

BIOBUSINESS BRIEFS

DEAL WATCH

Bristol–Myers Squibb and Exelixis collaborate on kinase inhibitors

Bristol–Myers Squibb (BMS) and Exelixis have entered into an agreement to co-develop two kinase inhibitors for oncology, including the multi-target kinase inhibitor XL184, which is currently in Phase III trials (TABLE 1).

Under the terms of the collaboration, BMS agreed to pay Exelixis US\$195 million for development and commercialization rights and to make additional license payments of \$45 million. The companies will share the worldwide development costs and profits of XL184 in the United States, and Exelixis will be eligible to receive up to \$150 million in sales related to payments outside the United States. The agreement also covers XL281, a RAF kinase inhibitor that is currently in Phase I trials.

Specific tyrosine kinases that are involved in oncogenesis, such as the epidermal growth factor receptor (EGFR), are validated targets in a number of cancers. However, one of the major problems leading to treatment failure is tumour heterogeneity, either within the cancer of an individual or between

patients with the same cancer diagnosis, says Janet Dancey, Program Leader, High Impact Clinical Trials, Ontario Institute for Cancer Research, Canada. “Even as we have become more sophisticated in identifying oncogenic kinases that may be driving specific types of cancer, inhibiting multiple targets simultaneously is likely to be more effective, because of tumour heterogeneity.”

The view that multi-target tyrosine kinase inhibitors may have better results than specific agents is also supported by Paolo Comoglio, Scientific Director, Institute for Cancer Research, Candiolo, Italy. “There is cross-talk between most, if not all, kinase receptors — the NEU/EGF receptor family is one example, the MET/hepatocyte growth factor receptor family is another — and so quenching the whole signal transduction machinery may turn out to be more effective in suppressing cell growth.”

Multi-target kinase inhibitors like XL184 (TABLE 1) might also provide therapeutic

benefit in various tumours driven by any one target, leading to broad applicability. “For example, XL184 may have a role for treating tumours that are sensitive to vascular endothelial growth factor receptor inhibition, such as renal, colorectal, lung or breast cancers; or in MET-driven tumours like papillary renal carcinoma and possibly EGFR-inhibitor resistant non-small-cell lung carcinoma; or in RET-driven tumours such as thyroid carcinoma,” notes Dancey. “Moreover, in tumours where more than one target may be relevant, the effects of a multi-target kinase inhibitor may be at least additive, if not synergistic. Although this might be achieved by a combination of multiple agents, patient adherence to and preference for a single drug would still favour the multi-target drug.”

“The prevention or reduction in the incidence of resistance to multi-target kinase inhibitors is another beneficial property,” adds Comoglio. There are, however, some potential downsides: if an agent has multiple targets, it is likely to have greater toxicity than selective agents, and it may be that no one drug can effectively and optimally inhibit multiple targets. “If dose-limiting toxicity occurs due to an effect on one target, the other targets may not be optimally inhibited,” concludes Dancey.

Table 1 | **Selected multi-target kinase inhibitors**

Drug (company)	Target	Highest phase	Indication*
Sorafenib (Bayer and Onyx)	PDGFR, VEGFR2 and 3, FLT3, KIT, RET, RAF	Launched	Hepatocellular carcinoma, RCC, renal tumour
Dasatinib (BMS)	BCR–ABL, FYN, SRC, LCK, EPH	Launched	ALL, CML
Nilotinib (Novartis)	PDGFR, ABL, KIT	Launched	CML
Sunitinib (Pfizer)	PDGFR, VEGF2, FLT3, KIT	Launched	Gastrointestinal tumour, RCC
Motesanib (Amgen and Takeda)	PDGFR, VEGFR, KIT	Phase III	NSCLC
Vandetanib (AstraZeneca)	EGFR, VEGFR2, RET	Phase III	Thyroid tumour, NSCLC
Lestaurtinib (Cephalon)	JAK2, FLT3, TRKA	Phase III	Myeloid leukaemia
XL184 (BMS and Exelixis)	VEGFR2, MET, KIT, FLT3, RET, TEK	Phase III	Thyroid tumour
Pazopanib (GSK)	PDGFR, VEGFR1, 2 and 3, KIT	Phase III	Renal tumour, sarcoma

*Indication given for highest phase; all drugs are also in lower phase clinical trials for other oncology indications. ALL, acute lymphoblastic leukaemia; BMS, Bristol–Myers Squibb; CML, chronic myeloid leukaemia; EGFR, epidermal growth factor receptor; GSK, GlaxoSmithKline; NSCLC, non-small-cell lung cancer; PDGFR, platelet-derived growth factor receptor; RCC, renal cell carcinoma; VEGFR, vascular endothelial growth factor receptor.