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A radiologist's guide to novel anticancer therapies in the era of precision medicine

Ali Khader, Rozan Bokhari, Reza Hakimelahi, Christopher Scheirey, Jalil Afnan, Marta Braschi-Amirfarzan, Richard Thomas *

Department of Radiology, Lahey Hospital and Medical Center, Tufts University School of Medicine, 41 Mall Road, Burlington 01805, MA, USA

HIGHLIGHTS

- Novel anticancer agents include small molecule inhibitors, antibodies and hormones.
- These agents are predominantly cytostatic and inhibit factors that provide a survival advantage to tumor cells.
- Modern cancer therapy employs a combination of novel anticancer agents and conventional chemotherapy.
- It is essential for radiologists to have a broad understanding of these agents and their mechanisms of action.

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ABSTRACT

Novel anticancer agents have replaced conventional chemotherapy as first line agents for many cancers, with continued new and expanding indications. Small molecule inhibitors act on cell surface or intracellular targets and prevent the downstream signaling that would otherwise permit tumor growth and spread. Anticancer antibodies can be directed against growth factors or may be immunotherapeutic agents. The latter act by inhibiting mechanisms that cancer cells use to evade the immune system. Hormonal agents act by decreasing levels of hormones that are necessary for the growth of certain cancer cells. Cancer therapy protocols often include novel anticancer agents and conventional chemotherapy used successively or in combination, in order to maximize survival and minimize morbidity. A working knowledge of anti-cancer drug classification will aid the radiologist in assessing response on imaging.

1. Overview of novel anticancer drugs – Mechanisms of action and indications

Over the past few decades, cancer therapy has evolved into a highly targeted and individualized process, with resultant improvement in morbidity and mortality [1–3]. This constant state of progress provides opportunities for research and improvements in clinical care as clinicians learn more about how different drugs affect the growth and spread of cancer [1,2,4]. Fine tuning the practice of precision medicine is an ongoing process that requires detailed understanding of the mechanisms of action of different drug classes, which can be used as single agents or as a combination of two or more drug classes [5].

The purpose of this review article is to provide a brief overview of the mechanisms of action of major targeted anticancer drug classes. The important current indications for these drugs have been listed in Table 1. Note that several individual drugs act on multiple targets and therefore need to be classified in multiple categories. Consequently, different drug classes included in Table 1 have overlapping indications. While it may be challenging for radiologists to be fully aware of every novel anticancer agent, it is beneficial to have an understanding of the mechanisms of action of broad drug classes and their current indications.

A working knowledge of anti-cancer drug classification will aid the radiologist in assessing response on imaging. In contrast to traditional chemotherapy agents, which are cytotoxic and result in cell killing, many of these novel agents are cytostatic and result in the shutdown of proliferative and survival mechanisms. Therefore, responses to these drugs can manifest differently on imaging and may require alternative assessment criteria for responses to be adequately captured. It is

* Corresponding author.
E-mail addresses: ali.khader@lahey.org (A. Khader), rozan.bokhari@lahey.org (R. Bokhari), reza.hakimelahi@lahey.org (R. Hakimelahi), christopher.scheirey@lahey.org (C. Scheirey), jail.afnan@lahey.org (J. Afnan), marta.braschiamirfarzan@lahey.org (M. Braschi-Amirfarzan), richard.thomas1@lahey.org (R. Thomas).

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Table 1
Important clinical indications for novel anticancer agents.

VEGF Inhibitors (Eg: bevacizumab, ziv-aflibercept, sorafenib, sunitinib)	Colorectal cancer, NSCLC, cervical cancer, epithelial ovarian cancer, fallopian tube cancer, primary peritoneal cancer, RCC, GIST, pancreatic neuroendocrine tumor, metastatic differentiated thyroid carcinoma, glioblastoma, advanced soft tissue sarcoma. Off label use in retinal vein occlusion, diabetic macular edema and age-related macular degeneration
ALK and ROS Inhibitors (Eg: crizotinib, entercitinib, alectinib, brigatinib, loratinib)	ALK positive NSCLC, ROS-1 positive NSCLC, NTRK gene fusion positive solid tumors
BCR-ABL Inhibitors and PDGFR Inhibitors (Eg: imatinib)	BCR-ABL mutated CML and ALL, GIST, HCC, colorectal cancer
PARP Inhibitors (Eg:olaparib)	BRCA mutated breast cancer, BRCA mutated ovarian cancer, BRCA mutated pancreatic cancer
EGFR inhibitors (Eg: erlotinib, osimertinib)	EGFR mutated NSCLC, metastatic colorectal cancer, metastatic head and neck cancer
RET, MET, KIT, PI3K (Eg: idelalisib, duvelisib)	Chronic lymphocytic leukemia, lymphoma, breast cancer
RAF Inhibitors (Eg: vemurafenib, dabrafenib)	BRAF V600E mutation positive Melanoma, BRAF V600E mutation positive Erdheim-Chester disease, BRAF V600E mutation positive NSCLC and anaplastic thyroid cancer
MEK Inhibitors (Eg: trametinib, cobimetinib)	Often used in combination with RAF inhibitors for BRAF V600E mutation positive NSCLC, melanoma and anaplastic thyroid cancer
mTOR Inhibitors (Eg: sirolimus)	Renal cell cancer, pancreatic/gastrointestinal/lung neuroendocrine tumor, breast cancer, TSC-associated partial-onset seizures, TSC-associated subependymal giant cell astrocytoma, TSC-associated renal angiomyolipoma
BTK Inhibitors (Eg: ibrutinib)	Mantle cell lymphoma, chronic lymphocytic leukemia, small lymphocytic lymphoma, Waldenstrom's macroglobulinemia, marginal zone lymphoma, chronic graft versus host disease
Hedgehog Pathway Inhibitors (Eg:vismodegib)	Basal cell carcinoma
CDK Inhibitors (Eg: palbociclib, abemaciclib)	HR+ /HER2 advanced or metastatic breast cancer (used in combination with hormonal agent)
HER2 Inhibitors (Eg: trastuzumab, pertuzumab)	HER2 positive breast cancer and HER2 positive gastric cancer
Immune Checkpoint Inhibitors (Eg: nivolumab, ipilimumab, pembrolizumab, durvalumab)	Melanoma, NSCLC, SCLC, RCC, HCC, Hodgkin's lymphoma, head and neck cancer, urothelial cancer, microsatellite instability high (msi-high) or DNA mismatch repair deficient (mmr-d) colorectal cancer and solid tumors, gastric cancer, esophageal cancer, cervical cancer, Merkel cell cancer, endometrial cancer, breast cancer
Anti-lymphocyte antibodies (Eg: rituximab, ofatumumab)	Lymphoma, waldenstrom's macroglobulinemia, granulomatosis with polyangiitis, microscopic polyangiitis, pemphigus vulgaris, rheumatoid arthritis, multiple sclerosis
Hormonal agents	SERM (tamoxifen) – HR+ breast cancer Selective estrogen degrader (fluvestrant) - HR+ breast cancer as monotherapy or in combination with abemaciclib Aromatase inhibitors (Letrozole, Anastrozole, exemestane) - post-menopausal women with HR+ breast cancer LHRH agonizts (euprolide, Goserelin, Triptorelin, Histrelin) - prostate cancer, endometriosis LHRH antagonists (Degarelix) – prostate cancer CYP17A1 inhibitor (abiraterone) – prostate cancer Androgen receptor antagonists (Flutamide, Nilutamide, Bicalutamide, enzalutamide, apalutamide, darolutamide) – prostate cancer

