Evaluate Vantage

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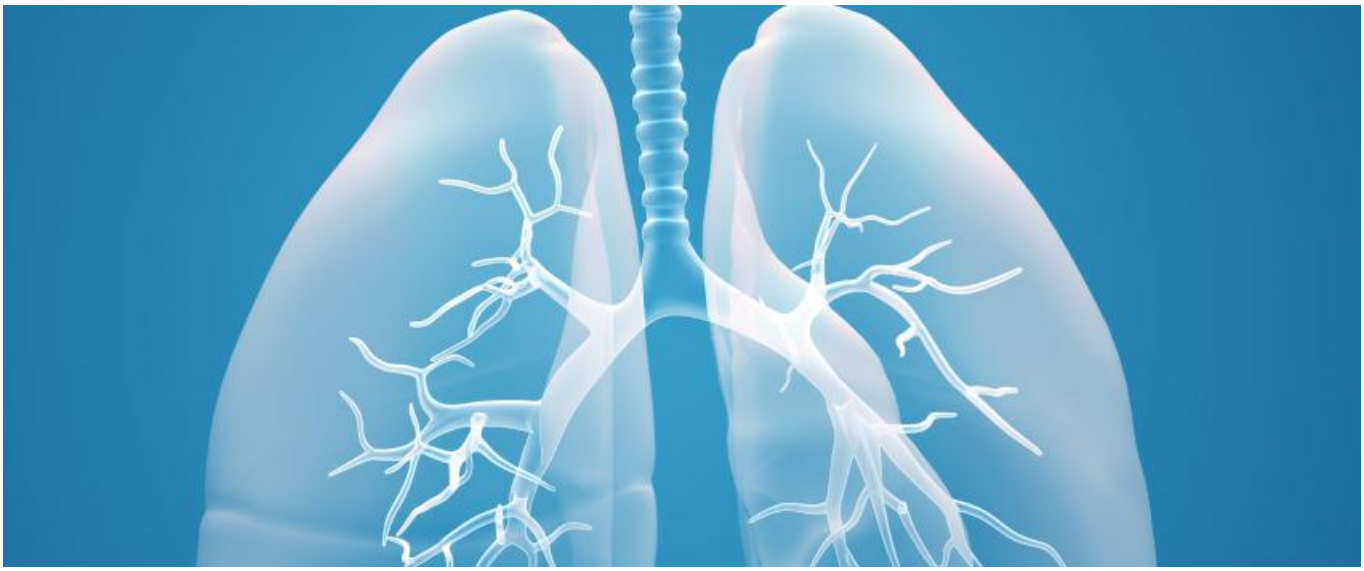
AACR 2019 – Chi-Med has savolitinib filing in its sights

Jacob Plieth



A patient death notwithstanding, Chi-Med reckons results from the Tatton study justify its US registration strategy.

Hutchison China Meditech reckons savolitinib could become the first selective cMet inhibitor to be approved. Investors were thus focused on today's AACR presentation of complete data from savolitinib's Tatton trial in lung cancer – its biggest potential use.

On the efficacy side there will be relief, as remission rates are broadly in line with the last Tatton data cut, 18 months ago, but now with many more patients. The big question mark is safety: investigators said there was toxicity, causing some discontinuations, and one death due to acute kidney injury was deemed possibly related to savolitinib.

Christian Hogg, Chi-Med's chief executive, told *Vantage* that Tatton included very frail patients, some of whom had failed multiple lines of chemotherapy, adding: "In all clinical trials of late-stage cancer patients you're going to have deaths. From these exploratory studies you learn about your patients."

Identifying patients

Tatton was exploratory because it aimed to identify amenable NSCLC patient populations. The AACR focus was on its two most market-relevant cohorts, testing the Astrazeneca-partnered savolitinib plus Astra's Tagrisso in subjects who had failed first or second-generation EGFR inhibitors, and in those who had failed Tagrisso or similar third-generation drugs.

