Evaluate Vantage

March 17, 2016

Revisiting a predictor of failure in the post-Celator world

Robin Davison

Celator's success in beating the notorious Feuerstein-Ratain rule, as well as bettering one of the longest-established standards of care in oncology, raises the question of whether this shortcut for predicting the outcome of phase III cancer trials still holds after the recent collapse in biotech share prices.

Perhaps the fact that a company has a sub-$300m market cap ahead of a pivotal readout now no longer guarantees a failed study. Maybe investors are losing their ability predict oncology clinical outcomes and price shares accordingly (see table below). Alternatively, the $300m threshold might be too high given the extent of the recent biotech sell-off.

Celator's stunning trial result is also not the only one that calls into question this otherwise trusty rule of thumb. Celldex had a market cap of over $2bn six months before its now-halted Act IV phase III trial of Rintega in glioblastoma multiforme, showing that having a significantly higher market cap is no guarantee of success (*No good reaction to Celldex's Act IV, March 7, 2016*).

The rule

The rule, named after the *TheStreet.com*'s biotech commentator Adam Feuerstein and University of Chicago oncologist Mark Ratain, forecasts the outcome of cancer drug phase III studies based on the sponsor companies' market capitalisation six months before the data due date.

Based on an exhaustive examination of phase III cancer readouts over the past 20 years or more, it has until this week had a 100% success record in predicting failure for companies whose market cap is below $300m. If a company's market value was above this figure success was not guaranteed but was at least possible.

Of course a few factors have come into play over the recent biotech stock market cycle. With three or four years of good access to capital markets, many more companies have been able fund pivotal trials alone and build up significant cash piles on their balance sheets. On the other hand, the sharp correction in share price since the middle of last year might have brought otherwise promising companies' valuations into the failure zone.

These changes notwithstanding, in recent weeks the Feuerstein-Ratain rule correctly predicted the interim futility stop for Peregrine Pharmaceuticals' phase III study of bavituximab in second-line non-squamous non-small cell lung cancer (NSCLC). Similarly, it certainly forecast Threshold Pharmaceuticals' simultaneous double phase III failure of evofosfamide in pancreatic cancer and soft tissue sarcoma in December.

Last year, the rule accurately predicted futility stops for Synta with ganetespib in NSCLC and for Verastem's defactinib in mesothelioma, among others. *EP Vantage* has screened the public company universe for sub-$300m market cap groups with phase III cancer trials.

Companies likely to test the Feuerstein-Ratain rule			
Market cap* ($m)	**Project**	**Company**	**Data**
150	Aldoxorubicin	CytRx	Q2 2016
157	DCVax-L	Northwest Biotherapeutics	Sep 2016**
25	Custirsen	OncoGenex	Q3 2016
15	Sapacitabine	Cyclacel	Dec 2016
23	SGX301	Soligenix	Dec 2016
36	Zoptarelin doxorubicin	Æterna Zentaris	Dec 2016
101	Tivantinib	ArQule	Dec 2016
160	NGR-hTNF	MolMed	Dec 2016
251	90Y-clivatuzumab tetraxetan	Immunomedics	Dec 2016
284	Xilonix	XBiotech	Dec 2016
259	NBTXR3	Nanobiotix	Mar 2017
112	Rocapuldencel-T	Argos Therapeutics	Apr 2017
138	Nanoplatin	Orient Europharma	Jun 2017
139	Galeterone	Tokai	Jun 2017
25	Custirsen	OncoGenex	Jul 2017
142	Livatag (doxorubicin transdrug)	Onxeo	Jul 2017
208	Entinostat	Syndax	Jul 2017
83	PV-10	Provectus	Sep 2017
105	Lefitolimod	Mologen	Oct 2017
121	Pexastimogene devacirepvec	Transgene	Oct 2017
83	VB-111	Vascular Biogenics	Dec 2017
82	Tedopi	OSE Pharma	Mar 2018
13	Rigosertib	Onconova	Jun 2018
18	Fosbretabulin	Oxigene	Jun 2018
33	ThermoDox	Celsion	Nov 2019
251	Sacituzumab govitecan	Immunomedics	Dec 2019
29	ICT-107	ImmunoCellular Therapeutics	Dec 2019
65	OncoVAX	Vaccinogen	Jul 2020
*Notes: *as at March 15; **recruitment suspended, data likely to be later.*			

First up to test the rule in this new environment is CytRx, whose 433-patient study of aldoxorubicin in soft-tissue sarcoma reads out in the second quarter. Aldoxorubicin is an albumin-linked prodrug designed to release doxorubicin in the acidic conditions inside the tumour.

This study could succeed since doxorubicin has long been used in the disease, but its dose is limited by cumulative toxicity. CytRx’s project might overcome this and a positive result here would add further strain on the Feuerstein-Ratain rule's validity.

Nine other companies are scheduled to report data in 2016, most towards the end of the year. If they report on

time, the six-month pre-data timing of the Feuerstein-Ratain rule will be coming up soon.

Double showing

Interestingly, two companies appear twice in the table thanks to a second phase III readout in later years. Perhaps a positive result in the first study will project them out of the sub-$300m zone – as was the case with Celator – and improve the odds for a second positive result.

The first is OncoGenex, which has two phase III trials under way with custirsen, in prostate and lung cancers, both of which have had their designs changed to reduce recruitment or focus on poor-prognosis patients after custirsen's earlier phase III failure in castrate-resistant prostate cancer.

And Immunomedics has two phase III studies under way, this time with different antibody-drug conjugates. The first is 90Y-clivatuzumab tetraxetan in metastatic pancreatic cancer, and the other sacituzumab govitecan in triple negative breast cancer.

Companies with the smallest market valuations are either poorly financed or have already endured some major setback. Cyclacel’s phase III study has, for example, already failed its interim analysis, but in its case the data safety monitoring board requested that the study continue to completion. Other companies might effectively be repeating a previously failed study with some minor changes, as is the case with Celsion.

One thing is certain: these companies will enjoy huge stock market gains if they deliver unambiguously positive phase III results.

To contact the writer of this story email Robin Davison in London at news@epvantage.com or follow @RobinDavison2 on Twitter