**Table 1**. Summary of kinase inhibitors approved by the FDA for treatment of solid tumors, their molecular targets and the studies demonstrating their regulatory roles on tumor immunogenicity or immune responses.

| TKI | Target | Approved for | Immunomodulation |
|---|---|---|---|
| **CDK4/6 inhibitors** | | | |
| Abemaciclib | CDK4/6 | BC | Increases antitumor immunity and synergizes with immunotherapy in CRC [1, 2], and in ES[3]. |
| Ribociclib | CDK4/6 | BC | Increases antitumor immunity [4] |
| Palbociclib | CDK4/6 | BC | Increases immunogenicity in breast cancer [5] and synergizes with immunotherapy in bladder cancer [6] |
| **Alk inhibitors** | | | |
| Alectinib | Alk, fusion/L1196M | NSCLC | Increases PD-L1 expression in NSCLC [7], increases HLA [8] |
| Brigatinib | Alk, EGFR and their mutants | NSCLC | Unknown; was approved on May 22, 2020 |
| Ceritinib | Alk, Alk fusion/point mutants | NSCLC | Altered immune responses, but did not alter immunogenicity to synergize with αPD-1 antibody in NSCLC mouse model [9] |
| Crizotinib | Alk, Alk fusion, c-Met | ALCL, NSCLC | Increases HLA, antigen presenting machinery [8] and increases T cell-APC interaction [10]. Synergizes with chemo and immunotherapy in mice model of NSCLS [11, 12]. Hepatoxicity observed when used with ICI [13] |
| Lorlatinib | Alk, Ros1 | NSCLC | Unknown; was approved on November 2, 2018 |
| Entrectinib | Trk, Ros1, Alk | NSCLC, ST | Unknown; was approved on August 15, 2019 |
| **MEK inhibitors** | | | |
| Binimetinib | MEK1/2 | MEL | Reviewed in [14] |
| Cobimetinib | MEK1 | MEL | Reduces B regulatory cells in colorectal cancer [15]. Impedes apoptosis of chronically stimulated, antigen-experienced CD8+T cells in colon cancer model and synergizes with αPD-L1 antibody to have tumoricidal activity [16], but did not show increased survival benefit when combined with atezolizumab in patients [17] |
| Trametinib | MEK1/2 | ATC, MEL, NSCLC | Reviewed in [14]. Partial inhibition of T cell function; increase CD8+ T cell infiltration with anti-PD-1 antibody in colon cancer line [18]. Increased HLA in melanoma [18]. Enhanced immune cell infiltration [19] and tumor control when combined with PD-1 blockade in melanoma mouse model [20, 21] |
| **RAF inhibitor** | | | |
| Dabrafenib | BRAF | ATC, MEL, NSCLC | Reviewed for melanoma [22]. Increases HLA in melanoma [18]. Doesn’t impair healthy T cell function [23]. |
| Encorafenib | RAF | CRC, MEL | Unknown; was approved on April 8, 2020. |
| Vemurafenib | BRAF(V600E) | ECD, MEL | Reviewed for melanoma [22]. Alters CD4+T cell function [24]. Suppresses MDSC [25]. Modulates both antitumor and protumor immunity in melanoma [19]. Enhances immunogenicity [26] |
| **EGFR family inhibitor** | | | |
| Afatinib | EGFR, HER2, HER4, EGFR L858R/T790M | NSCLC | Increases antitumor immunity in GC[27]. |
| Dacomitinib | EGFR family | NSCLC | Unknown; was approved September 18, 2018 |
| Erlotinib | EGFR | NSCLC, PC | Increases antitumor immunity [28], and synergizes with immunotherapy in colorectal cancer [29]. |

| | | | |
|---|---|---|---|
| Gefitinib | EGFR | NSCLC | Alters immune responses in mouse lung cancer model [30] |
| Lapatinib | EGFR, ERBB2 | BC | Increases antitumor immunity in gastric cancer [27] and IFNγ-driven antitumor adaptive immune response in breast cancer [31]. |
| Neratinib | HER2, EGFR | BC | Increases MHC and decreases PD-L1, PD-L2 in vitro; with HDAC inhibitor, sensitizes to immunotherapy in mouse [32] |
| Osimertinib | T790M EGFR | NSCLC | Alters immune responses in lung cancer mouse model [30] |
