Evaluate Vantage

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Esmo IO 2021 – Propel fails to propel Nektar

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The focus now falls on first-line melanoma data with bempegaldesleukin plus Opdivo, due in early 2022.

Nektar Therapeutics had hoped that data from the Propel study of bempegaldesleukin could help it revive its fortunes. In the event topline results, disclosed during the group's third-quarter earnings call last week, underwhelmed and shares fell 19% on Friday.

The latest data concern bempeg plus Merck & Co's Keytruda in first-line metastatic non-small cell lung cancer. Propel is an uncontrolled study, but Nektar had previously set out its expectations based on historic response rates achieved with Keytruda alone. Propel largely failed to meet these; the group will present more detailed data at the Esmo-IO meeting in December, but hopes will not now be high.

The group has expanded Propel to test a combination of bempeg, Keytruda and chemo, and results with this regimen are due in mid-2022. But the most important catalyst for Nektar now is a phase 3 first-line melanoma trial testing bempeg plus Bristol Myers Squibb's Opdivo versus Opdivo alone. Enrolment in that study is complete, with data due in early 2022.

Still, Propel is yet another dent in the theory that bempeg can turn cold tumours hot. Nektar reported data on 71 patients grouped by PD-L1 status: less than 1%, 1-49%, and 50% or more. In PD-L1-high patients bempeg plus Keytruda looks no better than Keytruda alone. Nektar played down expectations with the combo in this cohort, saying it was always going to be tough to beat single-agent Keytruda here.

Propel stalls: early data with bempeg + Keytruda

PD-L1 status	N	ORR Keytruda (historic)*	ORR bempeg + Keytruda
≥50%	15	40-45%	40%
1-49%	28	15%	"Low single digits"
<1%	28	8%	"Doubling" over historic Keytruda

**Benchmark given by Nektar. Source: company presentation & Leerink note, Nov 5, 2021.*

In non-expressers the result was more promising, with Nektar noting a doubling in overall response rate versus

that historically seen with Keytruda monotherapy, which the company said was 8%. However, response rates with Keytruda alone are in fact in the range of 8-10%; the difference between a 16% and 10% ORR is much less emphatic, especially given the small numbers of patients involved in Propel.

But it was in PD-L1-low patients that Propel really disappointed. A “low-single-digit” ORR is well below the 15% seen with Keytruda alone. The company had some explanations for this, including that a high number of patients in this arm of Propel had aggressive squamous cell disease, and the fact that 25% of subjects in this cohort had previously received chemotherapy for either stage three disease, or as adjuvant treatment for stage one or two disease. In the Keynote trials Nektar execs said this figure was only 4-6%.

On the positive side, bempeg plus Keytruda did result in some deep responses, with two complete remissions in the PD-L1-high arm, and two non-expressers seeing 100% reduction in target lesions.

Nektar will await the Keytruda and chemo-combo data from Propel before deciding on its filing strategy in NSCLC. The company might be looking for a path forward in PD-L1 low or non-expressers, who make up around 70% of patients, but the latest data suggest that even this is now far from clear.

Upcoming bempeg readouts		
Trial details	**Trial ID**	**Data due**
Ph3 in 1L melanoma +/- Opdivo	NCT03635983	Early 2022
Ph3 in 1L RCC + Opdivo vs TKI	NCT03729245	H1 2022
Ph2 Pivot-10 in 1L cisplatin-ineligible urothelial cancer + Opdivo vs	NCT03785925	H1 2022
Ph2 Propel 1L NSCLC + Keytruda + chemo	NCT03138889	Mid-2022
Source: company Q3 results.		