Innovation or repackaging? A global analysis of 929 checkpoint bispecific antibody trials

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Background

Immune checkpoint inhibitors (CPIs) are increasingly developed as combinations, most pairing separately administered agents. Bispecific and bifunctional antibodies, which engage a checkpoint and a second target in one molecule, are positioned as the successor strategy, intended to improve the therapeutic index over co-administered regimens [1]. To date, FDA-approved bispecifics have been largely for hematologic malignancies, and none target a checkpoint; only cadonilimab (PD-1/CTLA-4) and ivonescimab (PD-1/VEGF) are approved, both in China.

Whether this represents mechanistic innovation or empirical consolidation around PD-1/PD-L1 remains unknown. We characterized the clinical-stage pipeline to distinguish these possibilities.

Methods

- Source: GlobalData. We included all interventional trials initiated through 2025 that evaluated a bispecific or bifunctional agent targeting at least one immune checkpoint (PD-1, PD-L1, CTLA-4, LAG-3, TIGIT, or TIM-3).
- Each agent was classified into a mechanistic class defined by its second-checkpoint or non-checkpoint target.
- For dual-checkpoint agents, the partner checkpoint was identified.
- Trials were analyzed by start year.

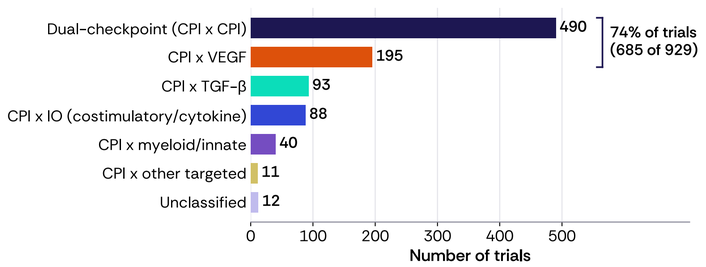


Figure 1a. Trials by mechanistic class (n = 929). Interventional trials initiated through 2025 evaluating a bispecific or bifunctional agent targeting at least one immune checkpoint, classified by the agent's second-checkpoint or non-checkpoint target. CPI x IO covers other immuno-oncology (IO) targets (costimulatory or cytokine). A trial with agents in two classes is counted in each. Unclassified: second target undisclosed or not listed in the source data (n = 10) or outside the defined classes (n = 2). Class bars sum to 929 because 16 trials fall in two classes; 913 distinct trials.

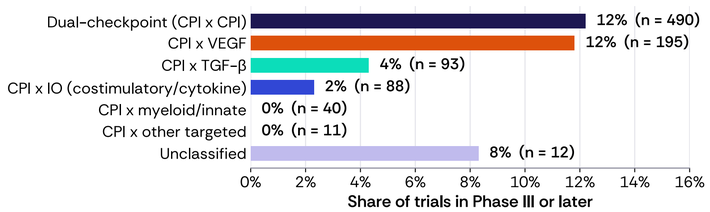


Figure 1b. Late-stage activity is concentrated in the same two classes. Share of trials in each mechanistic class that have reached Phase III or later. Labels show the share, with n = number of trials in the class. Dual-checkpoint and CPI x VEGF trials reached this stage at 12% each, versus 8% or less in every other class.

Results

We identified 929 trials. Activity was concentrated within a few mechanistic classes (Figure 1a) and predominantly anchored on PD-1 or PD-L1. Dual-checkpoint agents (n = 490) and CPI x VEGF agents (n = 195) together accounted for 74% of trials. These same two classes account for nearly all late-stage development: 12% of trials in each have reached Phase III or later, versus 8% or less in every other class (Figure 1b).

Among dual-checkpoint agents, 80% paired the checkpoint with CTLA-4 (n = 391), whereas LAG-3, TIGIT, and TIM-3 partners were uncommon (Figure 2).

Class-specific activity tracked individual late-phase clinical results rather than progressive mechanistic exploration (Figures 3 and 4): in the two largest classes after dual-checkpoint agents, CPI x VEGF trials rose from 14 in 2023 to 105 in 2025 after the ivonescimab readout, while CPI x TGF-β starts decreased from a 2021 peak of 25 to 1 by 2025 after the Phase III bintrafusp alfa failure in 2021.

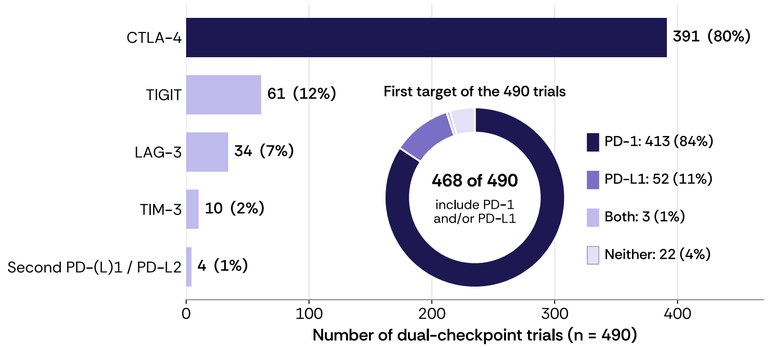


Figure 2. Partner checkpoint among dual-checkpoint trials (n = 490). Bars show the partner checkpoint; the donut shows the first target. 84% (413) pair with PD-1, 11% (52) with PD-L1, and 3 with both; 22 trials pair two non-PD-(L)1 checkpoints (commonly CTLA-4) with no PD-(L)1 target. Nine trials evaluate agents with more than one partner checkpoint and are counted under each bar.