| Tucatinib | HER2 | BC | Unknown; was approved on April 17, 2020 |
| Cetuximab | EGFR | CRC, SCCHN | Reviewed in [33]. Augments immune responses that are favorable for antitumor activity [34] |
| Margetuximab | HER2 | BC | Elicits improved ADCC compared to trastuzumab [35] and high HER2-specific antitumor immune response [36] |
| Necitumumab | EGFR | SNSCLC | Induces ADCC; reviewed for NSCLC [37] |
| Panitumumab | EGFR | CRC | Elicits antitumor immune response, albeit at lower level than does cetuximab [38] |
| Pertuzumab | HER2 | BC | Elicits antitumor immune responses, namely antibody-dependent cell-mediated cytotoxicity (ADCC) and phagocytosis (ADCP) by innate immune cells. Reviewed in [39] |
| trastuzumab* | HER2 | BC | Elicits ADCC and ADCP; reviewed in [39]. |
| **mTOR** | | | |
| Everolimus | mTOR | BC, PC, GIC, LC, RCC, SGCA. | Blocks T cell function and used as an immunosuppressant in organ transplantation [40, 41]. Associated with reduced CTL infiltration and increased T regulatory cells in prostate cancer [42]. Inhibits T cell and NK cell activity *in vitro* [43]. Using cyclophosphamide was shown to alleviate its immunosuppressive effects [44]. |
| Temsirolimus | mTOR | RCC | Increases antitumor immunity and synergizes with anti-tumour vaccine in RCC and MEL [45] |
| **Others** | | | |
| Alpelisib | PI3Kα | BC | When combined with Ribociclib, enhances tumor immunogenicity *in vitro* and elicits T cell infiltration that's associated with reduced breast cancer growth in mouse [4] |
| Avapritinib | Kit mutant, PDGFRa D842V | GIST | Unknown; was approved on January 9, 2020 |
| Axitinib | VEGFR1/2/3, Kit, PDGFR | RCC | Less adverse effects on T cell function compared to sorafenib *in vitro* [46] |
| Cabozantinib | c-Met, VEGFR1/2/3, FLT3, TIE2, TRKB, Axl, RET | HCC, MTC, RCC | Enhances antitumor immunity in colon cancer mouse model [47] and synergizes with tumor vaccine [48] |
| Capmatinib | MET | NSCLC | Suppresses T cells *in vitro*, upregulates PD-L1 in HCC cells; improves tumor killing when combined with αPD-1 antibody [49] |
| Erdafitinib | FGFR | UC | Synergizes with αPD-1 antibody to elicit antitumor immune response in lung cancer mouse model [50]. |
| Imatinib | c-kit, PDGFR | GIST, MDS/MPN, SM | Antitumor activity depends on host immune response and synergizes with immunotherapy [51]; reviewed for GIST [52]. Modulates various immune cells in cancer (reviewed in [53]). Affects macrophage activity in vitro [54, 55] |
| Larotrectinib | Trk | ST | Unknown; was approved on November 26, 2018 |

| | | | |
|---|---|---|---|
| Lenvatinib | VEGFR2 | EMC, HCC, RCC, TC | Reviewed for HCC in [56]. Reduces tumor-associated macrophages, increases CTLs, and synergizes with αPD-1 antibody [57, 58] |
| Fedratinib | JAK2, FLT3 | MF | Negatively regulates regulatory T cells and T helper cell cytokine secretion [59]. Downregulates PD-L1 expression in lung cancer [60] and lymphoma cell lines [61] |
| Pazopanib | PDGFR, VEGFR1/2/3, Kit | RCC, STS | Primes DC to confer antitumor immune response [62] |
| Pralsetinib | RET | TC, MTC, NSCLC | Unknown; was approved on December 1, 2020 |
| Pemigatinib | FGFR1/2/3 | CCC | Unknown; was approved on April 17, 2020 |
| Pexidartinib | KIT, CSF1R, FLT3 | TSGCT | Negatively affects tumor-associated macrophages, and synergizes with dendritic cell vaccination to eliminate mesothelioma in mouse model [63]. Reduces infiltration of immunosuppressive macrophages to improve immunotherapy [64] |
| Regorafenib | VEGFR2/3, Ret, Kit, PDGFR, Raf | CRC, GIST, HCC | Increases CTL driven antitumor immune response when used with αPD-1 antibody in HCC mouse model [65]. Reviewed in [56]. Modulates macrophage to enhance antitumor immunity; reviewed in [66] |
