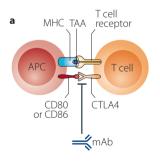


The clinical impact of checkpoint inhibitors and their anticipated position as linchpins of future cancer immunotherapy regimens has driven a wave of deal-making. In this feature, we chart the development progress and major deals for the leading checkpoint inhibitors.

BioPharma Dealmakers

Cancer immunotherapy—which harnesses the immune system to combat cancer—has revolutionized oncology drug development in the past 5 years. By modulating various components of the immune system, researchers have been able to develop highly promising new treatments for several cancers, including melanoma, non-small-cell lung cancer, renal cell carcinoma and Hodgkin lymphoma. A key approach that has proved particularly successful so far is the inhibition of immune checkpoint proteins that regulate the activity of T cells, thereby 'releasing the brakes' from T cells to enable them to attack cancer cells (Fig. 1a). Cytotoxic T lymphocyte-associated antigen 4 (CTLA4), programmed cell death protein 1 (PD1) and programmed cell death 1 ligand 1 (PDL1) are three checkpoint proteins that inhibitors have been successfully developed for (Fig. 1b).

The first checkpoint inhibitor to reach the market was Yervoy (ipilimumab), developed by Bristol-Myers Squibb, which was approved in March 2011 for unresectable or metastatic melanoma. Since then, three further checkpoint inhibitors—the PD1 inhibitors Opdivo (nivolumab) and Keytruda (pembrolizumab), and the PDL1 inhibitor Tecentriq (atezolizumab)—have been approved for various cancers. Given the huge impact of this first wave of checkpoint inhibitors, companies are now exploring the potential of combining checkpoint inhibitors with each other and with other cancer immunotherapies, as well as with drugs in different classes such as epigenetic modulators and kinase inhibitors. This has led to a flurry of deal activity involving many major pharma companies as each tries to establish its place in the rapidly growing cancer immunotherapies market. (Fig. 2) (March 2016 BioPharma Dealmakers, pB2).



PDL1 PD1 Tumor cell T cell

b CTLA4 inhibitors

Ipilimumab

Brand name: Yervoy
Developing company:
Bristol-Myers Squibb
FDA-approved indications:
unresectable or metastatic
melanoma; adjuvant
therapy for stage 3
melanoma

Tremelimumab

Brand name: N/A
Developing company:
MedImmune, the biologics
arm of AstraZeneca
FDA-approved indications:
none yet; in phase 3 trials

PD1 inhibitors

Nivolumab

Brand name: Opdivo
Developing company:
Bristol-Myers Squibb
FDA-approved indications:
unresectable or metastatic
melanoma, metastatic
NSCLC, advanced RCC,
Hodgkin lymphoma

Pembrolizumab

Brand name: Keytruda
Developing company:
Merck & Co.*
FDA-approved indications:
unresectable or metastatic
melanoma, metastatic
NSCLC, recurrent or
metastatic HNSCC

PDL1 inhibitors

Atezolizumab

Brand name: Tecentriq Developing company: Genentech/Roche FDA-approved indications: urothelial carcinoma

Durvalumab

Brand name: N/A
Developing company:
MedImmune, the biologics
arm of AstraZeneca
FDA-approved indications:
none yet; in phase 3 trials

Avelumab

Brand name: N/A
Developing companies:
Merck KGaA and Pfizer
FDA-approved indications:
none yet; in phase 3 trials

Figure 1: Characteristics of selected checkpoint inhibitors.

(a) Checkpoint inhibitors are monoclonal antibodies (mAbs) that target immunomodulatory molecules on the surface of immune cells and tumor cells, thereby enhancing T-cell-mediated antitumor responses. A simplified illustration of the interaction points of approved checkpoint inhibitors is shown. (b) The names and approval status of approved and selected late-stage checkpoint

inhibitors, color-coded according to their target. APC, antigen-presenting cell; CTLA4, cytotoxic Tlymphocyte-associated antigen 4; FDA, US Food and Drug Administration; HNSCC, head and neck squamous cell carcinoma; NSCLC, non-small-cell lung cancer; PD1, programmed cell death protein 1; PDL1, programmed cell death 1 ligand 1; RCC, renal cell carcinoma; TAA, tumor-associated antigen. *Known as MSD outside the United States and Canada.

