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Janux Soars On Early Efficacy, Safety For 'Masked' T-Cell Engagers

Phase Ia Studies Show Low Rates Of CRS

by Mandy Jackson

Janux reported early clinical trial data for its lead asset JANX007 that may show differentiated efficacy in the crowded PSMA space and for an EGFR agent with lung and kidney tumor shrinkage.

Early clinical trial results for *Janux Therapeutics Inc.*'s JANX007 and JANX008 appear to validate the company's Tumor Activated T-cell Engager (TRACTr) for the development of bispecific T-cell engagers that deliver cancer-killing activity with limited off-target toxicity. But what more than tripled Janux's share price on 27 January were data showing that PSMA-targeting JANX007 may have best-in-class efficacy in terms of decreasing PSA levels in prostate cancer patients.

The San Diego-based company reported initial Phase Ia trial results from 23 patients with advanced or metastatic castration-resistant prostate cancer (mCRPC) treated with JANX007 and from 11 patients with solid tumors known to express high levels of EGFR who were treated with JANX008 after the stock market closed on 26 January. Janux's stock rose 229.9% the following day to close at $49.75 per share. Janux went public in the US in 2021 at $17 per share. (Also see "*Finance Watch: Janux Offering Makes 47 Biopharma IPOs In 2021, So Far*"

Key Takeaways

- Janux reported early data for its PSMA-targeting bispecific T-cell engager (TCE) that analysts described as best in class, propelling a sharp rise in its valuation.
- The company's EGFR-targeting bispecific TCE also showed strong early efficacy.
- The anti-tumor activity and clean safety

- Scrip, 12 Jun, 2021.)

> profile relative to other TCEs could result in two blockbuster products if early data hold up, analysts said.

Both JANX007 and JANX008 come from the company's TRACTr technology platform, which uses peptides that bind to a bispecific T-cell engager (TCE) and mask the TCE until it is delivered to the tumor, where tumor proteases cleave the masks so that the bispecific can engage anti-tumor T-cells within cancer cells and not in healthy tissues. Initial clinical data show low levels of cytokine release syndrome (CRS) often associated with TCEs, with CRS severity to date only grade 1 or 2.

"It's an elegant approach to a class of therapeutics that have always had problems balancing systemic toxicity and selectivity issues," Evercore ISI analyst Jonathan Miller said in a 27 February note.

The PSMA- and EGFR-targeting candidates were tested in heavily pre-treated individuals, including mCRPC patients with a median of four-plus prior lines of therapy and people with solid tumors treated with multiple prior lines, including PD-1/L1 inhibitors. The data cutoff for the Phase Ia data reported on 26 February was 12 February for both JANX007 and JANX008.

Best-In-Class Potential In Prostate Cancer

Janux reported that at a starting dose of ⩾0.1mg with JANX007, 14 of 18 mCRPC patients (78%) achieved PSA30 declines and 10 of 18 (56%) achieved PSA50 declines, while at a starting dose of ⩾0.2mg, six of six patients (100%) achieved PSA30 declines and five of six (83%) achieved PSA50 declines. President and CEO David Campbell noted during a 26 February call on the data that about 45% of patients receiving *Novartis AG*'s PSMA-targeting radiopharmaceutical product Pluvicto (lutetium Lu 177 vipivotide textraetan) in trials achieved PSA50.

Miller pointed out that "mCRPC is getting complicated – radiotherapy, ADCs, CAR-T, IO ... [with] PSA50 rates for 'top-tier' therapies in late-line settings [that] hover around 50%." He noted that JANX007 "JANX gets to 57% PSA50 across all cohorts with high-dose patients in this current data set achieving an impressive ... 83% PSA50 – and [Janux] isn't even done escalating yet." The analyst said the results are the best early data he has seen in mCRPC.

"Acknowledging the low number of patients treated at dose levels with a first step-up dose of at least 0.2mg (n=6), this level of activity is clearly significant and above relevant benchmarks in such heavily pretreated patients," William Blair analyst Matt Phipps said in a 27 February note.

Pluvicto is the only approved PSMA-targeting therapy, cleared by the US Food and Drug Administration in 2022. (Also see "*Novartis Lays A New Foundation In Prostate Cancer With Second*

Radioligand Launch" - Scrip, 23 Mar, 2022.) However, 22 PSMA-targeting therapies are in the clinic, including eight radiotherapies, seven bispecific TCEs, three immunotherapies or vaccines, two chimeric antigen receptor T-cell (CAR-T) therapies, an antibody-drug conjugate (ADC) and a T-cell redirecting agent, according to Biomedtracker. Sixteen of the programs are in Phase I or Phase I/II trials.

