Evaluate Vantage

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Esmo 2020 – Lilly’s latecomer scores in early breast cancer

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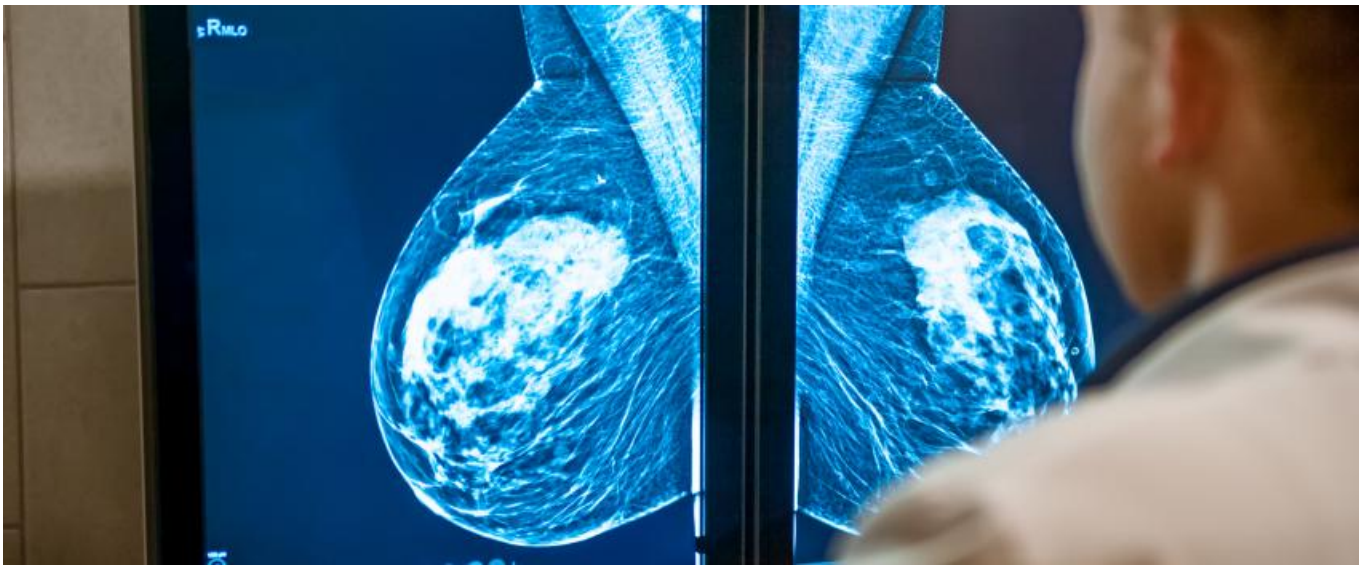


Verzenio looks set to move into a valuable adjuvant setting as Pfizer’s miss with Ibrance is laid bare.

The importance of picking the right population was demonstrated at the virtual Esmo conference today, which saw presentation of two adjuvant breast cancer trials with competing CDK4/6 inhibitors: Lilly’s Verzenio and Pfizer’s Ibrance. The results were dramatically different, with the former showing a 25% reduction in recurrence of cancer and the latter showing absolutely nothing.