| Ripretinib | SCFR KIT, PDGFRa, VEGFR2, TIE2, CSF1R | GIST | Unknown; was approved on May 15, 2020 |
| Ruxolitinib | JAK1/2 | MF, PV | Is immunosuppressive and anti-inflammatory through affecting various immune cells (reviewed in [67]). Suppresses cytokine release syndrome while not impeding CART cell therapy in AML mouse model [68]. Enhances T cell dependent antitumor immune response and synergizes with αPD-1 antibody in pancreatic cancer mouse model [69]. |
| Selpercatinib | RET, VEGFR1/3, FGFR1/2/3 | MTC, NSCLC, TC | Unknown; was approved on May 8, 2020 |
| Sorafenib | Raf, VEGFR2, PDGFRb | HCC, RCC, TC | Elicits antitumor immune response, regulates myeloid infiltrates and synergizes with cancer vaccine in colon cancer mouse model [70]. Adversely impacts T cell function *in vitro* [46]. Reduces regulatory T cell infiltration in RCC patients [71] |
| Sunitinib | PDGFR, FLT3 VEGFR1/2, Kit, | GIST, PC, RCC | Increases antitumor immunity [72-75] and reduces immunosuppression, synergizes with tumor vaccine in mouse model of colon cancer [70] |
| Vandetanib | VEGFR2, EGFR | MTC | Unknown; was approved on April 7, 2011 |
| Ramucirumab | VEGFR2 | CRC, HCC, NSCLC, SA, GEJA | Negatively regulates regulatory T cells, enhances CD8+ T cell infiltration and PD-L1 expression in gastric cancer patients [76]. Improves patient survival when used with pembrolizumab [77]. |

Source for drug, its target and designated cancer: National Cancer Institute. ↑ or ↓, increase or decrease in tumor intrinsic immunogenicity or association to increased antitumor immune responses. ▲or▼, increase or decrease in antitumor activity of immune cells directly impacted by the treatment. **ATC**, Anaplastic thyroid cancer. **ALL**, acute lymphoblastic leukemia. **ALCL**, anaplastic large cell lymphoma. **BC**, breast cancer. **CC**, cervical cancer. **CCC**, cholangiocarcinoma. **CRC**, colorectal cancer. **DFSP**, dermatofibrosarcoma protuberans. **ECD**, Erdheim-Chester disease. **EMC**, Endometrial cancer. **ES**, Ewing sarcoma. **GBM**, glioblastoma. **GC**, gastric cancer. **GIC**, gastrointestinal cancer. **GEJA**, gastroesophageal junction adenocarcinoma. **GIST**, Gastrointestinal Stromal Tumor. **HCC**, Hepatocellular carcinoma. **LC**, lung cancer. **LSCC**, lung squamous cell carcinoma. **MEL**, melanoma. **MF**, myelofibrosis. **MDS/MPN**, myelodysplastic/myeloproliferative neoplasms. **MTC**, Medullary thyroid cancer. **(S)NSCLC**, (Squamous) Non-small cell lung cancer. **OEC**, ovarian epithelial cancer. **FTC**, fallopian tube cancer. **PPC**, primary peritoneal cancer. **PC**, pancreatic cancer. **PV**, Polycythemia vera **RCC**, renal cell carcinoma. **SA**, stomach adenocarcinoma. **STS**, soft tissue sarcoma. **SCCHN**, squamous cell carcinoma of the head and neck. **ST**, certain solid tumors. **SGCA**, subependymal giant cell astrocytoma. **SM**, systemic mastocytosis. **TC**, thyroid cancer. **UC**, Urothelial cancer. **TSGCT**, tenosynovial giant cell tumor. *with hyaluronidase-oysk, or as antibody drug conjugate Ado-Trastuzumab emtansine, or in combination with pertuzumab and hyaluronidase-zzxf. fam-trastuzumab deruxtecan-nxki is approved for BC, GC, GEJA

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**Table 2**. Ongoing clinical trials of kinase inhibitors approved for breast cancer treatment in combination with immunotherapy. Only the kinase inhibitors and the immunotherapeutic agents that are combined are listed.

