

GlaxoSmithKline's One-Two Punch against Melanoma Will Two Kinase Inhibitors Be Better Than One?

Indication: Malignant melanoma

Companies:

GlaxoSmithKline (GSK)
Roche (RHHBY)
Daiichi Sankyo
Array BioPharma (ARRY)
AstraZeneca (AZN)
Novartis (NVS)

Products:

Dabrafenib (GSK2118436;
GlaxoSmithKline)
Trametinib (GSK1120212;
GlaxoSmithKline)
Zelboraf (vemurafenib; Roche /
Daiichi Sankyo)
Selumetinib (ARRY 886,
AZD6244; Array /
AstraZeneca)
ARRY 162 (Array / Novartis)

Probabilities of Approval:

Dabrafenib: 62%(C)
Trametinib: 52%(C)

The *inThought* **Approvability Index (IAI)** uses historical approval rates and detailed analysis of clinical trials to model the probability of FDA approval. The letter grade indicates relative progress in the current phase.

- The recent approval of Roche (RHHBY) and Daiichi Sankyo's BRAF^{V600E} inhibitor Zelboraf (vemurafenib) is good news for melanoma patients, but the development of resistance will hinder the drug's long-term effectiveness. The induction of squamous cell carcinomas is also a nuisance for patients on Zelboraf.
- Other kinase inhibitors may help to overcome these shortcomings. These include two oral phase III drugs from GlaxoSmithKline (GSK): dabrafenib, a BRAF^{V600E} inhibitor, and trametinib, a MEK inhibitor.
- Dabrafenib appears comparable in safety and efficacy to Zelboraf, and should have a straightforward path to approval. Whether its resistance profile is different from Zelboraf's remains to be seen.
- Trametinib is the most advanced MEK inhibitor program, with phase I data showing good safety and promising efficacy. Both trametinib and dabrafenib target the RAF-MEK-ERK pathway; the combination may have greater efficacy and safety than either monotherapy.
- Unfortunately, no phase II data are publicly available for either compound. On the basis of phase I data and reasonable assumptions regarding phase II results, we assign to dabrafenib and trametinib *inThought* Approvability Index (IAI) scores of 62%(C) and 52%(C), respectively.

The recent approval of Roche (RHHBY) and Daiichi Sankyo's BRAF inhibitor Zelboraf (vemurafenib) for the treatment of unresectable or metastatic melanoma with a BRAF^{V600E} mutation (see *inThought's* report of August 19, 2011) marks the first successful kinase inhibitor launched for melanoma. Despite Zelboraf's impressive activity, most patients develop resistance. Other agents are therefore needed to prevent or overcome resistance. Among the most advanced pipeline candidates for this role are two from GlaxoSmithKline (GSK): trametinib (GSK1120212) and dabrafenib (GSK2118436).

Dabrafenib

Like Zelboraf, dabrafenib is a highly specific inhibitor of mutant V600E BRAF (mt BRAF). In fact, it inhibits mt BRAF about four times more strongly than Zelboraf, while maintaining a comparable selectivity for mt BRAF over wild-type BRAF (wt BRAF). Phase I results appear to be at least as impressive as the phase I results for Zelboraf, both in terms of safety and efficacy. In addition, responses have been seen in melanoma patients with brain metastases.

Perhaps using Zelboraf's experience, GSK quickly moved dabrafenib into phase III development in January of this year. An important difference in the programs is that Zelboraf's phase III trial used overall survival (OS) as the primary endpoint whereas dabrafenib's phase III trial uses progression-free survival (PFS), a "softer" endpoint. Owing to the lack of phase II data available thus far, **we assign to dabrafenib an *inThought* Approvability Index (IAI) score of 62%(C).**

Trametinib

Trametinib is a highly specific inhibitor of MEK, the serine-threonine kinase that is activated by RAF in the RAF-MEK-ERK pathway. Phase I data show a good safety profile, with the most common serious adverse events being rash (5% of patients) and diarrhea (3%). For melanoma patients with mt BRAF, 27% had a partial response (PR) and 45% had stable disease (SD). Interestingly, 22% of melanoma patients with wt BRAF had PR.

As with dabrafenib, trametinib was quickly moved into phase III development in November 2010. Only

patients with mt BRAF are enrolled, and the primary endpoint is again PFS. As with dabrafenib, no phase II data are available. **We assign to trametinib an IAI score of 52%(C).**

Although trametinib is the most advanced MEK inhibitor program, Array BioPharma (ARRY) has two MEK inhibitors in phase II development for melanoma: selumetinib, which is partnered with AstraZeneca, and ARRY 162, which is partnered with Novartis. If trametinib is approved, one or both of these compounds may not be far behind.

Dabrafenib + Trametinib

As they do with the BRAF inhibitors, melanoma cells appear to develop resistance to trametinib relatively quickly. Preclinical studies suggest that inhibiting the RAF-MEK-ERK pathway at two points simultaneously may significantly delay development of resistance while offering an improved safety profile.

To test this hypothesis in the clinical setting, GSK has initiated a phase I/II study in which both the BRAF inhibitor dabrafenib and the MEK inhibitor trametinib are administered. **Preliminary results were presented at ASCO in June, showing that the combination is active (PR = 81%, SD = 19%) and possibly better tolerated than either agent alone.** The incidence of squamous cell carcinomas and other hyperproliferative skin lesions, which are hallmarks of Zelboraf and dabrafenib monotherapy, was markedly reduced (<1%) in the phase I portion of the combination trial. In addition, the incidence of rash, seen in 75-80% of patients on MEK inhibitors, was only 25%, with just a 2% incidence of grade 3 rash or higher.

Preliminary data from a phase I/II dabrafenib-trametinib combination study are encouraging.

A Bright Future

It has been a very good year for melanoma patients. Both Yervoy and Zelboraf have been approved for the indication, the first new drugs since 1992. And a healthy pipeline of targeted drugs and immunotherapies is looking promising.

In addition to the therapies recently approved and in advanced development, the use of combinations has barely begun to be explored. Not only might the combination of dabrafenib and trametinib provide an effective one-two punch against melanoma, but it and other combinations may also improve safety as well as efficacy.