Evaluate Vantage

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Asco 2021 – the exon 20 army lines up behind Rybrevant

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A new lung cancer niche is a major focus of Asco, with China's Dizal perhaps boasting the most intriguing dataset.

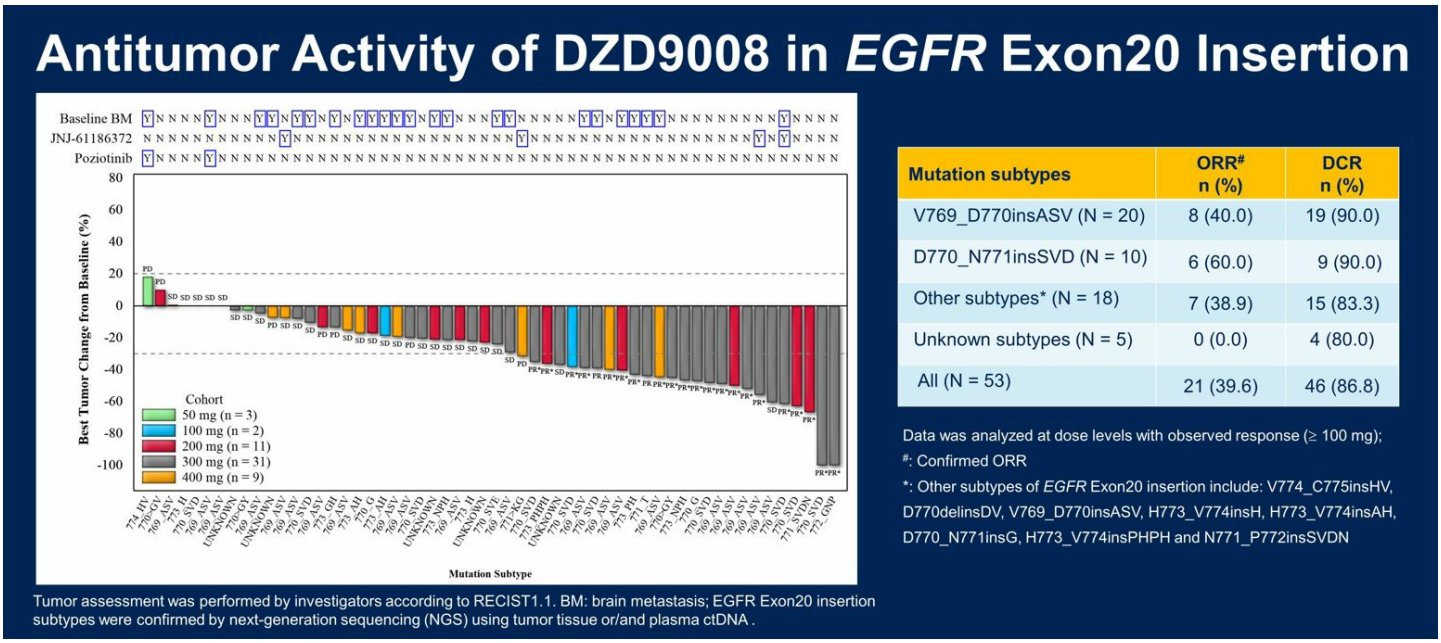
The approval last month of Johnson & Johnson's Rybrevant was an historic moment for treating EGFR exon 20 insertion-mutated lung cancer, but the company will probably not have this space to itself for long.

Next in line is Takeda's mobocertinib, whose US regulatory filing faces an October 26 action date, and which unlike Rybrevant is a small molecule. This weekend's Asco meeting saw much clinical data from companies also seeking to target this genetic niche, thought to account for 2-4% of NSCLC tumours – but mobocertinib's were not the most impressive.

DZD9008 (Dizal)

That honour is shared between Cullinan and a virtually unknown private Chinese company, Dizal Pharmaceuticals, which revealed its targeted small molecule DZD9008. Dizal's presentation concerned pooled data from two studies, one Chinese and the other global, and the headline number was a 40% ORR among 53 subjects with EGFR exon 20 insertions.

