumor activated					
XTX101 (Xilio)	Solid tumors, $N = 16$ (monotx)	6%	12.5%	N/A	Company Website
• Masked peptide, tumor activated					
• Fc engineered					
BMS-986249 (BMS)	Solid tumors, $N = 39$ (monotx)	0%	26%	23% (9/39)	ESMO/2022
• Probody (tumor activated)	Solid tumors ($N = 64$ (+ nivolumab)	16%	38%	38% (24/64)	ESMO/2022
• Conditionally active					
BMS-986218 (BMS)	Solid tumors, $N = 107$ (monotx)	1.9%	28%	17.8% (19/107)	SITC/2022
• IgG1	Solid tumors, $N = 48$ (+ nivolumab)	8.3%	29.1%	27% (13/48)	SITC/2022
• Fc engineered (afucosylated)					

[a]Fc, fragment crystallizable; IgG1, immunoglobulin G1.
[b]MSS-CRC, microsatellite stable colorectal cancer; NSCLC, non-small cell lung cancer; PD-1, programmed cell death protein 1; monotx, monotherapy treatment; r/r relapsed/refractory; N, sample size; L, lines of treatment.
[c]ORR, objective response rate.
[d]DCR, disease control rate.
[e]TRAE, treatment related adverse event, is reported for all treated patients.
[f]TRAE reported on all treated patients in this cohort, regardless of liver metastasis status.

novel FcγR-dependent mechanisms of action promoted superior priming and activation of T cells, as indicated by the expansion of new peripheral T cell clones in patients with advanced solid cancers.[7] Notably, botensilimab preferentially reduced suppressive intratumoral Tregs, a mechanism that remains controversial for conventional anti-CTLA-4.[7] Lastly, clinical response to botensilimab was independent of tumor neoantigen-burden and FCGR3A allele status,[7] unlike that reported for ipilimumab.[5]

While botensilimab can activate antigen-presenting cells (APCs) via FcγR-signaling, the benefit of combining it with RT and a CD40 agonist remains to be elucidated. Interestingly, botensilimab, but not conventional IgG1 anti-CTLA-4 antibodies, increased CD40 expression on APCs; essentially making APCs more responsive to CD40 agonism. This suggests that there may be additional benefits to combining botensilimab with an agonistic CD40 antibody, with or without RT, for the treatment of 'cold' and ICB refractory tumor types. It is also plausible that the dosage of the CD40 agonist antibodies can be reduced, potentially mitigating toxicity issues, a significant hurdle in the clinical development of relevant agonistic CD40 agents.[10] These observations warrant further investigation.

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