ESMO 2022 Round Up

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Evaluate Vantage

Introduction

Ahead of Esmo 2022 there were rumblings that attendees would remember this conference for 20 years, such was the anticipated wealth of innovation that would be on display. A bold statement and one that more seasoned biotech watchers may have taken with a pinch of salt. There was plenty of food for thought, however, even if the memory of the meal might not quite linger for decades to come.

The big expectations ahead of Esmo 2022 were all around Kras and while this targeted anti-cancer mechanism was certainly a big focus, there was plenty more to keep the audience – and shareholders – gripped throughout the conference.

For those on Kras-watch, there were a number of abstracts to chew on, from Amgen's Codebreak-200 and Codebreak-101 studies, as well as news from Mirati and Roche. All eyes are now on the FDA for pending decisions, meaning a stressful few months lay ahead for some of the key players.

Away from the Kras, the failure of Sanofi and Roche's Serds in Her2-negative breast cancer were laid bare. There was better news in another breast cancer subtype from Gilead's Trodelvy, although the commercial potential of that drug looks set to remain in rival Enhertu's shadow.

In this ebook, we've pulled together all our reporting on the clinical developments that emerged from Esmo. As always, we've also looked at the share price implications of everything that happened, providing plenty to chew over.

Contents

Preview – front-line liver cancer showdown

BY JACOB PLIETH | AUGUST 19, 2022

As Esmo yesterday briefly published the titles of late-breaking abstracts (most were gone this morning), investors have their first clues about what to expect at the oncology conference, which starts in Paris on September 9.

One of the highlights will be a trio of pivotal studies of anti-PD-1 MAbs in first-line hepatocellular cancer: Keytruda's Leap-002, known to have failed, camrelizumab's SHR-1210-III-310, toplined positive, and tislelizumab's Rationale-301, said to show non-inferiority versus Nexavar. Biotech watchers have key presentations on Relay's RLY-4008 – look out for toxicities – Biontech's BNT211 and Springworks' nirogacestat, not to mention Padcev's EV-103 cohort K, seen by some as smoothing the way to Seagen's takeover by Merck & Co. Also closely watched will be colorectal cancer data from Mirati's adagrasib, though a path for filing here has yet to be outlined, and of more immediate importance is the accelerated application for NSCLC, given upcoming release of confirmatory data on Amgen's competitor, Lumakras. Major failed studies being highlighted include Roche's Immotion-010 and Sanofi's Ameera-3; The French group recently discontinued amcenestrant on the basis of Ameera-3 and 5. With Gilead's Tropics-02 set to be one of the most picked-apart datasets Esmo is shaping up to be full of catalysts.

Selected Esmo 2022 abstracts			
Project (company)	**Study (use)**	**Note**	**Abstract**
Keytruda + Lenvima (Merck & Co/Eisai)	Leap-002 (1L liver)	Known to have failed OS & PFS vs Lenvima alone	LBA34
Camrelizumab + rivoceranib (Jiangsu Hengrui)	SHR-1210-III-310 (1L liver)	Known to have succeeded vs Nexavar; approved in China for 2L liver	LBA35
Tislelizumab (Beigene/ Novartis)	Rationale-301 (1L liver)	Known to have succeeded on non-inferiority vs Nexavar	LBA36
Dalpiciclib/ SHR 6390 (Jiangsu Hengrui)	SHR6390-III-302 (1L HR+/Her2- breast cancer)	CDK4/6 inhibitor	LBA16
Oleclumab (Astrazeneca)	Synergy (TNBC)	Anti-CD73 combos	LBA17
Trodelvy (Gilead)	Tropics-02 (2L HR+/Her2- breast cancer)	Modest PFS benefit, recently met 2nd interim OS analysis	214MO
Amcenestrant (Sanofi)	Ameera-3 (2L HR+/Her2- breast cancer)	Failed study, Serd recently discontinued by Sanofi	212MO
Nirogacestat (Springworks [ex Pfizer])	DeFi (desmoid tumours)	Known to have succeeded	LBA2
RLY-4008 (Relay)	ReFocus (FGFR inhibitor-naive cholangio)	Tox problems at Triple meeting 2021	LBA12
Adagrasib (Mirati)	Krystal-1 (Kras G12C+ve colorectal cancer)	Colorectal filing path unclear	LBA24
BNT211 (Biontech)	BNT211-01 (mRNA vaccine combo)	Anti-Claudin-6 Car-T, early data at AACR 2022	LBA38
Naporafenib/ LXH254 (Novartis)	Unclear (melanoma)	Various combos	LBA40
MEDI5752 (Astrazeneca)	D7980C00001 (1L NSCLC chemo combo)	PD-1xCTLA-4 bispecific vs vs Keytruda	LBA56
Tecentriq (Roche)	Immotion-010 (adjuvant renal)	Known to have failed	LBA66
Padcev + Keytruda (Seagen/ Merck & Co)	EV-103 cohort K (1L bladder)	Known to have succeeded; possible route to AA	LBA73

Source: Esmo website, company statements & clinicaltrials.gov.

Preview – duelling datasets

BY JACOB PLIETH | AUGUST 22, 2022

Most late-breaker titles for Esmo are now disclosed, and in terms of biotech catalysts the upcoming meeting's regular abstracts cannot be ignored either. In some cases the latter will allow a handy comparison to be made against the former.

For instance, investors in Springworks, whose nirogacestat features in a late-breaker, will pay attention to Ayala's rival gamma-secretase inhibitor AL102, which has a regular Esmo abstract; both datasets concern the niche area of desmoid tumours, but Ayala is worth just $20m, barely 2% of Springworks' market cap. Data on Daiichi Sankyo's B7H3-targeted DS-7300, which uses the same ADC technology as Enhertu, will be of interest to Macrogenics investors, while first-in-human results are due from studies of Deciphera's DCC-3116 and Regeneron's ubamatamab. An update to results at Esmo 2021 concerns Amgen's Lumakras in combination with Vectibix in colorectal cancer, while an earlier-stage Kras G12C inhibitor, Roche's GDC-6036, has phase 1 data. The main course at Esmo for Kras watchers is Mirati's adagrasib late-breaker, also in colorectal cancer. Indeed, Kras is something of an Esmo theme, with sessions including two satellite and several special symposia.

Selected Esmo 2022 abstracts

Project (company)	Study (use)	Note	Abstract
Lumakras + Vectibix (Amgen)	Codebreak-101 (Kras G12C+ve colorectal cancer)	Had data at Esmo 2021, cf LBA24 on Mirati's adagrasib	315O
GDC-6036 (Roche)	Ph 1 (Kras G12C+ve solid tumours)	Field getting crowded	459MO
CART-ddBCMA (Arcellx)	Interim ph1 (multiple myeloma)	Data at Asco 2022	620O
AL102 (Ayala, ex-Bristol Myers Squibb)	Ringside (desmoid tumours)	Gamma secretase inhibitor, cf LBA2 on Springworks' nirogacestat	1488MO
DS-7300 (Daiichi Sankyo)	Ph1/2 (solid tumours)	Anti-B7H3, cites durable responses, cf Macrogenics MGC018	453O
DCC-3116 (Deciphera)	First in human, incl MAPk combo (solid tumours)	ULK1/2 inhibitor (data at AACR 2022)	450O
Ubamatamab (REGN4018; Regeneron)	Ph1/2 monotherapy cohort (ovarian cancer)	Anti-Muc16 T-cell engager	523MO
Giredestrant (Roche)	AcelERA (2L HR+/Her2- breast cancer)	Failed Serd study	211MO
Amcenestrant (Sanofi)	Ameera-3 (2L HR+/Her2- breast cancer)	Failed study, Serd recently discontinued by Sanofi	212MO

Source: Esmo website, company statements & clinicaltrials.gov.

Last-minute Kras entry takes centre stage

BY JACOB PLIETH | SEPTEMBER 01, 2022

Amgen's confirmatory Codebreak-200 trial will feature as a surprising late-breaker at Esmo's presidential session.

A common theme of the long-running battle of Kras inhibitors has been how frequently Mirati has been outplayed by Amgen. The latest act in the saga took place yesterday, when Amgen somehow managed to get data from its confirmatory Codebreak-200 study of Lumakras accepted as a late-breaker for the Esmo meeting, which starts in eight days' time.

The deadline for late-breaker Esmo submissions was August 9, yet Amgen only toplined Codebreak-200 two days ago. True, Amgen will have had the results in house for some time before announcing, and if it additionally managed to use some of its connections to persuade Esmo to give it leeway then it has again played its hand well.

Esmo late-breaking titles went live on August 18, but one slot, LBA10, was noticeably left blank. Yesterday LBA10's title appeared on the Esmo website: "sotorasib versus docetaxel for previously treated NSCLC with KRAS G12C mutation, Codebreak-200 phase 3 study" is due to be presented at 5.40pm European time at the meeting's presidential symposium on September 12.

