Evaluate Vantage

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Asco 2020 – first-line lung cancer focus

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The upcoming cancer meeting shows Roche and Bristol trying to catch up with Merck & Co, with some read-across to biotech.

Last night's Asco abstract dump has revealed several results of interest to companies pursuing first-line non-small cell lung cancer. The keenly awaited Cityscape trial of the anti-Tigit MAb tiragolumab, for instance, shows why Roche is investing heavily in the project, though its real-world relevance seems marginal.

For Roche the most important thing is to find a way of catching up with Merck & Co's Keytruda – a similar consideration to Bristol-Myers Squibb, which has unveiled its Checkmate-9LA study, meant to support approval of Opdivo plus Yervoy and chemo. And Merck could do some catching up of its own: a study in stage III NSCLC shows that Keytruda could have Astrazeneca's Imfinzi in its sights.

Tigit became a closely watched immuno-oncology target after Roche began a wide-ranging clinical programme with tiragolumab this year, but until Asco data supporting it had been scant. Cityscape is only a phase II trial, but it has a robust design: tiragolumab plus Tecentriq versus Tecentriq alone.

The good news for Roche is that addition of Tigit blockade to PD-L1 shows an additive effect in terms of response rates and median progression-free survival. The bad is that this is strongly driven by the highest (≥50%) PD-L1 expressers, and the combo numbers only look good because Tecentriq alone performs particularly badly.

The first point is particularly relevant, as it is PD-L1-low subjects where the efficacy of PD-(L)1 blockade is in need of boosting. Yet Tigit blockade appears to add nothing, providing a clue to why Cityscape enrolled ≥1% PD-L1 expressers, and why Roche's phase III Tigit trial, Skyscraper-01, enrols ≥50% subjects.

On the plus side Tigit blockade appears to add no toxicity. But in and of itself a Tecentriq plus tiragolumab combo looks no better than Keytruda in its already approved first-line NSCLC use; Arcus, a biotech Tigit player that has traded up strongly in tandem with Roche's Tigit plans, opened off 11% this morning.

Cross-trial comparisons: Roche's Tigit data in context			
		Overall remission rate	
Study/subgroup	**Combo agent**	**Tecentriq combo**	**Tecentriq monotherapy**
Cityscape ITT (PD-L1 ≥1%)	*Tiragolumab*	*31.3%*	*16.2%*
Cityscape (PD-L1 ≥50%)	*Tiragolumab*	*55.2%*	*17.2%*
Cityscape (PD-L1 1-49%)	*Tiragolumab*	*13.2%*	*15.4%*
Birch (1L, PD-L1 ≥50%)	(none)	–	20.0%
Fir (1L, PD-L1 ≥50%)	(none)	–	43.0%
Impower-150 (all-comers)	Avastin + chemo	55.0%	–
Impower-150 (PD-L1 ≥50%)	Avastin + chemo	69.0%	–
Impower-130 (all-comers)	Abraxane	46.0%	–
		Keytruda combo	**Keytruda monotherapy**
Keynote-024 ITT (PD-L1 ≥50%)	(none)	–	45.0%
Keynote-189 (all-comers)	Chemo	48.0%	–
Source: Asco, company releases & product labels.			

In Bristol's case, Opdivo is due a double US FDA verdict on use in 1st-line NSCLC, first, by tomorrow, as a Yervoy combo based on the controversially overhauled Checkmate-227 trial, and then by August 6 on the basis of Checkmate-9LA, a study combining Opdivo with Yervoy and chemotherapy.

The Asco abstract reveals the first efficacy data from this second trial since it was said to have succeeded last October in improving overall survival. Indeed, the triple combo reduced risk of death by 31% versus chemo alone (p=0.0006), an interim analysis reveals; longer follow-up shows an improving picture, with median OS of 15.6 versus 10.9 months, and a 0.66 hazard ratio.

This looks promising for approval, but like Roche's Tigit it hardly challenges Keytruda, whose chemo combo study Keynote-189 yielded a 51% reduction in risk of death versus chemo alone. And the toxicity burden is considerable: in Checkmate-9LA 47% of patients on the combo experienced grade 3 and 4 toxicities, versus 38% for control.

Stage III

A separate NSCLC setting is pre-metastatic, stage III disease, where Astra's Imfinzi is carving out a niche thanks to approval based on its Pacific trial, notwithstanding doubts about its benefit in PD-L1 non-expressers.

The threat of other checkpoint blockers here has been looming, and Asco reveals the first data from Merck's Keynote-799 trial, in which a Keytruda regimen yielded a 56.6% remission rate, and six-month OS of 94.8%.

In Pacific Imfinzi showed a six-month OS of about 92% and ORR of 28.4%. But the important point is that in Keynote-799 Keytruda was given with chemoradiation, whereas Pacific enrolled subjects who had already been given chemoradiation and had not progressed; thus, the potential is for Keytruda to establish a niche in a setting before that in which Imfinzi is approved.

Keytruda already has a first-line stage III NSCLC label, courtesy of the Keynote-042 trial, but only in PD-L1 ≥1% patients who are not candidates for chemoradiation.

Of course, Keynote-799 is an uncontrolled study, and as with the Cityscape and Checkmate-9LA analyses the comparisons are across different studies that possibly recruited differing patient populations. But no doubt the data will be scrutinised further once Asco beings.

Study	Active cohort	Trial ID	Asco abstract
Cityscape	Tiragolumab + Tecentriq in 1L NSCLC	NCT03563716	9503
Checkmate-9LA	Opdivo + Yervoy + chemo in 1L NSCLC	NCT03215706	9501
Checkmate-227 cohort 1	Opdivo + Yervoy in 1L NSCLC	NCT02477826	9500
Keynote-799	Keytruda in 1L stage III NSCLC	NCT03631784	9008

The Asco virtual conference takes place on May 29-31.