VEGF – vascular endothelial growth factor, NSCLC – non small cell lung cancer, RCC – renal cell cancer, GIST – gastrointestinal stromal tumor, ALK – anaplastic lymphoma kinase, PDGFR – platelet derived growth factor receptor, CML – chronic myeloid leukemia, ALL – acute lymphocytic leukemia, HCC – hepatocellular carcinoma, EGFR – epidermal growth factor receptor, TSC – tuberous sclerosis, HR – hormone receptor, SERM – selective estrogen receptor modulator, LHRH – luteinizing hormone releasing hormone

important for the radiologist to understand and consider the specific anti-tumor agent(s) and mechanism of action when assessing restaging studies to be able to provide the highest quality and most accurate interpretations.

2. VEGF Inhibitors

Since the early 1970s when anti-angiogenic targeted therapy was first proposed as a means of controlling cancer growth [6], there has been tremendous progress in the understanding of tumor growth and angiogenesis [7]. The general understanding at the beginning of this era was that tumor growth results in hypoxic signaling of the tumor core, which causes vascular recruitment leading to further growth and additional hypoxic signaling [7]. We now know that the vascular endothelial growth factor (VEGF) family, primarily VEGF-A (previously called vascular permeability factor), plays a significant role in controlling angiogenesis [8]. Due to the abnormal angiogenesis associated with malignancy, VEGF has become an appealing target for antiangiogenic therapy [9]. The most commonly used classes of drugs that work against this angiogenic effect of VEGF are the anti-VEGF antibodies and the anti-VEGF receptor antibodies. The anti-VEGF antibodies, such as bevacizumab and ziv-aflibercept, neutralize VEGF by binding, thus eliminating VEGF signaling in the body [10]. The anti-VEGF receptor antibodies, such as sorafenib and sunitinib, are tyrosine kinase receptor inhibitors that bind to VEGF receptors, thus preventing the downstream intracellular cascade effects of the Ras and PI3K pathways and halting angiogenesis [11,12] (Fig. 1).

Other classes of anti-angiogenic drugs include soluble VEGF "decoy" receptors and newer antibodies that have more specific antiangiogenic effects on tumors with lesser effects on normal tissues [13–15].

Treatment with these agents generally results in a cytostatic response with stabilization or slight decrease in tumor size, as well as decreases in density/cavitation or enhancement.

3. ALK inhibitors

Anaplastic lymphoma kinase (ALK) is a tyrosine kinase receptor found on various tumors. It has been most closely studied in non-small cell lung cancer (NSCLC) with chromosomal rearrangement of ALK being found in approximately 5% of these tumors [16]. ALK receptors activate the signaling cascade of Ras, JAK and PI3K are responsible for cell proliferation and survival, making them an important target for therapy [17,18] (Fig. 2). Testing for the fusion oncogene responsible for the overexpression of ALK receptor in all cases of lung adenocarcinoma is important because positive tumors respond very well to ALK-targeted inhibitors [19]. Next generation ALK receptor inhibitors such as Alectinib and Brigatinib are the preferred first line treatment for those with ALK positive NSCLC as they demonstrate better systemic and CNS efficacy and less target resistance when compared to the first generation crizotinib [20–23]. Interestingly, the third generation ALK inhibitor, Loratinib, can overcome the majority of acquired ALK mutations and in one report even re-sensitized NSCLC to crizotinib when restarted under molecular guidance [21,24].

The typical treatment course with these agents is initial clinical and radiological response with eventual development of resistance. This may necessitate tissue sampling to evaluate for other mutations and guide changes in treatment.

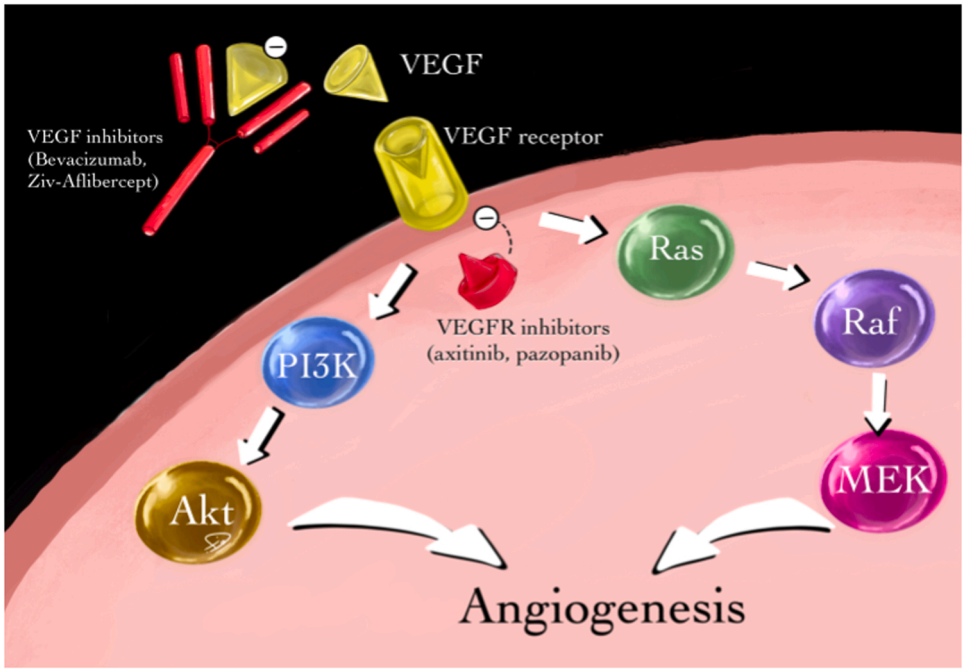

Fig. 1. VEGF inhibitors such as bevacizumab and ziv-aflibercept are antibodies that bind to VEGF and prevent its action on the receptor. VEGFR inhibitors such as axitinib and pazopanib block the VEGF receptor and prevent downstream signaling.