Amgen told Evaluate Vantage that it had submitted a "shell abstract" to the congress organisers in anticipation of having the data in time for Esmo. Its investors will welcome the group's strong connections. It will not go unnoticed, for instance, that its senior vice-president of oncology, Jean-

Charles Soria, worked at Gustave Roussy – which claims to be Europe's leading cancer hospital – for 15 years, most recently as director general.

The scientific co-chair of the Esmo 2022 congress is Dr Fabrice André, a medical oncologist at Gustave Roussy. He had recently tweeted that Esmo 2022 would be a conference that would be remembered for 20 years.

The question now, for Amgen as well as for Mirati, is how good the Codebreak-200 data are. All Amgen has said is that Lumakras showed "statistical significance and superiority over" docetaxel on the study's primary endpoint of progression-free survival.

There is little precedent on what to expect, as Codebreak-200 tested patients who had failed one systemic treatment, likely PD-(L)1 blockade. Wells Fargo analysts reckon "good data" would be a six-month or greater PFS benefit for Lumakras, versus four months or less for the chemo.

However, they also note that Gilead's Trodelvy and Astrazeneca/Daiichi Sankyo's datopotamab are aiming to replace docetaxel in post-PD-(L)1 NSCLC patients, so combos will be key for Lumakras to gain traction. Amgen has not fared well here: World Lung data showed unexpected levels of liver toxicity for Lumakras plus PD-(L)1 blockade.

Esmo will separately feature the Codebreak-101 trial of Lumakras plus Vectibix in colorectal cancer, as well as a late-breaker on a cut from Mirati's adagrasib's Krystal-1 study in the same setting.

Selected Esmo 2022 abstracts on Kras

Project (company)	Study (use)	Note	Abstract
Lumakras (Amgen)	Codebreak-200 (2nd-line Kras G12C+ve NSCLC, vs docetaxel)	Confirmatory trial for accelerated approval, toplined positive for PFS	LBA10
Adagrasib (Mirati)	Krystal-1 (Kras G12C+ve colorectal cancer)	Colorectal cancer filing path is unclear	LBA24
Lumakras + Vectibix (Amgen)	Codebreak-101 (Kras G12C+ve colorectal cancer)	Had data at Esmo 2021, but World Lung 2022 data on Lumakras + PD-(L)1 blockade showed liver tox	315O
GDC-6036 (Roche)	Ph 1 (Kras G12C+ve solid tumours)	Field is getting crowded	459MO

Source: Esmo & company statements.

Mirati shareholders appeared to welcome the toplining of Codebreak-200, sending the stock up 9% yesterday, but in NSCLC the company has a problem.

Adagrasib's US accelerated approval filing has a December 14 action date, but should the FDA grant Lumakras a full green light before then – on the basis of Codebreak-200 – it will be difficult for adagrasib to be approved on the basis of its surrogate endpoint of overall remission rate, as Evaluate Vantage has argued.

Still, Lumakras's formal approval is by no means assured. That will depend on the size of the benefit in Codebreak-200, and on whether the FDA deems PFS to be an appropriate second-line endpoint. Nothing has been said about overall survival, which does appear in the trial's secondary efficacy metrics.

Mirati and Amgen investors alike face a stressful few months.

This is an updated version of a story published earlier.

Sanofi and Roche's duelling Serd duds

BY JACOB PLIETH | SEPTEMBER 07, 2022

An Esmo abstract has shown why Sanofi was right to can amcenestrant: the Serd showed absolutely no benefit over physician's choice in the second-line Ameera-3 study in Her2-negative breast cancer.

Control numerically outperformed amcenestrant, with the PFS primary endpoint yielding a hazard ratio above 1.0, meaning that patients given amcenestrant were numerically more likely to progress than those on control. A second Serd failure, that of Roche's giredestrant in the Acelera trial, also features among Esmo's regular presentations, and appears slightly better: a non-significant 19% reduction in risk of progression favours giredestrant, while in ESR1 mutants the benefit was 40% – though there were not enough patients in this subgroup for this to be meaningful. Roche is pinning its hopes with giredestrant on front-line use, while Sanofi finally pulled the plug on amcenestrant when its first-line Ameera-5 trial also failed. The only novel oral Serd to work so far has been Radius/Menarini's elacestrant, likely thanks to its trial having been enriched for ESR1 mutants. Curiously, however, this project is not being tested in the front line.

Cross-trial comparison of novel oral Serds in 2nd-line HR+/Her2- breast cancer

		mPFS			
Project (company)	**Trial**	**All comers**		**ESR1mut**	
Elacestrant (Radius/ Menarini)	Emerald	2.8mth vs 1.9mth	HR=0.70, p=0.002	3.8mth vs 1.9mth	HR=0.55, p=0.0005
Giredestrant (Roche)	Acelera	Medians not disclosed in Esmo abstract 211MO	HR=0.81, p=0.18	Medians not disclosed in Esmo abstract 211MO	HR=0.60 (95% CI upper bound of 1.03)
Amcenestrant (Sanofi)	Ameera-3	3.6mth vs 3.7mth	HR=1.051, p=0.6437	Not given in Esmo abstract 212MO	

Source: Asco & Esmo.

Mirati needs some colorectal cancer urgency

BY MADELEINE ARMSTRONG | SEPTEMBER 07, 2022

Adagrasib data hold up, but filing timelines are still unclear.

This time last year it looked like colorectal cancer could be Mirati's golden ticket in its ongoing Kras battle with Amgen. At this year's Esmo meeting, the biotech again outdid its bigger rival – but it is still no clearer when Mirati's lead project, adagrasib, will be filed in this setting.

The group has pledged to "provide additional clarity" on its colorectal cancer regulatory strategy later this year, but this is a long overdue promise. Discussions with the FDA over colorectal cancer were to have taken place by the end of 2021, and an update on filing plans was then promised in the first half of 2022. Mirati's investors will have to hope that this will not end up being another case of good data being let down by poor execution.

Adagrasib and Amgen's Lumakras are not the only Kras contenders taking aim at colorectal cancer, with phase 1 results on Roche's GDC-6036 also due to be presented at Esmo. The overall response rate outlined in an abstract looks promising, and with a later cut of the data including more patients likely to emerge at the conference, it will be interesting to see if this holds up.

KRYSTAL CLEAR?

For now, though, Mirati appears to have the edge in late-line colorectal cancer patients with a Kras G12C mutation. Data just unveiled in a late-breaking abstract come from Krystal-1, which tested both adagrasib monotherapy and an Erbitux combo.

The results look similar to last year's update on the same trial (*Esmo 2021 – colorectal cancer could be Mirati's golden ticket*, September 17, 2021).

The adagrasib/Erbitux combo still looks better than a combination of Lumakras and Vectibix, updated results on which will also be available at Esmo. Amgen has deprioritised Lumakras monotherapy in colorectal after disappointing results.

Cross-trial comparison of Kras inhibitors in colorectal cancer				
Project (company)	**Adagrasib (Mirati)**		**Lumakras (Amgen)**	**GDC-6036 (Roche)**
Trial	Krystal-1		Codebreak-101	NCT04449874
Cutoff	Jun 16, 2022		Mar 25, 2022	Jan 28, 2022
	Adagrasib mono	Adagrasib + Erbitux	Lumakras + Vectibix	GDC-6036 mono
Median prior therapies	3	3	2	3
ORR	19% (8/43)	46% (13/28)	30% (12/40)	20% (8/41)
All TRAEs	-	-	93%	-
Grade 1/2 TRAEs	59%	84%	-	-
Grade 3/4 TRAEs*	34%	16%	23%**	-

*No grade 5 AEs seen; **no grade 4 AEs seen.

Source: Esmo abstracts LBA24, 315O & poster 362P.

Elsewhere, monotherapy data with GDC-6036 appear in line with solo adagrasib, and act as another reminder that the Kras space is getting crowded.

Still, efficacy is not the only consideration with Kras projects, with toxicity also high on the agenda, especially after liver enzyme elevations were recently seen with Lumakras and PD-(L)1 inhibitors in lung cancer.

The Esmo abstracts do not give a breakdown of adverse events, so it will be worth keeping an eye on these when the data are presented over the weekend.

As for future plans, Amgen is enrolling into a phase 3 trial of the Lumakras/Vectibix combo, Codebreak-300, in third-line disease, and this is due to complete next year.

Mirati, meanwhile, has said that an accelerated approval for late-line colorectal cancer could be on the cards, although it has been promising an update here for some time. The group expects full approval to be supported by the second-line Krystal-10 trial, testing an adagrasib/Erbitux combo against chemo.

The Esmo conference takes place in Paris on September 9-13. A recording of a discussion between Jacob Plieth and the biotech investor Brad Loncar about the meeting's themes is available here.

Trodelvy's improving trajectory might not matter much

BY AMY BROWN | SEPTEMBER 07, 2022

Later cuts of Tropics-02 make for better reading, but in Her2-driven breast cancer Gilead's Trodelvy will remain a footnote to Enhertu.

