

PD-1/VEGF Bispecifics: From China-Driven Breakthrough to Global Reality Check

When Biology, Capital, and Narrative Collide

Few oncology mechanisms have moved from obscurity to global prominence as rapidly as **dual PD-1/VEGF inhibition in a single molecular entity**. What was, until recently, a largely China-centric development story has, in under three years, become one of the most aggressively pursued immuno-oncology strategies globally—drawing capital, partnerships, and late-stage development bets from both biopharma and financial markets.

At the center of this momentum sits **ivonescimab (AK112)**, Akeso's PD-1/VEGF bispecific antibody, whose clinical and regulatory success in China catalyzed an industry-wide re-rating of the mechanism. However, as the program transitions from a China-optimized development environment into the far more stringent and precedent-driven **FDA regulatory ecosystem**, cracks are beginning to emerge between **perceived momentum** and **demonstrated global replicability**.

This paper examines how the PD-1/VEGF bispecific story took hold, why enthusiasm has outpaced evidence in FDA-track development, and why—despite real biological promise—the current late-stage risk profile remains materially underappreciated.

The Biological Rationale: Elegant, Intuitive, and Hard to Argue Against

From a mechanistic standpoint, the appeal of combining **immune checkpoint blockade (PD-1)** with **angiogenesis inhibition (VEGF)** is obvious and well supported:

- VEGF is immunosuppressive, impairing dendritic cell maturation, T-cell trafficking, and effector function.
- Anti-VEGF therapy can normalize tumor vasculature, improve immune infiltration, and synergize with checkpoint inhibition.
- Clinically, **IO + VEGF combinations** (e.g., PD-1 + bevacizumab, PD-1 + TKIs) have repeatedly demonstrated additive or synergistic effects across tumor types.

The bispecific thesis goes one step further:

If PD-1 and VEGF inhibition are synergistic as combinations, why not deliver them in a single molecule with fixed stoichiometry, optimized exposure, and simplified clinical development?

This logic is sound. The problem is not biology—it is **translation, comparability, and regulatory proof**.

China as the Spark: Ivonescimab's Rapid Ascent

Ivonescimab's rise is inseparable from its **China-first development strategy**.

- **May 2024**: First approval in China via **HARMONi-A (NCT05184712)**
- **April 2025**: Second approval via **HARMONi-2 (NCT05499390)**

Both approvals were achieved in **NSCLC**, a highly competitive indication globally, but one in which China's regulatory framework allows:

- Greater reliance on **PFS**
- Earlier approvals with **immature OS**
- Local comparator standards that may differ from US/EU expectations

The clinical data was compelling within this context: strong PFS gains, manageable safety, and a narrative of “best-of-both-worlds” IO biology. Importantly, ivonescimab did not just succeed—it **outperformed expectations relative to PD-1 monotherapy benchmarks**, creating the perception of a step-change rather than an incremental advance.

Capital followed quickly

From Breakthrough to Bandwagon: The Explosion of PD-1/VEGF Assets

In the three years following ivonescimab's clinical readouts:

- **Eight PD-1/VEGF bispecific assets** entered FDA-track development
- **All clinical programs initiated within the last ~36 months**
- **All programs are active**—none approved, none discontinued
- **Only two assets have reached Phase 3**:
 - Akeso/Summit's **ivonescimab**
 - Pfizer's **SSGJ-707**

This is a classic **early-signal amplification pattern**:

1. A single asset succeeds in a permissive regulatory environment
2. The mechanism is validated *in principle*
3. Capital, not attrition, becomes the dominant filter
4. Late-stage risk accumulates silently

Crucially, **ivonescimab itself dominates the Phase 3 evidence base**. Despite the growing pipeline, the field is effectively extrapolating from **one molecule, one geography, one sponsor experience**.

The Global Test: HARMONi and the OS Problem

That extrapolation met reality with the global HARMONi Phase 3 trial (NCT06396065).

- **Primary endpoints:** PFS and OS
- **Outcome:**
 - PFS met
 - **OS showed only a positive trend**, not statistical significance

The market reaction was immediate and instructive: Summit's stock declined sharply upon disclosure, reflecting a reassessment of **regulatory probability rather than biological promise**.

From an FDA perspective, this matters enormously.

In frontline or competitive solid tumor settings:

- **OS remains the gold standard**
- PFS-only approvals are increasingly rare without:
 - Clear unmet need
 - Large effect size
 - Or a compelling surrogate justification

Despite this, **Summit submitted a FDA BLA in January 2026**, signaling confidence—or at least willingness—to test the boundaries of regulatory discretion.

This is not unprecedented, but it is **high-risk behavior**.

Why China Success May Not Be Fully Portable

The divergence between China and US outcomes should not be dismissed as noise. Several structural factors are at play:

1. Comparator and Standard-of-Care Drift

US trials increasingly benchmark against optimized PD-1 backbones, combination regimens, and sequencing strategies that compress incremental benefit.

2. Post-Progression Therapy Confounding

OS separation is harder to demonstrate in markets with broad access to subsequent lines of therapy—particularly immunotherapy re-challenge.

3. Trial Powering Assumptions

China-based programs often assume larger effect sizes that do not replicate in more heterogeneous global populations.

4. Regulatory Philosophy

China rewards speed and access; the FDA rewards **durability and certainty**.

None of these invalidate the mechanism—but they **raise the bar**.

What the Data Is Quietly Saying: Elevated Late-Stage Risk

Intelligencia's **Probability of Technical and Regulatory Success (PTRS)** modeling flags **most Phase 3 PD-1/VEGF programs as high-risk**, reflecting a confluence of factors:

- Limited OS precedent
- Heavy reliance on a single clinical success narrative
- Compressed development timelines
- Mechanistic crowding in already competitive indications

Importantly, the absence of discontinued programs is **not reassurance**—it is a sign that **natural attrition has not yet occurred**.

History suggests it will.

So Is PD-1/VEGF a Fad—or the Next IO Backbone?

The honest answer is: **neither—and possibly both**.

- The **biology is real**
- The **China data is real**
- The **commercial upside is real**

But so are the risks:

- Regulatory skepticism without OS
- Difficulty reproducing effect sizes globally
- Portfolio crowding before true differentiation is established

Ivonescimab may yet secure FDA approval—regulatory outcomes are probabilistic, not deterministic. However, current evidence suggests that **clinical success in China should be viewed as enabling, not confirming, global approvability**.

For executives, portfolio managers, and BD leaders, the implication is clear:

PD-1/VEGF bispecifics are a high-conviction mechanism with low-conviction late-stage proof—at least for now.

Capital allocation, partnering strategy, and pipeline valuation should reflect that asymmetry.

Bottom Line: Proceed With Eyes Open

The PD-1/VEGF story is not over. But it is entering its most unforgiving chapter—the one where **biology meets regulation**, and where narrative must give way to endpoints.

In that transition, discipline—not hype—will separate durable winners from expensive lessons.

