Evaluate Vantage

June 04, 2016

Asco 2016 – Array to test Braf/Mek combo in colorectal cancer

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Array BioPharma's announcement yesterday of a plan to study its Braf/Mek inhibitor combination of encorafenib and binimetinib in a poor-performing subpopulation of colorectal cancer patients marks the first major expansion of the drugs' clinical programme since last year's European deal with Pierre Fabre.

Array and Pierre Fabre plan to initiate a phase III study in relapsed Braf-mutant colorectal cancer CRC in collaboration with Merck KGaA, codenamed Beacon CRC, which would allow the evaluation of a potential triple combination with Erbitux. The release was made in connection with the presentation of updated phase II data on encorafenib with Erbitux in Braf-mutant CRC at Asco.

Combination progress

Beacon CRC will enrol 615 patients, who will be randomised to the triple combination, a doublet of encorafenib and Erbitux, or a control arm of Erbitux plus investigator's choice of chemotherapy. Under the pre-existing arrangement, Array pays 60% of the Braf/Mek combo's development costs and Pierre Fabre the remainder; Merck's financial involvement in the trial has not been disclosed, although it will presumably underwrite a proportion of Beacon CRC's cost and supply the Erbitux.

Braf mutations are thought to affect 8-15% of CRC patients, and these have a poorer prognosis than wild-type. Furthermore, studies with Braf inhibitors as monotherapy in this patient group have, in contrast to melanoma, shown very limited efficacy. Historical data suggest that overall survival in relapsed Braf-mutant CRC is less than six months. Nevertheless, testing for Braf mutations, albeit usually as part of a panel, has become more common in CRC, despite the lack of any drug treatments, because of the possibility of enrolling patients into clinical trials.

Array presented updated results at Asco on Saturday from a phase II study of the doublet of encorafenib with Erbitux and a triplet with Novartis's investigational PI3K inhibitor alpelisib in advanced Braf-mutant CRC. The 102-patient phase II study showed a median progression-free survival of 4.2 months for the doublet and 5.4 months for the triplet regimens, with an early analysis suggesting median overall survival exceeding one year for the latter. The objective response rates were 22% for the doublet and 27% for the triplet regimen.

Array will hope that the triple therapy it intends to study in Beacon CRC can beat the encorafenib/Erbitux doublet and betters the PI3K triple. The phase II study tested a different triplet because all three drugs were, at the time of its initiation, under development by Novartis.

Array, which originated binimetinib, recovered rights to it last year and later acquired the Novartis-discovered encorafenib, to allow the Swiss group to comply with the antitrust review of its asset swap for GlaxoSmithKline's oncology business. This nifty two-step deal gave Array the potential third-to-market Braf/Mek combo, behind Novartis's Tafinlar/Mekinist and Roche's Zelboraf/Cotellic.

Both of those combinations are indicated for Braf-mutant melanoma, a market that Array might in due course enter, if the ongoing Columbus study is positive. The readout from that trial is now imminent. However, the readacross will be complicated as Columbus tests two doses of encorafenib in combination with binimetinib and a low dose of encorafenib as monotherapy, against Zelboraf alone.

Given the likely competition it would face from the two established Braf/Mek combos in melanoma, as well as from immuno-oncology agents, Array promised to pursue a differentiated development strategy, of which Braf-mutant CRC seems to be a part. Array appears to be the only company pursing this indication at present.

Different melanoma approach

Another possible element of this strategy is the development of binimetinib as monotherapy for Nras-mutant melanoma. This was studied in the 402-patient Nemo phase III study, which read out positively last December. Data from that trial will be presented at Asco on Monday.

The Nemo study met its primary endpoint, showing an improvement in PFS compared with dacarbazine (2.8

months versus 1.5 months), which achieved a hazard ratio of 0.62. Moreover, the improvement in PFS was observed in the prespecified subgroup of patients who received prior treatment with immunotherapy (5.5 months versus 1.6 months), a hazard ratio of 0.46.

While recent developments have been positive, Array has had one setback with binimetinib this year – the discontinuation for futility of the Milo phase III trial in low-grade serous ovarian cancer. The company looks set to file for Nras melanoma shortly.

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