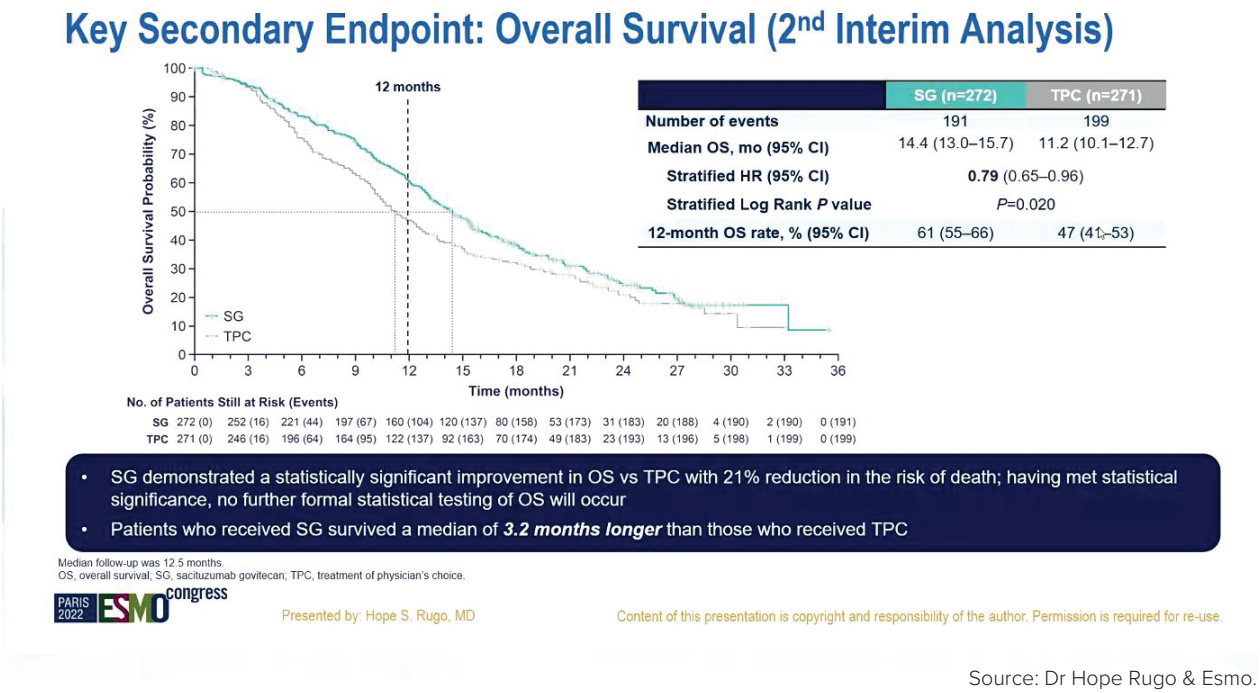
Hopes of an improving survival signal for Trodelvy in the disappointing Tropics-02 trial were the glimmers that Gilead had to hold on to coming out of Asco. Data to be presented at Esmo this weekend point to redemption of sorts, a newly released late-breaking abstract suggests.

This shows the overall survival benefit jumping from an underwhelming 1.6 months over control to a more respectable 3.2 months, with the hazard ratio improving to 0.79 and moving into statistical significance. Gilead had previously described this finding as "clinically meaningful" without providing actual numbers, and the absolute benefit shown is at the top end of expectations.

Whether this matters much is the big question. This is because of the performance of Astrazeneca and Daiichi's breast cancer rival, Enhertu, in the Destiny-Breast04 trial, which was conducted in a similar ER-positive and ostensibly Her2-negative population. That study wowed Asco and has established the concept of Her2-low disease.

True, direct comparison of the two datasets is imperfect: Tropics-02 recruited later-line patients with a poorer outlook, and included those without any Her2 expression. But the impressive Enhertu result means that it is already assumed that Trodelvy will be consigned to a salvage setting.

That perception is unlikely to shift with these latest data. However, clear signs of activity in a subgroup of Tropics-02 patients with no detectable Her2 receptor, deemed Her2 zero, on top of the the strengthening OS data, should bolster Gilead's case that Trodelvy does have a role to play in some ER-positive breast cancers.



Source: Dr Hope Rugo & Esmo.

Discussing the Tropics-02 data at Esmo, Dr Meritxell Bellet Ezquerra, from Vall d'Hebron Institute of Oncology, said: "No doubt this is a statistically positive trial. [It is] clinically meaningful and should lead to regulatory approval."

Still, Enhertu casts a long shadow. Asked about Trodelvy's positioning, University of California San Francisco's Dr Hope Rugo, the Tropics-02 lead investigator, told Esmo that she would use the drug in Her2-zero disease.

An improving picture: Tropics-02 median overall survival (months)			
	Trodelvy	**Control**	**Hazard ratio**
Asco 2022 cutoff	13.9	12.3	0.84 (p=0.143)
Esmo 2022 cutoff	14.4	11.2	0.79 (p=0.02)

Note: median duration of follow-up was 10.5 months at Asco and 12.5 months at Esmo. Source: conference abstracts.

In terms of expectations, Morgan Stanley noted recently that consensus among investors was sitting around a 2-2.5 month OS benefit for Trodelvy over chemo. The bank's analysts calculated that the benefit could fall within a 1.8-3.3 month range; SVB Securities thought that at least a 20% improvement over control would emerge.

This means that the actual numbers will come as a positive surprise, particularly as some were not expecting any meaningful improvement. It seems that OS has followed PFS with a late separation of the survival curves.

Why this happened is unclear. Biomarkers – Trodelvy is a conjugate targeted at Trop2 – might be playing a role. However, the trial enrolled during the Covid pandemic, and a lot of patients dropped out owing to progression before their first scan, Jefferies analysts wrote recently, citing the trial's primary investigator. This could mean that those who made it to the first or second scans were relatively healthier or more robust.

However, the Destiny-Breast04 result still looks much stronger, the problems with such a comparison notwithstanding. In that trial Enhertu generated a 6.4-month median OS benefit and 0.64 hazard ratio (p=0.003).

The numbers behind this – median OS was 23.9 months for Enhertu versus 17.5 months for control – illustrates how the Breast04 population had a better prognosis in the beginning. The trial was essentially conducted in a second-line setting, while Tropics-02 subjects were at least third line.

Another cut of Tropics-02 data being presented at Esmo does allow a slightly better comparison to be made. This shows PFS for the Her2-low and Her2-zero subgroups, with a stronger performance in the former but a decent enough result in the latter, albeit with a confidence interval that touches 1 at the upper bound.

Tropics-02 post-hoc subgroup analysis

	Her2 low		**Her2 zero**		**All patients***	
	Trodelvy	Control	Trodelvy	Control	Trodelvy	Control
Median PFS (months)	6.4mth	4.2mth	5.0mth	3.4mth	5.5mth	4.0mth
Hazard ratio	0.58		0.72		0.66 (p=0.0003)	

*Primary endpoint.

Source: Esmo.

Destiny-Breast04 did not allow patients deemed Her2 zero, and is therefore closer to the Her2-low subgroup. On median PFS, Enhertu generated 10.1 months versus 5.4 months for control, for a hazard ratio of 0.51 (p<0.001).

It is not inconceivable that Trodelvy could produce a more competitive result in an earlier setting. But proving that would be an expensive undertaking, and Gilead is already under pressure to justify the $21bn it spent acquiring the drug via Immunomedics.

In breast cancer Gilead's focus is in triple-negative disease, where Trodelvy is already approved third line. Considering Enhertu that feels like a wise niche in which to sit, but the company could be forgiven for wondering "what if?"

This is an updated version of a story published earlier.

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The new liver cancer entrants line up

BY JACOB PLIETH | SEPTEMBER 07, 2022

Late-breakers give tislelizumab, camrelizumab and Keytruda outside chances to add to the first-line armamentarium.

Front-line liver cancer, a setting into which immunotherapy has only made recent inroads, will soon see more competition. Whether that competition will include Beigene/Novartis, Jiangsu Hengrui or even Merck & Co/Eisai will be down to those companies and the FDA.

This is because pivotal data from their three anti-PD-1 approaches, just revealed in three Esmo late-breaking abstracts, show each to have some merit, but the studies in question also come with important caveats. The datasets will be picked apart at the meeting's Saturday morning session, and will be closely watched by the next expected entrant, Astrazeneca.

Astra's Imfinzi, with or without the anti-CTLA-4 MAb tremelimumab, is awaiting US approval based on a roughly three-month overall survival benefit over Nexavar in the Himalaya trial. The company's US filing was accepted with priority review in April, and the Pdufa date is expected to fall in the fourth quarter.

Nexavar as well as Lenvima are front-line standards of care in liver cancer. They were joined in 2020 by Roche's Tecentriq plus Avastin combo, which beat Nexavar in the Imbrave-150 trial and marked immunotherapy's first success in this tricky field, which had seen Bristol Myers Squibb trip up in Opdivo's Checkmate-459 trial.

UP NEXT

Now the stage is set for the next act. Pivotal studies of Jiangsu Hengrui's camrelizumab plus the tyrosine kinase inhibitor rivoceranib, and of Beigene/Novartis's tislelizumab monotherapy, were earlier toplined positive versus Nexavar, and Esmo has shown the actual numbers for the first time.

