June 03, 2021

Asco 2021 – Bristol makes more progress in stomach cancer

Jacob Plieth

But the space, a battle between Opdivo and Keytruda, is becoming extremely complex, and Bristol's win is not unequivocal.

If doctors thought that the use of immunotherapy in stomach/oesophageal cancers was complicated enough, data being revealed at Asco suggest that the picture is about to get even more byzantine.

Late-breaking data from Bristol Myers Squibb's Checkmate-648 study have been claimed to be the first to back a survival benefit for a chemo-free regimen in certain front-line oesophageal cancer patients. The nuance is in the word "certain", as this space has swiftly been carved up according to histology, precise location of the tumour and extent of PD-L1 expression.

Checkmate-648 concerned the squamous histology, looking primarily at PD-L1 ≥1% expressers and secondarily at all-comers, and tested Opdivo combined either with chemo or with Yervoy, compared against chemo alone. In April it was toplined positive for OS for both active cohorts, but PFS favoured only the chemo combo, and only in PD-L1 ≥1%.

The lack of significance shown in most PFS analyses is probably irrelevant given the trial's hit on OS, and might be explained by pseudoprogression. But there are other details, full data on which are being released at Asco for the first time, that will trouble prescribers.

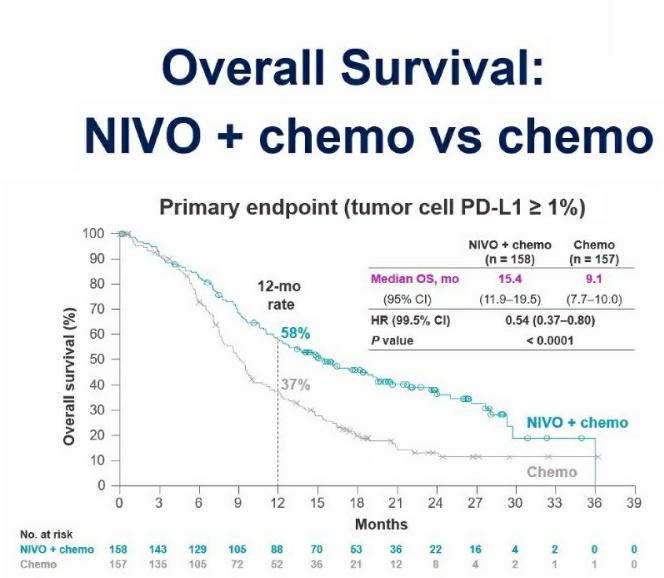
Summary of Checkmate-648 data				
Endpoint	**Opdivo + chemo**	**Opdivo + Yervoy**	**Chemo**	**Result**
mOS PD-L1 ≥1% (co-primary)	15.4mth	13.7mth	9.1mth	Positive for chemo combo (HR=0.54, p<0.0001) & Yervoy combo (HR=0.64, p=0.001)
mPFS PD-L1 ≥1% (co-primary)	?	?	?	Positive for chemo combo (HR=0.65), but not for Yervoy combo (HR=0.81)
mOS in all-comers (secondary)	13.2mth	12.8mth	10.7mth	Positive for chemo combo (HR=0.74, p=0.0021) & Yervoy combo (HR=0.78, p=0.011)
mPFS in all-comers (secondary)	?	?	?	Negative for chemo combo (HR=1.02) and Yervoy combo (HR=1.26)
Grade 3-4 TRAEs	147 (47%)	102 (32%)	108 (36%)	Said to be comparable across the three cohorts
Source: Asco.				

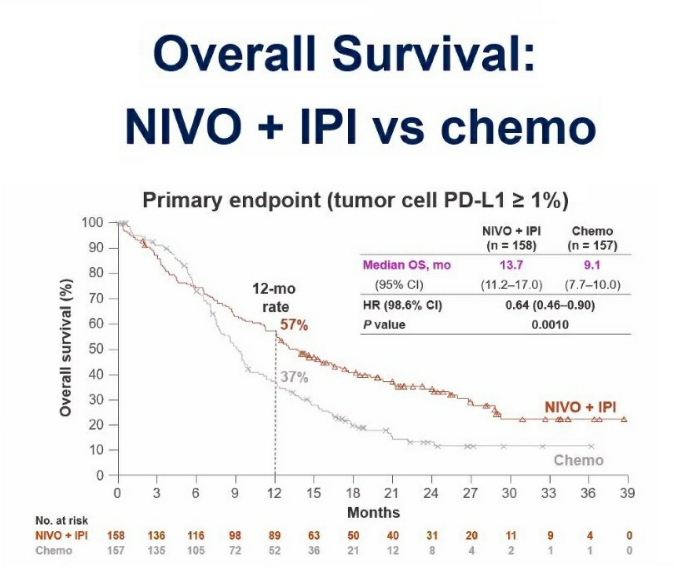
The most obvious oddity is that numerically Opdivo plus chemo did better than Opdivo plus Yervoy, and this cannot be explained by safety; toxicity was balanced across all three cohorts, and numerically the incidence of grade 3/4 events was lowest with Opdivo plus Yervoy.

