About the Expert

Dr Tony Rahman

Independent expert commentary is provided by Dr Tony Rahman. Tony is a Medical Oncologist at the Canterbury Regional Cancer and Haematology Service. One of his areas of subspecialisation is the care of patients with cancers of the lung. He is also involved in clinical trials of immunotherapy agents in the treatment of lung and genitourinary cancers.

Rationale for combining atezolizumab and bevacizumab

PD-L1 is an immune checkpoint that limits T-cell activity by binding to its receptors programmed death 1 (PD-1) or B7.1 (PD-L1). This inhibition prevents T-cells from leading their role in the immune system to treat cancer. However, PD-L1 is widely expressed across a number of malignancies, and interruption of T-cell infiltration into the tumour, which is an important step in the cancer immunity cycle, is also involved in clinical trials of immunotherapy agents in the treatment of lung and genitourinary cancers.

Background

Lung cancer is the leading cause of cancer-related deaths worldwide and in New Zealand. With the 5-year survival rate in lung cancer patients diagnosed between 2005-2009 at only 10%–20% further necessary advances in the treatment of NSCLC, including immunotherapy, have been made over the last decade. The standard of care for patients with treatment-naive metastatic NSCLC includes platinum-doublet chemotherapy with or without bevacizumab for patients with non-squamous cancer. Targeted therapies for patients with oncogenic alterations, anti–PD-1 monotherapy for those with PD-L1 expression on at least 50% of tumour cells, and anti–PD-1 plus platinum-doublet chemotherapy for patients with non-squamous cancer. However, the prognosis remains poor.

This review summarises the IMpower150 study, an open-label, phase III trial that evaluated Tecentriq® (atezolizumab) plus bevacizumab plus chemotherapy in patients with metastatic nonsquamous non-small-cell lung cancer (NSCLC) who had not previously received chemotherapy. The study concluded that the addition of atezolizumab to bevacizumab plus chemotherapy significantly improved progression-free survival and overall survival among patients with metastatic nonsquamous NSCLC, regardless of programmed death ligand-1 (PD-L1) expression and EGFR or ALK genetic alteration status. Atezolizumab is a monoclonal antibody targeting PD-L1. In New Zealand, atezolizumab is indicated (but not funded) for the treatment of adult patients with locally advanced or metastatic NSCLC after prior chemotherapy. It is also indicated (but not funded) for the treatment of extensive-stage small cell lung cancer, urothelial carcinoma, and triple-negative breast cancer. This publication has been commissioned by Roche Products (New Zealand) Limited.
There is a strong scientific rationale to support the combined use of atezolizumab plus the VEGF inhibitor bevacizumab (Figure 1). In addition to its antiangiogenic effects, bevacizumab may enhance the ability of atezolizumab to restore anti-cancer immunity by inhibiting VEGF-related immunosuppression, promoting T-cell infiltration into the tumour microenvironment and enabling priming and activation of T-cell responses against tumour antigens. Increased intratumoural T-cells promote an inflamed tumour microenvironment that is optimised for PD-L1 inhibition.

**Figure 1.** The complementary activity of PD-L1 and VEGF inhibitors through the cancer immunity cycle.

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**IMpower150: Methods**

IMpower150 was an international, open-label, randomised, phase III study that evaluated the addition of atezolizumab to carboplatin plus paclitaxel with or without bevacizumab. The following patients were eligible for the study: those who had stage IV or recurrent metastatic non-squamous NSCLC and were not treated with chemotherapy, those with a baseline Eastern Cooperative Oncology Group (ECOG) performance status score of 0/1, and those with any PD-L1 immunohistochemistry status. Additionally, patients with EGFR or ALK genomic alterations were eligible, provided they had received at least one approved TKI and had disease progression or unacceptable side effects. This is in contrast to other first-line lung immunotherapy trials which have excluded patients with EGFR or ALK mutations.

Patients received atezolizumab/carboplatin/paclitaxel (ACP) or atezolizumab/bevacizumab/carboplatin/paclitaxel (ABCP) or bevacizumab/carboplatin/paclitaxel (BCP) every 3 weeks for four or six cycles, followed by maintenance therapy with atezolizumab, bevacizumab, or both. In this first report, only the first two arms were analysed, whilst data were not shown for the third. Atezolizumab was administered at a dose of 1200 mg, bevacizumab at a dose of 15 mg/kg, paclitaxel at a dose of 200 mg/m², and carboplatin at an area under the concentration–time curve of 6 mg/mL/min. Continuation of atezolizumab after the occurrence of disease progression was allowed if evidence of clinical benefit existed. No crossover to atezolizumab was permitted.

Co-primary endpoints were investigator-assessed progression-free survival (PFS) in the intention-to-treat (ITT) wild-type (WT) (EGFR or ALK negative) population and in WT patients with expression of a tumour T-effector gene signature (Teff-WT), and overall survival (OS) in the ITT-WT population, for the ABCP versus BCP comparison. The Teff gene signature was described as PD-L1, CXCL9, and IFN-γ messenger RNA expression, as assessed using macro-dissected tumour tissue RNA measurements at baseline.

