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# Anyara sounds the death knell for 5T4-targeted anticancers

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The failure of Active Biotech's Anyara in a phase II/III renal cell carcinoma study could signal the end of the road for cancer projects targeting 5T4 – a once promising tumour antigen discovered by scientists at Cancer Research UK in the 1990s.

Followers of UK biotech will no doubt recall the disaster of Oxford Biomedica's Trovax in a 732-patient kidney cancer study in 2009; Trovax was a 5T4-targeted cancer vaccine, and *EvaluatePharma* reveals no other 5T4-based approaches in clinical development. Like Oxford before it, Active has pointed to positive signs seen in subgroup analyses but, given how crowded a field kidney cancer has become, finding a partner to fund further development seems improbable.

Active's shares fell 13% yesterday, although the company is still up almost 100% over the past 12 months – a rise that had been driven by hopes for Anyara, as well as its prostate cancer project tasquinimod. Still, analysts' expectations for Anyara had shrunk of late, perhaps explaining the somewhat muted share price reaction to the study's failure (*Active gets boost as pipeline hopes rise, May 22, 2012*).

**High-risk study**

The 526-patient Anyara trial had always been seen as high-risk, given that before it the project had only yielded data from small phase I studies. Its primary endpoint was missed, Anyara combined with interferon-alpha failing to increase overall survival compared with interferon-alpha alone.

Anyara (naptumomab estafenatox) is a conjugate combining an antibody against 5T4, an oncofetal protein displayed on the cell membrane of various carcinomas, with the SEA/E-120 staphylococcal enterotoxin. In contrast, Trovax was a vaccine comprising a 5T4-expressing vaccinia virus, but both it and Anyara worked broadly by engaging the host immune system to attack 5T4-expressing cells.

Active reckons it knows why its trial failed, saying that a high number of patients – around half of the 513 in the intent-to-treat population – had had unusually high levels of pre-formed antibodies against the enterotoxin "superantigen" component of Anyara. These patients would logically not be expected to mount an additional immune response against more enterotoxin.

Indeed, patients with normal antibody levels showed a numerical trend towards a survival benefit, although Active refused to be drawn on details. Moreover, a pre-specified analysis of a subgroup of 130 patients who had unusually high antibody levels, as well as low or normal baseline levels of interleukin-6 showed a statistically significant improvement in both overall and progression-free survival, with a p value of 0.02 for the former, Active said.

**Déjà vu**

In Oxford's phase III study Trovax had failed to improve survival across the overall 732-patient population, but showed hints of a survival advantage in those with a good baseline prognostic score who had been given interleukin-2 as standard of care. But, although this might have shown a way forward, no further development of Trovax in kidney cancer has taken place.

While Trovax could still be developed for other cancers, it has been sidelined by Oxford, and any further studies depend on securing a partner. Similarly, Active says it will not fund further trials of Anyara, although it would license the project out – presumably to a company willing to fund a confirmatory study in low-antibody/normal IL-6 patients.

But a major stumbling block is that Pfizer's Sutent has quickly established itself as standard of care in kidney cancer, meaning that even had the Anyara study worked its result could have been seen as irrelevant given the comparison against interferon-alpha. The current lack of interest in targeting 5T4 certainly suggests that this is an anticancer strategy whose time has come and gone.

Finding a partner for Anyara will be tough.

| Study | Trial ID |
| --- | --- |
| 526-pt, open-label phase II/III, renal cell carcinoma, addition to interferon-alpha | NCT00420888 |

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