Evaluate Vantage

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Snippet roundup: Clinical disappointments for Cara, Bioclin and Sumitomo

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Welcome to your weekly roundup of *EP Vantage*'s snippets – short takes on smaller news items.

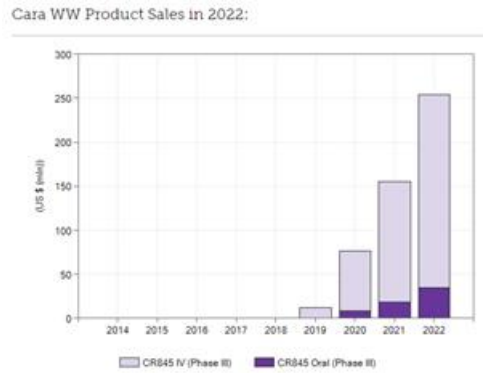
This week, June 26 to 30, 2017, we had thoughts on the following: Cara crashes on phase II mostly-miss; Bioclin flop sends an early warning for combination trials; Sumitomo's cancer push takes a stumble; Portola breezes past the FDA; EHA – With Eliana CAR-T payers have their work cut out.

These snippets were previously published daily via twitter.

Cara crashes on phase II mostly-miss

30 June, 2017

The phase IIb Clin2002 trial of Cara Therapeutics' oral painkiller CR845 has hit its primary efficacy measure – but only at one of the three dose levels studied, and only in a subset of patients. The study enrolled 476 patients with osteoarthritis of the hip or knee experiencing moderate to severe pain. The highest dose of the peripherally selective kappa opioid agonist, 5mg twice-daily, prompted a 39% reduction in mean joint pain score versus placebo at eight weeks (p=0.043) – but only in patients with OA of the hip. In both hip and knee patients, the same dose caused a 35% reduction, but this did not hit significance. The other two doses, 1mg and 2.5mg, did not hit. Cara says its next steps are to start another phase II trial with higher doses, prompted by the apparent dose-response: 5mg and 10mg tablets will be tested, and more patients with OA of the hip will be enrolled. It is true that it is the IV form, under investigation for postoperative pain and uraemic pruritis in kidney disease patients, that is forecast to become Cara's more important product. But this is a bad blow for the company, whose shares tanked 30% in the pre-market.



Bioclin flop sends an early warning for combination trials

29 June, 2017

With bad news for Bioclin's sole pipeline asset, B-701, comes a reminder that biopharma's monster effort to combine anything and everything with immuno-oncology will not be plain sailing. An investigator-initiated study of B-701 with Merck & Co's Keytruda in bladder cancer has been scrapped owing to safety concerns, its listing on Clinicaltrials.gov reveals. B-701 is an anti-FGFR3 MAb, and the trial was one of 54 involving Keytruda combined with an immuno-oncology agent, a recent *EP Vantage* report into anti-PD-(L)1 combos found. Not all is lost for Bioclin, which raised $30m in a series B round in March, and whose own phase I/II trial looks at B-701 monotherapy in relapsed bladder cancer. Another similarly acting compound, Lilly's LY3076226, is an anti-FGFR3 antibody-drug conjugate in phase I in various cancers. It is clear that without a strong mechanistic rationale, and a trial design that aims to establish the additive benefit of two agents, many of the industry's immuno-oncology combinations will underwhelm, and in the case of B-701 Bioclin must hope that any safety concerns likewise came not from its project but from the combo.

Sumitomo's cancer push takes a stumble

27 June, 2017

Sumitomo Dainippon seems to have confirmed that the cancer stem cell-targeting agent napabucasin is a dud. The early unblinding of the Brighter study, which tested the agent in combination with chemotherapy in gastric cancer and is not expected to show a survival advantage, follows the failure of a phase III monotherapy trial in 2014. And, though three large phase III chemo combo studies in colorectal, lung and pancreatic cancers are continuing, the chance of success elsewhere must now be considered low. The project, which targets the STAT3 signalling pathway, was considered Sumitomo's most valuable pipeline hope; the company has lost 9% or around $500m of market cap on the news. Napabuscasin was gained with the acquisition of Boston Biomedical in 2012 – the March exit of founder Chiang Li, who had continued to run the Boston-based developer for Sumitomo, was taken by some as a bad omen. Still, with the painful loss of Latuda to generics next year the Japanese company is unlikely to be deterred from its M&A strategy – and having recently completed the $220m takeover of Tolero it looks like oncology will remain a focus.