| Kinase inhibitor | Target | Immunotherapy | Phase | Subtype | Identifier |
|---|---|---|---|---|---|
| **CDK4/6 inhibitor** | | | | | |
| Abemaciclib | CDK4/6 | Pembrolizumab | Ib | HR+(A/M) | NCT02779751 |
| Abemaciclib | CDK4/6 | LY3300054 | Ia/b | HR+HER2- | NCT02791334 |
| Abemaciclib | CDK4/6 | Atezolizumab | Ib/II | HR+HER2-(A/M) | NCT03280563 |
| Palbociclib | CDK4/6 | Avelumab | Ib | AR+ER-HER- | NCT04360941 |
| Palbociclib | CDK4/6 | Avelumab | II | ER+ | NCT03573648 |
| Palbociclib | CDK4/6 | Pembrolizumab | II | ER+(M) HER2- | NCT02778685 |
| Palbociclib | CDK4/6 | Avelumab | II | ER+(M) HER2- | NCT03147287 |
| Palbociclib | CDK4/6 | Nivolumab | II | ER+/HER2- | NCT04075604 |
| Ribociclib | CDK4/6 | Spartalizumab | I | ER+(M) HER2- | NCT03294694 |
| **EGFR family inhibitors** | | | | | |
| Trastuzumab | HER2 | TPIV100 vaccine | II | HER2+,stage II-III | NCT04197687 |
| Trastuzumab | HER2 | Durvalumab | Ib | HER2+(M) | NCT02649686* |
| Trastuzumab | HER2 | Pembrolizumab | Ib/II | HER2+(M) | NCT04512261 |
| Trastuzumab | HER2 | Avelumab | II | HER2+(M) | NCT03414658 |
| Trastuzumab | HER2 | Envafolimab | II | HER2+(M) | NCT04034823 |
| Trastuzumab, Tucatinib | HER2 | Pembrolizumab | Ib/II | HER2+(M) | NCT04512261 |
| Trastuzumab emtansine | HER2 | Pembrolizumab | I | HER2+(M) | NCT03032107 |
| Trastuzumab emtansine | HER2 | Atezolizumab | II | HER2+(LA/M) | NCT02924883 |
| Trastuzumab emtansine | HER2 | Atezolizumab | III | HER2+,PDL1+ (LA/M) | NCT04740918 |
| Trastuzumab deruxtecan | HER2 | Durvalumab | Ib | HER2-low (A/M) | NCT04556773 |
| Trastuzumab deruxtecan | HER2 | Durvalumab | Ib/II | HER2+ (M) | NCT04538742 |
| Trastuzumab deruxtecan | HER2 | Nivolumab | Ib | HER2+(A/M) | NCT03523572 |
| Trastuzumab, pertuzumab | HER2 | Pembrolizumab | II | HER2+, LN positive | NCT03747120 |
| Trastuzumab, pertuzumab | HER2 | Atezolizumab | II | HER2 amplified | NCT03894007 |
| Trastuzumab, pertuzumab | HER2 | Atezolizumab | Ib | HER2+/- | NCT02605915 |
| Trastuzumab, pertuzumab | HER2 | Atezolizumab | III | HER2+ early | NCT03595592 |
| Trastuzumab, pertuzumab | HER2 | Atezolizumab | II | HER2+ | NCT03125928 |