The camrelizumab combo stands out in having yielded a 22.1-month median OS benefit – the highest ever on a cross-trial basis. However, the study was conducted largely in China, though it did include some US and European hospitals. Jiangsu is not known to have a US presence, and camrelizumab has never been filed in the US; it is approved in China, including for second-line liver cancer.

Meanwhile, Beigene plans a 2023 US filing for tislelizumab based on Rationale-301, a global study that also appears heavily weighted towards Chinese hospitals. A big caveat here, however, is that this has only shown non-inferiority to Nexavar, and the Esmo

abstract reveals a 15% reduction in risk of death, with the confidence interval's upper bound over 1.0.

The authors call tislelizumab's OS benefit "clinically meaningful", and Beigene might also point to Eisai's Lenvima, which secured its first-line label based on non-inferiority to Nexavar.

A separate problem for the FDA is the acceptability or otherwise of datasets that were generated largely outside the US. Moreover, Beigene and its partner Novartis have yet to get tislelizumab across the US regulatory line, with Covid delaying an FDA decision in oesophageal cancer, and a second-line lung cancer filing recently being abandoned.

Cross-trial comparisons in 1st-line liver cancer					
			mOS		
Drug(s)	**Company**	**Trial**	**Active**	**Control**	**Stats**
US approved					
Nexavar	Bayer	Sharp	10.7mth	7.9mth*	HR=0.69, p=0.00058
Lenvima	Eisai	Reflect	13.6mth	12.3mth	HR=0.92^
Tecentriq + Avastin	Roche	Imbrave-150	NE	13.2mth	HR=0.58, p=0.0006
Awaiting US approval					
Imfinzi	Astrazeneca	Himalaya	16.6mth	13.8mth	HR=0.86^
Imfinzi + tremelimumab			16.4mth		HR=0.78, p=0.0035
Not US approved					
Camrelizumab + rivoceranib	Jiangsu Hengrui	SHR-1210-III-310	22.1mth	15.2mth	HR=0.62, p<0.0001
Tislelizumab	Beigene/ Novartis	Rationale-301	15.9mth	14.1mth	HR=0.85^
Failed studies					
Opdivo	Bristol Myers Squibb	Checkmate-459	16.4mth	14.7mth	HR=0.85, p=0.075
Keytruda + Lenvima	Merck & Co/Eisai	Leap-002	21.2mth	19.0mth**	HR=0.84, p=0.0227

Note: ^successful only on a non-inferiority basis; *placebo; **Lenvima (all others used Nexavar as control). NE=not estimable

Source: product labels, The Lancet, Esmo & company statements.

Where does this leave Merck & Co? The Leap-002 study of Keytruda combined with Lenvima that features in its Esmo late-breaker was already known to have been a failure.

However, the trial's authors call the combo's median OS benefit, revealed as 21.2 months, "the longest … ever reported in first-line hepatocellular carcinoma phase 3 studies" (a claim clearly made before they had a chance to see Jiangsu Hengrui's camrelizumab plus rivoceranib data).

Merck/Eisai's problem is that Leap-002 logically used as a control not Nexavar but the numerically more efficacious Lenvima. Keytruda already carries a second-line liver cancer label, as does Opdivo, and Merck is not thought to be pursuing approval based on Leap-002.

"The median OS of 19.0 months with Lenvima monotherapy supports its role as a standard of care," the late-breaker's authors conclude.

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Keytruda secures a renal cancer monopoly

BY JACOB PLIETH | SEPTEMBER 07, 2022

Merck & Co should be able to make its recently won claim to have the first anti-PD-(L)1 drug approved for adjuvant treatment of kidney cancer for some time to come.

Judging by two late-breaking abstracts just revealed for the upcoming Esmo conference, its two rivals Bristol Myers Squibb and Roche slipped up here by similarly wide margins. The Checkmate-914 study of Opdivo plus Yervoy, and the Immotion-010 trial of Tecentriq, both showed sub-10% numerical improvements in risk of disease progression versus placebo, but with highly non-significant p values the datasets offer no meaningful value. The authors of each concede that primary endpoints were not met, and the Checkmate-914 investigators note higher discontinuations due to adverse events with Opdivo plus Yervoy than with placebo. Merck won US approval in adjuvant renal cancer based on a 32% reduction in disease progression favouring Keytruda in the Keynote-564 trial, and no doubt reasons for the differing readouts will be discussed at Esmo. Interestingly, Checkmate-914 also had an Opdivo monotherapy cohort, though nothing has been disclosed about this. Perhaps more will be forthcoming when Checkmate-914 is discussed at Esmo's presidential symposium on Sunday.

Cross-trial comparison in adjuvant renal cell carcinoma

		Disease-free survival		
Drug (company)	**Trial**	**Medians**	**Stats**	**Status**
Keytruda (Merck & Co)	Keynote-564	NR vs NR	HR=0.68 (0.53, 0.87), p=0.001	US approved Nov 2021
Opdivo + Yervoy (Bristol Myers Squibb)	Checkmate-914	NR vs 50.7mth	HR=0.92 (0.71, 1.19), p=0.535	Study fail
Tecentriq (Roche)	Immotion-010	57.2 vs 49.5mth	HR=0.93 (0.75, 1.15), p=0.495	Study fail

NR=not reached. HR=hazard ratio (95% confidence intervals in brackets).

Source: product label & Esmo.

Galleri's real-world exhibition disappoints

BY ELIZABETH CAIRNS | SEPTEMBER 08, 2022

Grail finds the path for its liquid biopsy less clear than it might have hoped.

Full data from a study assessing real-world use of a version of Grail's – or is it Illumina's? – multi-cancer screening test has revealed respectable predictive values. But not as respectable as they used to be: an interim data cut, reported last summer, looked better.

An updated version of the liquid biopsy, Galleri, is already on sale in the US as a lab-developed test, and the point of the Pathfinder trial is to convince doctors and payers of the test's utility as a screen for a variety of cancers in seemingly healthy patients. The data might also form part of a regulatory submission. But the diminishing accuracy is a disappointment, though arguably Illumina's investors have bigger problems to worry about.

The 6,600 participant-strong US-based Pathfinder study is the first time Galleri has been used in clinical practice to help guide diagnostic workups. The version of Galleri used in the study is an older one; the marketed version of the test, which sells for just under $1,000, has been tweaked to improve its performance.

Galleri was used to detect cell-free tumour DNA in blood samples from the Pathfinder subjects, all of whom were aged over 50 with or without additional cancer risk factors. The subjects' cancer status was then confirmed at one year.

According to the final cut of Pathfinder, to be presented at Esmo on Sunday, Galleri detected a cancer signal in 92 participants with analysable samples. Cancer was confirmed in 35 of these, giving a positive predictive value (PPV) of 38.0%. This is a drop from the 44.6% figure from the interim cut reported at last year's Asco.

Pathfinder data – accuracy		
	Initial test version	**Refined test version (prespecified analysis)**
True positives	35	25
True negatives	6,235	6,216
False positives	57	33
False negatives	86	95
Patients whose cancer origin was correctly identified	34	22
Sensitivity*	28.9%	20.8%
Specificity	99.1%	99.5%
Positive predictive value	38.0%	43.1%
Negative predictive value	98.6%	98.5%
Cancer origin prediction accuracy	97.1%	88.0%

*Vantage calculation.

Source: Esmo abstract #903O.

In a prespecified analysis, a refined version of the test was used to test participants' banked specimens, without the results being given to doctors or used to guide further steps. The data here were slightly better, with the exception of when Galleri was used to detect the origin of the cancer. The abstract does not say which tumour types were identified – or misidentified.

Accuracy figures were not the main thrust of the Pathfinder trial, however. Its primary endpoint actually concerns the number and types of subsequent tests required, and the time taken, to achieve a solid diagnosis in those in whom Galleri detected a cancer signal. Here, 24 of the true positives (73%) had a concrete diagnosis within three months.

Pathfinder data – primary endpoint			
	True positives	**False positives**	**Total**
N	35	57	92
Extent of diagnostic testing	33*	57	90
Proportion that had at least one imaging test	90.9%	93.0%	92.2%
Proportion that had at least one invasive procedure	81.8%	29.8%	48.9%
Median time to resolution (days)	57	162	79

*Excludes 2 true positives whose evaluation started before test results.

Source: Esmo abstract #903O.

When the interim cut of Pathfinder was released, Stifel analysts said an oncologist they had spoken to believed that the assay's performance was in line with expectations. To what degree the fall in PPV might disappoint cancer specialists is not yet clear, though a disappointment it will surely be.

And getting doctors on side is only part of the problem. Galleri has no reimbursement coverage; this almost never occurs ahead of FDA approval. When Grail filed its IPO in 2022, it said it intended to seek approval of the liquid biopsy in 2023.

A lot has happened since then. Someone will have to grapple with the problems of regulation, reimbursement and uptake, but with Illumina's purchase of Grail very much on the rocks it is uncertain who might will be.