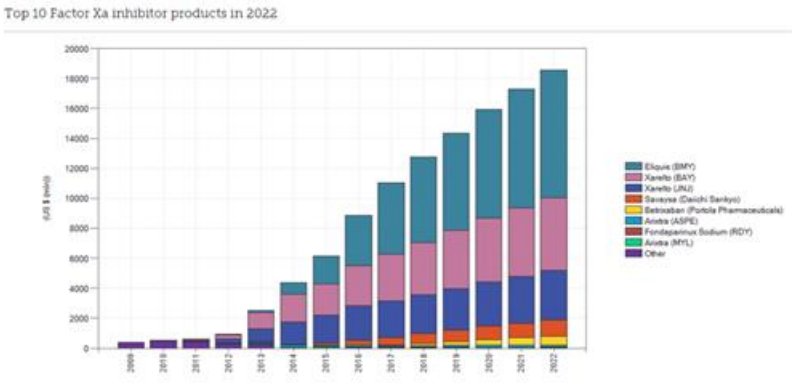
Napabucasin phase III programme

Trial	Conditions; regimens	Status	Enrollment	NCT ID
Brighter	Gastric cancer; + paclitaxel	Unblinded by DSMB June 2017: unlikely to meet primary endpoint of OS advantage, trial to continue open label.	700	NCT02178956
CanStem43L	Non-small-cell lung cancer; + paclitaxel	Recruiting (data due end 2019)	870	NCT02826161
CanStem303C	Colorectal cancer; + FOLFIRI	Recruiting (data due mid-2020)	1250	NCT02753127
CanStem111P	Pancreatic cancer; + nab-paclitaxel and gemcitabine	Recruiting (data due end 2020)	1132	NCT02993731

Portola breezes past the FDA

26 June, 2017

Considering the equivocal data Portola's blood thinner betrixaban posted in phase III it has had a remarkably clean run past the FDA. US approval of the factor Xa inhibitor on Friday for the treatment of venous thromboembolism in patients with acute medical illness seems to have taken shareholders by surprise, with the company's stock jumping 47% on the news. The drug, trademarked Bevyxxa, has an advantage over rivals in that it is the only once-daily oral VTE drug that can be used in the home setting – where, according to Portola, most deep-vein thrombosis events occur – as well as for hospitalised patients. But its chances of commercial success will depend on canny marketing by Portola, particularly after to its failure to beat Lovenox in high-risk patients in its pivotal trial, Apex. *EvaluatePharma*'s sellside consensus forecasts sales of $579m in 2022, putting Bevyxxa far behind the leaders of the factor Xa class, Bayer's Xarelto and Bristol-Myers Squibb's Eliquis.



EHA – With Eliana CAR-T payers have their work cut out

26 June, 2017

Assuming that the first wave of CAR-T projects secure approval, how likely they are to amount to a "cure" will weigh heavy with payers. And one reason why Saturday's update from Novartis's Eliana study of CTL019 in paediatric ALL should be scrutinised carefully is that numerous remitting subjects seem to relapse six months after treatment. The Swiss group was cagey about the six-month benefit – 83% of subjects had gone into complete remission at three months – but said "a majority" were likely to be disease-free still at six months. In fact the data, presented at the European Haematology Association meeting, allow a better guess to be made: the cited six-month probability of relapse-free survival is 75%, indicating – by extrapolation and in an admittedly small number of subjects who have data available – that the six-month complete remission rate falls to about 62%. What is worse, 16 subjects discontinued before infusion – this was also a problem in Novartis's lymphoma trial, Juliet – so the strict intent-to-treat remission rate is 62%, while the suggested six-month intent-to-treat overall response is 51%. No doubt these issues will be picked over at length at CTL019's July 12 US adcom.

Dissecting Novartis's Eliana study

		Note
Subjects enrolled	88	4 are still pending infusion
Subjects infused with CTL019	63	7 manufacturing failures, 9 deaths or AEs pre-infusion
3mth ORR	83%	52 of 63 evaluable subjects
3mth ORR (ITT)	62%	52 of 84 evaluable subjects
6mth ORR	62%	Indicative value, suggested by cited 6mth 75% relapse-free rates
6mth ORR (ITT)	51%	Indicative value, suggested by cited 6mth 75% relapse-free rates

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