PDL1 inhibitors **CTLA4** inhibitors **PD1** inhibitors July 2009: ipilimumab acquired 2009 by BMS through its \$2.4 billion purchase of Medarex January 2010: Debiopharm 2010 collaborates on the development of tremelimumab March 2011: ipilimumab 2011 approved by the FDA for unresectable or metastatic melanoma—the first checkpoint August 2014: Celgene partners with August 2014: Pfizer and inhibitor to be approved BMS to trial nivolumab in combination Merck & Co.* collaborate to with Abraxane (nab-paclitaxel) for trial Pfizer's kinase inhibitor 2014 November 2014: October 2011: MedImmune multiple cancers Xalkori (crizotinib) with Pfizer signs a \$2.85 obtains selected rights to pembrolizumab billion deal to access tremelimumab from Pfizer September 2014: pembrolizumab Merck KGaA's PDL1 approved by the FDA for unresectable October 2014: BMS program, including partners with Novartis to or metastatic melanoma an \$850 million trial nivolumab in two upfront payment phase 1/2 trials for NSCLC December 2014: nivolumab approved with three compounds by the FDA for unresectable or from Novartis metastatic melanoma April 2015: Juno partners with April 2015: tremelimumab is granted 'orphan drug AstraZeneca to study the combination of one of its CAR-T designation' as a potential January 2015: BMS and Lilly partner cell therapy candidates with treatment for malignant to trial nivolumab with Lilly's kinase durvalumah melanoma 2015 inhibitor galunisertib for advanced April 2015: Immunocore glioblastoma, hepatocellular January 2015: BMS collaborates April 2015: Celgene partners partners with AstraZeneca's with Seattle Genetics to trial carcinoma and NSCLC with AstraZeneca for the MedImmune for a phase nivolumab with its development of durvalumab for 1b/2 trial of tremelimumab antibody-drug conjugate March 2015: nivolumab approved a range of blood cancers with its immunotherapy Adcetris (brentuximab vedotin) by the FDA for metastatic NSCLC IMCqp100 for metastatic August 2015: Syndax Pharmaceuticals trials its for NHI and HI melanoma October 2015: pembrolizumab November 2015: Merck & Co.* approved by the FDA for epigenetic modulator October 2015: ipilimumab and GSK partner for a phase 1 entinostat with atezolizummetastatic NSCLC approved by the FDA as an trial testing a combination of ab for patients with breast adjuvant therapy for stage 3 the mAb GSK3174998 and cancer November 2015: nivolumab pembrolizumab in patients melanoma approved by the FDA for advanced with solid tumors October 2015: AstraZeneca October 2015: ipilimumab in and Lilly partner to trial combination with nivolumab selected Lilly candidates December 2015: Amgen December 2015: Lilly and Merck & approved by the FDA for (including galunisertib) collaborates with Merck & Co.* Co.* partner to test a combination unresectable or metastatic with durvalumab for to trial pembrolizumab with its of Lilly's kinase inhibitor abemacimelanoma—the first various solid tumors bispecific antibody Blincyto clib and pembrolizumab in a combination of checkpoint (blinatumomab) for NHL and its phase 1 trial inhibitors to be approved mAb AMG 820 in selected solid tumors January 2016: Syndax to test its epigenetic modulator entinostat with avelumab for ovarian cancer January 2016: Affimed to trial its bispecific antibody AFM13 with March 2016: Verastem February 2016: pembrolizumab to treat relapsed partners with Merck FDA grants or refractory HL May 2016: nivolumab durvalumab . KGaA to trial its kinase approved by the FDA for HL 2016 'breakthrough inhibitor defactinib in August 2016: pembrolizumab approved by the FDA for recurrent therapy combination with designation for avelumab in a phase or metastatic HNSCC 1/1b trial for ovarian metastatic urothelial cancer cancer March 2016: Kite Pharma April 2016: Astex Pharmapartners with Genentech ceuticals (part of Otsuka for a phase 1b/2 trial Pharmaceuticals) collabocombining its KTE-C19 rates with Genentech for a with atezolizumab for phase 1b trial combining PD1 inhibitors PDL1 inhibitors CTLA4 refractory NHL atezolizumab and the Nivolumab Atezolizumab inhibitors epigenetic Durvalumab Pembrolizumab | Ipilimumab ☐ Approved May 2016: Atezolizumab approved modulator Avelumab Tremelimumab guadecitabine by the FDA for urothelial carcinoma

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Figure 2: A timeline of selected approvals and collaborations for checkpoint inhibitors. BMS, Bristol-Myers Squibb; CAR, chimeric antigen receptor; FDA, US Food and Drug Administration; GSK, GlaxoSmithKline; mAb, monoclonal antibody; nab, nanoparticle-albumin-bound;

NHL, non-Hodgkin lymphoma; HL, Hodgkin lymphoma; HNSCC, head and neck squamous cell carcinoma; NSCLC, non-small-cell lung cancer; RCC, renal cell carcinoma. *Known as MSD outside the United States and Canada.