Lumakras's lung cancer shocker

BY JACOB PLIETH | SEPTEMBER 11, 2022

Having promised much, Esmo underdelivers with a late-breaker that appears to hand some advantage back to Mirati.

After a huge build-up, Amgen's Esmo appearance with Lumakras has taken a rather disappointing turn. The company's Codebreak-200 trial, intended to confirm Lumakras's US lung cancer approval, has yielded no overall survival benefit, as well as giving a reminder about liver toxicity, a special late-breaking Esmo abstract has just revealed.

On the face of it this is positive for Mirati, whose stock had traded up when Amgen's opaque topline Codebreak-200 disclosure hinted that all was not well. However, OS could be numerically positive, the Codebreak-200 dataset might yet be approvable, and Mirati still faces a tight deadline to get its competitor, adagrasib, across the US finish line.

The battle is coming down to the wire. Adagrasib faces a December 14 Pdufa date, but this accelerated approval might be under threat should the FDA earlier grant Lumakras a full green light. So has Amgen done enough in Codebreak-200 to secure full approval, and if it has how quickly will the US regulator act?

SURVIVAL REVEALED

Today's late-breaker, which Esmo had moved heaven and earth to include in the conference programme, helps with the first question. PFS, Codebreak-200's primary endpoint, was known to be positive, and the benefit here has been revealed as a 34% reduction in risk of progression versus docetaxel, with high statistical significance of p=0.002.

But this is where the good news ends. Overall survival, a key secondary endpoint, was "not significantly different between treatment arms", the late-breaker states, though it also cautions that Codebreak-200 had not been powered for OS. It is unclear what the statistical bar was for OS, and the abstract is silent on whether any numerical benefit was seen.

Further worry comes in the adverse events summary. 10% of patients experienced liver enzyme elevations, and the incidence of ALT and AST elevations at grade 3 or above was 7.7% and 5.3% respectively. Liver enzyme elevations became a major issue when Amgen recently reported data from Lumarkas's Keytruda combo trial at World Lung.

Still, this is by no means a new concern for Lumakras, whose label already includes dose-modification instructions in the event of grade 3 or 4 liver enzyme elevations, or grade 2 elevations with symptoms; there is no suggestion that Hy's law has been triggered. And the problem concerns

Cross-trial liver enzyme elevation comparisons for Kras inhibitor monotherapy in NSCLC					
		ALT		AST	
Project	Study	Any grade	Gr3+	Any grade	Gr3+
Lumakras	Codebreak-100	15.1%	6.3%	15.1%	5.6%
	Codebreak-200	10.1%	7.7%	10.1%	5.3%
Adagrasaib	Krystal-1	28.3%	4.3%	25.0%	3.4%

ALT=alanine aminotransferase; AST=aspartate aminotransferase.

Source: NEJM, Esmo & Asco.

adagrasib too, though (on a cross-trial basis) not to the same extent.

A separate question is how the market will perceive these findings, and whether the sellside had already done enough to rein in expectations.

Notably, initial hopes were that OS had been hit, albeit perhaps not convincingly, but once Amgen toplined the PFS result analysts started mooting the possibility of no OS benefit, citing study underpowering and extensive patient crossover. There was even some fear that Amgen would not report the OS number at all.

It might also come as a surprise that Codebreak-200, an open-label, second-line trial versus chemo, had PFS as primary endpoint. Typically the gold standard of OS is needed to confirm a remission rate benefit backing an accelerated approval, and using PFS to do this seems strange since PFS is itself a surrogate endpoint.

Still, the FDA will presumably have signed off on the acceptability of Codebreak-200's primary endpoint as confirmation. Some analysts had suggested that a median two-month PFS benefit would be good, but the abstract only provides a one-year landmark analysis – 28% versus 10% – in addition to the hazard ratio.

Investors have to wait until Monday's presidential session to see the curves for PFS and hopefully for OS too, to gauge the benefit fully and to look for positive signs as to the latter. The wait for the FDA's verdict will be longer.

Springworks aims to Defi expectations

BY MADELEINE ARMSTRONG AND JACOB PLIETH | SEPTEMBER 12, 2022

Data in the desmoid tumour niche look strong, but Ayala might provide a cheaper way for investors to play in gamma secretase inhibition.

Springworks Therapeutics looks on course to get its lead project, the gamma secretase inhibitor nirogacestat, approved for desmoid tumours, after presenting strong data over the weekend at Esmo.

However, this is a small niche, and the big hope for the group must be multiple myeloma, where nirogacestat is being trialled in combination with several BCMA-targeting agents – an approach underscored by the strengthened partnership between Springworks and GSK last week.

Still, there are doubts about this approach, with Allogene recently canning its ALLO-715/nirogacestat combo. And any investors seeking exposure to gamma secretase inhibitors might do well to look at Ayala Pharmaceuticals, which just reported early data with its contender, AL102, but which trades at a fraction of Springworks' valuation.

DESMOID NICHE

Ayala's $28m market cap is dwarfed by Springworks' $1.4bn, even with the latter's share price slide in spring, when reality hit for the group.

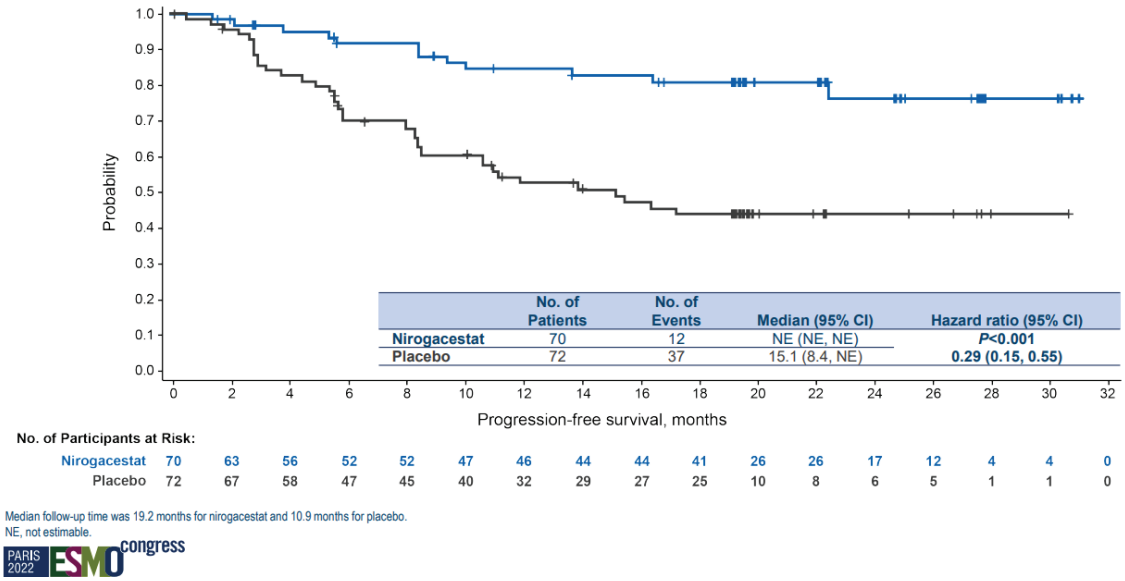
At least Springworks is closing in on desmoid tumours, which it says affect around 30,000 people in the US, with 5,000-7,000 of these under active treatment.

The phase 3 Defi study, which was presented at Esmo on Saturday, showed an impressive 71% reduction in the risk of disease progression with nirogacestat versus placebo; the overall response rate was 41% with drug versus 8% with placebo.

Springworks plans to file nirogacestat for desmoid tumours in the second half, but investors seem understandably nervous about the prospect of a solo launch for a use that looks unlikely ever to become profitable.

Meanwhile, Ayala today reported results from part A of its phase 2/3 Ringside trial, which tested three different doses of AL102. Of 29 patients evaluable at 16 weeks, one had a partial response that was later confirmed; there were also three more unconfirmed partial responses at later timepoints.

Nirogacestat Significantly Reduced Risk of Disease Progression



Source: Esmo & company presentation

Ayala is now taking the 1.2mg once-daily dose into part B of Ringside. The primary endpoint is progression-free survival, giving an opportunity for a cross-trial comparison against nirogacestat.

BCMA COMBOS

As for combo use, Springworks has various approaches in play, with GSK's buy-in the biggest endorsement here. The big pharma's motivation appears to be producing similar efficacy to Blenrep alone, but allowing a lower dose to reduce the ocular toxicity seen with the ADC.

However, as well as Allogene's decision to back away – which was not reflected in Springworks' Esmo presentation – Precision Biosciences does not seem to be getting much joy either with a combination of its allogeneic Car-T PBCAR269A and nirogacestat.

