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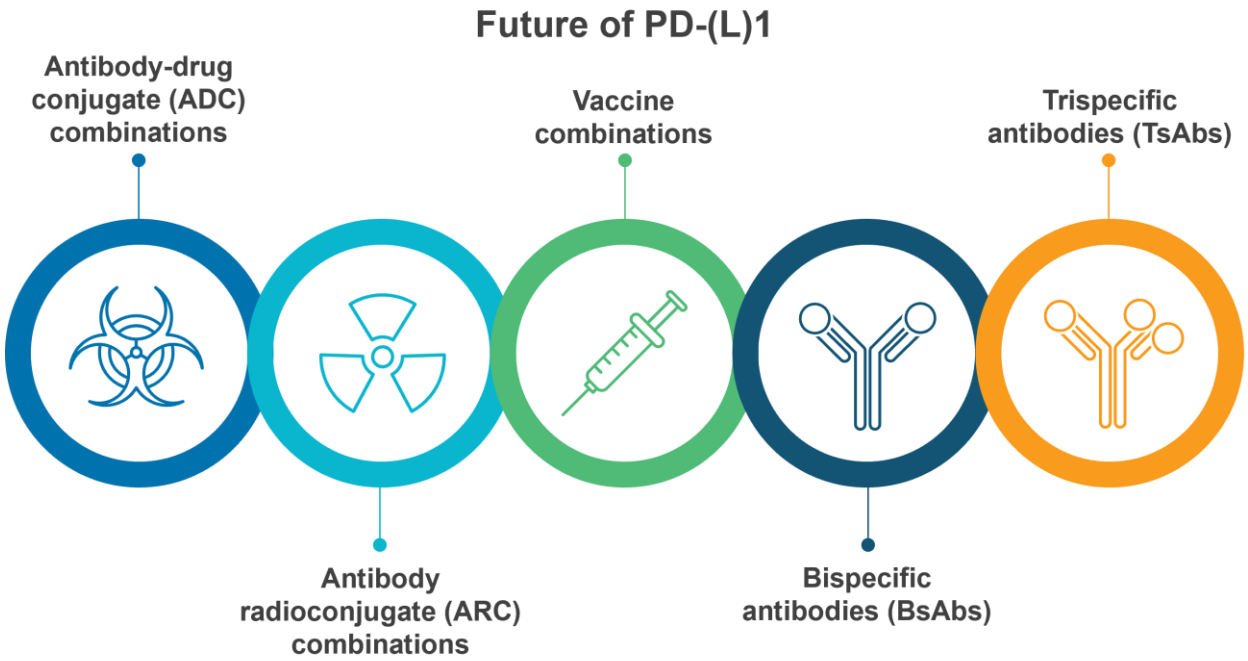
Keytruda and PD-(L)1 LoE: Life after programmed death (part 2)

Looking ahead to the future of oncology adds yet more weight to the conclusion that we not nearing "the end" of the PD-(L)1 era but are merely moving to the next chapter of its story, considering the number of avenues that are set to feature a PD-(L)1 component (Figure 1). Whilst new indications and posologies for existing products and a steady pipeline of new entrants represent two avenues that are important in securing a future role for the class, it is likely to continue to have a legacy role in a number of other forward-looking ways beyond monotherapy, single-target immune checkpoint inhibitor antibody approaches.

Figure 1: New product classes being investigated that contain a PD-(L)1 component.



Although we have seen a recent flurry of investment in antibody-drug conjugates (ADCs)1 and antibody radioconjugates (ARCs), which are focusing on a different selection of molecular targets away from

programmed death, the shadow of the PD-(L)1 class looms large. In particular, we are seeing multiple existing and pipeline ADCs in trial programs in combination with Keytruda and other PD-(L)1 agents. Notably, a more direct link to the class exists, with a Phase 1 trial underway for Pfizer's PF-08046054: a PD-L1-targeted ADC, which is leading the development race ahead of several preclinical PD-1 ADCs emerging from China.

ARCs are reemerging as future contenders in oncology. Fusion Pharmaceuticals (now part of AstraZeneca) are in the preclinical stages of investigating the role of their alpha-emitting actinium-225 FPI-1434 in insulin-like growth factor 1 receptor-positive solid tumours in combination with pembrolizumab. As with the ADCs, we are seeing signs that PD-(L)1 may also serve as a direct target of the ARCs and not just a combination partner, given supportive evidence arising from the academic and preclinical stages.2 This includes zirconium-89, which has been conjugated directly to pembrolizumab, a PD-1 inhibitor. However, conjugation to PD-L1 inhibitors is more commonplace, given the ligand's location on the tumour cells rather than T-cells. Whether these theranostics succeed and launch either as diagnostics and imaging approaches or as therapeutic treatment options, it is too early to tell, but this represents another route by which PD-(L)1 may continue to play a role in oncology.