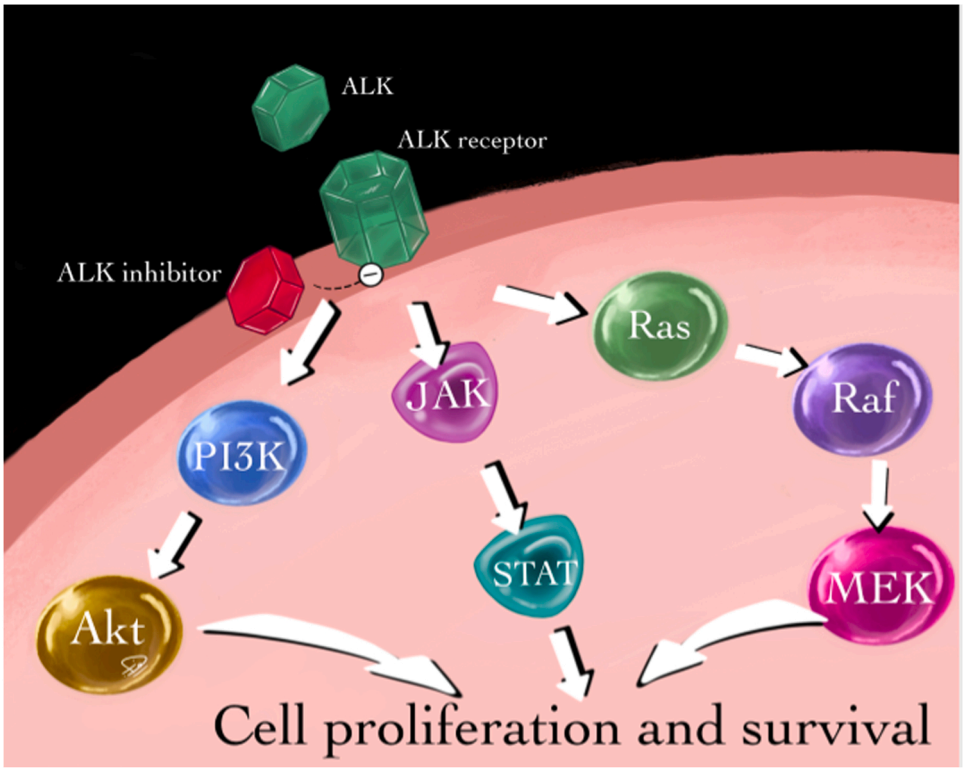

Fig. 2. ALK inhibitors bind to the ALK receptor and prevent downstream signaling through the PI3K, JAK and Ras pathways.

4. ROS inhibitors

ROS1 oncogene fusion proteins, manifested via gene translocation from ROS1 onto other genes such as CD4, are an important proto-oncogene found in certain tumors, primarily targeted and discussed in the literature with NSCLC [25–27]. These receptors are found in the cell membrane, cytosol or Golgi apparatus and are responsible for activation of growth and survival pathways similar to other tyrosine kinase receptors, including the RAS, PIK3 and JAK pathways [28]. ROS inhibitors act by blocking the cell membrane receptors (Fig. 3). An important aspect of this oncogene is its potential phosphorylation of extended synaptotagmin-like protein (E-SYT1), an intracellular protein which is postulated to be a driver of cell invasion in specific forms of ROS1 genomic fusions [29]. First line options of ROS inhibitors include

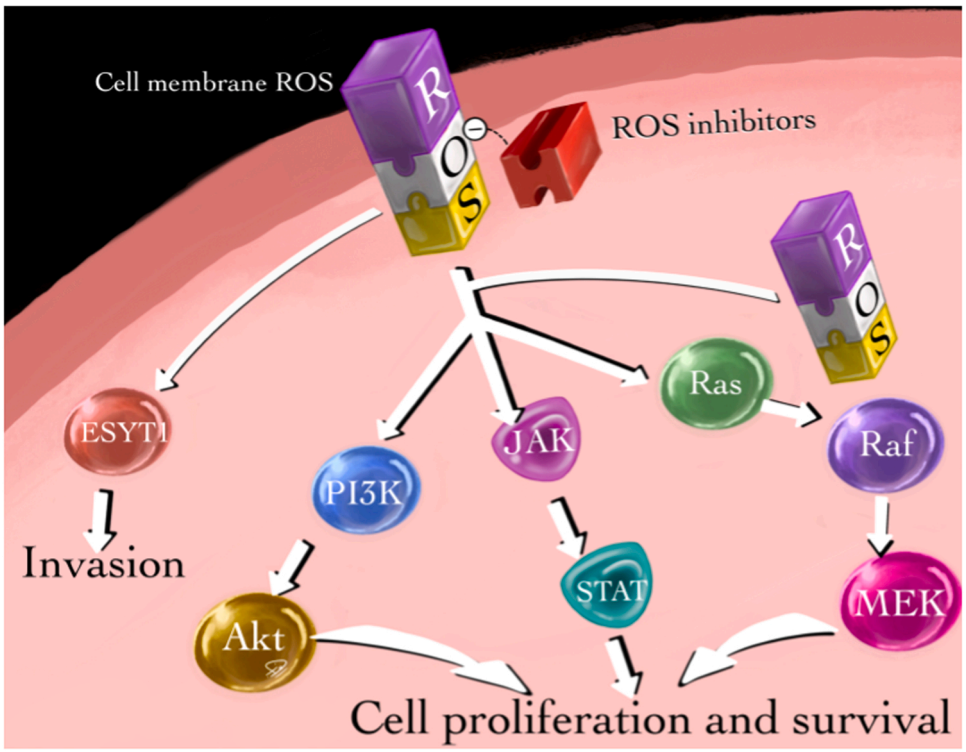

Fig. 3. ROS inhibitors bind to the cell surface ROS and prevent downstream signaling.

crizotinib and entercitinib, which are also ALK inhibitors [30].

The typical treatment course with these agents is initial clinical and radiological response with eventual development of resistance. This may necessitate tissue sampling to evaluate for other mutations and guide changes in treatment.

5. BCR-ABL inhibitors

The Philadelphia (Ph) chromosome is renowned as the first chromosomal abnormality associated with neoplasia. The reciprocal translocation that results in the oncogene BCR-ABL, codes for the constitutively active kinase oncoprotein of the same name [31]. The continuous activity of this intracytoplasmic tyrosine kinase leads to autophosphorylation and unregulated downstream activations of

