Evaluate Vantage

December 14, 2022

Ash 2022 – pirtobrutinib leads the post-Imbruvica charge

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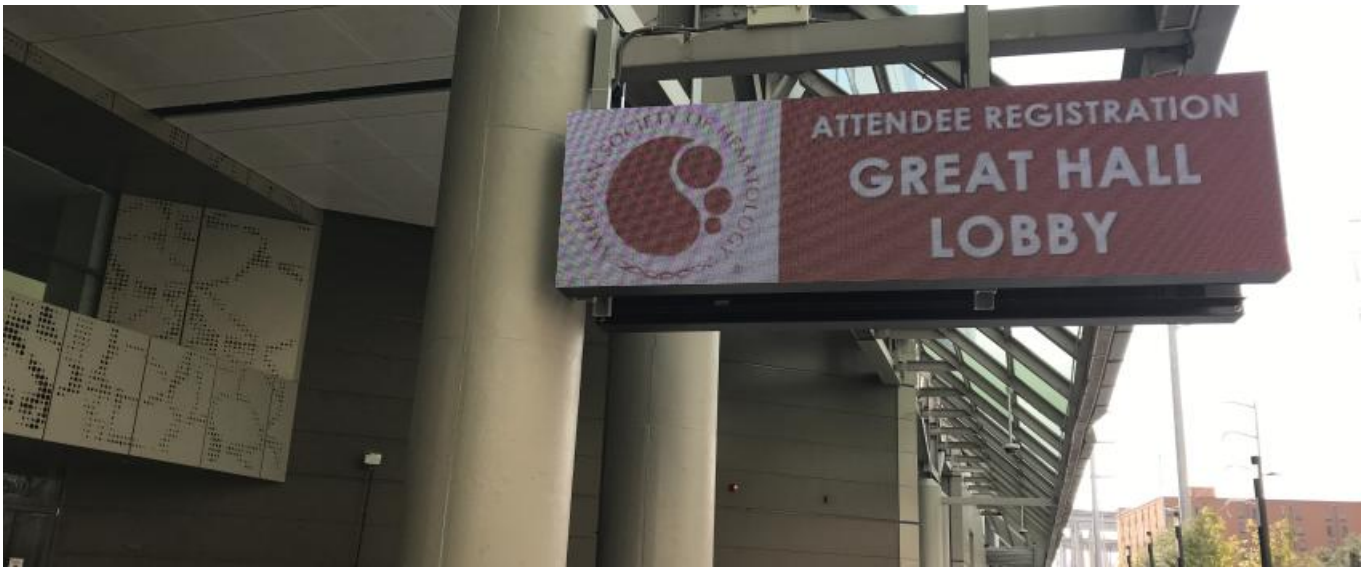


Lilly's non-covalent BTK inhibitor shines yet again, blunting the impact of early data with Nurix's BTK degrader.

If yesterday's Ash late-breaker on Beigene's Brukinsa signalled a changing of the guard in primary BTK inhibition, earlier data from Lilly's pirtobrutinib and Nurix's NX-2127 highlighted potential new options for patients who relapse on current BTK drugs.

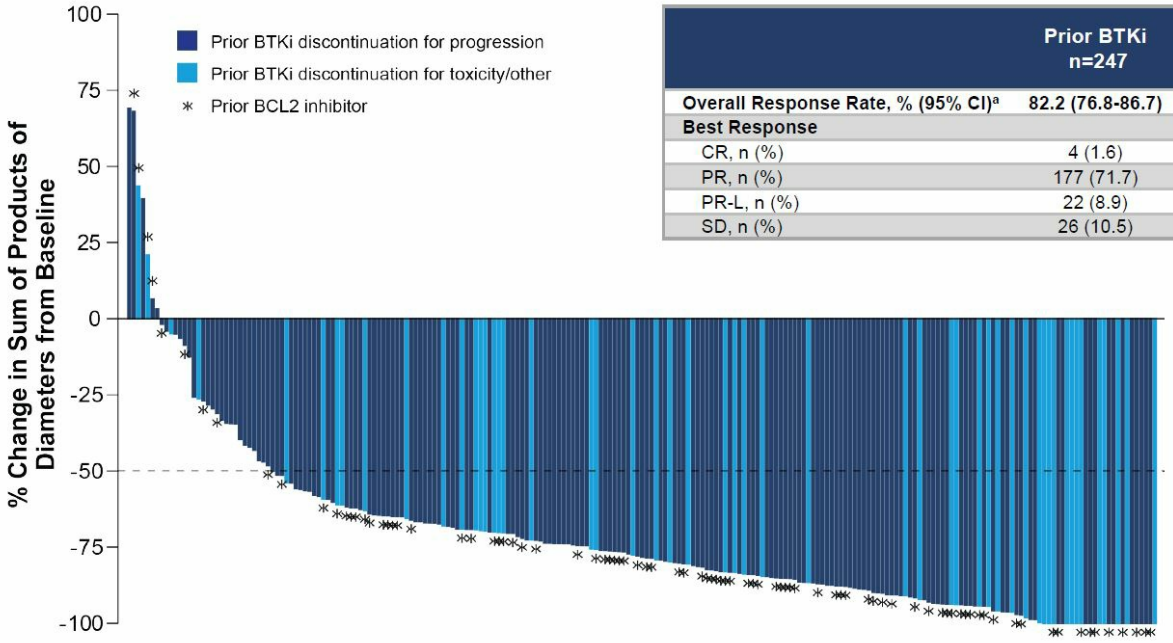
Nurix specialises in target degradation, a field that has seen the Serds post mixed success in breast cancer, but in which NX-2127, Nurix's lead asset, looks active, according to an early Ash dataset. Whether this really matters is unclear given that pirtobrutinib appears to have the immediate opportunity in BTK inhibitor-relapsed patients sewn up, and this could see Nurix relegated to an even later-line setting.