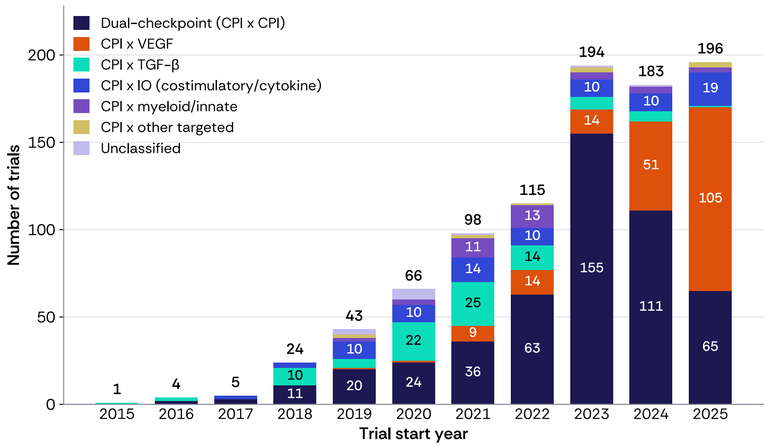


Figure 3. Trial starts per year by mechanistic class, 2015 to 2025. Segment labels show trials per class (values below 9 unlabelled). The label above each bar is the yearly total. Within these totals, the rise in CPI x VEGF trials and the fall in CPI x TGF-β trials coincide with the late-phase readouts described in Figure 4.

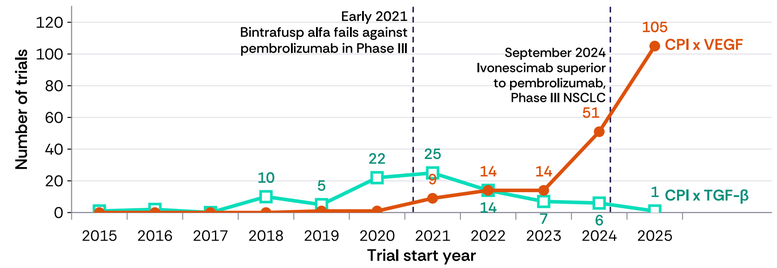


Figure 4. Class-specific activity tracked individual late-phase clinical results, 2015 to 2025. CPI x VEGF trials were stable through 2023 (9 to 14 per year), then rose to 105 in 2025, coinciding with ivonescimab becoming the first agent to show superiority over pembrolizumab (standard-of-care anti-PD-1) in a randomized Phase III non-small cell lung cancer (NSCLC) trial (September 2024) [2]. By 2025 CPI x VEGF was the most frequently initiated class, exceeding dual-checkpoint agents (Figure 3). In contrast, CPI x TGF-β trials peaked at 25 in 2021 and declined each year thereafter to 1 by 2025, following the Phase III failure of bintrafusp alfa against pembrolizumab in early 2021 [3] and termination of its development partnership. Dashed lines mark the two readouts within the year. Values below 5 are unlabelled, except the 2025 CPI x TGF-β value.

Key findings

929
checkpoint bispecific and bifunctional trials: 449 of 913 distinct trials (49%) active

74%
of trials in two classes: dual-checkpoint (490) and CPI x VEGF (195)

80%
of dual-checkpoint agents partner the checkpoint with CTLA-4 (391)

105
CPI x VEGF trials started in 2025, up from 14 in 2023

Conclusions

The clinical-stage pipeline of checkpoint-targeting bispecific and bifunctional agents is concentrated, predominantly PD-1/PD-L1–anchored, and responsive to individual clinical readouts.

These patterns indicate that the field is largely repackaging established PD-1/PD-L1 blockade with empirically chosen partners rather than diversifying checkpoint biology, with class prioritization following clinical results rather than prospective mechanistic rationale. This recapitulates, in a single-molecule format, the empirical and reactive development that produced high late-phase attrition among conventional checkpoint combinations.

However, mechanistic rationale and patient selection will be more important than molecular format in determining whether these agents succeed where co-administered combinations have not.

References

1. Klein C, Brinkmann U, Reichert JM, Kontermann RE. The present and future of bispecific antibodies for cancer therapy. Nat Rev Drug Discov. 2024;23:301–319.

2. Xiong A, Wang L, Chen J, et al. Ivonescimab versus pembrolizumab for PD-L1–positive non-small cell lung cancer (HARMONi-2): a randomised, double-blind, phase 3 study in China. Lancet. 2025;405:839–849.

3. Cho BC, Lee JS, Wu YL, et al. Bintrafusp alfa versus pembrolizumab in patients with treatment-naive, programmed death-ligand 1–high advanced NSCLC: a randomized, open-label, phase 3 trial. J Thorac Oncol. 2023;18:1731–1742.

Disclosure Statement

AI-assisted drafting was used to improve efficiency; all content was reviewed and approved by CRI staff.