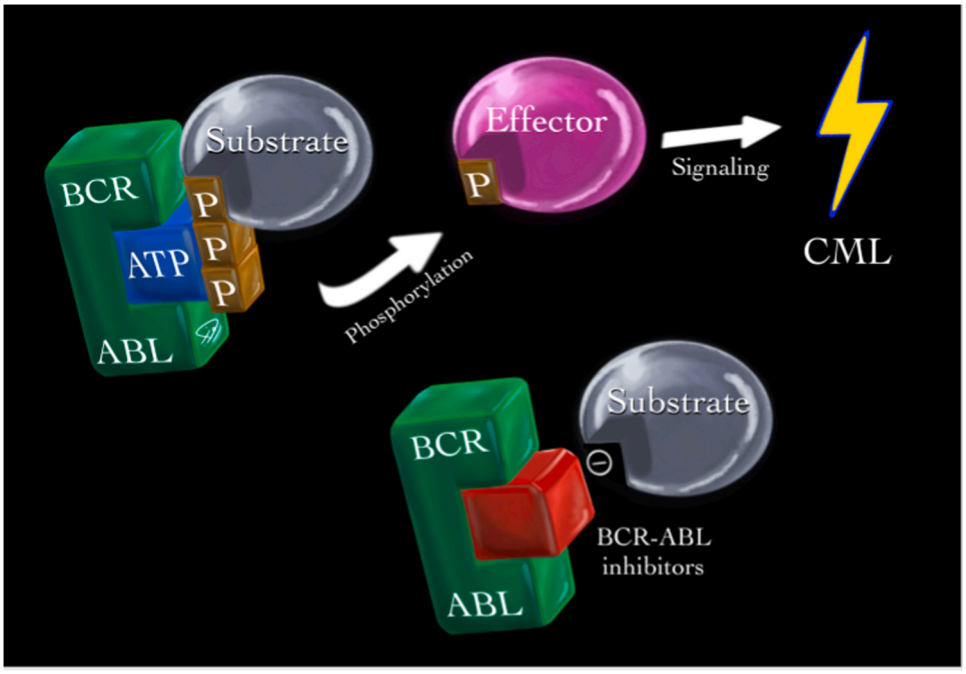

Fig. 4. BCR-ABL inhibitors prevent ATP from binding to the BCR-ABL protein and thereby prevent phosphorylation of its substrate. This leads to cessation of downstream signaling.

different substrates resulting in increased cell proliferation and survival [32,33]. Thus, utilizing an inhibitor of this tyrosine kinase (Fig. 4) is essential as a part of remission induction therapy in patients with blast crisis chronic myeloid leukemia (CML) or acute lymphocytic leukemia (ALL) as it results in significantly superior outcomes with relatively little toxicity [34–37]. Treatment with BCR-ABL inhibitor tyrosine kinase inhibitor should begin at diagnosis and continued into the post-remission management phase, as improved outcomes have been noted with continuous exposure when compared to pulsed or intermittent administration of these agents [38–40]. Response to treatment with these agents usually results in a decrease in tumor size.

6. PDGFR inhibitors

Platelet derived growth factor (PDGF) is a dimeric molecule which binds to two structurally similar tyrosine kinase receptors and this signal pathway acts as a mitogen for many cell types including connective tissue cells [41]. Autocrine and paracrine activation of the PDGF pathway is implicated in many different tumors including sarcomas and epithelial cancers, by increasing stromal recruitment and epithelial-mesenchymal transition and thus promoting tumor growth and proliferation [42]. Other than the usual tumorigenesis expected in tyrosine kinase signaling pathways described in above sections, PDGF receptors play an additional important role in certain tumors by facilitating deposition of type III collagen and signaling for rearrangement of actin and cell migration [43,44]. Certain tyrosine kinase receptor inhibitors (Fig. 5), such as Imatinib for gastrointestinal stromal tumor, are important to mitigate these downstream effects [45]. Response to treatment with these agents usually results in a cytostatic response with size stability but decrease in density/enhancement (e.g., peritoneal sarcomatosis in solitary fibrous tumor), T2 signal on MRI (e.g., desmoid type fibromatosis) and metabolic activity on PET (e.g., gastrointestinal stromal tumor).

7. PARP inhibitors

Poly (ADP-ribose) polymerase (PARP) inhibitors prevent the repair of single-strand DNA breaks (Fig. 6). Tissues with normal BRCA are able to repair such single-strand DNA breaks. However, in tumors with BRCA mutations, this action leads to double-strand DNA breaks and subsequent cell death [46,47]. Olaparib is now accepted as monotherapy in advanced cases of BRCA mutated tumors. It is especially effective against tumor cells which exhibit homologous recombinant deficient BRCA mutations [48]. PARP not only plays a role in DNA repair, but also aids in the regulation of certain transcription factors that play a role in cell growth and survival as seen in Androgen Receptor (AR) positive prostate cancers [49]. Response to treatment with these agents usually results in decrease in size/solid appearance of the tumor deposits, but usually without significant change in enhancement (e.g., peritoneal carcinomatosis in patients with ovarian cancer).

8. EGFR inhibitors

The epidermal growth factor receptor (EGFR) tyrosine kinases, also called HER1 and erbB-1, exist as monomers on the cell surface and dimerize upon stimulation to begin tyrosine kinase signaling [50]. Subsequent phosphorylation and activation of different signaling pathways including the KRAS-BRAF-MEK pathway, PI3K, STAT signaling pathway and the anti-apoptotic AKT kinase pathway promotes angiogenesis, survival/adhesion, migration and cell proliferation [51,52]. Specific onco-mutations of EGFR are seen in certain types of cancers, particularly NSCLC, making them a good target for EGFR inhibitors [53,54] (Fig. 7). It is important to note that amplification of EGFR does not correlate with improved outcomes with EGFR inhibitors, as opposed to presence of EGFR activating mutations [55–57].

The typical treatment course with these agents demonstrates initial radiologic responses, but eventual development of resistance leading to slow growth in one or more sites of disease. This may prompt the need for tissue sampling to evaluate for other mutations and determine changes in treatment.

9. RAF and MEK inhibitors

As described above, RAS and MEK activate many pathways which lead to downstream signaling causing transcription of genes, and in the setting of altered activation from mutations can cause inappropriate

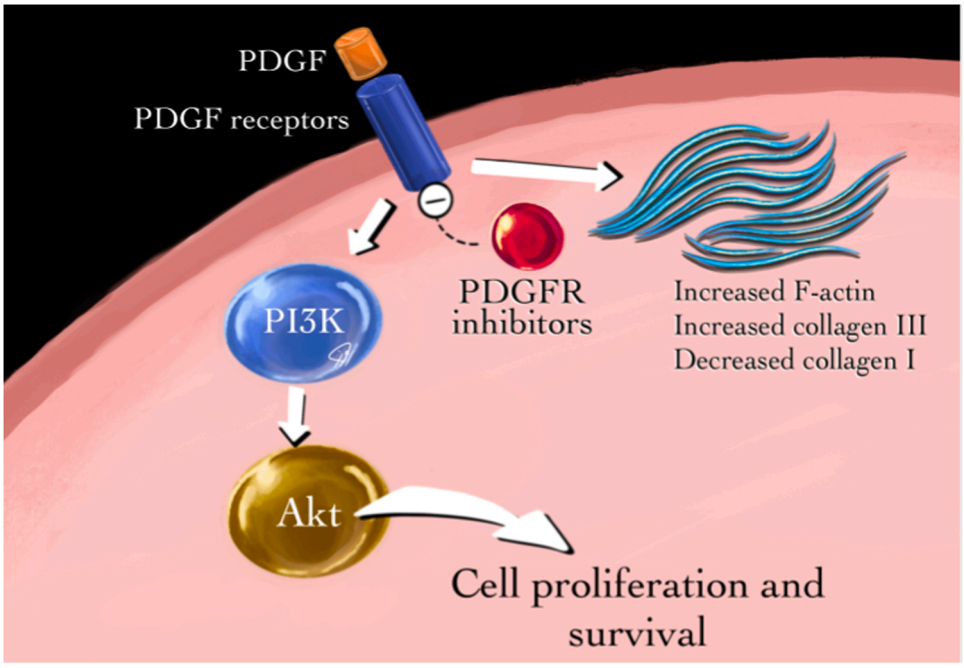

Fig. 5. PDGFR inhibitors bind to the PDGF receptor and prevent downstream signaling that decreases several processes such as cell proliferation /survival, and collagen and actin formation.