Pirtobrutinib is a non-covalent BTK inhibitor said to work after patients develop resistance mutations to covalently acting BTK drugs like Imbruvica, Calquence and Brukinsa, and made a big splash at Ash 2020. This year Lilly completed a rolling US filing for mantle cell lymphoma patients who relapse after prior BTK blockade, and first approval is expected in early 2023.

Still, mantle cell lymphoma is a relatively small use, and the big prize is chronic lymphoblastic leukaemia (CLL), the major indication for Imbruvica and other first-generation BTKs. It was an update of the CLL subset of pirtobrutinib's Bruin study that featured as the Lilly project's biggest Ash dataset.

This comprised an expansion cohort of 247 patients who had received a prior BTK inhibitor, and the group put up a stunning waterfall plot, showing tumour shrinkage in all but six patients, and an 82% overall remission rate. Not only that, but 100 of these patients had failed Abbvie's highly efficacious Bcl-2 inhibitor Venclexta as well as BTK blockade, and the ORR held up in these too, at 79%.

Pirtobrutinib Efficacy in CLL/SLL Patients who Received Prior BTKi Treatment



	Prior BTKi n=247	Prior BTKi+BCL2i n=100
Overall Response Rate, % (95% CI)[a]	**82.2 (76.8-86.7)**	**79.0 (69.7-86.5)**
Best Response		
CR, n (%)	4 (1.6)	0 (0.0)
PR, n (%)	177 (71.7)	70 (70.0)
PR-L, n (%)	22 (8.9)	9 (9.0)
SD, n (%)	26 (10.5)	11 (11.0)

Data cutoff date of 29 July 2022. Data for 24 patients are not shown in the waterfall plot due to no measurable target lesions identified by CT at baseline, discontinuation prior to first response assessment, or lack of adequate imaging in follow-up. [a]ORR includes patients with a best response of CR, PR, and PR-L. Response status per iwCLL 2018 according to independent review committee assessment.

Source: Dr Anthony Mato & Ash.

It was difficult for Nurix to compete against this kind of result, though a phase 1 trial of NK-2127 did show this BTK degrader to be active: an efficacy population of 15 post-BTK inhibitor patients with CLL presented at Ash on Monday showed five remissions.

This is all very well from an academic perspective, but Lilly's data puts up a significant roadblock; if pirtobrutinib is approved in CLL patients who fail covalent BTK therapy, as seems likely, what purpose is served by bringing forward a BTK degrader for the same use, however active the latter is proved to be mechanistically?

This must now be the main question for NX-2127, which carries a hefty sellside consensus for 2028 sales of $870m, according to *Evaluate Pharma*. This is only slightly short of pirtobrutinib's total of $1.1bn.

None of this is to say that NX-2127 has no future, but its use could be restricted to a very late setting. The Ash dataset includes five patients who had failed not only a covalent BTK inhibitor and Venclexta, but also a non-covalent BTK agent. One of these reported a partial response, ongoing at 12 months.

This is clearly an extremely early, albeit positive, signal. But, if this is a sign of NX-2127's future applicability, then that $870m number will have to come down. Already Nurix investors assume that the forecast is wildly optimistic, given that the market valuation of the entire group sits at $570m.

A further consideration is safety: 35% of CLL patients in the NX-2127 trial discontinued owing to an adverse event, versus just 3% of those treated with pirtobrutinib.