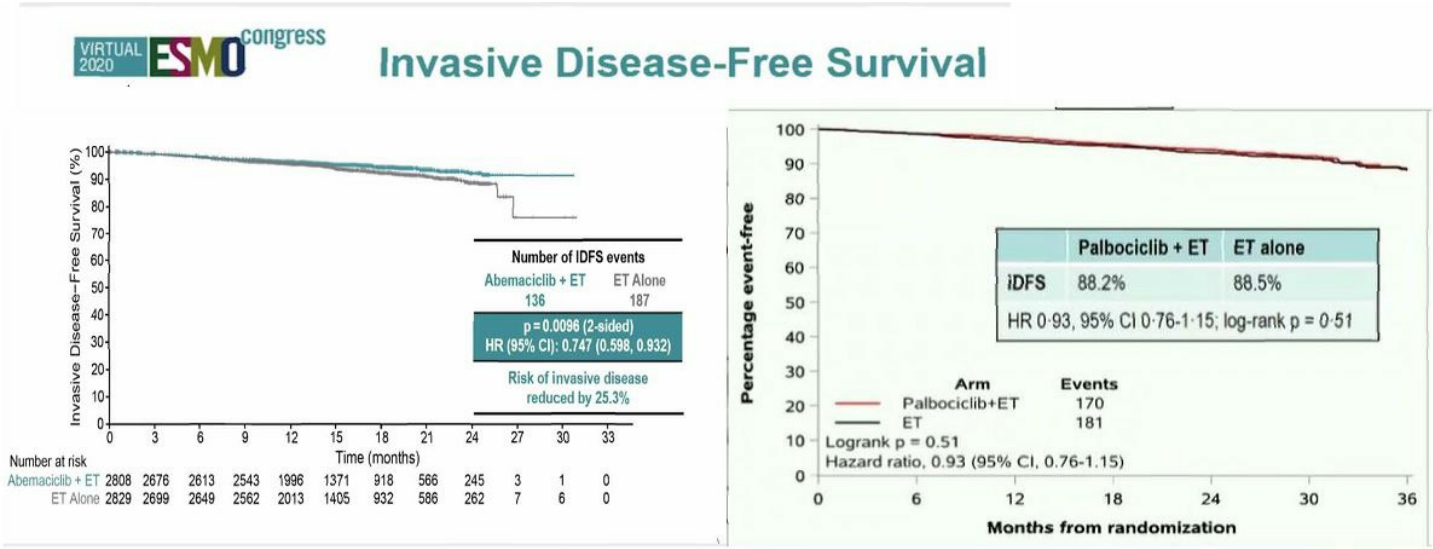
It was already known that the former’s MonarchE trial had succeeded and the latter’s Pallas study had failed; reviewing physicians concluded that MonarchE’s focus on patients at a very high risk of relapse most likely explained the divergent findings. And with a staggering 42% of Ibrance patients discontinuing treatment early in Pallas, with adverse events causing almost two-thirds of drop outs, it seems there is little for Pfizer to salvage here.

Both MonarchE and Pallas studied early-stage patients with the most common form of breast cancer – hormone receptor-positive/Her2-negative. Surgery, chemo or radiotherapy and hormone adjuvant therapy, which can be dosed for up to a decade, cure most patients. However, up to 30% relapse, and preventing or delaying this disease recurrence, by adding a CDK4/6 inhibitor to adjuvant endocrine therapy, was the aim of the trials.

MonarchE used clinical and pathological risk factors such as lymph node involvement and tumour size to guide enrolment. Pallas, meanwhile, simply stated that women must have stage II or III cancer. Both studies tested Verzenio or Ibrance dosed for two years on top of standard adjuvant endocrine therapy, and both used invasive disease-free survival (iDFS) as the primary endpoint.

While MonarchE produced an early and clear separation of the curves, virtually no difference could be seen in Pallas.

Primary endpoint analysis of MonarchE (left) and Pallas (right) trials



Two-year iDFS rates of 92.2% vs 88.7% in the Verzenio and hormone therapy alone arms were deemed statistically different, equating to 25.3% reduction in the risk of cancer returning within two years. The result is likely to beat expectations in the financial community; ahead of Esmo, sellside reports mentioned investor expectations of a 10-20% risk reduction.

Dr Stephen Johnston of Royal Marsden Hospital in London, MonarchE's lead investigator who presented the findings, said Verzenio prevented metastases mainly to the bone and liver. Overall, the risk of distant recurrence of cancer, a key secondary measure of the trial, was reduced by 28.3% (p=0.0085).