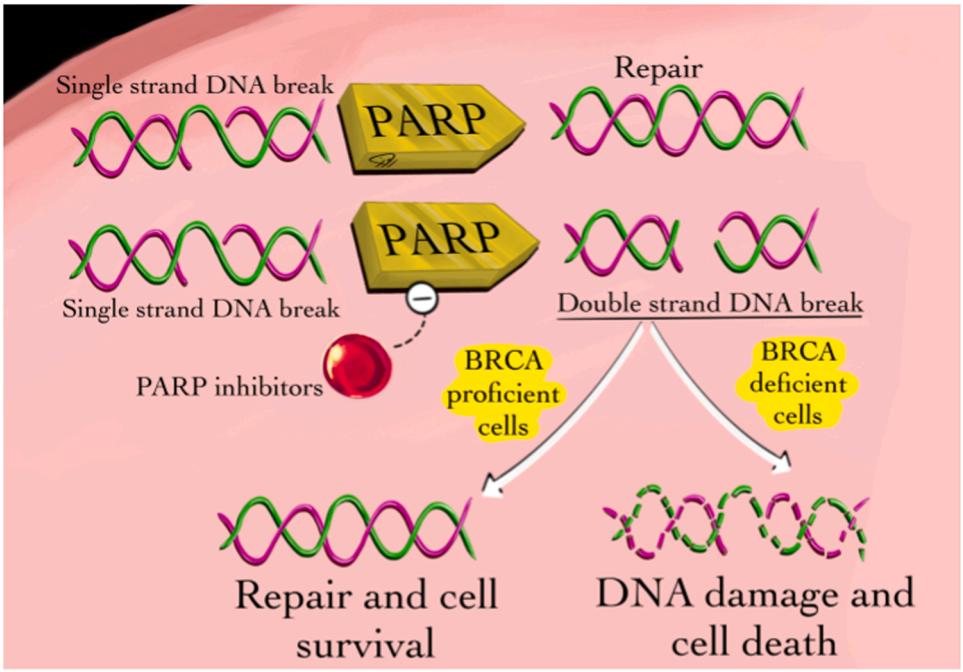

Fig. 6. PARP inhibitors inhibit repair of single strand DNA breaks. While BRCA proficient cells are able to repair these breaks, in BRCA deficient cells this leads to double strand DNA breaks and cell death.

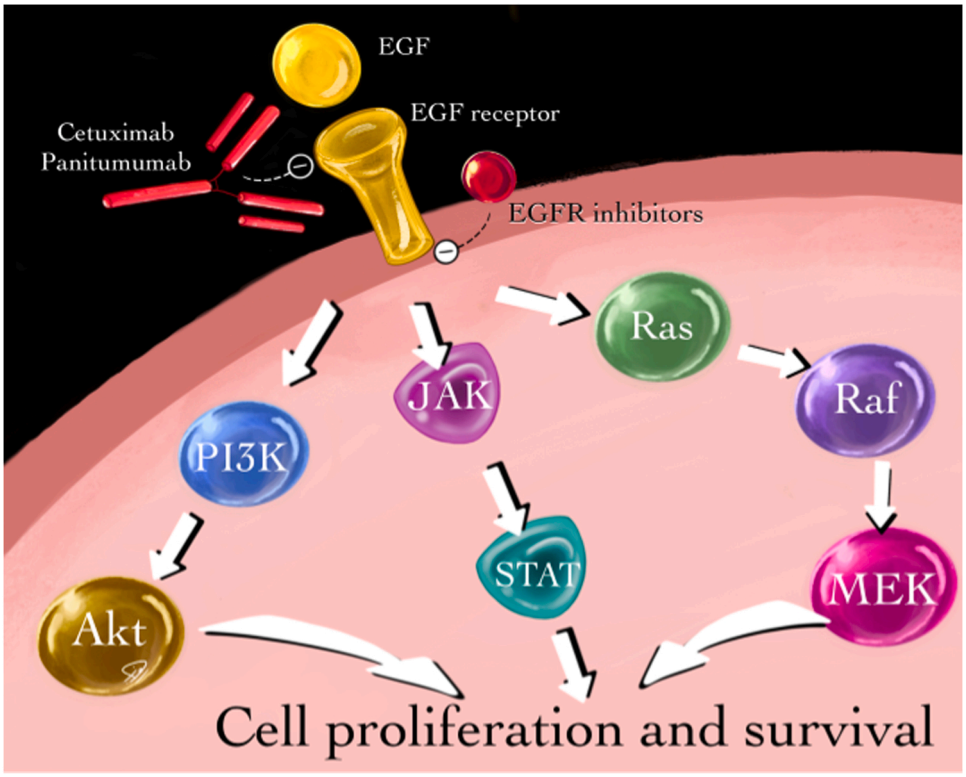

Fig. 7. EGFR inhibitors such as cetuximab and panitumumab are antibodies that bind to and inhibit EGFR. Small molecule EGFR inhibitors such as gefitinib and afatinib block the receptor and prevent downstream signaling.

cellular proliferation and survival [58–60]. Approximately 50% of metastatic melanoma demonstrate activating mutations of BRAF with the most common mutations including V600E and V600K [61–63]. Interestingly, selective RAS and MEK small molecule inhibitors (Fig. 8) are useful in cases of V600 mutations (BRAF), but can paradoxically cause cell growth in KRAS mutant and RAS/RAF wild type tumors by activating the RAF-MEK-ERK pathway in a RAS dependent manner [64]. Response to treatment with these agents usually results in decrease in size of the tumor burden, and associated decrease in enhancement (e.g., melanoma).

