Asco preview – lung cancer battle takes centre stage

Jacob Plieth

The battle for market share in first-line non-small-cell lung cancer – the first indication really to pit the leading anti-PD-(L)1 agents against each other – has reached fever pitch. Next, investors’ and doctors’ attention turns to tonight’s release of full abstracts for June’s Asco conference.

Asco will see hostilities continue from where they left off at April’s AACR meeting. Already, from available abstract titles, is it clear that squamous NSCLC will take centre stage, seeing experts do their best to compare data from the Keynote-407 trial of Merck & Co’s Keytruda against the Impower-131 study of Roche’s Tecentriq (see table below).

Bristol-Myers Squibb will also be trying again to make the case for use of Opdivo plus Yervoy in patients with high tumour mutation burden (TMB), based on further analyses of the Checkmate-227 trial in squamous and non-squamous disease.

But Keytruda’s first-line dominance is virtually assured. One way to look at the market is that the players aiming to compete against Keytruda are now fighting over parts of just one NSCLC subset: patients who express PD-L1 at less than 1% and are intolerant of chemotherapy.

Double whammy

In recent weeks Merck delivered two major blows. An astonishingly strong survival benefit in the Keynote-189 study, revealed at AACR, cemented Keytruda’s place in first-line non-squamous NSCLC irrespective of PD-L1 status, as part of an Alimta-containing chemotherapy regimen.

Keynote-407 looks set to see this accolade repeated in NSCLC with the tougher to treat squamous histology, this time for Keytruda as part of a chemo combo with Abraxane. All that is known so far about this trial is that it hit an interim overall remission rate (ORR) endpoint.

At Asco investors should expect revelation of these numbers, which prompted immediate US accelerated approval filing, and will be hoping for hints about survival, too.

Meanwhile, Tecentriq plus chemo recently showed a PFS advantage in Impower-131, a trial with a near-identical design to Keynote-407. All eyes are now on Roche’s presentation of the Impower-131 data at Asco, though since this is a late-breaker it will not be available when the abstracts are unveiled at 5pm Eastern time tonight.

For Bristol-Myers Squibb’s Opdivo things look distinctly bleaker, even if TMB is deemed to be a highly relevant biomarker. More on the Checkmate-227 trial, in combination with Yervoy and irrespective of histology, will come at Asco, and the abstract’s title suggests a focus on non-PD-L1-expressing patients – where Keytruda monotherapy has not made inroads.

That said, Keytruda will soon have a near stranglehold on first-line NSCLC: monotherapy is available for >50% PD-L1 expressers irrespective of histology (based on Keynote-024) – a bar likely to be lowered to >1% expressers (Keynote-042); and the chemo combo can be prescribed to all-comer non-squamous patients (Keynote-021G).

Asco will also feature an update to Keynote-021G, though this trial has effectively been superseded by the confirmatory Keynote-189 study that blew competitors out of the water at AACR (AACR – Keytruda cements its lead, April 16, 2018).

Check mate?

Checkmate-227 also gained prominence at AACR, though Bristol looks set to spend Asco fielding uncomfortable questions. Red flags include changes in co-primary endpoints, and the fact that just 139 Opdivo plus Yervoy subjects were confirmed as TMB-high, out of 1,739 enrolled into Checkmate-227 under its original
design.

For Bristol perhaps the best that can be said is that if a first-line NSCLC tumour does not express PD-L1, and the patient is TMB-high and cannot tolerate chemotherapy, they might benefit from Opdivo plus Yervoy – at the cost of Yervoy toxicity, of course.

Investors will also be looking to Roche to provide further data on the Impower-150 trial in non-squamous patients. While this study’s positive readout favoured Tecentriq plus Avastin plus chemo, it is still not clear how much benefit Avastin brings to the table.

Avastin is a key franchise for Roche, and bundling it with Tecentriq could be strategically important; the group might argue that many doctors are already familiar with it. At Asco investors should look for more detail comparing Tecentriq plus chemo versus Avastin plus chemo, and for evidence of consistency across PD-L1 expression levels and other biomarkers.

Ultimately what the markets really want to know now is whether, in NSCLC at least, Keytruda can now be said to be a better drug than Opdivo and Tecentriq.

<table>
<thead>
<tr>
<th>Study</th>
<th>Project</th>
<th>Company</th>
<th>Detail</th>
<th>Trial ID</th>
<th>Asco abstract</th>
</tr>
</thead>
<tbody>
<tr>
<td>Impower-131</td>
<td>Tecentriq + chemo</td>
<td>Roche</td>
<td>Squamous; PFS numbers?</td>
<td>NCT02367794</td>
<td>LBA9000</td>
</tr>
<tr>
<td>Keynote-407</td>
<td>Keytruda + chemo</td>
<td>Merck &amp; Co</td>
<td>Squamous; ORR numbers? OS?</td>
<td>NCT02775435</td>
<td>105</td>
</tr>
<tr>
<td>Checkmate-227</td>
<td>Opdivo + Yervoy</td>
<td>Bristol-Myers Squibb</td>
<td>Update on &lt;1% PD-L1 expressers</td>
<td>NCT02477826</td>
<td>9001</td>
</tr>
<tr>
<td>Impower-150</td>
<td>Tecentriq + Avastin + chemo</td>
<td>Roche</td>
<td>Non-squamous; OS update?</td>
<td>NCT02366143</td>
<td>9002</td>
</tr>
<tr>
<td>Keynote-021G</td>
<td>Keytruda + chemo</td>
<td>Merck &amp; Co</td>
<td>Non-squamous; 2yr OS update?</td>
<td>NCT02039674</td>
<td>9026</td>
</tr>
</tbody>
</table>

EP Vantage will be reporting from Asco, which begins in Chicago on June 1. For live tweets follow @ByAmyBrown and @BylonGardner on Twitter.

© Copyright 2019 Evaluate Ltd.