A PERSPECTIVE ON RADIOLIGAND THERAPY

The Second Wave Should Go Narrow

The first generation of radioligand therapy proved the modality works. The next generation will decide whether it earns a permanent seat in oncology — and the way to earn it is to treat fewer patients, more deliberately, against a harder standard of proof.

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I spent a decade helping bring targeted radiation to market — through the Axumin launch at Blue Earth, and later inside Novartis on Locametz and Pluvicto. I want the modality to win. That is exactly why I think the field is about to make the same mistake twice, and why the second wave of agents should do the opposite of what the first wave did.

Radioligand therapy is roughly where immunotherapy stood around 2012. The foundational question has been answered. Targeted radiation works: it delivers dose to tumor, it produces meaningful responses, and it does so with a tolerability profile most oncologists can live with. That question is closed. The one that replaces it is harder and more consequential — not *does it work*, but do we know how to use it well enough to prove it deserves *to move earlier in the treatment sequence.*

The instinct across the field is to answer that question by expanding: more patients, earlier lines, broader labels. I think that instinct is wrong, and the evidence from the first wave already shows why. The second wave — Blue Earth Therapeutics' rhPSMA program and the agents following it — has a narrow window to establish a different pattern. Go narrow. Select harder. Pick fights you can win cleanly. Build the proof the first wave skipped.

01

What the first wave actually proved — and what it skipped

The headline achievement of the first generation is real and shouldn't be minimized. Pluvicto became the first PSMA-targeted radioligand therapy approved by the FDA, and demand has grown steadily — quarterly sales moved past half a billion dollars in 2025 on the strength of the pre-taxane expansion.[1] The modality is commercially validated. Patients are being treated who would not otherwise have had this option.

But look at how the expansion was won, because the mechanism matters more than the milestone. The pre-taxane approval rested on PSMAfore, a trial that roughly tripled the eligible patient population[2] by moving Pluvicto ahead of chemotherapy. The primary endpoint — radiographic progression-free survival — came in strong. The commercial logic was clean: prove you can move earlier, and the addressable market multiplies.

The problem is what that trial was built to answer. PSMAfore compared Pluvicto against a change in androgen-receptor pathway inhibitor — a second ARPI — in patients who had already progressed on one. It delivered a progression-free survival win. It did not deliver an overall survival win, and the design allowed control-arm patients to cross over once they progressed, which muddied the survival read from the start.

> *The first wave optimized for the size of the eligible population. It did not optimize for the specificity of the patient or the strength of the proof. Those are different goals, and the gap between them is where the trouble lives.*

This is the part of the story the field would rather not dwell on, and it's the part that should shape everything the second wave does.

02

Europe already returned the verdict

In March 2026, Novartis withdrew its application to bring Pluvicto into the earlier, pre-chemotherapy setting in the European Union.

The reasons are worth stating precisely, because they are not the reasons people assume. The EMA's committee signaled it would not support the expansion. The comparator in PSMAfore — a second ARPI — was considered inadequate therapy for patients at that stage of disease, which made the progression-free survival advantage difficult to interpret. And there was no demonstrated overall survival benefit.[3] Novartis was careful to note the withdrawal did not touch the drug's existing approvals, its safety, or its efficacy.[4] That framing is true and also beside the point.

Here is the point. A US regulator accepted a progression-free survival win against a weak comparator and roughly tripled the label. A European regulator looked at the same data and said: this comparison isn't fair, and you haven't shown people live longer. Same evidence. Two verdicts. The modality didn't fail in Europe because it treated too many patients. It failed because the proof wasn't built to survive a demanding reviewer.

I want to be careful here, because it would be easy to tell a simpler story than the facts support. The common framing — including one I used to reach for myself — is that the first wave went "too broad" and that breadth diluted the modality. That's close, but it's imprecise, and the imprecise version leads to the wrong lesson. The failure wasn't volume as such. A modality can treat a large population well. The failure had two linked halves, and they fed each other.

The first half is about who was studied. By defining the trial population broadly — in effect, PSMA-positive and appropriate to delay chemotherapy — PSMAfore enrolled a clinically heterogeneous group: patients with very different tumor biology, different aggressiveness, different likelihoods of deep response, all averaged into a single result. Heterogeneous populations regress toward a muddier mean. When you don't specify who you're actually trying to treat, the responders and the non-responders blur together, and the magnitude of benefit you report is smaller than the magnitude the drug is capable of in the patients it truly helps. Novartis didn't only pick a soft comparator. It diluted its own effect size by declining to be specific about the population.

The second half is about what it was measured against. A muted effect size needs a weak comparator to still look like a win — and a second ARPI in patients who had already failed one is a weak comparator. So the two failures compound: broad selection softens the result, the softened result needs a soft control to clear the bar, and the soft control is exactly what a serious regulator refuses. Breadth of ambition produced narrowness of proof, on both axes. That inversion is the whole lesson.

THE DISTINCTION THAT MATTERS

Going broad at the bedside — treating a wide range of eligible patients — is a clinical and commercial choice that can be entirely defensible.

Going broad in your evidence — designing trials to clear the lowest bar that unlocks the largest label — is what erodes a modality's standing. The first wave conflated the two. The second wave must separate them.

03

Why the second wave is built to go narrow

What makes this moment genuinely interesting is that the second-generation agents are engineered around a different premise — whether or not their developers have framed it this way.

