Evaluate Vantage

June 06, 2023

Asco 2023 – Dizal heralds a “super-Tagrisso”

Jacob Plieth

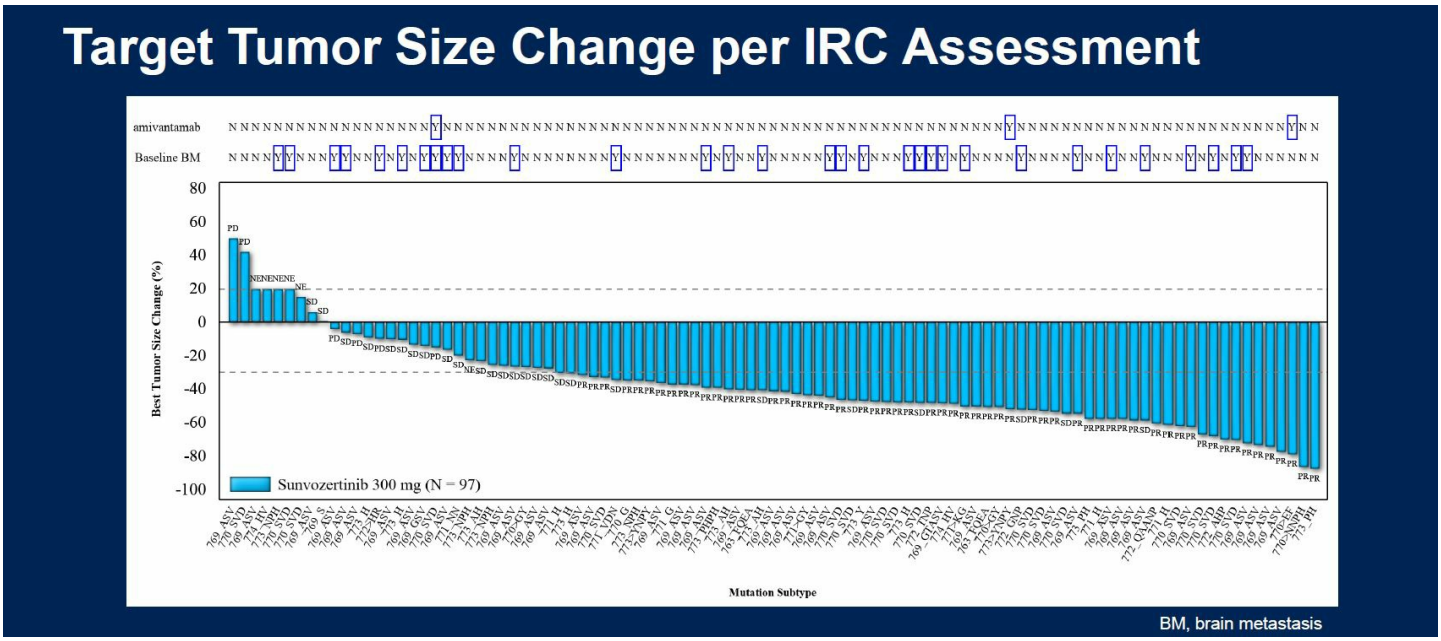
China’s Dizal, an unexpected targeted therapy star of Asco 2021, is back with even more impressive data.

Since presenting apparently industry-leading data in a targeted lung cancer niche at Asco 2021 Dizal has not had a major presence outside China. But the group, an offshoot of Astrazeneca, has been busy with its lead project, sunvozertinib, and this weekend’s Asco showed the fruits of those efforts.

Not only is sunvozertinib yielding even higher efficacy in a pivotal Chinese trial than in its earlier studies two years ago, it has made inroads into first-line use, as well as into a hitherto separate setting dominated by Astra’s Tagrisso. Dizal nearly floated on Nasdaq, its chief executive, Xiaolin Zhang, tells *Evaluate Vantage*, and the goal now is to extract maximum value in a licensing deal.

Some might be surprised that sunvozertinib still remains unpartnered. The initial NSCLC setting in question, EGFR exon 20 insertions, has seen the approval of two drugs, Johnson & Johnson’s MAb Rybrevant and Takeda’s small molecule Exkivity. Meanwhile, Otsuka paid $275m for Cullinan’s CLN-081 while Blueprint handed across $275m for Lengo’s BLU-451.

Even two years ago sunvozertinib looked as good as Rybrevant, and better than Exkivity, on a cross-trial basis. Now come Asco data just presented from the Chinese Wu-Kong6 trial showing an even better 61% remission rate, including in two of three post-Rybrevant subjects; the results backed a filing in China, where Zhang expects sunvozertinib to be approved within months.