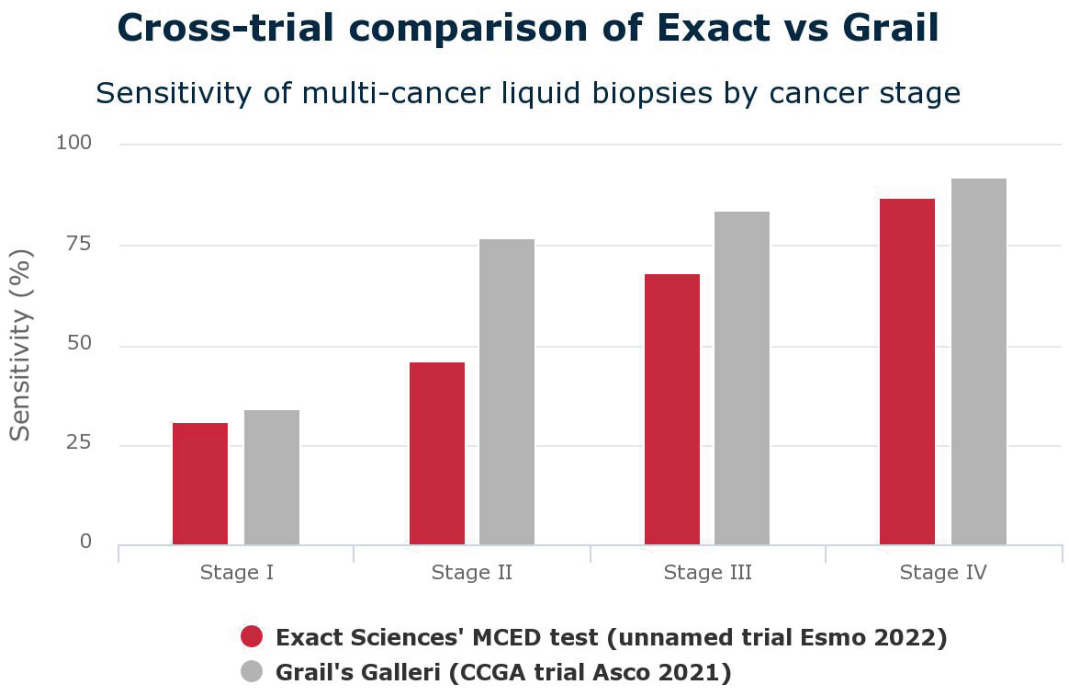
AL102, meanwhile, is being trialled with Novartis's WVT078 in multiple myeloma. Ayala recently said it would start a study of its project in T-cell acute lymphoblastic leukaemia around year-end.

Exact trails Grail on sensitivity

BY ELIZABETH CAIRNS | SEPTEMBER 12, 2022

Exact Sciences spent $1.7bn on Thrive in 2020 to get its hands on that company's liquid biopsy, then called CancerSeek.

Data presented on Friday at Esmo, however, suggest that this assay, which Exact now refers to simply as its multi-cancer early detection (MCED) test, might not be quite as good as the competition. The data come from a retrospective, case-control study intended to validate four blood biomarkers – aneuploidy, DNA methylation, mutations and proteins – detected by the assay. They indicated that the test could detect cancers from 15 organ sites with a mean sensitivity of 61% and mean specificity of 98%. But splitting the data by stage of the cancer suggests that Exact's assay might not be quite as sensitive as Grail/Illumina's Galleri pan-cancer test was in a similar trial, as the graph below shows. This is not a strictly fair juxtaposition, of course, since cross-trial comparisons never are; moreover the tests picked up different tumour types, which will have affected their accuracy figures. Exact is currently conducting a larger case-control trial, results of which will determine the final design of the MCED test, which will next year go into a pivotal US study called Soar.



Source: Company communications, Asco, Esmo.

Double trouble for Lumakras

BY JACOB PLIETH | SEPTEMBER 12, 2022

Key data omitted from Codebreak-200's late-breaking abstract reveal cases of drug-induced liver injury, and overall survival that points the wrong way.

Anyone thinking that concerns over Amgen's Lumakras, raised when the drug's late-breaking abstract went live last night, were over was in for a second surprise today. The presentation just given at Esmo heaps more worries on the Kras inhibitor, approved for lung cancer on an accelerated basis.

The biggest concerns from the potentially confirmatory Codebreak-200 trial are a disappointing median progression-free survival benefit, overall survival favouring docetaxel, and two cases of drug-induced liver injury on top of the liver enzyme elevations already disclosed. Individually each might be allayed, but taken together they boost Mirati, whose investors will see fresh doubts about Lumakras's full approvability.

Full lung cancer approval will be down to the FDA, which will now scrutinise Codebreak-200. Mirati's rival Kras inhibitor adagrasib faces a December 14 Pdufa date, and depending on timelines full Lumakras approval risks jeopardising Mirati's chances of obtaining an accelerated green light for adagrasib.

For Codebreak-200's lead investigator, Dr Melisa Johnson from the Sarah Cannon Research Institute at Tennessee Oncology, this was a highly positive study. "It supports [Lumakras] as a new second-line standard for patients with Kras G12C NSCLC," she told an Esmo press conference this morning.

Others were not so sure. Another lung cancer

doctor, City of Hope's Dr Jack West, tweeted in light of the abstract that hepatotoxicity concerns and lack of an OS benefit were disappointing given the cost difference between Lumakras and docetaxel, $18,000 versus about $2,000 a month respectively. He also questioned whether docetaxel represented a real comparator, and said few doctors gave this chemotherapy with enthusiasm.

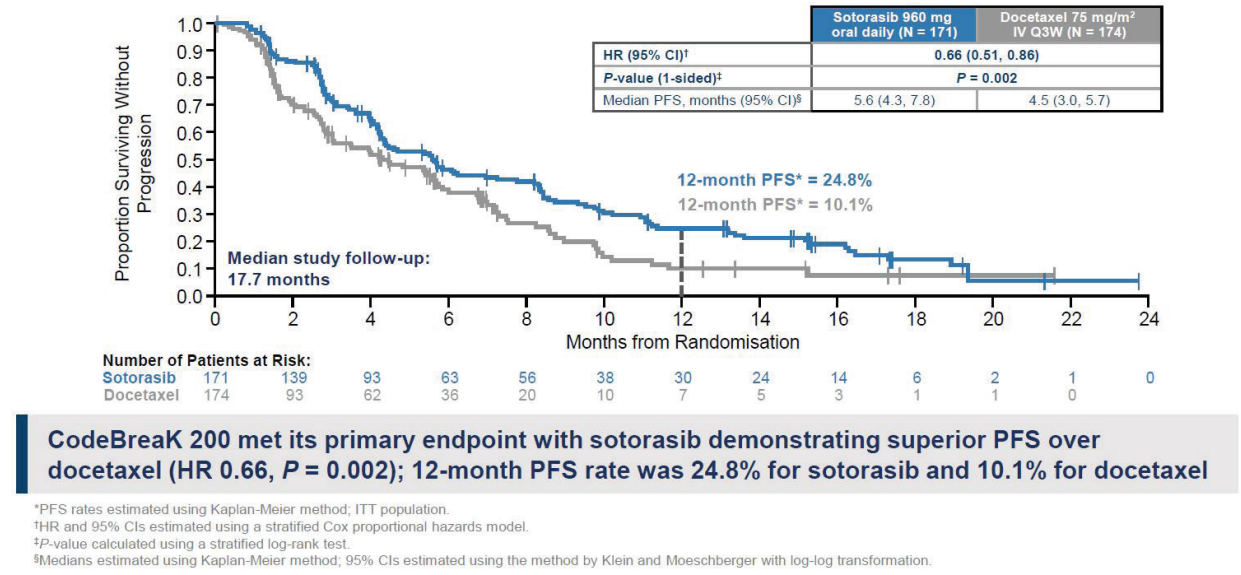
MISSING

It is noteworthy that Esmo, having first gone out of its way to let Amgen to present Codebreak-200 as a late-breaker, then allowed an abstract to be published that omitted vital aspects of the data and painted the result in a better light than became evident at today's full presentation.

Perhaps the biggest red flag is liver toxicity. The abstract had revealed a slightly higher rate of grade 3 or higher ALT elevation versus the earlier Codebreak-100 trial, but today it was disclosed that six patients quit treatment because of this, and another two discontinued owing to drug-induced liver injury.

How close is Hy's law, the rule suggesting that patients are at high risk of fatal drug-induced liver injury, to being triggered, Evaluate Vantage asked during the press conference? "Not close," Dr Johnson replied. "The safety signal was pretty similar between [Codebreak-200 and Codebreak-100]. It was amenable to dose reduction."

It also cannot be denied that docetaxel is fairly toxic, explaining doctors' reluctance to use it and desire to find something better. The rates of all severe and serious toxicities in Codebreak-200 were higher for the chemo than for Lumakras, though liver enzyme elevation is not an issue for docetaxel.



CodeBreaK 200 met its primary endpoint with sotorasib demonstrating superior PFS over docetaxel (HR 0.66, *P* = 0.002); 12-month PFS rate was 24.8% for sotorasib and 10.1% for docetaxel

*PFS rates estimated using Kaplan-Meier method; ITT population.
†HR and 95% CIs estimated using a stratified Cox proportional hazards model.
‡*P*-value calculated using a stratified log-rank test.
§Medians estimated using Kaplan-Meier method; 95% CIs estimated using the method by Klein and Moeschberger with log-log transformation.