Pluvicto's sales have generated a lot of interest in treatments that target PSMA. Novartis reported $273m in fourth quarter 2023 sales, up 53% from Q4 2022. The radiotherapy produced $980m in sales for all of 2023, up 262% year-over-year. *Johnson & Johnson*, which already has two PSMA-targeting agents in Phase I trials – the bispecific JNJ-87189401 and the T-cell redirecting agent JNJ-80038114, announced at the start of 2024 that it will pay $2bn for ADC developer *Ambrx Biopharma, Inc.*, whose lead drug candidates include the PSMA-targeting asset ARX517. (Also see "*J&J Makes Its Biggest Bet Yet On Antibody-Drug Conjugates With Ambrx Buyout*" - Scrip, 8 Jan, 2024.)

Safety Differentiates JANX007 From Other TCEs

JANX007 also appears to be a differentiated cancer therapy in terms of safety as compared with other TCEs, with CRS observed in 91% of mCRPC patients, but all of those events were grade 1 or 2. Patients were given dexamethasone prophylaxis, primarily during the first treatment cycle, to prevent CRS and reduce its severity. Campbell noted that grade 1 CRS generally amounts to a fever, while grade 2 is a fever with some other side effects, all of which are manageable, he said.

The majority of non-CRS treatment-related adverse events (TRAEs) were also grade 1 or 2 and, as with the occurrence of CRS, primarily occurred during the initial treatment cycle. There was a low incidence of grade 3 TRAEs, and no grade 4 or 5 events.

"We still don't know exactly how tox will track as dose continues to escalate (no clear trend in CRS rate from data we're given – but granularity is low), but this profile certainly supports continued escalation," Miller said.

Phipps noted that he was "particularly encouraged by the safety profile of JANX007 holding up even at doses up to 3mg, which are above maximally tolerated doses with standard T-cell engagers, owing to the reduced systemic exposure of the TRACTr platform."

The Phase Ia study of JANX007 will continue until Janux identifies maximum tolerated doses for the drug. The company will provide updates on doses selected for a Phase Ib dose expansion study during the second half of 2024.

"At this point, we believe we have already identified a dose level that is worthy of development, but because we still have such a good CRS and safety window, we are continuing our dose optimization," Campbell said. "We expect to continue that through the rest of the year. We have

the goal to further deepen our PSA responses, drive these patients to PSA50s and beyond as well as durability, while maintaining this safety profile, but the early data is already competitive with those also undergoing clinical development at this point."

EGFR Data Show Lung, Liver Cancer Elimination

Efficacy data from the first 11 patients treated with JANX008 are limited, but Janux reported a confirmed partial response (PR) in one non-small cell lung cancer (NSCLC) patient treated with 0.15mg once-weekly dose, with 100% reduction of the target lung lesion and elimination of liver metastasis with no CRS or TRAEs. The patient remains on treatment with their PR maintained through a week 18 scan.

In addition, the company said a patient with renal cell carcinoma (RCC) had a 12% reduction in the size of a large RCC mass and "significant clinical benefit," and that individual experienced only grade 1 CRS.

Grade 1 CRS was observed in only two and there were no cases of grade 2 or higher CRS among the 11 subjects who received JANX008 at doses of up to 1.25mg. The majority of non-CRS TRAEs were also grade 1 or 2 and predominantly occurred during the first dosing cycle. No treatment-related serious adverse events or dose-limiting toxicities were observed.

The Phase Ia dose escalation and optimization study of JANX008 is ongoing with an update planned for later in 2024.

"While the data was from a small set of patients, it was encouraging to note that both products were relatively safe with no patient experiencing higher than grade 2 CRS, a major toxicity issue that led to discontinuation of multiple T-cell engager clinical candidates," H.C Wainwright analyst Swayampakula Ramakanth said in a 27 February note. "Both drugs showed single-agent anti-tumor efficacy and if they continue to be successful in their respective clinical programs, we believe they have the potential to be best-in-class therapies."

Phipps said William Blair sees $1.5bn in peak sales potential for JANX007 in chemotherapy refractory metastatic prostate cancer with multibillion-dollar potential beyond that in earlier lines of treatment. He forecast $1.3bn in peak sales in metastatic colorectal cancer for JANX008 with additional blockbuster potential if the drug shows efficacy across EGFR-expressing tumor types.

Campbell noted that Janux plans to test JANX007 as a monotherapy in third-line or later prostate cancer but move the TCE into first- and second-line treatment in combination with established drugs, including enzalutamide.