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Hard knocks for brain cancer, again

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In the wake of two phase III glioblastoma failures this month, from Abbvie and Bristol-Myers Squibb, hopes dim for another big readout from Tocagen.

Glioblastoma's intractable and aggressive nature means that few novel agents make it to late-stage testing. Two phase III blow-ups this month have left the pipeline looking particularly bare, and news from Tocagen last night suggests that another asset could be heading for the scrapheap.

A pivotal trial of the viral gene therapy Toca511/FC will continue to final readout, the company said, dashing hopes of an early stop for efficacy. There is a small chance that a survival benefit will ultimately be seen, but the recent failures, of an antibody-drug conjugate from Abbvie and Bristol-Myers Squibb's Opdivo, show just how hard it is to make progress in this disease.

These two setbacks arguably leave five active phase III trials of novel glioblastoma agents, including Tocagen's. There were nine ongoing studies flagged as worth tracking last year, when *Vantage* last looked at the space, and no new names have made it into phase III since then (*Therapy focus: no giving up on brain cancer, 12 March 2018*).

This amounts to a disappointing lack of progress. True, there are many agents in earlier stages of testing: *EvaluatePharma* counts 49 phase I or II glioblastoma assets that are considered their respective developers' lead, but in reality a number of these have probably already been quietly abandoned, and few will make it into larger trials.

Notable phase III novel agents targeting glioblastoma multiforme				
Project	**Mechanism**	**Company**	**Trial ID**	**Notes**
Opdivo	Anti-PD-1 MAb	Bristol-Myers Squibb	NCT02617589 NCT02667587	Checkmate-4 vs Temodar: May 2019. Checkmate-5 top of Temod due this year
Depatuxizumab mafodotin	Anti-EGFR ADC	Abbvie	NCT02573324	Intellance-1 s top of Temod patients with amplification May 2019.
Toca 511 & Toca FC	Gene therapy & pyrimidine analogue	Tocagen	NCT02414165	Toca 5 study, of Temodar o In May 2019 to continue t readout, due 2019.
DCVax-L	Cancer vaccine	Northwest Biotherapeutics	NCT00045968	On top of Ter Recruitment 2015; still no readout.
Trans sodium crocetinate	Vitamin A analogue	Diffusion Pharmaceuticals	NCT03393000	Intact study, Temodar, bio patients: prin completion 2
Marizomib	Proteasome inhibitor	Celgene	NCT03345095	EORTC-1709- study, on top of Temodar: completion 2
Source: EvaluatePharma and Clinicaltrials.gov.				

First to Tocagen, which disappointed investors last night by saying the Toca 5 trial would continue to the final readout, due by year end. Shares plunged 34% this morning.

The interim look was conducted after 75% of the deaths required to trigger final analysis had occurred. With so few events remaining the chances of the trial ultimately showing a survival benefit are vanishingly small.

A small band of believers remain, however. They argue that because Toca511/FC works partly by boosting the immune system a separation of the survival curves should not have been expected at this stage.

Tocagen also reckons that a survival benefit will take time to develop. But, with little reason to believe that regulators will accept anything other than a clear hit on overall survival, the primary endpoint of the trial must be met at the final analysis for unequivocal success to be declared.

Setbacks and ways forward

The field would receive a well-needed boost should Tocagen succeed, given the two phase III failures earlier this month.

Abbvie said last week that the Intellance-1 study of its antibody-drug conjugate depatuxizumab mafodotin found no survival benefit at interim analysis. This was based on data from 638 patients, and the lack of any signal must have been indisputable; the company has halted enrolment into other studies.

Depatuxizumab mafodotin was designed to treat patients whose tumours have EGFR amplification. Whether the failure was a problem with the biomarker or the ADC itself is as yet unknown.

Opdivo's stumble with Checkmate-498, meanwhile, marked the second phase III flop for the Bristol-Myers Squibb checkpoint inhibitor in glioblastoma, after the failure of the second-line Checkmate-143 in 2017.

The anti-PD-1 antibody failed to provide an overall survival benefit at the final analysis of 498, a first-line study, the company said earlier this month, without giving further detail. Bristol's last remaining shot here is Checkmate-548, which tests Opdivo on top of Temodar.

The odds of success must be considered low, and the 498 setback seems to confirm what many believe: that immunotherapy has yet to find its place in this cancer. This probably partly explains why Merck & Co has declined to commit serious research dollars to Keytruda in this space. Several mid-stage academic studies of the checkpoint inhibitor are ongoing in various brain cancer settings, with Merck named as collaborator in only a handful.

Still, there are signs that the company is looking for a way in: it recently initiated the phase II Leap-005 study, of Keytruda plus Lenvima, which has a glioblastoma cohort among other tumour types. Meanwhile, a signal of activity was reported earlier this year in a small academic study that is no doubt being closely scrutinised at Merck. Patients treated with Keytruda before surgery lived twice as long as those who received it afterwards.

Other immune system harnessing techniques, CAR-T for example, are being trialled in earlier glioblastoma studies with varying levels of success. And in Norway academics recently launched a fairly large phase II/III trial of a trivalent dendritic cell therapy.

Elsewhere in the pivotal pipeline

Another project is Northwest Biotherapeutics' controversial DCvax-L, though this company has been sitting on phase III data for years now, and the cancer vaccine seems unlikely to go anywhere.

Privately held Diffusion, meanwhile, continues to enrol inoperable glioblastoma subjects into its trial of trans sodium crocetinate. The company claims that this can re-oxygenate hypoxic tumour tissues, increasing susceptibility to radiation and chemotherapy. Results are some way off, according to clinical trial database entries.

And finally marizomib, a proteasome inhibitor owned by Celgene, is being put through a pivotal trial by an academic group. Researchers hope that the agent's ability to eradicate glioblastoma stem cells, and the fact that it is an irreversible inhibitor of all three subunits of the proteasome, give it a chance to make a mark in this disease.

The trial only started last year, so data are not imminent. But, given the setbacks elsewhere, marizomib could yet turn into glioblastoma's biggest late-stage hope.