Evaluate Vantage

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World Lung 2021 – front-line competition lines up behind Keytruda

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Cstone/EQRX and Shanghai Junshi/Coherus might have approvable anti-PD-(L)1 projects, but can Keytruda be challenged on price?

When it comes to combining immuno-oncology drugs with chemotherapy in front-line lung cancer doctors are spoilt for choice. Yesterday the IASLC World Conference on Lung Cancer featured two more me-too anti-PD-(L)1/chemo combos, from Chinese groups that could soon challenge the US dominance of Merck & Co's Keytruda.

With caveats the data, for Cstone's sugemalimab and Shanghai Junshi's toripalimab, looked comparable to Keytruda, with sugemalimab coming out on top on a cross-trial basis. All that remains now is for the two projects' US licensees, EQRX and Coherus, to seek approval and challenge the Merck drug on price.

Though EQRX and Coherus have both expressed a desire to pursue discounting in the US, complex and opaque existing payer arrangements mean that this is more easily said than done. And whether the FDA would accept as a basis for US approval trials run mostly in China, as these two were, is a question yet to be answered.

Choice

Toripalimab's first-line NSCLC chemo combo trial Choice-01 had been toplined positive for PFS last month, and the World Lung presentation added an immature OS analysis to this.

However, no breakdown was provided by PD-L1 expression – a vital consideration in a scenario where PD-L1-positives might be driving most of the survival benefit. Moreover, on a cross-trial basis the absolute PFS and OS benefits, and hazard ratios, looked less impressive than Keytruda's Keynote-189 and 407 studies.

Presenting the Choice-01 data, Dr Jie Wang, from the Chinese Academy of Medical Sciences, said placebo recipients who progressed could cross over to active checkpoint blockade, perhaps confounding the OS readout. Nevertheless, the Merck studies, as well as Cstone's rival Gemstone-302 dataset presented at World Lung, also allowed such crossover.

And Choice-01 included stage IIIB NSCLC too, while rival trials stuck to relatively more advanced stage IV patients.

Other than this, Cstone's Gemstone-302 had a similar design to Choice-01, comparing front-line sugemalimab plus chemo against chemo alone. Sugemalimab's separate Gemstone-301 study, in stage III patients, was toplined positive in May and has a late-breaker at Esmo this weekend.

Cross-trial comparison of World Lung first-line NSCLC data						
			mOS		**mPFS**	
Study	**Company**	**Design**	**PD-(L)1+chemo**	**Chemo**	**PD-(L)1+chemo**	**Chemo**
Choice-01*	Shanghai Junshi/Coherus	Toripalimab + chemo vs chemo (all-comers)	21.0mth	16.0mth	8.3mth	5.6mth
			HR=0.81 (immature)**		HR=0.58 (p=0.0001)	
Gemstone-302	Cstone/EQRX	Sugemalimab + chemo vs chemo (all-comers)	22.8mth	17.7mth	9.0mth	4.9mth
			HR=0.67 (immature)		HR=0.48 (p<0.0001)	
		Sugemalimab + chemo vs chemo (PD-L1 ≥1%)	NR	19.8mth	10.9mth	4.9mth
		Sugemalimab + chemo vs chemo (PD-L1 <1%)	19.4mth	14.8mth	7.4mth	4.9mth
			Not given**		HR=0.55	
*Note: *included stage IIIB as well as stage IV (Gemstone-302 was stage IV only); **confidence interval's upper bound >1.00. Source: World Lung 2021.*						

Significant detail was given at World Lung regarding Gemstone-302’s benefit in biomarker and histology-defined subgroups, and in general Cstone’s data looked better than Junshi’s and competitive against Keytruda. Not only that, but sugemalimab plus chemo looked active even in PD-L1 non-expressers, at least numerically, in PFS as well as OS terms.

Sugemalimab is not approved anywhere. Toripalimab is available in China and a rolling US filing was initiated in March, though in neither case do the indications include NSCLC.

One curiosity about Gemstone-302 was that the survival benefit favouring sugemalimab appeared to be much stronger in squamous than in non-squamous patients. The former represents the more aggressive NSCLC histology, and in Choice-01 the hazard ratios for PFS were very similar for squames and non-squames.

Cross-trial comparison of World Lung data vs established drugs across histologies						
			mOS		**mPFS**	
Study	**Company**	**Design**	**PD-(L)1+chemo**	**Chemo**	**PD-(L)1+chemo**	**Chemo**
Keynote-407	Merck & Co	Keytruda + chemo vs chemo (squam)	15.9mth	11.3mth	6.4mth	4.8mth
			HR=0.64 (p=0.0017)		HR=0.56 (p<0.0001)	
Gemstone-302	Cstone/EQRX	Sugemalimab + chemo vs chemo (squam)	23.3mth	12.2mth	8.3mth	4.8mth
			Not given		HR=0.34	
Choice-01*	Shanghai Junshi/Coherus	Toripalimab + chemo vs chemo (squam)	Not given		HR=0.55	
Keynote-189	Merck & Co	Keytruda + chemo vs chemo (non-squam)	NR	11.3mth	8.8mth	4.9mth
			HR=0.49 (p<0.0001)		HR=0.52 (p<0.0001)	
Impower-130	Roche	Tecentriq + chemo vs chemo (non-squam)	18.6mth	13.9mth	7.2mth	6.5mth
			HR=0.80 (p=0.0384)		HR=0.75 (p=0.0024)	
Gemstone-302	Cstone/EQRX	Sugemalimab + chemo vs chemo (non-squam)	22.8mth	20.8mth	9.6mth	5.9mth
			Not given**		HR=0.59	
Choice-01*	Shanghai Junshi/Coherus	Toripalimab + chemo vs chemo (non-squam)	Not given		HR=0.59	

*Note: *included stage IIIB as well as stage IV (all others stage IV only); **confidence interval's upper bound >1.00. Source: World Lung 2021 & product labels.*

The datasets will also be held up against Astrazeneca's Poseidon study of Imfinzi plus chemo, with or without tremelimumab, which also looks approvable and was presented at a World Lung presidential session last week.

Discussing Choice-01 and Gemstone-302, Dr Keunchil Park, of Samsung Medical Center, said both supported new treatment options for first-line metastatic NSCLC.

But he also pointed out that there was already plenty of choice in terms of anti-PD-(L)1/chemo combos, citing no fewer than 15 controlled studies of various such treatments that have been shown to reduce risk of progression.

A perusal of drug approvals reveals seven anti-PD-(L)1 drugs already available in the US, and nine in China. Of these, four and five respectively have first-line NSCLC labels. Who will be first to throw down the pricing gauntlet?

Plenty of first-line PD-(L)1+chemo combo: HR of PFS

Non-Squamous HR of PFS	Non-Squamous & Squamous HR of PFS	Squamous HR of PFS
KEYNOTE-189 0.49	CheckMate 9LA 0.70	KEYNOTE-407 0.59
IMpower150 0.59		IMpower131 0.71
IMpower130 0.64		
IMpower132 0.60		
CameL (Camrelizumab) 0.60		CameL-sq 0.37
ORIENT-11 (Sintilimab) 0.48	GEMSTONE-302 (Sugemalimab) 0.48	
ORIENT-12 0.54	CHOICE-01 (Toripalimab) 0.58	
RATIONALE-304 (Tislelizumab) 0.64		RATIONALE-307 0.53/0.48
GEMSTONE-302 (Sugemalimab) 0.59		GEMSTONE-302 (Sugemalimab) 0.34

Source: Dr Keunchil Park & IASLC.

Remember to download for free the recent Evaluate Vantage update on developments in the PD-(L)1 inhibitor space.