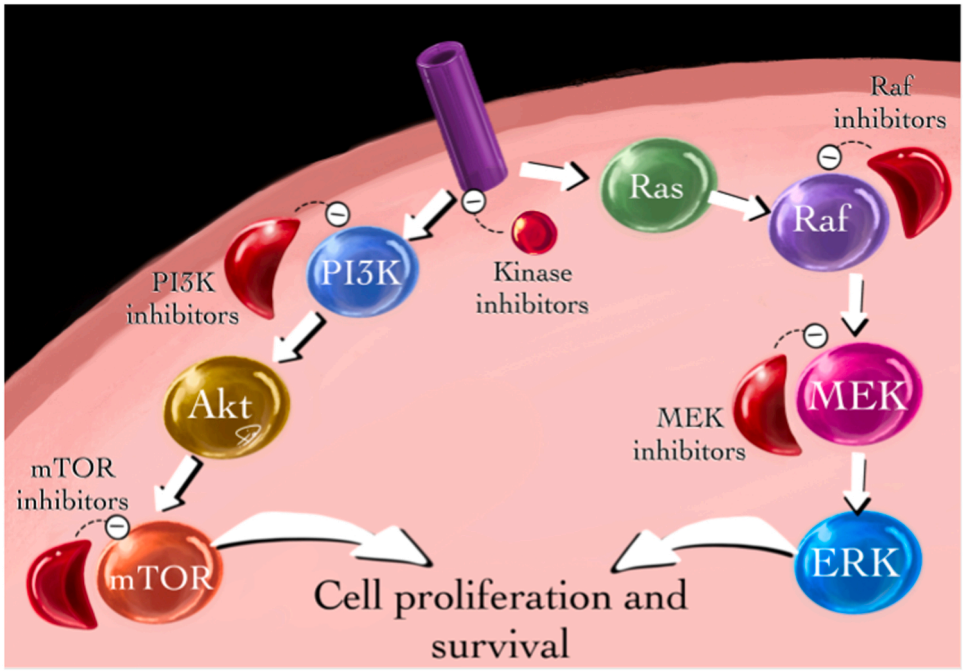

Fig. 8. Raf, MEK, PI3K and mTOR inhibitors bind to their respective targets and block signaling in the PI3K and Ras pathways.

10. mTOR inhibitors

Sirolimus, the first mammalian target of rapamycin (mTOR) inhibitor in use, was discovered in a soil sample. Initially used as an antifungal, it was later found to have immunosuppressive and antiproliferative properties and began to be used against different disorders such as malignancy, psoriasis and tuberous sclerosis [65]. Upon gaining entry into the cytoplasm, mTOR inhibitors bind the FK binding protein (Fig. 8) and are thought to modulate the activity of mTOR leading to inhibition of interleukin (IL)– 2 mediated signal transduction. This arrests cell cycle in the G1-S phase [66]. Some mTOR inhibitors additionally act on T and B cells to block response to cytokines, preventing cell-cycle progression and proliferation [67]. Inhibition of smooth muscle cell proliferation and the activating factors in tuberous sclerosis by mTOR inhibitors may dampen the progression of tuberous sclerosis associated tumors, such as angiomyolipoma and subependymal giant cell

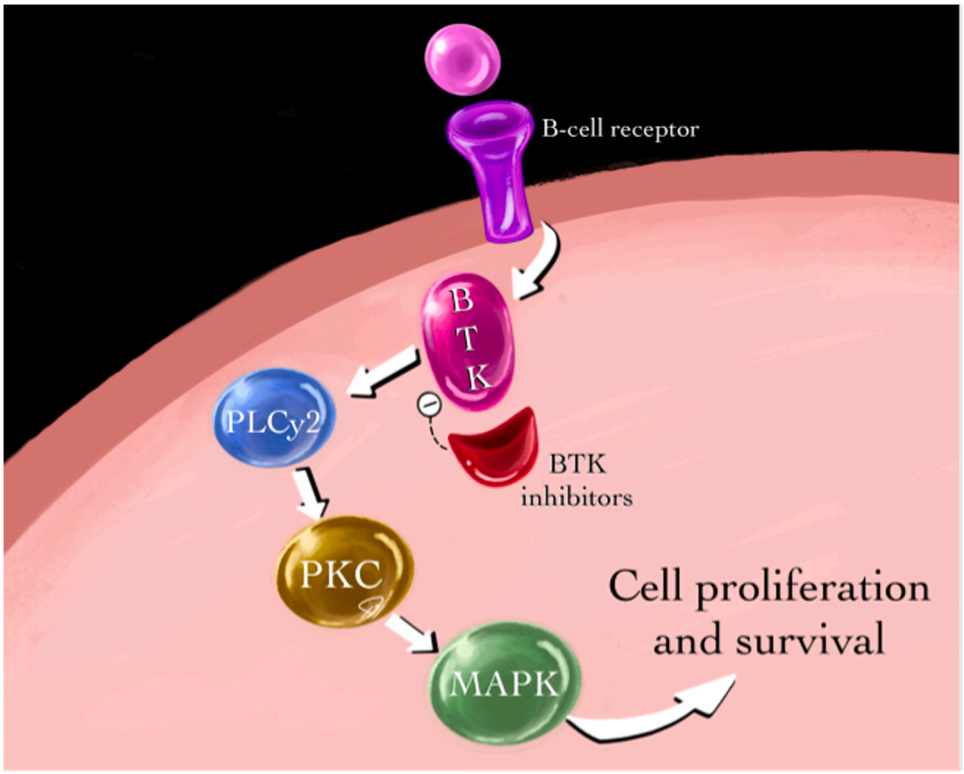

Fig. 9. BTK inhibitors bind to the intracellular signaling protein BTK and block its downstream activation.

astrocytoma [68,69]. Response to treatment with these agents results in decreased size (e.g. Waldenstrom's Macroglobulinemia) and can result in decreased enhancement of the metastatic deposits (e.g. neuroendocrine tumors).

11. BTK inhibitors

Bruton tyrosine kinase (BTK) is an early signaling molecule in the B-cell antigen receptor (BCR) pathway which plays a major role in cellular proliferation and survival [70]. Activation of the BCR signaling pathway leads to phosphorylation of BTK. This in turn phosphorylates and activates phospholipase-Cy (PLCy), which allows calcium to mobilize and activate certain regulatory steps including mitogen-activated protein kinase (MAPK) [71]. These processes result in uncontrolled activation of the BCR signaling cascade leading to unregulated proliferation of B-cells and different kinds of B-cell lymphoma such as diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma, and B-cell chronic lymphocytic lymphoma (CLL) [72,73]. BTK inhibitors, primarily ibrutinib, act as an effective and irreversible inhibitor of BTK (Fig. 9), which inhibits the BCR and cytokine receptor pathways [74,75]. Response to treatment with these agents usually results in decrease in tumor size, occasionally accompanied by adipocytic maturation (e.g., chronic lymphocytic leukemia).

12. CDK inhibitors

Cyclin dependant kinases (CDK) are major regulators of specific cell cycle checkpoints that proliferating cells must traverse. CDK alterations are found in many cancer cells, making them an appealing target for oncologic management of certain tumors [76]. In combination with other anti-neoplastic agents, CDK inhibitors can block cell cycle progression (Fig. 10), preventing cell proliferation and selectively inducing apoptosis in rapidly dividing cancer cells [77]. Notably, CDK inhibitors can have dual targets and effects beyond cell cycle regulation, and these include important roles in transcriptional regulation, cell fate determination, cell migration and cytoskeletal dynamics. These processes occur via a complex reaction involving phosphorylation of different intracellular molecules such as the Cip/Kip proteins [78]. Response to treatment with these agents usually results in decrease in tumor size.

