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Asco 2018 – Small cell lung data underwhelm but big readouts approach

Amy Brown

The tough-to-treat lung cancer type featured in several Asco presentations.

Researchers have made great advances in non-small cell lung cancer in the past few years, but small cell disease has proven much harder to crack. Survival rates in the latter have not improved since the 1980s, though hopes are high that this might soon change – several pivotal tests of various immunotherapies in front-line disease should start to report later this year.

In later-stage patients, this year's Asco saw a handful of trials yield data, most notably Merck & Co's Keynote-158 and Abbvie's Trinity. However, they failed to impress the conference's official reviewer, Dr Apar Kishor Ganti of the University of Nebraska Medical Center, who concluded that the studies have merely added a couple more options to a long list of drugs that do not work very well in relapsed patients.

He did describe the Keytruda data in patients with high PD-L1 expression as encouraging, though he cautioned that patient numbers were small. Keynote-158 was a basket trial of several tumour types – the small cell lung cohort comprised 107 patients, most of whom were on their second line of therapy.

Dr Ganti's assessment of the Rova-T data from Trinity, which enrolled patients on their third to seventh line of therapy, was more damning. He concluded that responses were not much different from those seen with other targeted agents that have been tried and failed in this disease, and noted that in clinical practice very few DLL3-high patients are seen.

This was the population that the Trinity presenter focused on, and in which stronger responses were seen. Rova-T is an antibody-drug conjugate that targets DLL3, an antigen that is present in around 80% of small cell lung tumours. The DLL3 high population is thought to only account for around a third of these, however.

Relapsed small cell lung cancer – treatment responses by therapy		
	ORR (%)	**Median OS (months)**
Keynote-158 (Keytruda)		
All comers	19	9.1
PD-L1 positive (n=42)	36	14.9
PD-L1 negative (n=50)	6	5.9
Trinity (Rova-T)		
All comers (n=339)	12	5.6
DLL3 high (n=238)	14	5.7
Cytotoxic agents		
Topotecan	20-27	6-9
Amrubicin	30	7.5
Targeted agents		
Pazopanib	14	6
Sorafenib	6	6
Checkmate-032 (Opdivo + Yervoy)		
All comers	23	7.7
Source: Asco 2018 presentation.		

Still, even in DLL3-high patients responses were not markedly stronger, and the final data appear to have been even more disappointing than assumed, particularly on tolerability, which was very poor. The trial was already known to have failed, and even though the presentation struck a surprisingly optimistic tone, it seems highly unlikely that Rova-T is going anywhere.

“It seems unlikely in our view that Rova-T, or perhaps any variant of DLL3 antibody-drug conjugate medicine, will come to market, at least while the profile looks the way it did in Trinity,” Leerink analysts concluded today.

Two further phase III trials in front-line maintenance and a second-line setting are ongoing, though the chances of a different outcome are surely very low.

First-line combos

Merck too must hope for a stronger signal in its ongoing phase III study in first-line disease, Keynote-604, from which results could emerge next year. The trial is testing Keytruda in combination with chemotherapy, so Merck will be hoping for a better response in PD-L1 low patients, where almost no activity was seen in ‘158, a monotherapy trial.

Bristol-Myers Squibb and Roche are slightly ahead in this earlier setting – both have studies that could read out in the coming months, though they have taken very different approaches with their trial design.

Roche could unveil the Impower-133 results any day now; this pits Tecentriq in combination with chemotherapy against chemo alone in newly diagnosed patients. Bristol, meanwhile, has taken the maintenance road with Checkmate-451, which should read out later this year and looks at the combination of Opdivo with Yervoy.

While small cell lung cancer is an aggressive disease, a high proportion of patients do respond initially to platinum doublet chemotherapy, which remains standard of care for front-line patients. However, progression occurs very quickly – typically within five to 15 months – and median survival in relapsed disease is only two to six months.

Nothing is specifically approved for patients deemed refractory. For those who respond and then relapse, the type of chemotherapy used second line depends on how quickly the cancer starts to grow again.

Pharmamar's second-line bet

Thus the second-line space in small cell is important for now, and this is where a small rival, Pharmamar, is hoping to make its mark. Its phase III Atlantic trial is expected to complete enrolment very soon – 600 patients are sought – and results could emerge next year. The study pits its new chemotherapy agent Zepsyre in combination with doxorubicin against platinum chemotherapies.

Presumably if the I-O trials above read out positively the opportunities in this setting could diminish, although Jose Antonio Lopez-Vilarino de Ramos, Pharmamar's clinical oncology specialist, believes that the second-line setting still represents an important space.

"Around 80% of patients respond to first-line platinum doublets, so it's going to be very hard to improve on that," he told *EP Vantage*.

At the upcoming World Lung conference in September Pharmamar will present results from a phase Ib cohort that was taken into its phase III trial – the results will provide insight into the potential of Zepsyre, which has produced disappointing results in the past.

If immunotherapy has the same impact on small cell lung cancer as it has had in non-small cell, Pharmamar might struggle to argue for a place for Zepsyre, even if Atlantis is a success. Physicians would probably judge that scenario a nice problem to have. For the time being, small cell lung cancer remains a very tough disease to treat.

Trials to watch in small cell lung cancer

Company	Trial	Regimen	Design	Data	Trial ID
Roche	Impower-133 (n=400)	Tecentriq + chemo combo	First-line	1H '18	NCT02763579
Bristol-Myers Squibb	Checkmate-451 (n=940)	Opdivo, Opdivo + Yervoy	First-line maintenance	End 2018	NCT02538666
Merck	Keynote-604 (n=430)	Keytruda + chemo	First-line	2019	NCT03066778
Astrazeneca	Caspian (n=795)	Imfinzi + chemo, Imfinzi + tremi + chemo	First-line	2019	NCT03043872
Abbvie	Meru (n=740)	Rova-T + chemo	First-line maintenance	2020	NCT03033511
Abbvie	Tahoe (n=411)	Rova-T vs chemo, DLL3 high	Second-line	2019	NCT03061812
Pharmamar	Atlantis (n= 600)	Zepsyre + chemo vs chemo	Second-line	2019	NCT02566993

Source: Clinicaltrials.gov, Asco 2018 presentations, company statements.