Evaluate Vantage

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Sarcoma field digests evofosfamide failure

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The failure of the phase III study of evofosfamide in soft tissue sarcoma – which was itself only half of an unprecedented double dose of disappointment meted out to Threshold Pharmaceuticals yesterday – has left observers pondering the implications for future development in this cancer field.

Most obviously, Threshold's discontinuation of evofosfamide leaves an already thin pipeline in this indication even thinner (see table below). And the sarcoma field has never had a very strong flow of new agents.

That industry pipeline for soft tissue sarcoma is now reduced to just five molecules in late-stage or pivotal studies – two in phase III and three in phase II/III – with a similar number in company-sponsored, randomised phase II studies. There are of course a number of other agents in investigator-sponsored or exploratory, single-arm studies in sarcoma, but these have been excluded from *EP Vantage's* analysis as they do not, or do not yet, represent programmes working towards a regulatory approval.

Curiously, the fact that evofosfamide did not show an additive benefit to doxorubicin in the pivotal study had to some extent been anticipated by investors (*Event – Threshold hopes to buck the F-R rule, December 3, 2015*).

This was based on concerns that the study had underestimated control arm survival and thus would be underpowered to show an effect. While this may or may not have been evofosfamide's undoing, what was unexpected was an exceptional performance in the doxorubicin-only control arm.

The study showed a median overall survival of 19 months for the control arm, by far the longest seen yet for the existing agent. It contrasts with an original 10 and later 12 months that were assumed for the Threshold trial's powering calculations, and even the 17 months seen in the control arm for another failed pivotal study in sarcoma, that of Ziopharm Oncology's palifosfamide.

Standard of care improves

The only comment that Threshold could make was that the standard of care for sarcoma has clearly improved. If this is the case, it could have implications for both what are now the two lead agents in the sarcoma pipeline, CytRx's aldoxorubicin and Lilly's olaratumab.

The first of these, aldoxorubicin, is a possible beneficiary, as it is closely related to doxorubicin and is its natural successor. The albumin-linked conjugate is designed to release doxorubicin but only in the acidic conditions inside the tumour. The strategy is to allow higher effective doses, and greater cumulative doses, of doxorubicin to be administered to patients. This could be important as use of the conventional agent is limited by increasing cardiac toxicity over time.

However, CytRx is studying its agent in the second-line setting and therefore cannot use this to position the agent in preference to doxorubicin. The pivotal study compares aldoxorubicin with investigator's choice of chemotherapy from dacarbazine, Votrient, gemcitabine/docetaxel, doxorubicin or ifosfamide. There is also the question that if doxorubicin performs better than widley appreciated, it may leave little room to show a benefit in later lines of therapy.

Cytrx has conducted a Phase II study in first line sarcoma, which showed median OS of 15.8 months for aldoxorubicin versus 14.3 months for doxorubicin, with a slightly greater difference in treatment-naïve patients. who represented 90% of those enrolled in the trial.

Meanwhile, Lilly's olaratumab has more obvious problems. It is in a 460-patient phase III as an add-on to doxorubicin in first line sarcoma. The phase Ib/II study of doxorubicin +/- olaratumab used to generate powering assumptions showed a two month increase in progression free survival (6.6 vs 4.1 months) and a just over 10 month gain in overall survival (25.0 vs 14.7 months) for the combination relative to control. Although the design assumptions used in the trial have not been disclosed, it is unlikely they anticipate survival in the control arm of 19 months, the figure seen in Threshold's phase III study.

So it seems that the sarcoma field, which had hitherto been enjoying a period of optimism engendered by positive study readouts for J&J/Pharmamar's Yondelis and Eisai's Halven, now faces a nervous period until these questions can be answered.

Project	Company	Stage	Study	Setting	Trial ID
Olaratumab (LY3012207)	Eli Lilly	III	doxorubicin +/- olaratumab	first line	NCT02451943
Aldoxorubicin	CytRx	III	aldoxorubicin vs investigator's choice	second line	NCT02049905
NBTXR3	Nanobiotix	II/III	Radiotherapy +/- NBTXR3	neo-adjuvant	NCT02379845
Anlotinib	Sino Biopharma	II/III	anlotinib vs placebo	second line	NCT02449343
Selinexor	Karyopharm	II/III	selinexor vs placebo	>second line	NCT02606461
MORAb-004	Eisai	II	gemcitabine+ docetaxel +/- MORAb-004	<third line	NCT01574716
Vigil (Bi-shRNAfurin and GMCSF autologous tumour cell immunotherapy)	Gradalis	II	Vigil vs gemcitabine + docetaxel	third line	NCT02511132
CMB305 +atezolizumab	Immune Design/Roche	II	atezolizumab +/- CMB305	n/a	NCT02609984
Votrient	Novartis	II	pazopanib vs placebo	first-line maintenance	NCT02367651

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