Evaluate Vantage

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Karyopharm comes to Boston for the springtime

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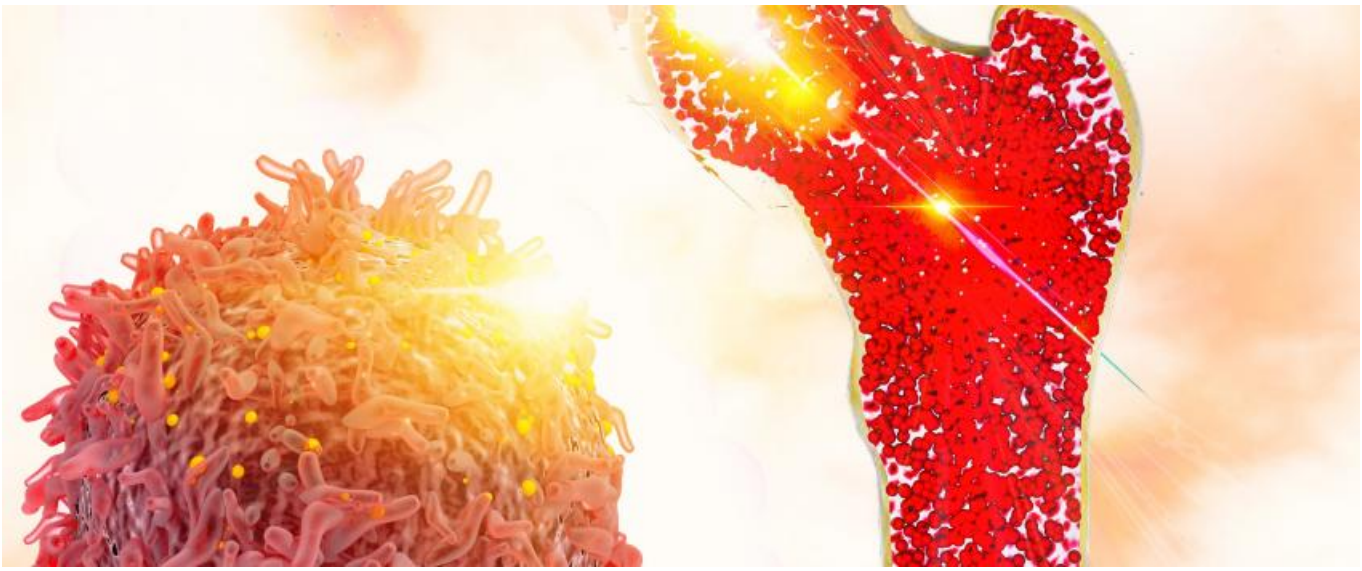

Karyopharm's newly approved myeloma drug, Xpovio, has shown promise in earlier lines of therapy, but toxicity could still cap its potential.

Karyopharm bulls who believed that FDA approval of Xpovio last year boded well for future label expansion will be congratulating themselves this morning. Shares in the company surged 50% at the open, to a five-year high, on news that the Boston study in second-line multiple myeloma had succeeded.

The trial pitted a combination of Xpovio, Velcade and dexamethasone (SVd) against Velcade and dex alone (Vd), and detected a significant extension in progression-free survival, with a hazard ratio of 0.70, in the Xpovio-containing cohort. Importantly, the company said there were "no new safety signals" on the SVd arm, and no imbalance in deaths; with few further details available, more cautious investors might choose to wait for full disclosure to declare Boston a runaway success.

This is because of the known toxicity profile of Xpovio, which includes very high rates of thrombocytopenia and discontinuations. The phase II Storm trial in much later-line patients had a fatal adverse event rate of 9%.

Not that this record prevented the FDA from granting approval last year, albeit on an accelerated basis, for very late-line myeloma patients. Given the high toxicity burden, approval even in this very refractory population was not thought a given (*Karyopharm rollercoaster ends in selinexor approval, July 4, 2019*).

On a conference call this morning company executives said the Boston data would be filed in the second quarter, making approval in this much larger and more valuable setting a possibility before the year is over.

Cross-trial comparison of second-line multiple myeloma trials						
	Xpovio: Boston trial NCT03110562		**Darzalex: Castor trial NCT02136134**		**Pomylast: Optimismm trial NCT01734928**	
	SVd (n=201)	Vd (n=201)	DVd (n=251)	Vd (n=247)	PVd (n=281)	Vd (n=278)
mPFS	13.93	9.46	not reached	7.2 months	11.2	7.1
P value	0.0066		<0.0001		<0.0001	
Hazard ratio	0.70		0.39		0.61	
Rate of peripheral neuropathy (any grade)	"Significantly lower" in SVd than on Vd		47%	38%	48%	37%

Vd = Velcade plus dexamethasone; SVd = Xpovio, Velcade and dexamethasone; DVd - Darzalex, Velcade and dexamethasone; PVd = Pomalyst, Velcade and dexamethasone. Source: Company statements, US drug labels.

Multiple myeloma is a very crowded space, with various treatments available for patients who relapse. First-line therapy is typically Revlimid, on top of which Darzalex is increasingly now used. Use of Velcade, which comes with its own toxicity burden – peripheral neuropathy – is thought be declining in the second-line setting, in favour of Kyprolis, a newer proteasome inhibitor.

Lack of relevance in the real world could be a real problem for Xpovio, then, despite the ostensibly positive result. This is despite Karyopharm's attempt at clever trial design: the SVd arm, but not the control, tested a once-weekly Velcade dose – label indications say the proteasome inhibitor should be dosed twice a week, but physicians frequently reduce the dosage to avoid peripheral neuropathy. Steroid use was also lowered in Boston.

All of this, the company believes, will prove the SVd regimen to be a safer and effective new option. In fact, the difference in rate of peripheral neuropathy was a prespecified secondary endpoint included in the statistical plan, so it is clear that the company is gunning for better tolerability on the label.

Much depends on full disclosure of the Boston data, a trial that could prove pretty tricky to interpret in many ways. All Karyopharm would say today was that rates of peripheral neuropathy were "significantly lower" in the SVd arm. A look at other trials that have used Vd for a comparator arm, in similar settings, provide a benchmark of sorts.

Investors added $600m to Karyopharm's valuation today, as they bet on Xpovio's chances of label expansion. Given the FDA's recent lenient record, perhaps this is a reasonable wager. Physicians with many other options on the table might be harder to convince.