Secondary endpoints included investigator-assessed PFS, and OS in the ITT population, which comprised all enrolled patients, including those with EGFR or ALK genomic alterations (oncogenic driver mutations). In addition, the following endpoints were evaluated in the WT population: PFS, as assessed at an independent review facility; investigator-assessed PFS in the PD-L1 expression subgroups; and the rate of objective response (complete response or partial response, as assessed by the investigators), as well as the duration of response among the patients who had an objective response; and safety.

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**Expert commentary on methods**

**IMpower150 was a phase III trial asking two important questions:**

1. Does an immune checkpoint inhibitor (ICI) (targeting the PD-L1 to PD-1 interaction) combine effectively with chemotherapy to improve outcomes for fit patients with stage IV non-squamous NSCLC?
2. Does VEGF blockade enhance the efficacy of an immune checkpoint inhibitor in fit patients with stage IV non-squamous NSCLC?

- **The study included lung cancer patients with oncogenic driver mutations after disease progression on a TKI or, in certain countries, if a TKI was not available to the patient.**
- **There was a protocol amendment during the study which changed the primary analysis populations from the ITT and PD-L1 positive population to patients without driver mutations (WT population) and Teff gene signature high. It was stated that emerging data had shown patients with driver mutations did not gain benefit from single agent checkpoint inhibitors in second line compared with chemotherapy alone.**
- **The study was not stratified to compare outcomes for driver mutation patients compared with WT patients nor outcomes between Teff high and Teff low patients.**
- **The study was stratified to compare outcomes with regard to PD-L1 expression, the presence or absence of liver metastases and gender.**
**IMpower150: Results**

A total of 1202 patients (ITT population) were enrolled. The WT population comprised 1040 of these patients (86.5%). Teff gene-signature expression could be evaluated in 95.6% of the patients in the WT population. A total of 445 of the 1040 patients in the WT population (42.8%) had high Teff gene-signature expression (Teff-high WT population).

**Progression-free survival**

Among the WT population, the median PFS was longer in the ABCP group than in the BCP group (8.3 months vs 6.8 months; P < 0.001) (Figure 2). At 12 months, the rate of PFS was twice as high in the ABCP group than in the BCP group (36.5% vs 18%) (Figure 2). The corresponding PFS values in the Teff-high WT population were 11.3 months and 6.8 months (hazard ratio [HR], 0.51; 95% confidence interval [CI], 0.38–0.68; P < 0.001), with 12-month PFS of 46% versus 18%, respectively.

Subgroup analysis showed that PFS among patients with EGRF mutations or ALK rearrangements increased with ABCP compared to that with BCP (9.7 vs 6.1 months; HR, 0.59; 95% CI, 0.37–0.94). This observed benefit is notable, given that clinical trials of PD-L1 or PD-1 inhibitors as monotherapy after the failure of TKI therapy have not shown that such therapies are more effective than standard chemotherapy. In addition, such patients have limited proven treatment options, and data are scarce from phase III trials examining the effectiveness of platinum-based regimens with or without PD-L1 or PD-1 inhibitors in this patient population.

Prolonged PFS was also observed regardless of PD-L1 status including in the PD-L1-negative subgroup (7.1 months with ABCP vs 6.9 months with BCP; HR, 0.77; 95% CI, 0.61–0.99) and the PD-L1-low subgroup (8.3 months vs 6.6 months; HR, 0.56; 95% CI, 0.41–0.77), as well as in the subgroup of patients with low expression of a Teff gene signature (7.3 months vs 7.0 months; HR, 0.76; 95% CI, 0.60–0.96). The benefit of ABCP in patients regardless of PD-L1 status is particularly relevant because the use of PD-1 inhibitors as first-line monotherapy is presently restricted to patients with high PD-L1 expression, and most patients with metastatic NSCLC have tumours with low, negative, or unknown PD-L1 expression.

A benefit with respect to PFS was observed with ABCP in key clinical and biomarker subgroups, including patients with liver metastases (7.4 months with ABCP vs 4.9 months with BCP; HR, 0.42; 95% CI, 0.26–0.66). Of note, patients with liver metastases previously had limited therapeutic benefit with checkpoint-inhibitor monotherapy.

**Overall survival**

At the time of the interim analysis of OS in the WT population the median duration of follow-up was approximately 20 months. Median OS among the patients in the WT population was significantly longer in the ABCP group than in the BCP group (19.2 months vs 14.7 months; Figure 3).

Further analyses found that the survival advantage of ABCP extended to patients with EGRF mutations (median OS not reached vs 18.7 months; HR, 0.61; 95% CI, 0.29–1.28) and those with liver metastases (13.3 months vs 9.4 months; HR, 0.52; 95% CI 0.33–0.82).

**Objective response and duration of response**

The investigator-assessed unconfirmed objective response rates in the WT population were 63.5% in the ABCP group and 48.0% in the BCP, 3.7% of the patients in the ABCP group had complete responses, compared with 1.2% of the patients in the BCP group. The results were similar in the Teff-high WT population. In the WT population, the median response durations were 9.0 and 5.7 months in the ABCP and BCP groups, respectively; in the Teff-high WT population, these were 11.2 and 5.7 months in the ABCP and BCP groups, respectively.

