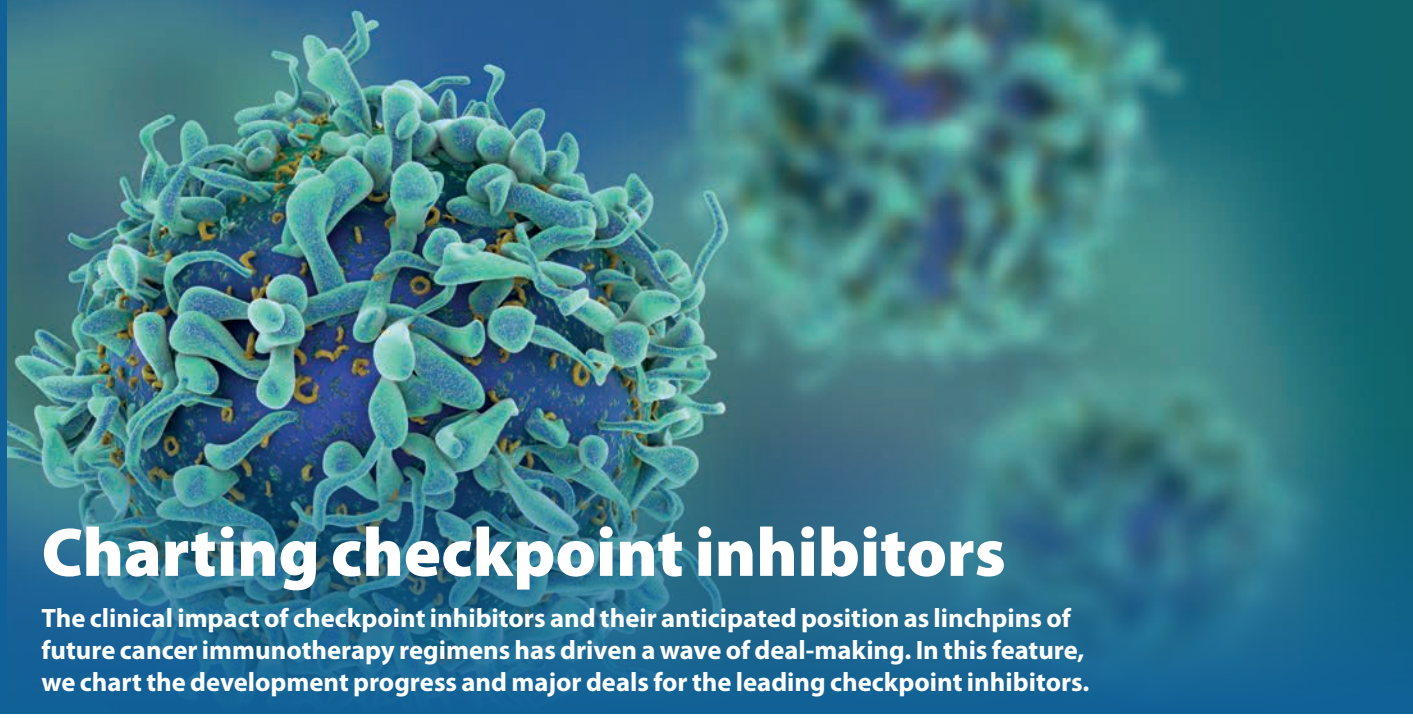


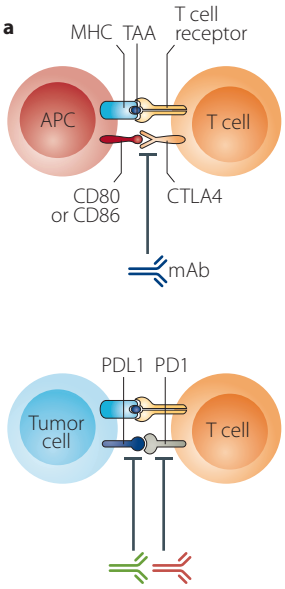
Charting checkpoint inhibitors

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).



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 anti-tumor 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 T lymphocyte-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.

