Evaluate Vantage

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Imbruvica resistance provides early but fertile development ground

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Targeting a mechanism of resistance to first-generation BTK inhibitors has caught the attention of biotechs like Arqule, which claimed a major success last week.

The approval in 2013 of Imbruvica marked a first for the BTK inhibitor class. Now, in a scenario familiar to followers of targeted cancer treatments, attention is turning to treating patients carrying a BTK mutation that renders them resistant to Imbruvica.

The mutation is called C481S, and causes a conformational change in the kinase domain of BTK, preventing Imbruvica from binding to its target. Last week Arqule claimed a major success with its own BTK inhibitor in a subject carrying this C481S mutation, and hot on its heels come similar follow-ons from Sunesis, Lilly, Aptose and Carna Biosciences.

What all of these next-generation inhibitors have in common is that they bind BTK non-covalently, and thus reversibly. Meanwhile, Imbruvica, as well as the only other approved BTK inhibitor, Astrazeneca's Calquence, bind covalently and irreversibly to the C481 domain of BTK.

Arqule's first?

Arqule's success in chronic lymphoblastic leukaemia came courtesy of ARQ 531, and might even have been the first time a therapy specifically aiming to treat a C481S mutant had managed to do so.

That said, the trial in which this single case report was observed does not only enrol C481S mutants. Rather, it recruits subjects who have failed BTK inhibitor treatment; the relevant patient had progressed on Calquence, and their C481S status was only determined subsequently.

In an earlier poster at last year's Ash meeting Arqule had reported one partial remission, but this patient's lymphoma was not said to be C481S-positive. Eight subjects determined to be C481S mutants had stable disease after ARQ 531 treatment at that time.

These findings raise a separate point, namely that non-covalent BTK inhibitors are thought to have activity not only against C481S-mutated BTK, but also against the wild-type kinase. After all, the mere fact that they do not interact with the C481 binding site might not preclude activity at wild-type BTK.

In the unrelated setting of EGFR-mutated lung cancer, similar thinking guided Astrazeneca's development of the targeted agent Tagrisso. Efficacy against EGFR-T790m led to Tagrisso's approval specifically in patients

who had this resistance mutation and had failed EGFR inhibitor therapy; subsequently the drug was approved in a broader first-line EGFR-positive population.

Selected follow-on BTK inhibitors			
Project	**Company**	**Attributes**	**Trial ID**
Filed			
BGB-3111 (zanubrutinib)	Beigene	Covalent	NCT03053440
Phase II			
GS-4059 (tirabrutinib)	Gilead/Ono	Covalent	NCT02983617
M7583	Merck KGaA	Covalent	NCT02825836
Phase I			
ARQ 531	Arqule	Non-covalent	NCT03162536
LOXO-305	Lilly (ex Loxo, ex Redx)	Non-covalent	NCT03740529
SNS-062 (vecabrutinib)	Sunesis (ex Biogen)	Non-covalent	NCT03037645
TG-1701	TG Therapeutics	Covalent	NCT03671590
RG7845 (fenebrutinib)	Roche	Non-covalent	None in oncology
BMS-986142	Bristol-Myers Squibb	Non-covalent	None in oncology
Preclinical			
CG-806	Aptose	Non-covalent	NA (IND filed)
AS-1763	Carna Biosciences (ex Evotec)	Non-covalent	NA
Source: company filings & clinicaltrials.gov.			

In contrast to the ARQ 531 trial, an early study of Lilly's rival asset, LOXO-305, includes BTK inhibitor-relapsed subjects known prospectively to be C481S mutants, as well as others known not to have the mutation. Lilly gained rights to this asset through the takeover of Loxo Oncology, which had earlier acquired it from Redx Pharma.

The only other relevant clinical player known to be targeting C481S-positive haematological cancers is Sunesis, which has started a phase I trial of vecabrutinib. The struggling company claims that vecabrutinib might avoid serious rash, but in reality this could be down to not dosing vecabrutinib high enough; indeed, Sunesis has yet to report any clinical efficacy.

Aptose's CG-806 is in preclinical trials, and the company last month filed an IND to begin human trials.

"Second-generation"

So what about more advanced, so-called second-generation BTK inhibitors like Calquence, Beigene's zanubrutinib and Gilead's tirabrutinib?

It seems that the selling point of such assets is their increased activity at BTK, though all these are still covalent inhibitors, and thus would be expected to result in development of resistance via the C481S mutation just like with Imbruvica. At least one paper suggests that Calquence, zanubrutinib and tirabrutinib have activity at C481S, but logic – and Arqule's case report – surely suggests that this is wrong.

Still, a dearth of big pharma involvement in the non-covalent space signals caution. Roche is also developing a reversible, non-covalently binding BTK inhibitor, fenebrutinib, but after running a small trial in haematological malignancies it switched focus to autoimmune disease.

And Bristol-Myers Squibb's BMS-986142 seems to have been shelved, having never been studied in cancer patients. Such a lack of endorsement from what are two huge global oncology players could temper enthusiasm about smaller developers of non-covalent BTK inhibitors like Arqule and Sunesis.

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