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Asco-GI 2023 – zolbetuximab opens up a stomach cancer niche

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Clinical data back Claudin18.2 as a target for treating stomach cancer – but biomarker diagnosis is needed.

Last year saw Claudin18.2 emerge as a sought-after novel oncology target. Now here come positive survival data in the first setting in which the most advanced anti-Claudin18.2 antibody, Astellas's zolbetuximab, might be approved.

The results, from the Spotlight chemo combo study in front-line gastric/gastroesophageal junction (GEJ) cancer, have just been unveiled in a late-breaking abstract at the Asco Gastrointestinal Cancers symposium. On the face of it zolbetuximab looks approvable, but the data raise several questions, most notably about the need for mandatory Claudin18.2 testing.

Claudin18.2 is a protein said to be expressed in normal gastric mucosa cells and retained in metastatic gastric/GEJ tumour cells, but testing for its presence is not currently standard practice in these cancers. Spotlight, which Astellas had toplined as positive last November, enrolled only those patients whose tumours tested positive for at least moderate expression of this biomarker.

Tumours of Spotlight patients also had to have adenocarcinoma histology, as well as being negative for Her2. Thus, since the comparator in Spotlight was chemo alone, the results raise a second unanswered question: how might these patients have performed if given Bristol Myers Squibb's Opdivo, which can already be used as a chemo combo in Her2-negative gastric/GEJ adenocarcinoma?

Perhaps some of these questions will be answered, and more detail on safety given, at the full presentation of the Spotlight data, due to take place today at 1:30pm Pacific time.

Trials in 1st-line gastroesophageal junction (GEJ) cancer				
	Trial	**Setting, histology & biomarker**	**Design**	**Result**
Opdivo (Bristol Myers Squibb, approved)	Checkmate-649	Gastric/GEJ, adeno, Her2-ve	On top of chemo	mOS 13.8mth vs 11.6mth (HR=0.80) mPFS 7.7mth vs 6.9mth (HR=0.77)
Keytruda (Merck & Co, approved)	Keynote-811	Gastric/GEJ, adeno, Her2+ve	On top of Herceptin+chemo	ORR 74% vs 52%
	Keynote-590	Oesophageal/GEJ, squamous or adeno	On top of chemo	mOS 12.4mth vs 9.8mth (HR=0.73) mPFS 6.3mth vs 5.8mth (HR=0.65)
		Oesophageal/GEJ, squamous or adeno, PD-L1 ≥10%*		mOS 13.5mth vs 9.4mth (HR=0.62) mPFS 7.5mth vs 5.5mth (HR=0.51)
Tislelizumab (Beigene/ Novartis)	Rationale-305	Gastric/GEJ, adeno, Her2-ve, PD-L1+ve**	On top of chemo	mOS 17.2mth vs 12.6mth (HR=0.74) mPFS 7.2mth vs 5.9mth (HR=0.67)
Zolbetuximab (Astellas)	Spotlight	Gastric/GEJ, adeno, Her2-ve, Claudin18.2+ve^	On top of chemo	mOS 18.2mth vs 15.5mth (HR=0.75) mPFS 10.6mth vs 8.7mth (HR=0.75)
	Glow	Gastric/GEJ, adeno, Her2-ve, Claudin18.2+ve^	On top of chemo	Toplined +ve for mOS & mPFS

*Notes: *setting to which EMA restricted Keytruda's use;**trial enrolled patients irrespective of PD-L1 expression; ^defined as moderate-to-strong membrane staining in ≥75% tumour cells by IHC. Source: product labels & Asco-GI.*

For now Astellas can boast a strongly statistically significant result in the Spotlight population on the trial's primary endpoint, median PFS, as well as in the key OS secondary. Both measures have been hit, with zolbetuximab plus chemo cutting risk by 25% versus chemo alone.

On a cross-trial basis zolbetuximab in Spotlight outperformed Opdivo in the Bristol drug's registrational Checkmate-649 trial on both survival measures – but the comparator in Astellas's study also outperformed Bristol's.

In this complicated cancer space Keytruda plus chemo is also available for GEJ cancer of either adeno or squamous histology, but specifically in gastric cancer it only has accelerated approval in Her2-positives in combination with Herceptin.

Beigene in PD-L1-positives

A separate pivotal study in Her2-negative gastric/GEJ adenocarcinoma, Beigene's Rationale-305, is also being presented at Asco-GI. However, in this trial, 74% of whose patients were enrolled at Asian hospitals, tislelizumab plus chemo appears to have beaten chemo only in those expressing PD-L1.

Rationale-305 is the basis for approval in China, where a tislelizumab filing was accepted last June, as well as for a US submission, which Beigene and its partner Novartis last said was being planned for this year. Full data from the trial, due at 4:15pm Pacific time, should shed more light on any efficacy in the intent-to-treat population.

That said, given the interest in Claudin18.2, Astellas's Spotlight late-breaker will likely overshadow the Rationale-305 results at Asco-GI today. That interest was on show just two days ago, when Leap Therapeutics acquired Flame Biosciences, a private biotech with two very early-stage assets against Claudin18.2.

Interestingly, Spotlight is one of two pivotal zolbetuximab chemo combo trials in first-line gastric/GEJ cancer, the other being the Glow study. The difference between the two extremely similar trials lies in the chemo:

Spotlight uses Folfox (leucovorin, 5-FU and oxaliplatin) while in Glow zolbetuximab is given on top of Capox (capecitabine and oxaliplatin).

Astellas toplined Glow as positive for PFS and OS in December, but has yet to present the full data.