This was especially impressive given the late-line nature of subjects' disease, and the fact that two of four patients who had relapsed on Rybrevant experienced remission. There were no responses among two patients who had failed Spectrum's poziotinib.



Source: Dr James Chin-Hsin Yang & Asco.

Also noteworthy was the 5% rate of DZD9008-related diarrhoea at grade 3 or above, which is in line with Rybrevant's 3%, and well below the 21% seen in a separate study of Takeda's mobocertinib.

Mobocertinib (Takeda)

This study was the complex phase 1/2 trial that Takeda has taken to the US FDA. Its post-chemo EGFR exon 20 insertion cohort yielded data at the World Lung conference in February, and Takeda's Asco update included the same 114 patients, with ORR of 28% by independent review (35% by investigator assessment) at a November 1, 2020 data cutoff.

BDTX-189 (Black Diamond)

Diarrhoea is also apparently troubling Black Diamond's small molecule BDTX-189, with phase 1 data at Asco showing rates of about 10% grade 3 or above, rising to 33% at the highest dose, in addition to liver enzyme elevation. The very early results show one partial remission in an EGFR mutant, out of six evaluable heavily pretreated EGFR or Her2 exon 20 insertion-positive subjects.

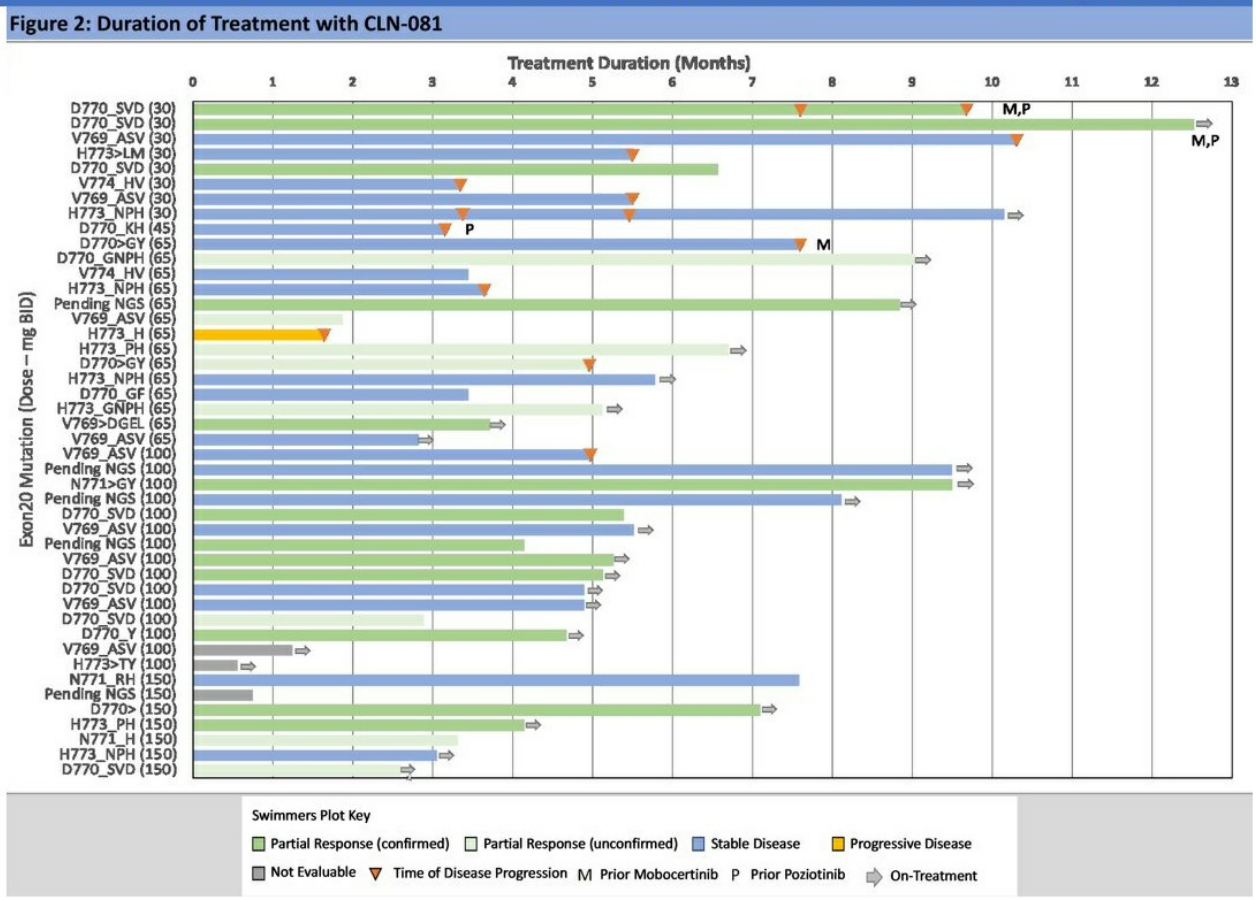
CLN-081 (Cullinan)

