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June 04, 2019

Asco 2019 – tepotinib and capmatinib fight over a new lung cancer niche

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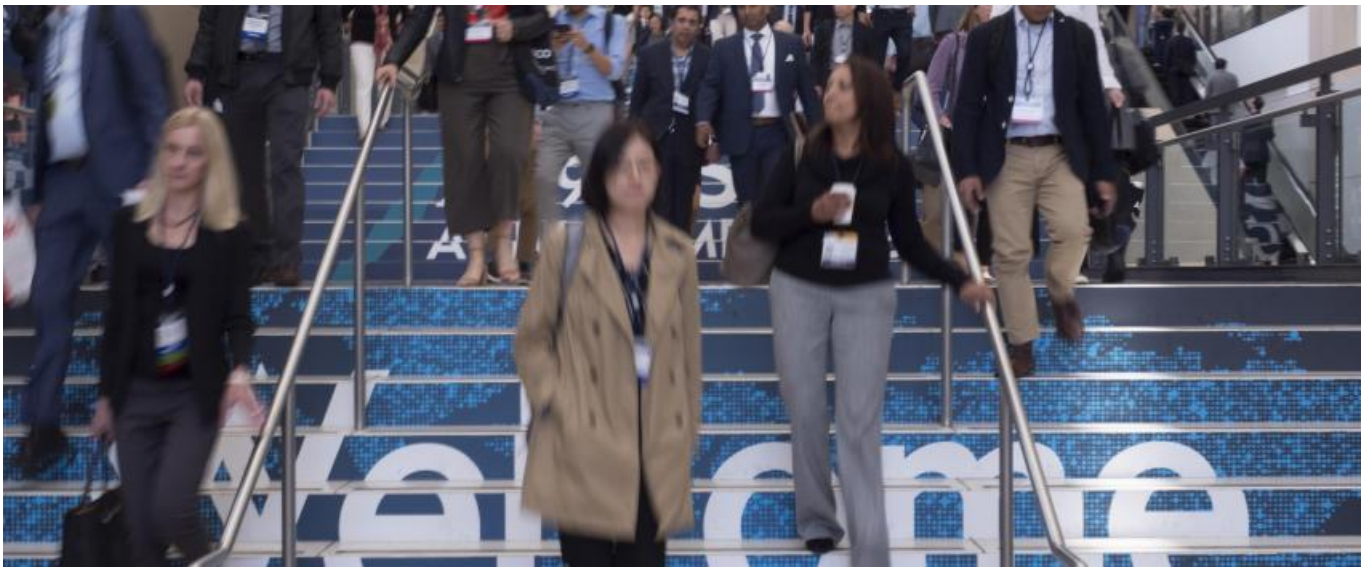

cMet emerges as the latest genetic mutation that could soon see targeted treatments become available.

Targeted therapy has revolutionised the treatment of lung cancers with known genetic mutations such as EGFR, ALK and Ros. Judging by data presented at Asco the segmentation of this disease is set to continue, with cMet emerging as the next mutation to watch.

Yesterday two duelling cMet inhibitors, Merck KGaA's tepotinib and Incyte/Novartis's capmatinib, squared off, and showed clearly that patients with this mutation could soon see an efficacious treatment. What remains to be ironed out is which project is safer and/or most potent, and how precisely a cMet mutation should be diagnosed.

It must also be remembered that cMet can be implicated in at least two different settings. In 3-5% of NSCLC tumours a cMet variant known as exon 14 deletion can be the cancer's primary driver. In later NSCLC treatment cMet amplification can develop as a resistance mechanism to an inhibitor of EGFR.

It was the first of these that concerned tepotinib and capmatinib's Asco datasets, respectively from the Vision and Geometry mono-1 trials. The issue was further complicated by the fact that some NSCLC subjects in both trials were first line, while others had failed one or two rounds of chemotherapy.

For reasons that are not entirely clear, first-line treatment of an exon 14 deleted NSCLC tumour with a cMet inhibitor yielded the highest overall response rates – 59% and 68% were seen with tepotinib and capmatinib respectively – though in later lines the rates were only slightly less impressive.

	Capmatinib (Incyte/Novartis)		Tepotinib (Merck KGaA)	
	Geometry mono-1 study		Vision study	
	1st line	2nd/3rd line	1st line	2nd/3rd line
Patients evaluable	28	69	17	31
Mutation	cMet exon 14 del (by tissue biopsy)		cMet exon 14 del (by liquid biopsy)	
ORR	19 (68%)	28 (41%)	10 (59%)	14 (45%)
Median response duration	11.4mth	9.72mth	Not disclosed	12.4mth
Grade 4 adverse events	4.5%		0.0%	
Treatment-related disc.	11.4%		4.6%	
Source: Asco.				

