

World Lung 2021 - treme stands up to scrutiny



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Full data from the Poseidon study confirm the anti-CTLA-4 MAb's activity; with three chemo combos established, however, will it be enough?

Full data from AstraZeneca's Poseidon study have confirmed the surprising positive effect of adding tremelimumab to Imfinzi and chemo in front-line non-small cell lung cancer, a presidential session of the IASLC World Conference on Lung Cancer meeting has heard.

Despite treme's dismal clinical history it is difficult to pick holes in the data, and the full results show two patient groups appearing to derive an especially strong benefit from the anti-CTLA-4 MAb. Still, on a cross-trial basis Poseidon will be unlikely to give doctors a reason to prescribe the Astra combo in preference to Merck & Co's, Roche's or Bristol Myers Squibb's incumbents.

Nevertheless, Astra has said it wants to file with regulators on the basis of Poseidon in the second half of this year. Imfinzi is already established in stage III NSCLC, but securing a front-line metastatic NSCLC label would be a first; treme is not approved in any indication.

Poseidon was [toplined as positive last October for PFS](#), a measure that favoured Imfinzi/treme/chemo as well as just Imfinzi plus chemo, and then [in May for OS, this time favouring only the treme-containing triple](#). Poseidon's primary survival endpoints concerned only the Imfinzi/chemo doublet, but even after this failed for mOS sufficient statistical power remained to confirm the triple's OS benefit, a secondary endpoint.

Good news

At World Lung today Dr Melissa Johnson of the Sarah Cannon Research Institute revealed numerical increases in median PFS and OS as first Imfinzi and then treme are added to chemo. There was also good news on safety, as "most adverse events were driven by the chemotherapy", she stated; severe and serious adverse events were highest for the triple, but AE-related discontinuations were even throughout.

This is all very well in isolation, but if Poseidon leads to approval Astra will contend with three already available chemo combos in first-line NSCLC: Merck's Keytruda, Roche's Tecentriq and Bristol's Opdivo/Yervoy-containing triple.

This will lead to cross-trial comparisons, however unreliable these might be. Perhaps the most obvious is to weigh Poseidon against Bristol's Checkmate-9LA, which also concerned a PD-1/CTLA-4/chemo combination.

The comparison below makes it clear that Astra will have no obvious advantage, Poseidon showing the group's triple adding 1.4 and 2.3 months of median PFS and OS respectively to chemo alone, versus 1.8 and 3.4

months for the Bristol incumbent.

Cross-trial comparison of Poseidon and Checkmate-9LA					
	Poseidon			Checkmate-9LA	
	Imfinzi + treme + chemo	Imfinzi + chemo	Chemo	Opdivo + Yervoy + chemo	Chemo
N	338	338	337	361	358
mPFS	6.2 mth	5.5 mth	4.8 mth	6.8 mth	5.0 mth
PFS HR	0.72	0.74	-	0.70	-
PFS p value	0.00031	0.00093	-	0.0001	-
mOS	14.0 mth	13.3 mth	11.7 mth	14.1 mth	10.7 mth
OS HR	0.77	0.86	-	0.69	-
OS p value	0.00304*	0.07581**	-	0.0006	-

*Source: World Lung 2021 & Opdivo prescribing information. Note: *significant at 0.01 threshold; **not statistically significant.*

A particularly illuminating part of Dr Johnson's presentation concerned Poseidon's forest plot, which revealed two subgroups of patients who benefited especially strongly from the triple: PD-L1 negatives, in whom the dual combo had no survival benefit but the triple reduced risk of death by 30%, and those with non-squamous NSCLC histology.

Dr Johnson said the survival benefit was more pronounced in non-squamous versus squamous subjects, and in Poseidon risk of death in non-squames was cut by 30% for the triplet but only 18% for Imfinzi plus chemo. Thus one possibility is that the benefit in Poseidon of the triple versus the doublet was driven by PD-L1-negative and/or non-squamous patients.

Even so, further comparisons of different trials show that this might cut little ice with prescribers. Keytruda and Tecentriq both carry front-line NSCLC chemo combo labels on the basis of separate studies in subjects with non-squamous histology, Keynote-189 and Impower-130 respectively.

Again, on a cross-study basis, Poseidon's PFS and OS benefit is little to write home about. Treme looks approvable, but the incumbents have little to worry about.

Cross-trial comparison in 1st-line non-squamous NSCLC

		N	mPFS	PFS HR	mOS	OS HR
Poseidon (subset)	Imfinzi + treme + chemo	209	6.8 mth	0.66	17.2 mth	0.70
	Imfinzi + chemo	214	6.4 mth	0.77	14.8 mth	0.82
	Chemo	214	5.5 mth	-	13.1 mth	-
Keynote-189	Keytruda + chemo	410	8.8 mth	0.52	NR	0.49
	Chemo	206	4.9 mth	-	11.3 mth	-
Impower-130	Tecentriq + Abraxane	453	7.2 mth	0.75	18.6 mth	0.80
	Abraxane	228	6.5 mth	-	13.9 mth	-

Source: World Lung 2021 & prescribing information for Keytruda & Tecentriq.

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