But the picture gets more troubling: the overall survival curves for the Yervoy combo crossed over at six months, showing that before this point patients on Opdivo plus Yervoy were actually dying more quickly than those on chemo alone, and the overall benefit was only due to a positive effect in longer-term survivors.

Despite this, Asco highlighted the fact that Opdivo plus Yervoy was “chemotherapy-free”, though the combo’s added cost, and deleterious effects on early death, will concern others. Presenting Checkmate-648 data at an embargoed Asco presscast last week, Royal Marsden Hospital’s Dr Ian Chau supported Opdivo plus Yervoy, saying that up-front chemo might not be suitable in patients with numerous co-morbidities.

But he accepted that the curves’ crossing over was something his team was looking at very closely, to identify specifically the patients who might do worse on the Yervoy combo. “We may or may not find this subgroup,” he said in response to a question from *Evaluate Vantage*, but cautioned that this type of survival pattern was not uncommon in gastrointestinal cancers.





Source: adapted from Dr Ian Chau & Asco.

A separate and equally live question is the one regarding PD-L1 positivity. Though OS benefits in Checkmate-

648 are clearly seen in all-comers, the effect is stronger in ≥1% PD-L1 expressers, and it could be that PD-L1-positive patients are driving the overall benefit.

Dr Chau was unclear about whether the effect specifically in PD-L1 non-expressers would be revealed at Asco over the weekend, but said he "would not limit prescribing" the Opdivo combo to ≥1% PD-L1 expressers only. Additional data that he will show include ≥5% and ≥10% PD-L1 expression cut points, which he said did not suggest an improved benefit.

Growing complexity

Of course the breadth of a potential label here will be down to regulators, and perhaps the most important thing about Checkmate-648 is that it has shown a positive effect on the gold-standard endpoint of OS.

However, US doctors prescribing immunotherapy for gastric, oesophageal and gastroesophageal junction (GEJ) cancers will face considerable complexity. Opdivo monotherapy has an all-comers label in second-line squamous oesophageal cancer, while a front-line patient with the adenocarcinoma histology could get Opdivo plus chemo (*Esmo 2020 – double win complicates the gastric cancer picture, September 21, 2021*).

Alternatively, a US front-line patient with any histology can get Keytruda – as long as they can also tolerate chemotherapy. In the EU the picture is even more complex, with the CHMP recommending that this Keytruda/chemo be limited to PD-L1 ≥10% expressers.

The Checkmate-649 study backing the front-line Opdivo/chemo combo included the related gastric and GEJ cancers, a battleground also complicated by histology and biomarkers. Finally, Opdivo monotherapy was recently approved for the adjuvant treatment of oesophageal and GEJ cancers irrespective of histology.

Selected studies in gastric/oesophageal cancer				
Study	**Setting**	**Histology**	**PD-L1 status**	**Note**
Keytruda (Merck & Co)				
Keynote-059	Gastric & GEJ (3L)	Adenocarcinoma	≥1%	Monotherapy US accelerated approval Sep 2017, maintained despite failing KN-061 below
Keynote-061	Gastric & GEJ (2L)	Adenocarcinoma	≥1%	Failed study
Keynote-062	Gastric & GEJ (1L)	Adenocarcinoma	≥1%	Inconclusive data
Keynote-180 & 181	Oesophageal & GEJ (2L)	Mixed, except GEJ (Siewert type 1 adeno only)	≥10%	Monotherapy full US approval in squamous Jul 2019; EU filing pulled Jan 2020
Keynote-590	Oesophageal & GEJ (1L)	Mixed, except GEJ (Siewert type 1 adeno only)	≥10% (& all-comers)	Chemo combo full US approval in all-comers Mar 2021; EU proposing to approve in ≥10% PD-L1 only
Keynote-811	Gastric & GEJ (1L)	Adenocarcinoma	All-comers, Her2-positive	Herceptin + chemo combo US accelerated approval May 2021
Opdivo (Bristol Myers Squibb)				
Attraction-3	Oesophageal (2L)	Squamous	All-comers	Monotherapy US accelerated approval Jun 2020, later converted to full
Checkmate-649	Gastric, GEJ & oesophageal (1L)	Mixed, except oesophageal (adeno only)	≥5% (& all-comers), Her2-negative	Chemo combo full US approval in all-comers Apr 2021; Yervoy combo arm immature
Checkmate-577	Oesophageal & GEJ (adjuvant)	Mixed	All-comers	Monotherapy full US approval May 2021
Checkmate-648	Oesophageal (1L)	Squamous	≥1% (& all-comers)	Chemo combo & Yervoy combo, data at Asco 2021
Source: Esmo, Asco & company reports. GEJ=gastroesophageal junction cancer.				