13. HER2 inhibitors

Part of the epidermal growth factor receptor (EGFR) family, the HER2 receptor is a vital activator of the signaling cascade leading to epithelial cell growth, differentiation, and potential angiogenesis [79–81]. Part of HER2 receptor's proto-oncogene effect comes from the activation of the PI3K-AKT and RAS-MAPK pathways leading to cell proliferation and survival [82,83]. Testing for HER2 expression becomes important as it offers a novel target to supress the growth of cancers overexpressing the HER2 oncogene such as HER2 + breast cancers [84,85]. HER2 receptors can be inhibited by antibodies blocking receptor activation, and small molecule inhibitors which enter cells and act intracellularly to prevent activation [86] (Fig. 11). Response to treatment with these agents usually results in decrease in tumor size.

14. Immune Checkpoint Inhibitors

There are numerous immunological approaches to cancer therapy. This section discusses inhibition of programmed cell death 1 (PD1), programmed cell death ligand 1 (PD-L1; also known as B7-H1), PD-L2 (B7-H2) and cytotoxic T-lymphocyte antigen 4 (CTLA-4).

PD1 is an inhibitory transmembrane protein that is expressed by T cells, natural killer (NK) cells and B cells. It binds to PD-L1/2 on tissue cells resulting in inhibition of apoptosis, peripheral T effector cell exhaustion and conversion of T effector cells to T regulatory cells [87,88]. Overexpression of PD1 allows tumor cells to avoid cell death by decreasing T cell activation, proliferation, cytokine release, and T cell survival [89]. Antibodies targeting PD1 or PD-L1/2 (Fig. 12) have proved efficacious in circumventing tumor cells' ability to bypass immune system regulation [89–91].

CTLA-4, discovered in 1987, is a negative regulator of CD4 + and CD8 + T lymphocyte activation [92–94]. CTLA-4 expression acts as a

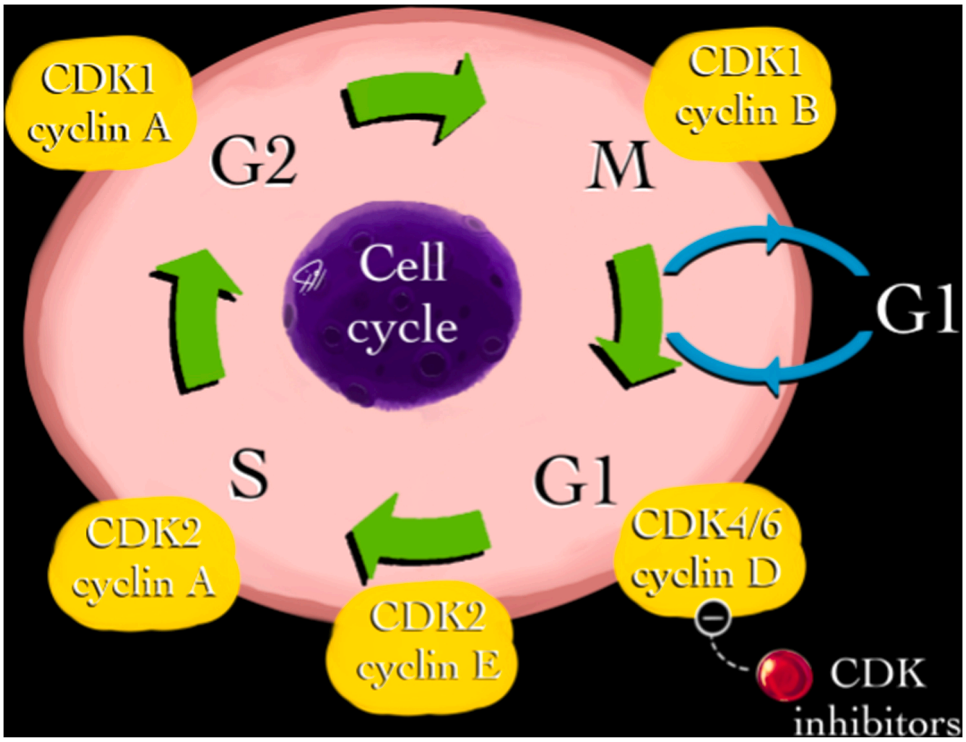

Fig. 10. CDK inhibitors block cell cycle and arrest it at the G1 phase.

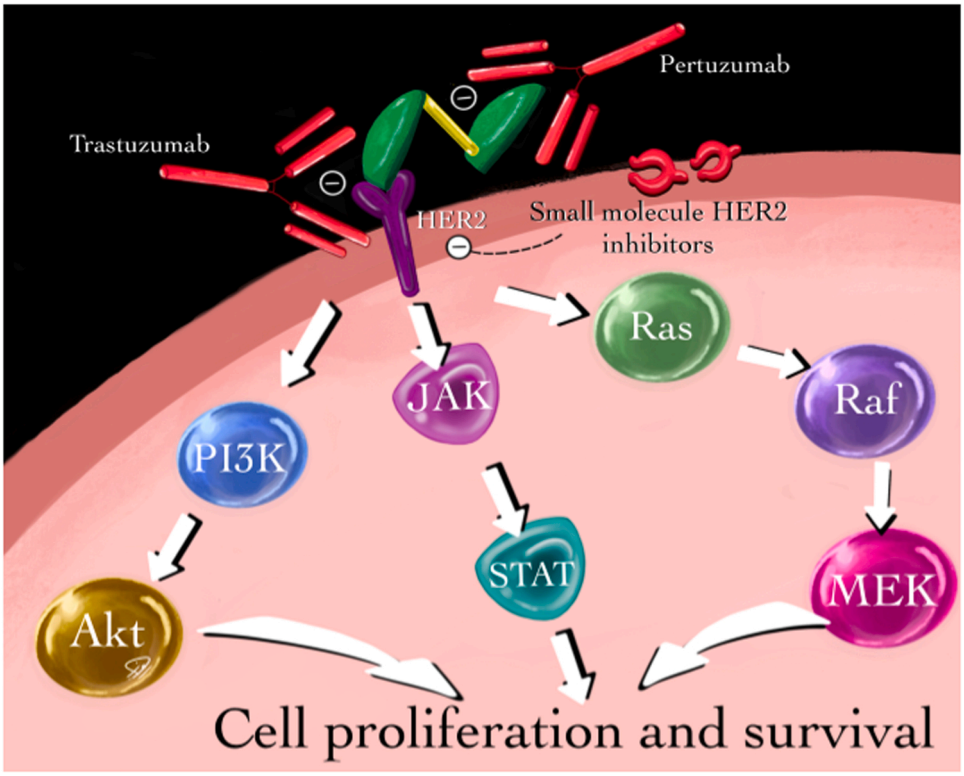

Fig. 11. HER2 inhibitors such as trastuzumab and pertuzumab are antibodies that bind to and inhibit the HER2 receptor. Small molecule HER2 inhibitors such as neratinib and lapatinib block the receptor and prevent downstream signaling.