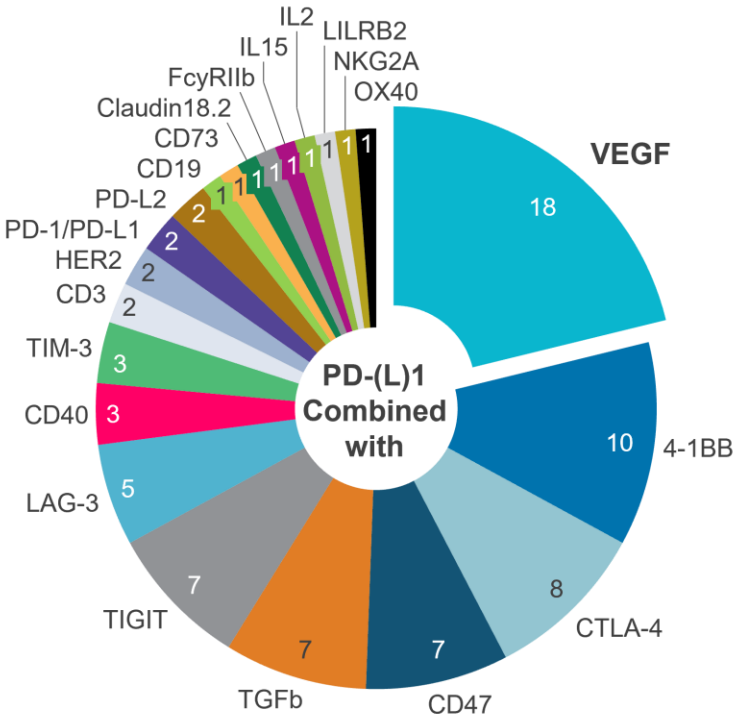
Vaccines—particularly mRNA-based immunotherapies—are an additional modality that might be able to leverage PD-(L)1 either directly or through combination use. As we have previously discussed,3 investigational products including Moderna's neoantigen therapy V940 (mRNA-4157) represent one of these approaches, with Phase 3 trials now underway in combination with Keytruda as an adjuvant treatment in resected high-risk melanoma, which builds on encouraging results from the Phase 2b KEYNOTE-942 trial that read out in 2024.4 Similar mRNA-based iNeST (individualised neoantigen-specific immunotherapy) approaches are also underway from BioNTech, in collaboration with Roche and other companies—many of which are in combination with PD-(L)1 antibodies. However, this is not the only vaccine-based approach that leverages a PD-(L)1 component, as we are also seeing trials underway for "off-the-shelf" DNA, RNA and antigen-based vaccines that directly focus on the production of anti-PD-(L)1 antibodies—either alone or in combination with a second antigen, such as IDO1 , as with Moderna's mRNA-4359.

Unlike the antibody-based technologies listed in Figure 1 above, the oncology vaccines represent a truly new approach to treating non-pathogen-driven cancer, which we have previously explored.3 As such, little is known about the potential role they will play in patients' treatment, how they will be commercialised, or whether vaccines should be a complementary arm to existing PD-(L)1 therapies in the form of an additive or synergistic combination regimen.

A more established yet still relatively new approach to solid-tumour oncology is the emerging cohort of bispecific antibodies (BsAbs) and those that look to cover PD-(L)1 as one of their targets. The initial BsAb entry into oncology was Amgen's Blincyto (blinatumomab) in 2015, which targets both CD3 and CD19, with the subsequent entry of a handful of other products for various haematological indications, largely targeting CD3 too. PD-(L)1 is now emerging as one of the expected targets in a future wave of BsAbs in solid tumours.

Some of these solid tumour-focused antibodies are being directed towards co-targets that have previously been tackled with monotherapies, including VEGF and CTLA-4, as well as other new and upcoming proteins (Figure 2). The likes of AstraZeneca, BioNTech, Merck, Roche and Servier, along with others, are looking into the PD-(L)1 BsAb space. As with the field of ADCs under development across the globe, these drugs are casting a wide net at present across key tumour targets, but it is clear where industry and researchers believe they are most likely to uncover significant, synergistic outcomes.