The Merck project emerged as the more tolerable. And the two are neck and neck in development: Incyte recently said it expected capmatinib to be filed in the US by the end of 2019, while Merck pointedly referred to Vision as a "potentially registrational" study.

One key difference is the way cMet exon 14 deletion is detected – a vital consideration. Both groups used traditional biopsy to sequence prospective patients' tumour samples, but Merck also enrolled NSCLC subjects who had tested positive using a proprietary liquid biopsy.

"This is the future of precision medicine," Merck's head of R&D, Luciano Rossetti, told *Vantage* of the liquid biopsy approach. "We are the very first to do this."

This gave Vision an added level of complexity, however: 87 subjects comprised the total dataset (around 1,000 had been screened), with 48 and 51 testing positive for exon 14 deletion by liquid and tissue biopsy respectively, implying that 12 had been identified using both methods.

EGFR and beyond

All this shows the extent to which a knowledge of genetics, in addition to an understanding of immunology, is needed to appreciate the way cancer is increasingly being treated.

Asco also heard of promise in a separate EGFR-mutant NSCLC use – exon 20 insertion – where current anti-EGFR tyrosine kinase inhibitors like Iressa, Tarceva and Tagrisso tend not to work. Here, Takeda's phase I asset TAK-788 put 12 of 28 subjects, some of whom had failed immunotherapy, into partial remission, said Memorial Sloan Kettering's Dr Gregory Riely.

However, there was a 14% rate of treatment-related discontinuations. TAK-788 is an inhibitor of EGFR and Her2; not long ago the clinical development landscape for exon 20 insertion mutations was a desert, but now includes Spectrum's poziotinib and Rain Therapeutics' tarloxotinib, in addition to TAK-788.

The cMet inhibitors, meanwhile, have a potential use beyond *de novo* exon 14 deletion: patients who have failed Iressa, Tarceva or Tagrisso. This represents a later-stage focus for the developers of tepotinib and capmatinib, via the projects' respective combination studies Insight and Geometry duo-1.

Mr Rossetti said he viewed capmatinib as tepotinib's most relevant competitor in the setting of the Vision trial, but that in post-EGFR inhibitor use its opposite number was Chi-Med/Astrazeneca's savolitinib, which has shown promise in the Tatton trial (*AACR 2019 – Chi-Med has savolitinib filing in its sights, March 31, 2019*).

If nothing else this demonstrates how complex targeted NSCLC treatment is becoming. It is not about to get any less complicated.

NSCLC therapy landscape for selected small-molecule targeted treatments			
	Line of targeted therapy/mutation		
Drug (company)	**1st line**	**2nd line**	**Note**
Approved			
Tarceva (Roche)	EGFR+	EGFR+	Approved broadly; EGFR testing advised
Iressa (Astrazeneca)	EGFR+		Exon 19 deletion or exon 21 substitution
Gilotrif (Boehringer Ingelheim)	EGFR+		Broad EGFR+ label
Tagrisso (Astrazeneca)	EGFR+	T790M+	T790M+ use is post EGFR TKI therapy
Vizimpro (Pfizer)	EGFR+		Exon 19 deletion or exon 21 substitution
Investigational			
Tepotinib (Merck KGaA)	cMet+	cMet+	Exon 14 deletion or post EGFR TKI therapy
Capmatinib (Incyte/Novartis)	cMet+	cMet+	Exon 14 deletion or post EGFR TKI therapy
Savolitinib (Chi-Med/Astrazeneca)	cMet+	cMet+	Post EGFR TKI therapy or exon 14 deletion
Cyramza (Lilly) + Tarceva	EGFR+		Exon 19 deletion or exon 21 substitution
Poziotinib (Spectrum)	EGFR+		Exon 20 insertion
TAK-788 (Takeda/Ariad)	EGFR+		Exon 20 insertion
Tarloxotinib (Rain Therapeutics)	EGFR+		Exon 20 insertion
TAS6417 (Otsuka)	EGFR+		Exon 20 insertion
BLU-667 (Blueprint)		Ret+	Post EGFR TKI therapy
LOXO-292 (Lilly, ex Loxo)		Ret+	Post EGFR TKI therapy
SL-1001 (Stemline)		Ret+	Licensed from Cancer Research UK