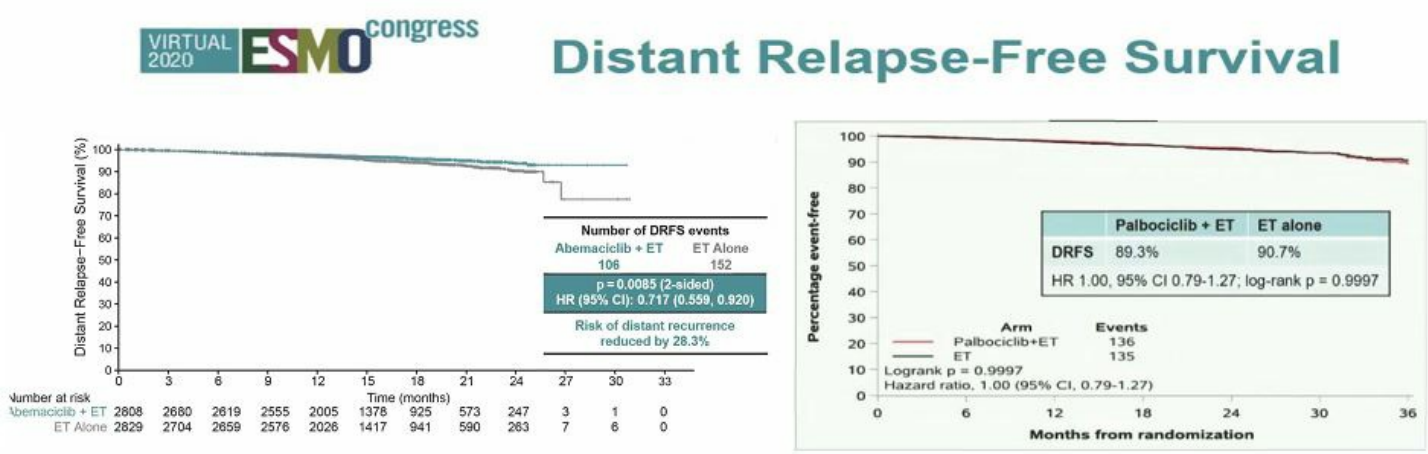
In Pallas, iDFS rates came in at 88.2% for Ibrance and 88.5% for control, with no difference seen on the secondary measure either. The Ibrance arm was closed at a second interim readout, but lead investigator Dr Erica Mayer said women would continue to be followed. "These are early days for the Pallas trial, and for MonarchE too," she said.

This is certainly true, with median follow-up in MonarchE at 15 months and 23.7 months for Pallas. Still, with more than 75% of planned events having occurred in MonarchE, which triggered the interim readout presented, Dr Johnston believes that the findings should prove robust.

Relatively low rates of disease recurrence makes designing studies in this setting difficult, and Dr Johnston said a lot of time was spent figuring out what to expect in the control arm of MonarchE. The study was powered on the assumption that 20% of patients would relapse within five years.

"So many times these adjuvant trials fail because the control arm does better than predicted," he said in a telephone interview. "We really tried to nail down the patients [via enrolment criteria] with up to 20% risk of relapse. That's where we thought we would be able to make a difference, and we have."

Secondary endpoint analysis of MonarchE (left) and Pallas (right) trials



Many of the high-risk patients in MonarchE probably already had micro-metastases, Milan University's Dr Giuseppe Curigliano told *Evaluate Vantage*, which could help explain the benefit seen. CDK4/6 inhibitors are known to work in metastatic disease, with Verzenio and Ibrance both approved in this setting.

Dr Curigliano said another theory for Pallas's failure was a high proportion of patients with endocrine resistance

and/or less sensitivity to CDK4/6 inhibition. He also pointed to the 42% dropout rate in Pallas, due to Ibrance toxicities.

This compares with a 16.6% dropout rate in the Verenzio arm of MonarchE, though encouragingly only 5% of these were due to diarrhoea, which is thought to be the most troubling side-effect of the Lilly drug.

“In my opinion the different outcome is much more likely to be because of the different patient populations,” he concluded. Dr Curigliano reviewed MonarchE for an Esmo press conference.

Of course different efficacy of the two drugs cannot be ruled out, although Dr Johnston noted that Ibrance and Verenzio were considered to work to the same extent in metastatic disease, despite having different side effects and dosing schedules. Pfizer can also take comfort from the fact that physicians widely precluded any implications for the metastatic setting.

Still, Pfizer can surely rule out any adjuvant use for Ibrance – the sellside has slashed almost $2bn from 2026 sales as a result, according to *EvaluatePharma's* consensus forecasts.

Verzenio arrived in the metastatic setting four years after Ibrance, sales of which are set to breach $5bn this year. This situation is therefore unquestionably a win for Lilly, which looks set to launch Verzenio in a substantial new patient population – perhaps 50% larger than metastatic breast cancer – with no competition from the incumbent.

This story has been corrected to clarify that of the 42% drop out rate in Pallas, only two-thirds were due to adverse events.