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Triple meeting – early data give and they take away

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Turning Point and Repare are left nursing heavy losses, while Relay just about weathers a storm.

With extremely early data nowadays providing significant impetus behind many biotech acquisition and flotation valuations, they can also have the opposite effect. A case in point is the share price collapses in recent days of Turning Point and Repare Therapeutics.

Both groups had presentations at the EORTC-NCI-AACR (Triple) symposium that finished yesterday, and both ended the meeting in the red. A third group, Relay Therapeutics, also turned heads for all the wrong reasons, but in the event it managed to weather the storm and is currently trading flat. But Turning Point investors might today be wondering whether their company's targeted approach is all it has been cracked up to be.

Turning Point

Turning Point had already seen a dramatic desertion of investor support this year, its shares having halved even before the Triple meeting started, and a couple of updates at the conference prompted further declines.

Two presentations were given on the Trident-1 study of the company's lead project, repotrectinib, a kinase inhibitor designed to target tumours driven by defects in Ros1, Alk and NKTR. Ros1 is the biggest focus, a setting where Turning Point hopes to compete against Roche's Rozlytrek, which has already has a first-line label in Ros-positive NSCLC.

The first repotrectinib dataset concerned the latest results from cohorts of second-line or later NSCLC patients, who had already failed on Rozlytrek. Response rates deteriorated significantly in EXP-4, a cohort progressed on one TKI and no platinum chemo, which at World Lung earlier this year was showing an ORR of 67%; at the Triple meeting this fell to 38%.

Still, analysts believe that the project should be approvable in salvage settings, given the lack of other options, and data in expansion cohorts of more advanced patients seemed just about to hold up.

Whether repotrectinib can win a first-line NSCLC label is a bigger question. Even if this is granted the project's safety profile – mainly high rates of dizziness – versus Rozlytrek could prevent much front-line use, analysts at Stifel believe. An update from the first-line (EXP-1) cohort of Trident-1 is expected early next year.

Turning Point's Trident-1 study						
Cohort	**EXP-1 (n=55)**	**EXP-2 (n=60)**	**EXP-3 (n=40)**	**EXP-4 (n=60)**	**EXP-5 (n=55)**	**EXP-6 (n=40)**
Mutation	Ros1+	Ros1+	Ros1+	Ros1+	NTRK+	NTRK+
Treatment line	Naive	1 TKI + 1 prior chemo	2 TKIs, no prior chemo	1 TKI, no prior chemo	Naive	TKI pretreated
Previously reported ORR	91% (n=22)	50% (n=12)	0% (n=10)*	67% all PRs (n=9)	–	50% (n=6)
ORR at Triple meeting 2021	Not updated	39% (n=23)	30% (n=10)	38% (n=39)	41% (n=17)	48% (n=23)
*Note: Ros1+ cohorts are NSCLC, while NTRK+ are tumour agnostic; *before modification this cohort allowed prior chemo; Rozlytrek approved first line on 67% ORR; Lorbrena used second line off-label on 35% ORR (has CNS tox).*						

A second repotrectinib presentation, which was awarded a plenary spot, concerned patients with NTRK fusions, irrespective of cancer type, and did show highly impressive response rates: 41% in TKI-naive subjects and 48% in those pretreated appear to make approval likely, though the apparently stellar data cut little ice with investors.

One problem is that Turning Point has been working hard not to be seen as a one-trick, repotrectinib-focused pony, including at last year's Triple meeting. And unfortunately new data on its follow-on asset, the Met inhibitor elzovantinib (TPX-0022), underwhelmed in a separate Triple meeting update.

An ORR of 20% in five TKI-naive Met exon 14 deletion NSCLC patients was achieved, around half of that shown by Novartis's Tabrecta and Merck KGaA's Tepmetko. Elzovantinib also failed to generate any responses in pretreated patients.

Meanwhile, in a separate cohort of Met-altered gastric cancer subjects, ORR fell from 100% a year ago to 33% in nine patients.

On a call executives said they would probably seek a line-agnostic label for repotrectinib next year, which analysts reckon could delay any launch to 2023. Little wonder the stock was this morning trading 24% below its close last Wednesday, before the Triple abstract went live.

Repare

Similarly failing to hit expectations was Repare, which claimed a meaningful clinical benefit with its ATR inhibitor RP-3500 in almost half of the 69 evaluable patients with cancers with synthetic lethal genomic alterations including CDK12, Brca and ATM mutations.

However, actual efficacy here amounted to just 12 partial responses, mostly seen in Brca1-mutated cancers. Though the data were early this 17% ORR fell well short of Stifel's expectations of 36%, which would have been in line with Bayer's rival ATR inhibitor BAY 1895344.

Moreover, the Bayer ORR figure comes specifically from 11 patients with ATM aberrations, where Repare's RP-3500 could only manage an 8% ORR among 37 subjects. Given the activity signs in Brca mutants Stifel suggested the possibility of combining RP-3500 with Parp inhibition, but investors did not buy it: compared with Wednesday the stock is today off 20%.

Relay

The markets also remain unconvinced about Relay's bold claims for RLY-4008, an inhibitor of FGFR2, a mutation seen most often in cholangiocarcinoma (bile duct cancer).

Three of six treatment-naive patients in a first-in-human trial achieved a partial response, according to the Triple meeting update, but it was toxicity that caused problems. Relay claims that RLY-4008's high selectivity helps it avoid the side effects seen with similarly targeted drugs, Incyte's Pemazyre and Bridgebio/Helsinn's Truseltiq, but data do not bear this out.

A twice-daily dose has been scrapped owing to dose-limiting toxicities, and even the once-daily schedule highlighted at the Triple meeting and being taken forward has raised questions. Mouth sores and nail toxicities are side effects of concern, as well as hyperphosphataemia.

Thursday's Triple abstract caused a share price dip, but the stock recovered some losses, and is currently off

about 8%. Relay’s $2.5bn valuation remains punchy, and is largely based on hopes for a supercomputer-driven discovery technology; RLY-4008 is only one of two phase 1 assets.

Evaluate Vantage has also published a story covering data that impressed at the symposium that can be found here.