Evaluate Vantage

May 15, 2020

Asco 2020 – small-cell lung cancer and the role of CTLA-4

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Astra and Merck & Co present mixed small-cell lung cancer data, while Innovent, Xencor, Alphamab and Alligator bang the drum for CTLA-4.

Much of the lung cancer focus at this year's virtual Asco meeting is on non-small cell histology, but how Roche's Tecentriq might be challenged in front-line small-cell disease should not be ignored either. For one, it will raise fresh concerns about the deleterious effect of inhibiting CTLA-4, courtesy of further data from Astrazeneca's Caspian trial.

Despite this several biotechs continue to investigate CTLA-4, albeit not necessarily in lung cancer, an early look at the Asco abstracts reveals. And, still in SCLC, Merck & Co seems now to be arguing that its Keynote-604 study of Keytruda was positive, though its commercial potential is likely zero.

Keynote-604, a trial combining Keytruda not with CTLA-4 inhibition but with chemo, was toplined in January as a success on progression-free but a failure on the more important overall survival endpoint. Merck said a seemingly numerically positive 20% reduction in risk of death did not meet its statistical plan's significance threshold, but did not disclose the absolute time figures or a p value.

Its Asco abstract does, however: median OS is 10.8 versus 9.7 months, with p=0.0164 for the hazard ratio. Why is this statistically non-significant? Because, apparently, Merck had assigned very little alpha to the OS analysis, and the threshold for significance had been set at p=0.0128.

The abstract's authors add that "a post hoc analysis" yielded a p value that did meet this threshold, but do not elaborate further. They conclude that Keytruda "significantly ... prolonged OS", supporting its benefit in SCLC.

Selected Asco 1st-line SCLC abstracts				
Company	**Project(s)**	**Study**	**Abstract**	**Detail**
Merck & Co	Keytruda + chemo	Keynote-604	9001	mOS 10.8mth vs 9.7mth (not stat sig); mPFS 4.5mth vs 4.3mth (p=0.0023)
Astrazeneca	Imfinzi + chemo +/- tremelimumab	Caspian	9002	Updated mOS 12.9mth (doublet; nominal p=0.0032) and 10.4mth (triplet; not stat sig) vs 10.5mth

Ignoring the intricacies of statistical analysis, a 1.1-month survival improvement seems to offer little hope, however. It underperforms even the underwhelming two-month benefit on which Tecentriq was approved in its Impower-133 study.

For now the first-line SCLC battle is between Roche and Astra's Imfinzi plus chemo combo, approved in March on the basis of a 2.7-month OS advantage in one cohort of the Caspian study. But it is the second active cohort, Imfinzi and chemo plus the anti-CTLA-4 MAb tremelimumab, that doctors will be scrutinising at Asco.

This is because these subjects actually did worse than chemo alone in numerical terms: median OS for the treme-containing triplet was 10.4 versus 10.5 months, while median PFS came in at 4.9 months, half a month worse than control. The fact that rates of adverse events leading to discontinuation were twice as high with the triplet than the doublet or control provides a clue.

Selected Asco abstracts on CTLA-4 targeting				
Company	**Project**	**Mechanism**	**Abstract**	**Detail**
Innovent	IBI310 +/- sintilimab	CTLA-4 +/- PD-1 MAb	e15111	ORR 0% in 10 monotherapy subjects, and 14% in 7 combo subjects
Bristol-Myers Squibb/ Cytomx	BMS-986249 +/- Opdivo	CTLA-4 +/- PD-1 MAb	3058	First-in-human data: TRAEs in 23/39 subjects on monotherapy, and in 32/43 on combo
Xencor	XmAb20717	PD-1 x CTLA-4 bispecific MAb	e15001	1/34 CR in Keytruda-relapsed melanoma
Alphamab	KN046	PD-1 x CTLA-4 bispecific MAb	3020	12% ORR in 25 solid tumour subjects progressed after checkpoint blockade
Alligator	ATOR-1015	CTLA-4 x Ox40 bispecific MAb	3061	First-in-human data: 6 of 15 solid tumour subjects experienced drug-related AEs, grade ≤2

Nevertheless, research into blocking CTLA-4 is far from dead. Innovent, for instance, is presenting data on its own CTLA-4 MAb, IBI310, with or without the PD-1 MAb sintilimab, in melanoma, while Alligator, Xencor and Alphamab have abstracts on CTLA-4-targeting bispecific antibodies.

There are some hints of activity, the most important of which will be in patients who have already failed PD-(L)1 blockade, and the hope is that many datasets will be updated at Asco; some, including Cytomx's and Alligator's, have no efficacy results in the abstracts.

Also undisclosed are the virtual meeting's late-breaking abstracts, whose titles are known but which Asco will not make public until May 28. There is still much to play for.

Selected Asco late-breakers, which go live on May 28			
Company	**Drug**	**Presentation**	**Abstract**
Pfizer & Merck KGaA	Bavencio	Javelin Bladder 100 phase III interim analysis	LBA1
Amgen	Kyprolis	Endurance study in 1st-line multiple myeloma	LBA3
Merck & Co	Keytruda	First data from Keynote-177 study in MSI-high/MMR-deficient colorectal cancer	LBA4
Astrazeneca	Tagrisso	Adaura lung cancer maintenance study	LBA5

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

Further reading:

Asco 2020 – abstract dump triggers first moves

Asco 2020 – first-line lung cancer focus

Asco 2020 – early allogeneic Car-T promise

Asco 2020 starts to take shape