Evaluate Vantage

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Asco 2019 – Abstract drop fires the starting gun

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Amgen's KRAS inhibitor, Macrogenics' breast cancer project and Roche's entrectinib stand out as the curtain lifts on thousands of abstracts due to be presented at the huge cancer conference.

The big hitting studies remain under wraps but the release today of the main body of abstracts due to be presented at Asco next month will give the medical and financial communities plenty to chew over in the coming weeks.

Firm conclusions are often hard to draw from these brief summaries of the studies, but *Vantage* has taken a quick look at some of the most hotly anticipated abstracts. The most notable presentation being held back concerns the results from the Polo study of Astrazeneca's Lynparza in pancreatic cancer, which is known to have improved progression free survival, and which will feature at the conference's main plenary session.

Amgen and AMG 510: abstract 3003

The first clinical data on Amgen's Kras G12C inhibitor are among the most keenly awaited at this year's Asco, despite the project only being in phase I.

The abstract describes 22 subjects enrolled by the time of data cut off, with tumour response measured in nine. One patient had a partial response, while six had stable disease and two had progressive disease. A second partial response was reported after data cut off, and investors looking to glean insight into the potential of this agent will be hoping for a later readout at the conference.

Drawing any firm conclusions about the potency of AMG 510 is almost impossible at this stage, though those with high expectations could be disappointed by these initial signals.

At its first quarter results Amgen said that the dose escalation phase of the study had been completed and that it intended to start an anti-PD-1 combination arm; some took this to mean that monotherapy activity was looking underwhelming. The full presentation of the data will remain a key date on investors' Asco schedules.

Roche and entrectinib: abstract 10009

Results from a phase I/Ib study of Roche's tumour agnostic candidate entrectinib were highlighted in an Asco press conference earlier today, underlining just how impressive physicians consider this agent to be. The study was conducted in children and young adults with rare central nervous system tumours, neuroblastoma or other solid tumours, and as expected responses were only seen in patients with fusions and alterations in the

genes that entrectinib targets: NTRK1/2/3, ROS1, or ALK.

But in those subjects, remission rates were unequivocal: all of those evaluated responded, including three complete responses and nine partial responses. US and European regulators are due to rule on entrectinib's approval later this year, and a green light looks highly likely based on these data and previous results from other studies.

Giles Robinson, a pediatric neuro-oncologist at St Jude Children's Research Hospital who presented the data at the press conference, described the responses as "striking, rapid and durable", and pointed to entrectinib's action on central nervous system tumours as particularly impressive.

He cautioned that the data remain early, however, and drew attention to weight gain, which is a known toxicity of entrectinib. Dr Robinson said that this has proved to be a significant worry for some patients, and is something investors will want to keep an eye on.

Macrogenics and margetuximab: abstract 1000

A surprise hit on progression free survival earlier this year put Macrogenics' margetuximab back on investors' radars. A closer look at the data from the phase III Sophia study, in advanced Her2 positive breast cancer, shows it is too soon to declare this a slam dunk.

The company had previously only unveiled hazard ratios and the first look at absolute PFS numbers show a marginal advantage for margetuximab. The Fc-optimised anti-Her2 MAb generated 5.8 months of PFS versus 4.9 for Herceptin; in patients with a particular genotype associated with poor response to Herceptin, who largely drove the win in the study, PFS increased to 6.9 months, versus 5.1 months for the Roche antibody.

The company set out immature overall survival data in an accompanying press release, which will presumably be included in the conference presentation. Based on 158 events, margetuximab improved median OS by 1.7 months over Herceptin in all patients and by 6.8 months in the "exploratory subpopulation" of patients carrying the CD16A 158F allele. A pre-specified interim OS analysis is likely to happen in the second half of this year, while the final cut of this data is slated for 2020.

Shares in Macrogenics rose 9% on Thursday on hopes that the company might be able to win approval in the subpopulation showing greater efficacy. The final OS readout needs to hit significance for any of chance of this happening, however.