Figure 2: Current range of molecular co-targets under investigation across active clinical trials for PD-(L)1 BsAbs.



Source: CRA analysis

The VEGF pathway is one that has been repeatedly targeted. Avastin (bevacizumab), a previous blockbuster drug in its own right, represented the first biologic approach to interrupting VEGF signalling in the tumour microenvironment. Since then, we have seen multiple tyrosine kinase inhibitors that also block VEGF activity across a diverse range of solid tumours—again, several of which have become blockbusters themselves. It is perhaps unsurprising that the concept of co-targeting both PD-(L)1 and VEGF has been a tantalising one, even if past attempts at combining two monoclonal antibody therapies have so far delivered mostly muted, non-synergistic efficacy outcomes, although exceptions are notable, e.g. Tecentriq (atezolizumab) combined with bevacizumab in hepatocellular carcinoma. It is hoped that approaching these two targets in this new way—via BsAbs— will be the key to unlocking their broader potential.

One of the most promising new BsAbs targeting PD-1 and VEGF is Akeso Inc.'s (partnered with Summit Therapeutics outside China) ivonescimab , which has already launched in their domestic market of China as Idafang (Table 1). The results from their China-based Phase 3 HARMONi-2 trial, which were reported in September 20245 and published in March 2025,6 garnered significant attention given that Idafang demonstrated superiority to Keytruda in a head-to-head comparison in first-line PD-L1-positive non-small-cell lung cancer. It should be noted that evidence on overall survival (OS), which remains the gold-standard barometer for efficacy in oncology, is not yet mature, so comparisons thus far have been on progression-free survival and overall response rate, amongst others. Although this positive evidence needs to be validated in a broader, international trial population, it could potentially represent the next step into a post-PD-(L)1 monotherapy era.

Further, it is important to note that ivonescimab's trial programs are not solely focused on the monotherapy approach, with Summit and Pfizer now confirming a collaboration to combine ivonescimab with Pfizer's suite of vedotin-carrying ADCs across multiple solid tumours.7 Although an exciting clinical proposition, it likely opens up many of the same issues that present barriers for today's branded oncology combinations when seeking reimbursement, not to mention the likely tolerability challenges that these drugs can present to patients. However, if such combinations can replicate the OS successes recently seen with Pfizer and Astellas' Padcev (enfortumab vedotin) when combined with Keytruda in advanced urothelial cancer, this too could be a winning strategy for the future.

Table 1: Ongoing research programs investigating the use of PD-(L)1 x VEGF BsAbs across the globe.

Molecule	Target	Company	Most advanced clinical phase
Ivonescimab	PD-1 x VEGF-A	Akeso and Summit Therapeutics	Marketed (China only: Idafang)
BNT327	PD-L1 x VEGF-A	BioNTech and Bristol-Myers Squibb	Phase 3
AI-081	PD-1 x VEGF	OncoC4 and Accroimmune	Phase 2
MK-2010	PD-1 x VEGF	Merck & Co.	Phase 2
RC-148	PD-1 x VEGF	RemeGen	Phase 2
SSGJ-707	PD-1 x VEGF	3SBio and Pfizer	Phase 2
SCTB-14	PD-1 x VEGF	Sinocelltech	Phase 1/2
AP-505 (B1962)	PD-L1 x VEGF	Tasly Pharmaceutical Group and AP Biosciences	Phase 1
IMM-2510	PD-L1 x VEGF	ImmuneOnco and Instil Bio	Phase 1
JS-207	PD-1 x VEGF-A	Shanghai Junshi	Phase 1
MHB-039A	PD-1 x VEGF	Shanghai Minghui Pharmaceutical	Phase 1
SG1408	PD-L1 x VEGF	Hangzhou Sumgen Biotech	Phase 1
B-006	PD-L1 x VEGF	Convalife Pharmaceuticals	Preclinical
CR-001	PD-1 x VEGF	Crescent Biopharma	Preclinical
CTX-10726	PD-1 x VEGF-A	Compass Therapeutics	Preclinical
Jankistomig	PD-1 x VEGFR2	Ottimo Pharma	Preclinical
NY-500	PD-1 x VEGF	NAYA Biosciences	Preclinical
PD-L1/VEGF Trap	PD-L1 x VEGF	Immunowake	Preclinical

Source: CRA analysis

As shown in Table 1, Akeso and Summit are not alone in understanding the potential of PD-(L)1 x VEGF BsAbs in oncology, with 18 publicly announced molecules under investigation from preclinical stage to advanced human trials. The majority of these new antibodies originated in China, which is again proving

to be a hotbed of biotechnology innovation. Other BsAbs looking for this synergistic effect are also likely to emerge in time or may currently be under examination as “undisclosed target” assets.