| Trastuzumab, pertuzumab | HER2 | Atezolizumab | III | HER2+ early | NCT03726879 |
| Trastuzumab, pertuzumab | HER2 | TAA vaccine | II | HER2+ | NCT04329065 |
| Trastuzumab, pertuzumab | HER2 | Atezolizumab | III | HER2+(M) | NCT03199885 |
| Trastuzumab, pertuzumab | HER2 | Durvalumab | II | HER2+ | NCT03820141 |
| Trastuzumab, pertuzumab | HER2 | IFNγ | I/II | HER2+ | NCT03112590 |
| Trastuzumab, pertuzumab | HER2 | DC vaccine | I | HER2+ | NCT03387553 |
| Pertuzumab | HER2 | Atezolizumab | II | HER2+ | NCT03894007 |
| Pertuzumab, ABP 980 | HER2 | Pembrolizumab | II | HER2+ | NCT03988036 |
| MEK inhibitors | | | | | |
| Binimetinib | MEK | Avelumab | II | TNBC | NCT03971409 |
| Binimetinib | MEK | Pembrolizumab | Ib | all | NCT02779751 |
| Binimetinib | MEK | Pembrolizumab | I/II | TNBC(LA/M) | NCT03106415 |
| Cobimetinib | MEK | Atezolizumab | II | TNBC(M) | NCT02322814 |
| Cobimetinib | MEK | Atezolizumab | I/II | ER+ Stage IV | NCT03566485 |
| Cobimetinib | MEK | Atezolizumab | II | Inflammatory BC | NCT03202316 |
| Cobimetinib | MEK | Atezolizumab | II | ER+HER2- | NCT03395899 |
| Trametinib | MEK | PDR001 (anti-PD-1) | Ib | TNBC | NCT02900664 |
| **Others** | | | | | |
| BGB324 | Axl | Pembrolizumab | II | TNBC(M) | NCT03184558 |
| Capmatinib | MET | spartalizumab +LAG525 | I | TNBC | NCT03742349 |
| Cabozantinib | c-Met, VEGFR1/2/3, FLT3, TIE2, TRKB, Axl, RET | Atezolizumab | Ib | LABC, TNBC | NCT03170960 |
| Cabozantinib | c-Met, VEGFR1/2/3, | Nivolumab | I | TNBC | NCT04514484 |

| | | | | | |
|---|---|---|---|---|---|
| | FLT3, TIE2, TRKB, Axl, RET | | | | |
| Cabozantinib | c-Met, VEGFR1/2/3, FLT3, TIE2, TRKB, Axl, RET | Nivolumab | II | TNBC(M) | NCT03316586 |
| Lenvatinib | VEGFR2 | Pembrolizumab | II | TNBC | NCT03797326 |
| Lenvatinib | VEGFR2 | Pembrolizumab | I | TNBC | NCT04427293 |
| Ruxolitinib | JAK2 | Pembrolizumab | I | HR-, TNBC(M) | NCT03012230 |
| Everolimus | mTOR | Spartalizumab | Ib | TNBC | NCT02890069 |

Source: Clinicaltrials.gov. **P**, early phase 1/pilot. **(L)A/M**, (locally) advanced and/or metastatic. **LABC**, locally advanced. Breast cancer. **ABP 980**: trastuzumab biosimilar ABP980. ***** = completed. **LN**, lymph node. **HR**, hormone receptor