An overall response rate of 22% will also not help lift hopes in the light of a clinical win claimed by Daiichi Sankyo and Astrazeneca for their anti-Her2 antibody-drug conjugate, DS-8201, earlier this month. This too is trying to prove itself a better Herceptin. Last week the partners said a pivotal phase II DESTINY-Breast01 study confirmed the "unprecedented clinical activity" seen in a phase I trial, which generated an ORR of 60% (*Astra and Daiichi lay out their plan for a better Herceptin, May 8, 2019*.

Nektar and NKTR-214: Abstract 11010

Data on Nektar's NKTR-214 suggest that a combination with Opdivo might be a viable therapy for treatment-refractory patients with various kinds of sarcoma. This is a disease in which checkpoint inhibitor monotherapy has minimal efficacy, meaning the clinical bar to success is relatively low.

An investigator-initiated pilot study in 50 patients showed partial responses in one patient with leiomyosarcoma (LMS) and another with chondrosarcoma (CS); two patients with undifferentiated pleomorphic sarcoma (UPS) also had partial responses. PFS ranged from 5.1 to 7.7 months. This compares with one complete response in a 40-patient trial of Keytruda in soft tissue sarcoma, according to Leerink analysts.

Clinical benefit rate ranged from 20% to 40% in the different tumours; this is roughly in line with the objective response rate target of more than 20% that Leerink analysts believe would constitute proof-of-concept for NKTR-214 in this setting.

NKTR-214 Asco data					
Tumour type	**LMS**	**UPS**	**DDLPS**	**CS**	**OS**
Confirmed partial response	1	2	0	1	0
CBR (partial and complete responses plus stable disease) at 6mths	20%	20%	40%	20%	0
Duration of response (mths)	3.8	5.8	-	9.3	-
Median PFS (mths)	1.8	2.4	3.9	1.8	2
Median OS (mths)	7.7	7.7	NE	5.1	6.4
Source: Asco abstract #11010.					

Aduro and ADU-S100: abstract 2507

Expectations around novel immuno-oncology combinations has dived over the last year and an early update from Aduro looks unlikely to reignite hopes for Sting agonism. The company's ADU-S100 is being tested with Novartis's anti-PD1 spartalizumab, and an update from an early trial will be scrutinised for signs of efficacy.

The trial recruited 66 patients with advanced or metastatic solid tumours or lymphoma.Treatment was discontinued in 49 patients (74%), 28 of whom had disease progression. Two patients discontinued after adverse events, and one patient died. The abstract gives little away on firm results, saying only that partial responses have been observed in patients with PD-1-naive triple-negative breast cancer and PD-1-relapsed or refractory melanoma.

Again, the actual presentation, which will include response data, remains of interest.

Analysts at Leerink said they want to see an objective response rate of 20-30% higher than anti-PD(L)1 therapy alone, though lower increases in ORR might still be considered promising. Aduro shares opened slightly lower on Thursday.

Daiichi Sankyo and DS-1062: abstracts 9051 and 9010

Daiichi's antibody-drug conjugate programme has entered the spotlight in the last few months following a substantial deal with Astrazeneca over its lead candidate, DS-8201, and Asco will see data on two earlier-stage projects.

DS-1062, a Trop2-targeted conjugate being tested in advanced non-small cell lung cancer, generated one partial response and eight cases of stable disease, out of 18 evaluable subjects. Fatigue was the biggest toxicity concern noted.

U3-1402 meanwhile is a Her3 targeted conjugate, also being trialled in lung cancer, this time in refractory EGFR-positive patients. The early-stage study being presented enrolled 15 patients, five of whom discontinued, one due to an adverse event. Of 13 patients evaluable for response, two had a partial response.

Both studies are ongoing and though these projects are early stage these presentations should mark them as ones to watch for the future.

This story was originally published on May 15th when abstracts went live, and has been updated to include some share price reactions.