Her2 and EGFR are related, an indeed EGFR is sometimes called Her1, but they do represent distinct driver mutations. One small molecule believed to work only with EGFR exon 20 insertion, and not with Her2 exon 20 mutants (or indeed EGFR wild-type NSCLC), is Cullinan's CLN-081, said to be built on a unique pyrrolopyrimidine scaffold.

Its first-in-human study now comprises 42 evaluable subjects, at an April 1 cutoff, and its Asco presentation revealed an impressive 21 partial responses across all dose levels, including a 54% ORR at 100mg twice daily, the dose for phase 2 expansion.

Cullinan also said two of the longest remissions concerned patients who had failed both mobocertinib and poziotinib; two other subjects, one post poziotinib and one post mobocertinib, did not experience remission.

activity of CLN-081 in NSCLC with EGFR Exon 20 insertion mutations (Ins20)



Source: Dr Zofia Piotrowska & Asco.

J&J also presented Rybrevant data at Asco, though this concerned a separate NSCLC niche, EGFR exon 19 deletion/exon 21 L858R patients resistant to Astrazeneca's Tagrisso in a separate cohort of its registrational Chrysalis trial.

This was noteworthy not only for the 36% ORR in patients with a range of downstream mutations, but also for the fact that Rybrevant here was being combined with J&J's small molecule lazertinib. A Rybrevant/lazertinib combo represents J&J's push into the front-line setting, courtesy of the separate Mariposa study.

Meanwhile, Spectrum's poziotinib had a low-key Asco presence focused on patients with brain metastases, but after the group's setback in the EGFR setting poziotinib's regulatory filing this year will be in Her2 exon 20 insertions.

Poziotinib thus represents one of the disappointments in the EGFR exon 20 space, but other projects look set to challenge Rybrevant sooner rather than later.

Selected EGFR exon 20 insertion NSCLC projects with data at Asco 2021			
Project	**Company**	**Trial**	**Summary of Asco data**
Rybrevant	Johnson & Johnson	Chrysalis	mPFS 8.3mth, mOS 22.8mth (vs 2.9mth & 12.8mth for separate "real-world" cohort); main Asco presentation was on lazertinib combo in exon 19 Tagrisso failures
DZD9008	Dizal Pharma	Wu-Kong-1 & 2	40% confirmed ORR in 53 pts; 2/4 PRs in post Rybrevant pts; 0/2 PRs in post poziotinib pts; 5% drug-related diarrhoea
CLN-081	Cullinan	NCT04036682	50% ORR (8 PRs unconfirmed/pending confirmation) in 42 EGFR exon 20 patients; 2/4 PRs in mobo/pozio failures
Mobocertinib	Takeda	NCT02716116	28% confirmed ORR (35% unconfirmed) in 114 pts post platinum chemo; mPFS 7.3mth; mOS 24.0mth; 21% treatment-related diarrhoea
BDTX-189	Black Diamond	Masterkey-01	1/3 unconfirmed PR at ≥800mg QD (patient had relapsed on poziotinib); activity separately seen in Her2-amplified NSCLC; evidence of grade 3 diarrhoea
Poziotinib	Spectrum	Zenith20	22% ORR among Her2 & EGFR exon 20 ins cohorts with CNS disease (n=36); US filing to focus on Her2 exon 20
Source: Asco.			