TRIAL WATCH

Comparing development strategies for PD1/PDL1-based immunotherapies

Inhibitors of the PD1/PDL1 immune checkpoint have revolutionized cancer treatment. Here, we discuss the differing development strategies of global and Chinese biopharma companies for PD1/PDL1-targeted agents by comparing the landscapes for approvals and pivotal trials.

Differences in development strategies are notable with regards to the first indication for marketing authorization. As of September 2021, 14 anti-PD1/PDL1 monoclonal antibodies (mAbs) have reached at least one major market, six of which were discovered in China. Global companies have often attempted to differentiate their agents in the US or European markets by aiming to be first-in-indication. Examples include avelumab for Merkel cell carcinoma, cemiplimab for cutaneous squamous cell carcinoma and dostarlimab for dMMR/MSI-H endometrial cancer (FIG. 1). Even for the same cancer, products were pursued for distinct subtypes or disease stages. For instance, durvalumab stood out as the first consolidation therapy after chemoradiotherapy in stage III non-small-cell lung cancer.

By contrast, Chinese companies have almost exclusively adopted the approach of targeting 'rare' and life-threatening indications to access the market quickly. Five out of the six approved PD1-targeted mAbs discovered in China received their first conditional approvals by the Chinese National Medical Products Administration (NMPA) for Hodgkin's lymphoma (FIG. 1). These divergent development approaches between companies in China and elsewhere resulted, at least partially, from differences in the ecosystems for pharmaceutical R&D, regulation, capital and reimbursement.

Both in China and overseas, there are robust development pipelines for PD1/PDL1 agents. Since 2020, the number of pivotal clinical trials (defined as sponsor-initiated studies that could potentially be used to obtain marketing approval or post-marketing confirmatory efficacy studies) of domestic PD1/PDL1 agents in China has outpaced the number of trials of products discovered in other major countries (Supplementary Fig. 1). When looking at indication distribution, we found that domestic agents are especially being pursued in efficacy-proven common malignancies, such as lung and hepatic cancer (Supplementary Fig. 2). Interestingly, the unique geographic variation of nasopharyngeal carcinoma and head and neck squamous cell carcinomas accounted for the divergent developmental focuses for these two diseases in China and elsewhere.

In light of the potential excessive development of similar PD1/PDL1 agents, the bar for regulatory approvals seems to be becoming higher. For instance, an application to the FDA for accelerated approval for balstilimab in cervical cancer was withdrawn owing to the recent full approval of pembrolizumab for the same indication.

In China, recently published oncology R&D guidance emphasizes unmet medical needs and clinical value. To demonstrate 'advance-in-class', several domestic agents, such as tislelizumab (NCT04866017) and pucotenlimab (NCT04750083) were tested in trials designed to show superiority over other approved PD1/PDL1 agents.

Next-generation agents have been designed to exceed the therapeutic threshold of PD1/PDL1 mAbs. Bispecific antibodies dominate the clinical pipelines inside and outside of China (Supplementary Fig. 3), either blocking multiple immunosuppressive pathways such as CTLA4 and LAG3 or activating co-stimulating receptors such as 4-1BB and OX40 (Supplementary Fig. 4). Products developed in China that could be the first of the type approved globally include the subcutaneously administered nanobody envafolimab for dMMR/MSI-H cancer (approved in China in November 2021) and the bispecific PD1×CTLA4 antibody cadonilimab for cervical cancer (under consideration for approval).

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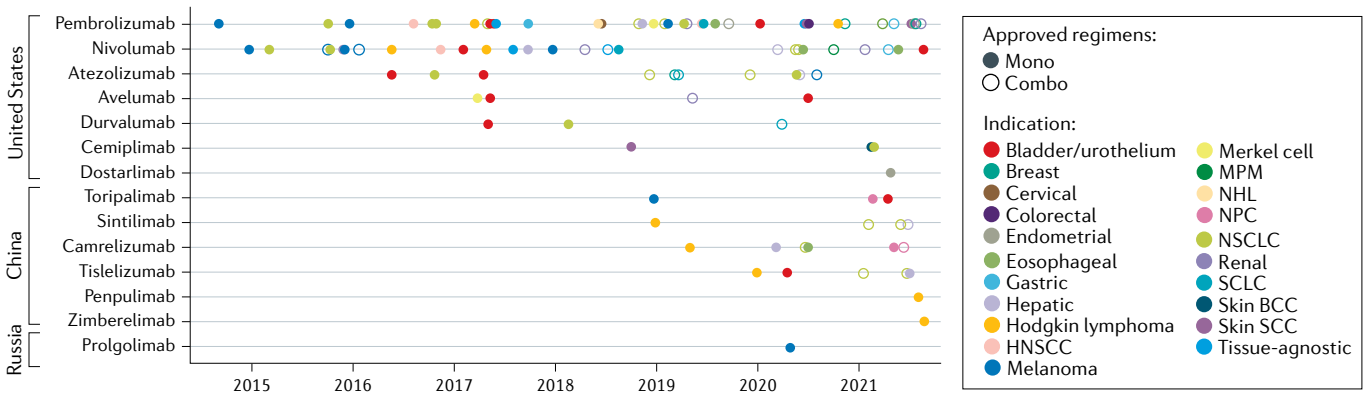

Fig. 1 | **Timelines of marketing approvals for PD1/PDL1 checkpoint inhibitors.** One solid or hollow dot indicates one marketing approval as a PD1/PDL1 monotherapy or combination therapy, respectively in the countries shown. Tissue-agnostic indications are DNA mismatch repair deficiency (dMMR) or high tumour-mutation burden (TMB-H) cancers. HNSCC, head and neck squamous cell carcinoma; MPM, malignant pleural mesothelioma; NHL, non-Hodgkin lymphoma; NPC, nasopharyngeal carcinoma; NSCLC, non-small-cell lung cancer; SCLC, small-cell lung cancer; skin BCC, basal cell carcinoma of the skin; skin SCC, squamous cell carcinoma of the skin. Data sourced 10 September 2021. See Supplementary Box 1 for details.