Source: Dr Melissa Johnson & Esmo.

A second key aspect of the Codebreak-200 data that had been left out of the abstract was the median PFS benefit, the trial's primary endpoint. Instead the abstract touted a 12-month landmark analysis – in hindsight the most flattering part of the survival curves – an unusual move given that the survival analysis was mature.

Today it was revealed that Lumakras extended median PFS by just over a month. Hopes were that the Amgen drug would give mPFS of at least six months, yielding a delta of two months or more, considering a benefit of 6.3 months seen in Codebreak-100. This decline in the data is typical of the move from a single-arm to a randomised phase 3 study.

On a webinar previewing Codebreak-200 yesterday Evercore ISI analysts had opined that a one-month delta, with docetaxel around 4.5 months, would "start to look like a disappointing result". In a press release issued last night Amgen spoke about "the totality of evidence" supporting Lumakras as a treatment option.

Dr Johnson argued that PFS was a meaningful primary endpoint, and insisted that the curves were robust, separating early and remaining separated.

OVERALL SURVIVAL DETRIMENT

No such luck for the gold standard of OS, however, which in the Codebreak-200 abstract was said to be not statistically different between Lumakras and docetaxel.

Today the failure to hit this key secondary endpoint was quantified: not only was there no numerical benefit for Lumakras, but at median the survival analysis favoured docetaxel by nearly a month. Across the whole study the hazard ratio was above 1.0, meaning that patients on Lumakras were at numerically greater risk of death than those taking docetaxel.

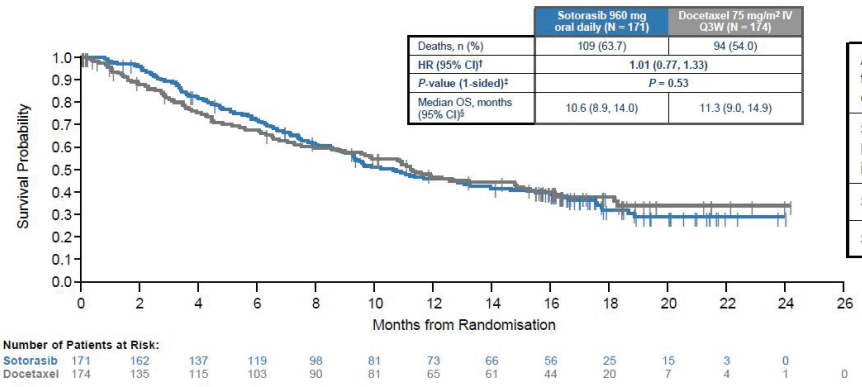
Of course there are caveats here, the biggest of which is patient crossover: Dr Johnson said 34% of control cohort patients switched to a Kras G12C inhibitor after progressing on docetaxel. This will clearly have confounded the OS analysis, though some might say that it just undermines the case for Lumakras to be given before docetaxel.

It must also be stressed that Codebreak-200 suffered from underpowering; it had originally been envisaged as a 650-patient trial, but an FDA-requested February 2021 protocol amendment implemented in the wake of Amgen's Codebreak-100 data halved the targeted recruitment and allowed crossover.

Whether Lumakras consolidates its status as a second-line treatment for Kras-mutated NSCLC now depends on the FDA upholding the accelerated approval and formalising it, and on a real-world balance of other factors including toxicity profiles and cost.

This is an updated version of a story published earlier.

OS: Sotorasib vs Docetaxel*



	Sotorasib 960 mg oral daily (N = 171)	Docetaxel 75 mg/m² IV Q3W (N = 174)
Deaths, n (%)	109 (63.7)	94 (54.0)
HR (95% CI)†	1.01 (0.77, 1.33)	
P-value (1-sided)‡	*P* = 0.53	
Median OS, months (95% CI)§	10.6 (8.9, 14.0)	11.3 (9.0, 14.9)

	Sotorasib	Docetaxel
Any subsequent treatment, including crossover**	36%	42%
Subsequent $KRAS^{G12C}$ inhibitor, including crossover	4%	34%
Subsequent chemo	21%	12%
Subsequent IO	9%	6%

*OS rates estimated using Kaplan-Meier method; ITT population.
†HR and 95% CIs estimated using a stratified Cox proportional hazards model
‡ *P*-value calculated using a stratified log-rank test.
§Medians estimated using Kaplan-Meier method; 95% CIs estimated using the method by Klein and Moeschberger with log-log transformation.
**Patients (16.4% in sotorasib arm, 5.2% in docetaxel arm) were treated beyond progression

Source: Dr Melissa Johnson & Esmo.

Regeneron stakes its Lag3 claim

BY JACOB PLIETH | SEPTEMBER 13, 2022

Fianlimab maintains its leading activity, but more Opdualag competition is not far behind.

Bristol Myers Squibb got to the market first with relatlimab, but competition in Lag3 blockade is slowly mounting. At Esmo Regeneron nailed its colours to the mast, claiming efficacy for its anti-Lag3 MAb fianlimab, combined with Libtayo, that on a cross-trial basis exceeded that of Bristol's Opdualag.

Notably this was in front-line melanoma, the indication in which Bristol markets Opdualag, a fixed-dose combo of relatlimab and Opdivo. Melanoma is well served by immuno-oncology, something acknowledged by the other most advanced Lag3 player, Merck & Co, which is instead running pivotal studies of favezelimab in Hodgkin's and colorectal cancers.

Like Bristol and Regeneron, Merck is combining its Lag3 offering with an in-house anti-PD-(L)1, namely Keytruda. This is the case with all earlier-stage assets too, Opdualag seemingly having set a blueprint for biopharma to follow in terms of building intellectual property protection.

FIANLIMAB

Regeneron's fianlimab had already shown promising signs of efficacy at 2021's Asco meeting, where an initial 33 PD-(L)1 inhibitor-naive melanoma patients given a Libtayo combo yielded a 64% overall remission rate by investigator review.

At Esmo over the weekend Regeneron updated efficacy in these and seven additional patients,

as well as presenting data in a further 40 subjects in a separate treatment-naive melanoma cohort. Together these yielded a 64% ORR, which on a cross-trial basis beat the 43% in Bristol's registrational Relativity-047 trial, though this number had been assessed by more robust independent review.

Regeneron also provided an analysis estimating that median progression-free survival was 24 months, seemingly far superior to the 10.1 months in Opdualag's label. However, caution must be used here: the survival curve for fianlimab plus Libtayo is heavily censored, and with just a few more early events the median could easily halve.

But there is no denying that Regeneron has a promising pipeline project on its hands. Not long ago it started a pivotal front-line melanoma trial, and says it is planning a second in the adjuvant setting. The group also recently took control of Libtayo from its partner, Sanofi.

Cross-trial comparison in 1st-line melanoma					
Project	**Trial**	**ORR***	**mPFS**	**Grade ≥3 AEs^**	**AE-related discontinuation**
Opdualag vs Opdivo	Relativity-047	43% vs 33%	10.1mth vs 4.6mth (HR=0.75)	40%	18%
Fianlimab + Libtayo	NCT03005782	64%	24mth**	20%	15%

Notes: *by independent review for Opdualag, and investigator-assessed for fianlimab; **cross-trial comparison not appropriate owing to extensive censoring of PFS curve; ^rate of treatment-related AEs leading to death was 0.8% for Opdualag, and 2.5% for fianlimab.
Source: prescribing information & Esmo.

Merck had also reported initial favezelimab data at last year's Asco, in late-line microsatellite-stable colorectal cancer, where the activity it saw was mostly in PD-L1-positive patients.

Favezelimab plus Keytruda is now in phase 3 in relapsed PD-L1-positive colorectal cancer, and in relapsed/refractory Hodgkin lymphoma. As for melanoma, Merck is running the phase 1/2 Keymaker-U02 trial, whose "substudy 02C" recruits stage III melanoma patients who are candidates for neoadjuvant therapy, and one of the many combos it tests is favezelimab plus Keytruda.

Selected R&D projects with activity at Lag3		
Project	**Company**	**Status**
Anti-Lag3 MAbs		
Favezelimab (MK-4280)	Merck & Co	Ph3 Keytruda combo for r/r Hodgkin lymphoma
		Ph3 Keytruda combo for 2nd-line PD-L1+ve colorectal cancer
Fianlimab (REGN3767)	Regeneron	Ph3 Libtayo combo for 1st-line melanoma
INCAGN2385	Incyte	Ph2 retifanlimab combo
BI 754111	Boehringer Ingelheim	Ph2 BI 754091 combo
LBL-007	Beigene/Leads Biolabs	Ph1/2 tislelizumab combo
Encelimab (TSR-033)	GSK/Anaptysbio	Ph1 solid tumours
IBI110	Innovent Biologics	Various ph1 trials
Sym022	Symphogen	Various ph1 trials
HLX26	Shanghai Henlius/Fosun	Ph1 HLX10 combo
Anti-Lag3 x PD-1 bispecific MAbs		
Tebotelimab	Macrogenics/Zai Lab	Ph2/3 combos in Her2+ve gastric cancer
RO7247669/ RG6139	Roche	Ph2 vs Opdivo in squamous oesophageal carcinoma
EMB-02	Epimab Biotherapeutics	Ph1/2 solid tumours
FS118	F-star Therapeutics	Ph1/2
IBI323	Innovent Biologics	Ph1

Source: Evaluate Pharma & clinicaltrials.gov.