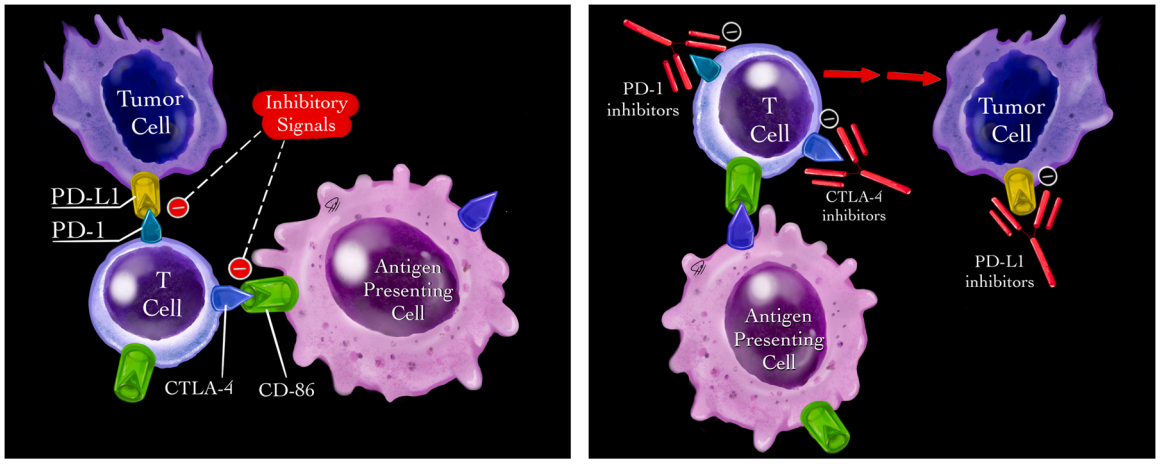

Fig. 12. PD-1 and PD-L1 inhibitors block the inhibitory effects of these receptors at the T-cell and tumor cell interface. CTLA-4 inhibitors block the inhibitory effects of CTLA-4 at the T-cell and antigen presenting cell interface.

physiologic stop to the CD4 + and CD8 + T cell activation triggered by antigen presenting cells [92,94]. The understanding is that in certain malignancies, upregulation of CTLA-4 leads to weakening of the immune response to the tumor. Thus antibodies blocking CTLA-4 activation (Fig. 12) result in improved immune mediated tumor damage [95,96]. The unique mechanism of action of these agents can result in transient increases in tumor burden due to infiltration by immune cells and resultant inflammatory changes – a phenomenon referred to as pseudoprogression or atypical response [97].

15. Hormonal agents

Selective estrogen receptor modulators (SERMs) are a class of drugs that competitively inhibit estrogen binding to estrogen receptors and have mixed agonist and antagonist properties depending on the target tissue. These are used in the management of hormone positive breast cancer [98,99].

Selective estrogen receptor down-regulators (SERDs) are also competitive inhibitors of the estrogen receptor. These are different compared to the SERMs in that these are full antagonists with no agoniztic properties [100,101]. Fulvestrant, the novel SERD medication, exerts its anticancer effects by not only acting as an antagonist to estrogen receptors but also by degrading the estrogen receptor protein [102,103].

Aromatase inhibitors exert their antiestrogenic effects by inhibiting the enzyme aromatase which leads to decreased peripheral conversion

of androgens to estrogens [104]. Aromatase inhibitors are the standard treatment for postmenopausal patients with hormone positive breast cancer [105].

Androgen deprivation therapy (ADT) can be accomplished medically or surgically and is the cornerstone management in castration sensitive prostate cancer [106,107]. The most commonly used medical method is continuous use of a gonadotrophin releasing hormone (GnRH) agonist which will stop production of luteinizing hormone and thus decrease testosterone levels [108,109]. GnRH antagonists are an alternative, rapid option for ADT and are preferred over GnRH agonizts as they avoid the initial surge in luteinizing hormone levels caused by the latter [110]. Second generation androgen receptor antagonists, which bind directly and inhibit androgen receptors, can be utilized along with ADT in the treatment of prostate cancer [111].

Response to treatment with these agents usually results in decrease in tumor size. Response may also manifest as increased sclerosis of the osseous metastases, indicating increased osteoblastic activity (e.g., breast Ca).

16. Anti-lymphocyte antibody

Antibodies targeting CD20, the cluster of differentiation cell surface protein denoting most B cells, lead to B cell depletion by several mechanisms including antibody dependant cytotoxicity and phagocytosis, complement mediated cell lysis, growth arrest and B cell apoptosis [112,113].

Anti CD52 antibodies are widely used in the treatment of certain B cell malignancies and autoimmune disorders including multiple sclerosis [114]. These antibodies lead to rapid and prolonged depletion of T and B cells expressing CD52 in a manner similar to that of anti CD20 antibodies, with reprogramming effects on downstream immune cell composition [115,116].

CD30 antibodies are slightly different in that the therapeutic agent, Brentuximab vedotin, is a drug-antibody conjugate and consists of multiple molecular components that work to bind to cells expressing CD30 [117]. Once bound, it forms a complex on the cell surface that is then internalized releasing its maytansine and monomethyl auristatin E (MMAE) component, a potent microtubule destabilizer which induces cell cycle arrest and apoptosis [118,119]. Response to treatment with these agents usually results in decrease in tumor size and metabolic activity (e.g., diffuse large B-cell lymphoma).

17. Future trends

Advancements in cancer therapy continue to develop at a rapid pace. It is anticipated this field will continue to grow exponentially in the foreseeable future. A recent analysis of the research and development (R&D) pipeline of novel anticancer therapies in the USA and China identified 34 new drugs approved in 2020 alone [119]. This impressive growth in the field occurred despite the impact of COVID-19. In addition to clinical trials of new therapies, an additional line of research and meta-analysis has identified the utility of combination therapies that may prove more efficacious or be able to treat other conditions, currently beyond the ability of single therapies.

The future direction of anticancer therapy remains at the forefront of medical research efforts and a part of an ever-growing industry. To provide the best possible care to their patients, it is necessary for every clinician, including radiologists, to remain informed with the most current available therapies and developments in this novel frontier of anti-cancer research. Knowledge and integration of anti-cancer drug classification will keep the radiologist as an important, valuable, and relied upon member of the cancer care team.

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Ali Khader – manuscript writing, review of literature. **Rozan Bokhari** – illustrations, manuscript editing. **Reza Hakimelahi** – manuscript editing, table, review of literature. **Christopher Scheirey** – manuscript editing, table, review of literature. **Jalil Afnan** – manuscript editing, table, review of literature. **Marta Braschi-Amirfarzan** – manuscript editing, table, illustrations, review of literature. **Richard Thomas** – manuscript writing and editing, table, illustrations, review of literature.

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Conflict of interest statement

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