Consider Blue Earth Therapeutics' lead candidate, 177Lu-rhPSMA-10.1. The Phase 1 data that read out through 2025 didn't lead with population size. It led with dose ratios: a mean tumor-to-salivary-gland ratio of 73 and a tumor-to-kidney ratio of 32, delivering proportionately higher absorbed dose to tumor than to the critical healthy organs that limit how much radiation you can give.[5] The design thesis is that a cleaner therapeutic ratio lets you push tumor dose without pushing toxicity in step.

That is a narrow-strategy instrument. A better therapeutic ratio is not an argument for treating more people. It's an argument for treating the right people more effectively — for front-loaded dosing, adaptive regimens, and dose intensity matched to the individual rather than fixed by convention. The second wave's central advantage is precision. Precision and breadth-of-label are strategically opposed. You cannot lead with "we deliver dose more selectively" and then define success as "we qualified the widest possible population." The instrument and the strategy have to agree.

What going narrow actually means in practice

Three commitments, each of which trades near-term addressable market for durable standing:

Select patients on biology, not just eligibility. The first-wave question was essentially binary: is the tumor PSMA-positive? That's a gate, not a prediction — and a gate lets in a heterogeneous crowd whose blended result understates what the drug does in its best responders. The next selection paradigm integrates PSMA PET with markers of discordant and aggressive biology to identify the tumors where deep, durable response is most likely. Fewer patients enter. More of them benefit meaningfully. And critically, the reported effect size climbs, because you've stopped averaging your responders against patients who were never going to respond. Specificity isn't only kinder to the patient who's spared a therapy that won't help — it's what makes the trial result impressive enough to defend.

Optimize dose intensity instead of inheriting it. Much of the first-wave dosing paradigm — fixed activity, spaced cycles, a marrow-protection mindset — was carried over conservatively rather than derived. The second wave has the therapeutic ratio to do better: front-load where early tumor control matters most, adapt to response, individualize delivery. This only works in a defined population where the biology is understood.

Run trials against comparators you'll be proud of. This is the discipline the first wave lacked, and the one Europe just punished. If the goal is a modality that endures, the second wave has to design trials against the therapy a patient would actually, reasonably receive — and it has to be willing to be measured on overall survival, not only on progression delayed. A narrower, cleaner win against a real standard is worth more than a broad win against a soft one. The broad win is exactly what got withdrawn.

> *A narrow, unambiguous proof of benefit is the most valuable asset the second wave can build. It's also the only one that travels across every regulator, every payer, and every skeptical tumor board.*

04

Future shaping: getting ahead of the verdict

Most strategy in this field is reactive — you read the trial result, then you build the messaging around whatever you got. The more valuable discipline is what I've come to call *future shaping*: working several years out, deciding what you want to be true about the modality, and making the design choices now that let that future actually arrive.

Applied here, future shaping asks a different opening question than the one the first wave asked. Not how large a label can this data unlock? but *what will a demanding reviewer, a cost*-conscious payer, and a cautious oncologist need to believe three years from now — *and what evidence, designed today, earns that belief?* The EU withdrawal was foreseeable. The comparator problem was visible in the trial design before the data ever read out. A future-shaping posture treats that foreseeability as an instruction: build the proof that survives the room you'll eventually be standing in, not the room you're in now.

The second wave has one advantage the first wave never had — it gets to watch the first wave's verdict come in before committing its own pivotal trials. That is a gift. Squandering it by chasing the same broad labels against the same soft comparators would be the single most avoidable mistake available to the field.

The company that shapes the next phase of radioligand therapy will not be the one with the widest label. It will be the one that proves, cleanly and against a fair standard, that targeted radiation works dramatically better when it's aimed with discipline. That proof is narrow by construction. It's also the only thing that turns a promising therapy into a permanent pillar of oncology — and the first wave has already shown us, at real cost, what happens when we reach for breadth before we've earned it.

NOTES & SOURCES

1. Novartis Q3 2025 financial reporting (Form 6-K): Pluvicto quarterly net sales of USD 564 million, +46%, driven by sustained US demand following the pre-taxane mCRPC approval and continued ex-US access expansion in the post-taxane setting; described as the only FDA- and PMDA-approved PSMA-targeted radioligand therapy for use after one ARPI and before chemotherapy.

2. FDA expanded-indication approval, 28 March 2025, based on PSMAfore (NCT04689828); the pre-taxane label was reported to approximately triple the number of patients eligible for Pluvicto. PSMAfore enrolled ~468 PSMA-positive mCRPC patients who had progressed on one ARPI and were considered appropriate to delay taxane chemotherapy.

3. European Medicines Agency, withdrawal of the type II variation to extend Pluvicto into the pre-chemotherapy setting; application withdrawn 23 March 2026. Per the CHMP's provisional assessment: the ARPI comparator was not considered adequate therapy for patients at that disease stage, complicating interpretation of the radiographic progression-free survival advantage, and no overall survival benefit was demonstrated versus the comparator arm.

4. Novartis statement, 24 April 2026: withdrawal followed CHMP feedback on the PSMAfore control arm and was not related to the quality, efficacy, or safety of Pluvicto, and did not affect ongoing trials, existing approvals, or pending submissions inside or outside the EU.

5. Blue Earth Therapeutics, Phase 1 dosimetry results for 177Lu-rhPSMA-10.1 (NCT05413850), reported March 2025 and presented at SNMMI, June 2025: mean tumor-to-salivary-gland ratio of 73 and tumor-to-kidney ratio of 32 across 13 mCRPC patients; data described by the company as comparing favorably to published first-generation PSMA-targeted radioligand therapy dosimetry.

This perspective reflects the author's independent analysis of publicly available information and does not represent the position of any company referenced. It is commentary on the direction of the modality, not clinical or investment guidance.