Source: Dr Mengzhao Wang & Asco.

The chief exec puts the success down to “quite a bit of clever chemistry”. Armed with his 20 years’ experience at Astra he founded Dizal in 2017 as a spin-out of Astra’s Shanghai-based Asian R&D centre, which he had helped set up; Dizal floated on the Shanghai stock exchange in late 2021.

Astra retains a 25% equity stake in Dizal, and other investors include Lilly Asia Ventures, Sequoia Capital and STIC Ventures. Zhang tells *Vantage* that Dizal draws heavily on its Astra heritage, using English as its “working language”, and he even appointed Goldman Sachs to run a Nasdaq IPO before being put off by the US’s cooling stance on China.

But exon 20 insertions was never the key focus behind sunvozertinib, Zhang reveals. Rather, this was seen as “low-hanging fruit” at a time before that genetically defined niche really matured, and the ultimate aim was to design “a super-Tagrisso” with broad activity across EGFR mutations.

It is noteworthy that Tagrisso, and Astra’s earlier iteration Iressa, both work on EGFR activating mutations, which have not been actionable with a molecule that also hits exon 20 – until now, apparently. A separate Asco poster, in NSCLC patients with EGFR activating mutations, reveals a 27% remission rate.

“One of the design criteria [for sunvozertinib] was that it had to be equally potent against all insertion mutations,” says Zhang, and so in addition to EGFR activating mutation activity the molecule shows “almost equal potency across around 30 types of exon 20 insertions”. And then there is front-line use in exon 20 insertions, where ORR stands at 71%.

Another better Tagrisso?

Remarkably, Dizal and sunvozertinib are not the only ricochet of Astra’s EGFR-targeted lung cancer bullet. Years ago Astra was working on a better Tagrisso with CNS penetration, and designed a molecule coded AZD3759 – of which coincidentally Zhang is one of the inventors.

Though Zhang says AZD3759 won prestigious design awards Astra did not take it forward, and instead sold it to a private Chinese group called Alpha Biopharma. The compound now has the generic name zorifertinib, and is awaiting China approval; Asco data show numerically better front-line activity than Iressa, but that comparator seems obsolete given that Tagrisso is now firmly established here.

Blueprint’s early-stage assets also featured at Asco over the weekend, though there was nothing major to suggest a threat to Astra or Dizal. Perhaps most intriguing will be BLU-945’s combination with Tagrisso in patients who have progressed on the Astra drug, though perhaps such a combo is necessitated by BLU-945’s incomplete coverage of EGFR activating mutations, and a 22% rate of severe liver enzyme elevations could be disastrous.

Cross-trial comparisons in EGFR-mutated NSCLC				
Project	**Company**	**Mutation/setting**	**Trial**	**Asco data**
BLU-451	Blueprint (ex Lengo)	EGFR exon 20 ins, ~4L NSCLC	NCT04862780	1 PR cited in exon20, none in "atypical EGFRm"
Sunvozertinib	Dizal	EGFR exon 20 insertions, 2-4L NSCLC	Wu-Kong6	ORR 61% (59/97), including in 2/3 patients who failed Rybrevant
		EGFR exon 20 insertions, 1L NSCLC	Wu-Kong1 & 15	ORR 71% (20/28), including in 8/9 patients with brain mets
		EGFR activating muts, NSCLC post EGFR inhibitor	Wu-Kong1, 2 & 15	ORR 27% (10/37), including in 5/25 patients who failed 3rd-gen TKI like Tagrisso
BLU-945	Blueprint	EGFR activating muts, NSCLC post Tagrisso	Symphony	ORR 4% (2/44), 22% gr≥3 ALT elevation
BLU-945 (Tagrisso combo)		EGFR activating muts, NSCLC refractory to Tagrisso		ORR 10% (4/41)
AZD3759 (zorifertinib)	Alpha Biopharma (ex Astrazeneca)	EGFR activating muts, 1L NSCLC	Everest	ORR 69%, versus 58% for Iressa/ Tarceva
Source: Asco.				

While Wu-Kong6 is a Chinese study, part B of a phase 1/2 trial called Wu-Kong1 is international, and should yield data later this year. This, Zhang says, will back sunvozertinib's US and Europe filings, with Dizal then leaving commercialisation to a partner.

Zhang says he has had lots of interest already, and it is easy to see why. Interestingly, Astra does not have first-refusal rights, and the chief exec says there is no special advantage to seeking a deal with his former employer: "My only criterion is to maximise the benefit to our shareholders."