Among competitors Immutep's ieramilimab is notable for having relied on another company to provide the PD-1 part of a combo – being the subject of a deal with Novartis. However, that PD-1 was spartalizumab, which the Swiss firm has since deprioritised in favour of the Beigene-derived tislelizumab.

The pipeline is notable also for including several projects that combine Lag3 with PD-1 blockade in a single, bispecific MAb. It includes Macrogenics' tebotelimab, and RG6139, an asset about which Roche has so far said relatively little.

And Esmo also featured a poster on another anti-Lag3 MAb, Incyte's INCAGN02385. This concerned a monotherapy trial in solid tumour patients in the salvage setting, and the company was unable to report anything beyond stable diseases.

Nevertheless, Incyte boasted of good tolerability, linear pharmacokinetics and promising receptor occupancy, on the basis of which it selected 350mg once every two weeks as the dose for mid-stage studies in combination with retifanlimab.

Movers – Kras backfires

BY JACOB PLIETH, AMY BROWN, MADELEINE ARMSTRONG & EDWIN ELMHIRST | SEPTEMBER 12, 2022

Inhibition of Kras dominated Esmo, though probably not in the way some had hoped.

Esmo promised to be a conference whose most important topic was Kras, and this is how it turned out. However, investors were left bemoaning Amgen's move to push a Lumakras late-breaker into the meeting, an ultimately costly strategy that contributed to $12bn of value being wiped from their company's market cap.

The jury is still out on how this affects Amgen's rival Mirati, but there was better news for several small biotechs, Evaluate Vantage's analysis of stock movers over the Esmo period finds. Relay and Deciphera have come out of Esmo as clear small-cap successes, and there were some big moves during the actual meeting, even if overall the losers outnumbered the winners.

To be fair, only part of the $12.2bn in market cap lost by Amgen can be accounted for by Lumakras's disappointment in the Codebreak-200 trial. Amgen

also had to contend with US approval of Bristol Myers Squibb's Tyk2 inhibitor Sotyktu; the psoriasis drug, greenlit with an unexpectedly clean label, will likely hit sales of Amgen's blockbuster Otezla.

This analysis calculates share price moves from the close before the titles of presentations and abstracts briefly appeared on Esmo's website on August 18, and yesterday, September 13, when the conference formally ended.

Selected Esmo 2022 risers*		
Company	**Share price gain**	**Comment**
Relay Therapeutics	22%	See text
Deciphera	21%	See text
Regeneron	12%	Regeneron stakes its Lag3 claim
Clovis Oncology	9%	See text
Ayala	8%	Springworks aims to Defi expectations
Daiichi Sankyo	7%	Esmo 2022 preview
Springworks	6%	Springworks aims to Defi expectations
Mirati	5%	Mirati needs some colorectal cancer urgency
Roche	1%	Sanofi and Roche's duelling Serd duds

Note: *share price change calculated from Aug 18 to Sep 13.

Among the risers Relay stood out, with data on its FGFR2 inhibitor RLY-4008 being impressive enough to fuel a $300m secondary; the stock had been up 60%, but the raise managed to wipe out a big chunk of the Esmo-driven gains.

An 88% overall response rate in the RLY-4008 dose selected to take forward in cholangiocarcinoma represented double that of what existing pan-FGFR inhibitors have shown, noted Dr Chiara Braconi of the University of Glasgow, who discussed the data at Esmo. RLY-4008's selectivity might explain why a different toxicity profile seems to be emerging.

Diarrhoea and hyperphosphotaemia, the biggest problems with pan-FGFR agents, were seen at "clinically insignificant" levels with RLY-4008, though stomatitis and nail toxicities were more common. Still, the data are early, and Dr Braconi said open questions included ensuring that the trial's population was not biased for good responders, and whether RLY-4008 can also keep secondary resistance mechanisms under control.

Relay will report full data from the trial next year – the phase 1 portion included other FGFR-driven tumour types – and have the pivotal cholangiocarcinoma cohort fully enrolled by the first half.

Regeneron reported promising melanoma data with its anti-Lag3 MAb fianlimab, but its 12% climb owed much to positive results with high-dose Eylea. Concerns over the desmoid tumour market hit Springworks and Ayala, though both rose over the Esmo period, while Clovis got a lift from the Athena-Mono trial of Rubraca in first-line ovarian cancer maintenance showing further benefit across various subgroups.

Mirati was up 5%, though this belies a 4% fall yesterday on concerns that lack of an overall survival benefit, revealed in Lumakras's Esmo presentation, might jeopardise the chances of Mirati's adagrasib securing US approval without randomised data.

Deciphera is struggling to rebuild confidence after a big setback with its marketed GI tumour drug Qinlock, and updates on two follow-on assets were well received. Most encouraging were phase 2 data on vimseltinib, a CSF1 receptor kinase inhibitor for tenosynovial giant cell tumours, a rare cancer of joint tissue.

ORR hit 53% in a cohort of patients with no prior targeted therapy, and 46% in those previously treated with Daiichi Sankyo's Turalio, which also hits CSF1R. Turalio last year became the first drug to win approval for TGCT based on ORR of 38%, with no responses seen for control; it carries a boxed warning of potentially fatal liver injury.

MANY FALLERS

Amgen's $12bn of lost valuation dwarfed all other Esmo fallers, of which there were many. Immunocore made the classic mistake of cherrypicking data for an IMC-F106C abstract that overpromised, and paid the price when its Esmo presentation disappointed accordingly.

Merck & Co also lost $12bn, though this had more to do with ongoing questions over a possible bid for Seagen and less with the group's own low-key meeting, which featured several clinical failures. Seagen itself fell 15% even though an Esmo update backed the potential of a Padcev plus Keytruda combo in bladder cancer.

Exelixis scored a presidential session slot with full presentation of the Cosmic-313 trial that largely confirmed what was suspected when the company toplined the data in July: despite significantly extending progression-free survival, adding Cabometyx to Opdivo and Yervoy in first-line renal cancer means more toxicity.

The fact that Cosmic-313 met its primary endpoint of progression-free survival was pretty much where the good news ended. "Response rates we saw in both arms, as well as the complete response rates, fell short of what we in the RCC community had hoped for," said Dr Sumanta Pal of City of Hope, who reviewed the study for Esmo.

Complete responses of 3% were seen in both arms, which tested Cabometyx, Opdivo and Yervoy versus Opdivo and Yervoy. Stifel analysts say this showed that adding Cabometyx did not produce deeper responses, possibly because Yervoy use had to be dialled back to rein in liver toxicity. Whether an overall survival benefit will emerge remains a crucial unknown – final OS analysis has yet to happen.

And it was a Kras setting that featured Esmo's biggest share price loser: an update from a phase 1/2 study of Cardiff Oncology's PLK1 inhibitor onvansertib in second-line Kras-mutated colorectal cancer did not look any better than the earlier look at the Asco-GI meeting that disappointed investors.

Meanwhile, Gritstone climbed after presenting early molecular response data with its vaccine-based immunotherapies, Slate v1 and Slate-Kras, in combination with Opdivo and Yervoy in Kras-mutated solid tumours – but was a loser over the whole Esmo period.

Selected Esmo 2022 fallers*		
Company	**Share price fall**	**Comment**
Cardiff Oncology	-28%	See text
Plus Therapeutics	-26%	Early data on rhenium-186 nanoliposome from Respect-GBM glioblastoma trial
Immunocore	-22%	Actual ORR with IMC-F106C is 23%, versus 38% cited in abstract
Zymeworks	-22%	Questions raised over how ZW49 is differentiated vs Enhertu
Adaptimmune	-17%	44% ORR with ADP-A2M4CD8 across various cancers
Immutep	-16%	Regeneron stakes its Lag3 claim
Seagen	-15%	Cohort K of EV-103 trial gives ORR of 45% for Padcev, vs 65% for Padcev + Keytruda
I-Mab Biopharma	-13%	Lemzoparlimab continues to disappoint
Exelixis	-11%	See text
Gritstone Bio	-10%	See text
Amgen	-9%	Double trouble for Lumakras
Incyte	-7%	Regeneron stakes its Lag3 claim
Merck & Co	-6%	The new liver cancer entrants line up
Immatics	-6%	Readacross from Immunocore's disappointment in Prame
Biontech	-4%	ORR in trial of BNT211 fell from 43% to 25%
Bristol Myers Squibb	-4%	Keytruda secures a renal cancer monopoly

Note: *share price change calculated from Aug 18 to Sep 13.

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