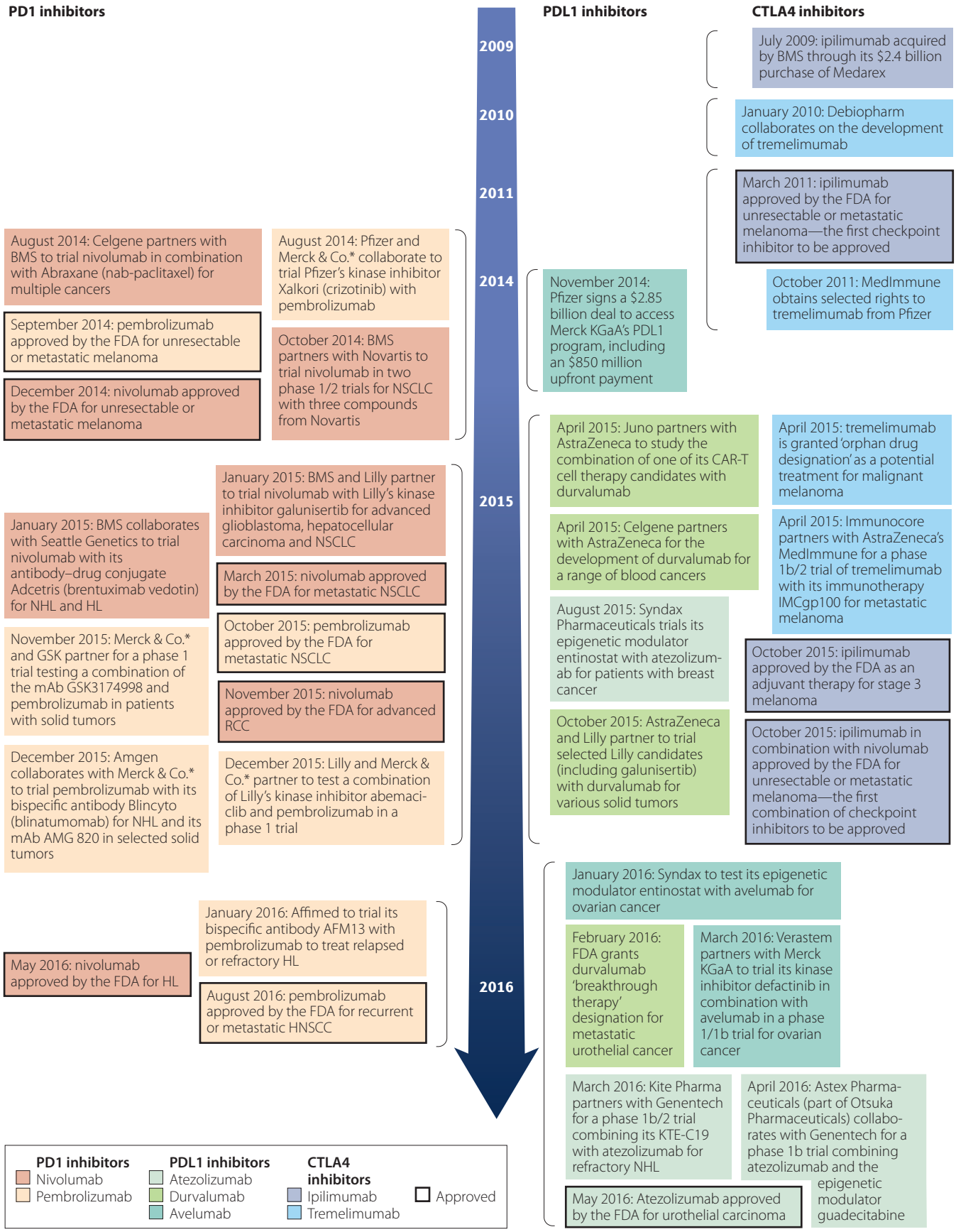


Figure 2: A timeline of selected approvals and collaborations for checkpoint inhibitors. BMS, Bristol-Myers Squibb; CAR, chimeric antigen receptor; FDA, US Food and Drug Administration; GSK, GlaxoSmithKline; mAb, monoclonal antibody; nab, nanoparticle-albumin-bound; NHL, non-Hodgkin lymphoma; HL, Hodgkin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