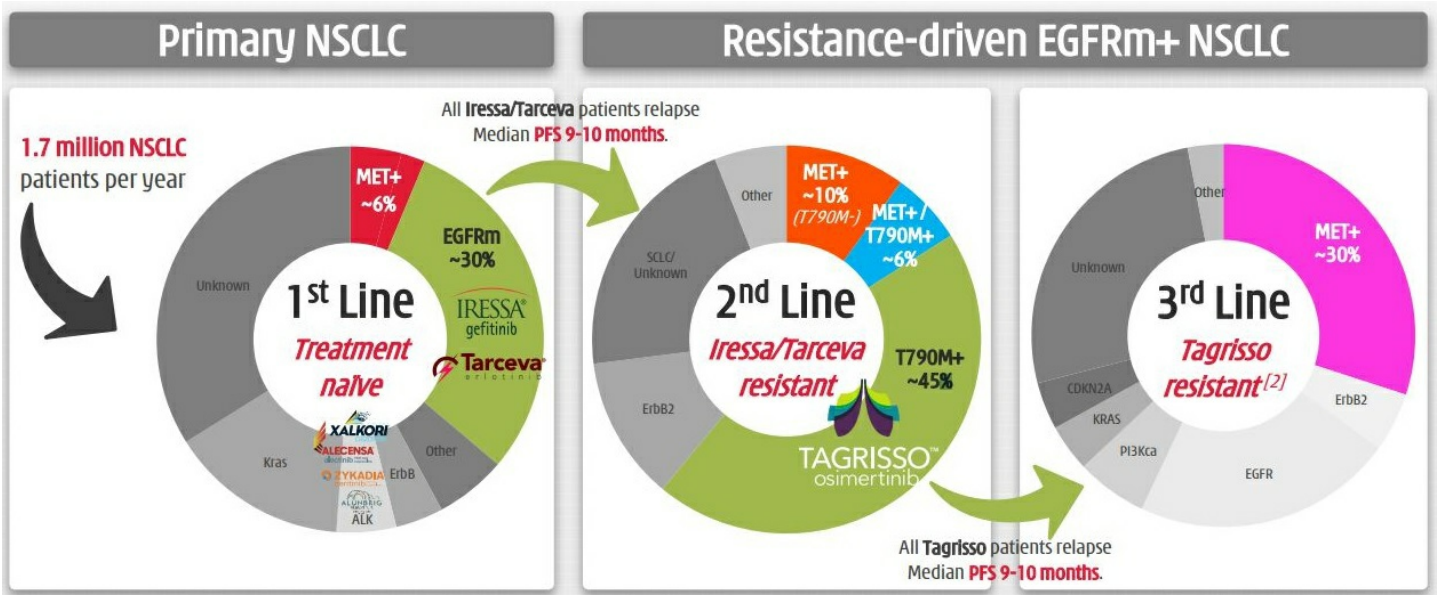
Similar but not identical patient groups are being studied in Savannah, a more tightly controlled phase II study that should yield response data in early 2021. This, Mr Hogg hopes, will provide a dataset that can be filed for accelerated approval.

The efficacy numbers from Tatton are promising: subjects in the two cohorts had overall remission rates of 52% and 28% respectively. Tatton's earlier data cut, presented at World Lung in 2017, showed respective 61% and 33% remission rates, but Mr Hogg stressed that these included patients whose genetic status – all had to have cMet-positive tumours – had not been confirmed by central review.

Savolitinib + Tagrisso NSCLC data from the Tatton study					
		Efficacy			
Setting	**Genetic status**	**WCLC 2017***	**WCLC 2017 (confirmed)**	**AACR 2019 (confirmed)**	**Note**
Post Iressa or Tarceva	cMet+ve, T790M-ve	14/23 PRs, ORR 61%	8/15 PRs, ORR 53%	24/46 PRs, ORR 52%	2 deaths, 1 possibly savolitinib related
Post Tagrisso (or similar 3rd-gen TKI)	cMet+ve	10/33 PRs, ORR 33%	7/25 PRs, ORR 28%	12/43 PRs, ORR 28%	2 deaths, both unrelated
*Note: PRs=partial responses; ORR=overall remission rate; *includes subjects whose cMet status had not been centrally confirmed.*					

On a like-for-like basis the final results are in line with those presented in 2017. And Mr Hogg highlighted the duration of response data, which can approximate to progression-free survival, and which amounted to 7.1 and 9.7 months in the respective Tatton cohorts.

The two relevant settings approximate to second or third-line targeted uses. Median PFS amounts to 18-19 months with Tagrisso, either first line, or second line including the benefit of Iressa or Tarceva; Mr Hogg called the 9.7-month duration of response in Tagrisso failures “uncharted territory”.



Source: Chi-Med presentation.

The basis for treating patients with cMet-driven cancers is that EGFR targeting often causes tumours to escape via the T790M resistance mutation, and cMet amplification can be a subsequent resistance mechanism. It is also possible, though rare, for an untreated tumour to be cMet-driven, for instance through cMet exon 14 deletion, and in this case the EGFR pathway is not activated.

This is why savolitinib is also being studied as monotherapy in NSCLC subjects with *de novo* cMet exon 14 deletions, and along with other settings this is also a focus for the project’s two closest competitors: Novartis/Incyte’s capmatinib and Merck KGaA’s tepotinib.

To have a shot at being first to market Chi-Med will depend on Savannah matching the responses seen in Tatton, and on toxicity being manageable, though on the latter point Mr Hogg remains confident, stating: “If there was a big concern on the safety side we wouldn’t have started a global registrational study.”

Selected other studies of cMet inhibitors			
Trial	**Setting**	**Genetic status**	**Treatment**
Novartis/Incyte			
NCT02335944	No restriction	cMet+ve, EGFR+ve	Capmatinib + EGF816
NCT02468661	Post 1st/2nd-gen TKI	cMet+ve, EGFR+ve	Capmatinib +/- Tarceva
NCT02414139	No restriction	cMet exon 14 del, EGFR-ve	Capmatinib monotherapy
NCT02750215	Post Met inhibitor	cMet exon 14 alt, EGFR-ve	Capmatinib monotherapy
NCT03693339	No restriction	cMet exon 14 alt	Capmatinib monotherapy
Merck KGaA			
Insight (NCT01982955)	Post Iressa or Tarceva	cMet+ve, T790M-ve	Tepotinib + Iressa
Vision (NCT02864992)	No restriction	cMet+ve/exon 14 alt	Tepotinib monotherapy
Chi-Med/Astrazeneca			
Savannah (NCT03778229)	Post 1st or 2nd-line Tagrisso	cMet+ve, T790M+/-ve	Savolitinib + Tagrisso
NCT02897479	No restriction	cMet exon 14 del	Savolitinib monotherapy