Encouraging head-to-head studies pitting next generation tyrosine kinase inhibitors (TKIs) Sprycel and Tasigna against incumbent Gleevec were presented at Asco this year, serving to underline how researchers expect newer and more potent agents to eventually become the mainstay of treatment of chronic myeloid leukaemia (CML).

The questions that remain are how soon the medical profession will become comfortable enough to start switching patients over to a front line setting and which agent they should choose. There are currently three new TKIs – Sprycel, Tasigna and a bit further behind bosutinib – vying to replace $4bn a year Gleevec, a drug sold by Novartis that dramatically improved the life expectancy of patients with CML when it reached the market almost a decade ago. At Asco doctors agreed that it will be some time before their relative effectiveness will be determined, but that it seems likely demand for newer agents will rise in the meantime.

First line goal

Both Sprycel and Tasigna are already approved to treat patients for whom Gleevec is no longer working, but being allowed to market them for first-line use is the ultimate goal here. The most high profile study at the conference was the first look at data from a phase III study of Bristol-Myers Squibb’s Sprycel (dasatinib) versus Gleevec (imatinib) in patients with newly diagnosed CML in chronic phase (CML-CP), a trial called Dasision. At 12 months the new kid on the block was showing significantly higher and faster rates of responses, with a lower rate of progression. Given that life expectancy in CML patients is around 80% after 10 years, survival data from this study will not be available for some time. But doctors agreed that the surrogate measures were looking very encouraging.

Additionally, 18-month data were presented from the ENESTnd trial, a second look at results from this study which pitted Gleevec against Novartis’ own Tasigna. The newer agent generated double the molecular response rates.

Researchers believe that because these drugs are more potent, they are less likely to lead to the resistance issues that are seen with Gleevec. And importantly, the side effect profiles of these newer agents appear to be similar if not better than the incumbent.

High bar

These data were also published by the New England Journal of Medicine this week, accompanied by an editorial by Dr Charles Sawyers of Memorial Sloan-Kettering Cancer Center in New York. He wrote that the success of Gleevec, in terms of improving survival so dramatically, is rare in oncology. Before Gleevec was available interferon therapy meant 10 year survival rates were about 15-20% for CML, yet that figure is now closer to 80% researchers believe.

Essentially, the hope is that these newer agents can produce even deeper, longer lasting remissions. However, all doctors emphasised that longer term data is probably going to be required before doctors embrace these new therapies whole heartedly, given how well known and respected Gleevec already is.

As Dr Sonali Smith, who was not involved in either trial, commented at a presentation of the data, the two main challenges with CML therapy is both primary and secondary resistance to Gleevec, and these newer TKIs definitely provide a treatment option for these patients. But, so far only very short follow up is available from these trials and further long term data is going to be required before they are used widely in the first line setting.

“The bottom line is that we would like to see three to five years of survival data first, although the surrogate endpoints are excellent,” added Dr Hagop Kantarjian, one of the lead authors of the Dasision study.
However, in his editorial Dr Sawyers points out that resistance could still become an issue with these newer therapies. He also stresses that longer term follow up should happen, to confirm that these markers for survival materialise into real benefit.

And these therapies do have side effects; Tasigna has a black box warning about cardiovascular risks, including sudden death, and food restrictions, while Sprycel has been associated with pleural effusions. In fact the comparative side effect profiles of these agents could well define which agent is used more widely. The table below shows that despite the black box warning the Novartis drug is seen having a clear edge at this point.

Dr Sawyers' final point on cost is also likely to have a big impact on the commercial potential of these newer agents. With Gleevec going off patent in the US in mid 2015, the two newer agents could have trouble competing given that the older agent is still viewed as a very effective drug.

“With rising pressure to balance cost and efficacy, patients and payers may be forced to select the cheapest among three excellent treatment options,” Dr Sawyers says. By 2015 that cheapest option will be Gleevec by some distance.

Marketing push

Despite these cost pressures and the prospect of generic Gleevec in 2015, analysts are still projecting strong sales growth of the newer agents through 2015 and into 2016. With Gleevec's patent expiry only five years away definitive proof of improved survival in CML will not be available by then, given patients can live for 10 years or more with Gleevec.

It could certainly be the case that the makers of Tasigna and Sprycel, and possibly others behind them, struggle to convince payers that these newer agents are worth the extra cost, when cheaper generic Gleevec is available.

As such, the speed with which BMS and Novartis can convince doctors to start switching patients now will be very important for the commercial success of these franchises. Novartis has already sought first-line regulatory approval for Tasigna in Europe and the US, the FDA's ruling could arrive within the next few weeks. BMS has yet to file Sprycel for first-line use so approval is unlikely until the first half of 2011.

The lack of long term survival data probably means a big pick up in off label use, prior to approval, is unlikely to happen. However should these agents be approved in a first line setting, no doubt a big marketing push will commence.

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<th>Archive Consensus Forecast Analysis</th>
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