Evaluate Vantage

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EHA 2019 – Sunesis chases Arqule, but remissions prove elusive

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Sunesis's vecabrutinib has yet to put a patient into remission, so hope rests on higher dosing of this next-generation BTK inhibitor.

The escalating battle between non-covalent BTK inhibitors in patients who develop resistance to Imbruvica or Calquence saw Sunesis and Aptose mount challenges over the weekend to Arqule, which looks to have generated the strongest results so far.

Sunesis can at least boast clinical data, though its poster at the European Hematology Association meeting showed that it has yet to put a patient into remission, having evaluated five of 23 treated subjects so far. To be fair, dose escalation is continuing, and with a clean profile Sunesis could yet show efficacy at higher doses. But that means investors have to sit and wait.

This all concerns very early data, but the markets are taking note. Sunesis surged 35% on Thursday in anticipation of Arqule's own highly positive EHA update (*EHA 2019 – turnaround puts Arqule in the takeover frame, June 14, 2019*). Arqule climbed 30% on Friday, while this morning Sunesis opened off 15% before recovering some losses.

Minutiae

Investors now will be delving into the two studies' minutiae. On Friday Arqule reported partial responses in four of six evaluable chronic lymphoblastic leukaemia subjects who had relapsed with a C481S resistance mutation and had been started on a 65mg daily dose of its project, ARQ 531.

The following day Sunesis said its dose-escalation trial of vecabrutinib had efficacy data available on five C481S-mutated CLL subjects: two of these, dosed at 50mg and 100mg twice daily, showed decreased tumour load, but neither was enough to be recorded as a response.

Sunesis is now enrolling subjects at 200mg twice daily, and its trial design calls for a further cohort, 300mg twice daily. The group said pharmacology suggested that vecabrutinib concentrations capable of producing consistent BTK inhibition were likely to be achieved only at above 100mg twice daily.

Why Arqule is able to boast efficacy at 65mg while Sunesis apparently needs a dose above 200mg clearly comes down to the relative pharmacology profiles and half lives of ARQ 531 and vecabrutinib. The most important thing for vecabrutinib is not to hit a toxicity barrier before an effective dose is found.

Sunesis said so far grade 3 drug-related adverse events had been seen in three of 20 subjects. The most common events of any grade at the doses tested were anaemia, neutropenia and night sweats; Arqule also saw decreased neutrophil count and anaemia with ARQ 531, while one subject discontinued after developing a sudden rash.

Kinase inhibition profiles of non-covalent BTK inhibitors

	TEC Family Kinases					Inhibition of Other Kinases
IC_{50} (nM)	BTK	ITK	Tec#	TXK*	BMX*	Notable Target Kinases
Vecabrutinib[1]	3	14	14	474	224	Selective: only 4, including SRC family, NEK11
ARQ 531[5]	4.23	>10000	5.8	36.4	5.23	>20 more: SRC & TRK families, RAF1, MEK1
Loxo-305[6]	3.15	>5000	1234	209	1155	Very Selective
CG-806[7] (Aptose)	8.4	4.3	>1000	n/a	14.5	18 w/ IC_{50} <10 nM: FLT3 (wt, ITD) c-MET, TRK family & Aurora kinases

n/a=not available
* Determined with vecabrutinib free base (also relevant for SRC and EGFR)
# Activated
[1] Neuman et al., ASH 2016
[5] Eathiraj et al., Pan Pacific Lymphoma Conference 2016
[6] Brandhuber et al., SOHO 2018
[7] Zhang et al., EHA 2018

Source: Sunesis.

For its part Aptose was only able to report preclinical data with its non-covalent BTK contender, CG-806, which has only just started phase I.

Its EHA poster described no observed toxicity in a mouse model, and the compound was said not to inhibit other kinases that are related to Imbruvica-related intolerance. However, as well as BTK CG-806 hits the Flt3 kinase, giving it a different profile from the Sunesis and Arqule projects.

Indeed, the Aptose poster was presented at an acute myelogenous leukaemia session, where researchers highlighted CG-806's potential in combination with Venclexta. AML has recently seen the introduction of two Flt3-targeting drugs, Novartis's Rydapt and Astellas's Xospata.

And a still unknown quantity is Lilly's LOXO-305, licensed from Redx, said to be the most selective non-covalent BTK inhibitor of the bunch. That asset remains a future threat, but for now Sunesis investors must lick their wounds and hope for future efficacy.