Hot on the heels of Akeso and Summit are Germany’s BioNTech with BNT327 (formerly PM8002), following the recently completed acquisition of Biotheus,8 and Keytruda owners Merck with MK-2010 (formerly LM-299), which was recently gained in an exclusive license from LaNova Medicines.9 We have now also seen Pfizer more fully commit to the field through exclusively licensing 3SBio’s SSGJ-707 in May 2025.10 At the beginning of the American Society of Clinical Oncology annual meeting in June this year, we also heard that Bristol-Myers Squibb has entered into a co-commercialisation deal with BioNTech on BNT327, bringing the majority of key players in the PD-(L)1 field into this new treatment avenue. Interestingly, it is BNT327 that leads the way in terms of the number and breadth of international investigative trials, with a total of 12 in Phase 2 or 3.

These high-profile acquisitions, alliances and ambitious trial programs speak to the expectation that the synergy between PD-(L)1 and VEGF in the BsAb approach might overcome the high clinical bar set by Keytruda and the PD-(L)1 class to become the new standard of care, particularly in terms of the key OS measure of efficacy. It remains to be seen how differences in the biochemical structure of these molecules and their slight variations in targeting (e.g. PD-1 vs PD-L1, VEGF vs VEGF-A vs VEGFR2) could influence their overall efficacy and tolerability profiles.

Even further on the horizon lie the PD-(L)1 inhibitors that form part of trispecific antibodies (TsAbs) and tetraspecific antibodies (Table 2). As with the BsAbs, it is likely that haematological malignancies will be the first cancers to be broadly targeted with this class, but it is interesting nevertheless to note that PD-(L)1 is already being thought of as a component of future applications.

Table 2: Selection of ongoing research programs across the globe investigating the use of PD-(L)1 as part of a trispecific or tetraspecific antibody approach.

Molecule	Target	Company	Most advanced clinical phase
GNC-035	PD-L1 x CD3 x 4-1BB x ROR1	Systimmune	Phase 2
Emfizatamab (GNC-038)	PD-L1 x CD3 x 4-1BB x CD19	Systimmune	Phase 2
CS-2009	PD-1 x VEGF-A x CTLA-4	CStone Pharmaceuticals	Phase 1
DR-30206	PD-L1 x VEGF x TGF-B	Huadong Medicines	Phase 1
HC-010	PD-1 x VEGF x CTLA-4	HC Biopharma	Phase 1
Umizortamig (GNC-039)	PD-L1 x CD3 x 4-1BB x EGFRvIII	Systimmune	Phase 1
GB268	PD-1 x VEGF x CTLA-4	Genor Biopharma	Preclinical

Source: CRA analysis

Following a period marked by manufacturers mostly pursuing single-target antibodies in oncology, it now appears that a multi-target approach may come to characterise the next generation of anti-cancer therapies. Just as BsAbs are looking to take an important step forward for unconjugated antibodies with several late-stage trials now underway—both with and without PD-(L)1 as a co-target—we are also

seeing early signals that the bispecific approach may unlock new clinical avenues through a fusion with ADC technology to create bispecific antibody-drug conjugates.11 Over 35 of these candidates are under investigation in China alone, and it is perhaps unsurprising to note that PD-(L)1 appears as one of the co-targets amongst the small but growing number of early investigational drugs in this new class.

To inherit the mantle of “most successful next-generation oncology products”, which is arguably the title held by the PD-(L)1 products at present, these new technologies will not only need to demonstrate clinical superiority to the incumbent class but also prove to be useful in a diverse range of cancers and across lines of therapy from early, neoadjuvant uses to late-line metastatic interventions. This latter characteristic is only partially being met by recent ADC launches, with several of them restricted by their biomarker specificity. Although this was initially also true of the PD-(L)1 products, they soon broadened their use beyond constraining PD-L1 expression levels. It is therefore perhaps unsurprising that having one foot firmly planted in this PD-(L)1 field, as the BsAb and TsAb approaches do, may prove to be a pragmatic clinical and commercial approach to drive future success.

In the upcoming final part of this article, we will focus on some of the key strategies that will enable new competitors, whether originator or biosimilar, to succeed in a peri- and post-LoE PD-(L)1 setting.

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