**Expert commentary on efficacy**

- Final analysis data on PFS and interim data on OS was published for the ABCP vs BCP arms. No data was published for the ACP arm.
- IMpower150 showed a significant 1.5-month improvement in median PFS in favour of ABCP in the ITT analysis as well as significant improvement in the PFS rate at 6 (67% vs 56%) and 12 months (36.5% vs 18%) with a stratified HR of 0.62.
- In the WT and Teff high WT populations response rates were higher and the median durations of response were longer in the ABCP arm.
- Median OS was 4.5 months longer in the ABCP arm (19.2 months vs 14.7 months) than in the BCP arm in the WT population with a stratified HR of 0.78.
- Other results are as described above, however, the HRs are unstratified.
Safety

The safety profile of ABCP was consistent with previously reported safety risks of the individual medicines.1 The most commonly observed grade 3 or 4 treatment-related adverse events were neutropenia (13.7%) in the ABCP group vs 11.2% in the BCP group and hypertension (6.4% vs 6.3%, respectively).1 The incidences of rash, stomatitis, febrile neutropenia, and haemoptysis were higher by <10% among patients in the ABCP group than among those in the BCP group.1 Deaths from treatment occurred in 11 (2.8%) and 9 (2.3%) patients in the ABCP and BCP groups, respectively.1 Five deaths in the ABCP group were due to pulmonary haemorrhage or haemoptysis.1

The incidence and nature of immune-related adverse events in the ABCP group were similar to those with atezolizumab monotherapy.1 Overall, 77.4% of the immune-related adverse events observed in the ABCP group were grade 1 or 2, and none were grade 5.1 The most common immune-related adverse events included rash, hepatitis, hypothyroidism, hyperthyroidism, pneumonitis, and colitis (Table 1).1 Most adverse events were transient and were limited to the chemotherapy induction phase.1 The rate of serious adverse events during the chemotherapy-free maintenance treatment was low, a finding that is clinically relevant, given that induction represents a short time (approximately 2.2 months), whereas maintenance treatment can be prolonged.1

Table 1. Immune-related adverse events by treatment phase in the ABCP group and the BCP group

<table>
<thead>
<tr>
<th>Incidence, n (%)</th>
<th>Induction phase</th>
<th>Maintenance phase</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ABCP (n=393)</td>
<td>BCP (n=394)</td>
</tr>
<tr>
<td>All grades</td>
<td>131 (33.3)</td>
<td>85 (21.6)</td>
</tr>
<tr>
<td>Grade 3-4</td>
<td>30 (7.6)</td>
<td>12 (3.0)</td>
</tr>
<tr>
<td>Rash</td>
<td>81 (20.6)</td>
<td>46 (11.7)</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>17 (4.3)</td>
<td>10 (2.5)</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>6 (1.5)</td>
<td>4 (1.0)</td>
</tr>
<tr>
<td>Colitis</td>
<td>4 (1.0)</td>
<td>2 (0.5)</td>
</tr>
<tr>
<td>Hepatitis lab abnormalities</td>
<td>31 (7.9)</td>
<td>17 (4.3)</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>17 (4.3)</td>
<td>10 (2.5)</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>6 (1.5)</td>
<td>4 (1.0)</td>
</tr>
<tr>
<td>Colitis</td>
<td>4 (1.0)</td>
<td>2 (0.5)</td>
</tr>
<tr>
<td>All grades</td>
<td>116 (37.2)</td>
<td>20 (6.4)</td>
</tr>
<tr>
<td>Grade 3-4</td>
<td>35 (13.0)</td>
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</tr>
<tr>
<td>Rash</td>
<td>48 (15.4)</td>
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<td>Hypothyroidism</td>
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</tr>
<tr>
<td>Colitis</td>
<td>6 (1.9)</td>
<td>5 (1.6)</td>
</tr>
</tbody>
</table>

**Expert commentary on safety**

- Safety data is consistent with previous immunotherapy trials with regard to immune-related adverse events.1
- Four deaths from pulmonary haemorrhage/haemoptysis in the ABCP cohort were associated with high risk features (e.g. cavitation, tumour necrosis and infiltration of the great vessels).1
- The use of bevacizumab in patients with these high risk features should be carefully considered.

**TAKE HOME MESSAGES**

- IMpower150 demonstrated significantly improved PFS and OS with the addition of atezolizumab to the regimen of bevacizumab plus chemotherapy as a first-line treatment for non-squamous metastatic NSCLC.1
- PFS was longer in the ABCP group than in the BCP group (8.3 months vs 6.8 months).1
- The rate of PFS at 12 months was twice as high with ABCP as with BCP (36.5% vs 18.0%).1
- OS was longer in the ABCP group than in the BCP group (19.2 months vs 14.7 months).1
- The rate of objective response was higher with ABCP than with BCP (63.5% vs 48.0%).1
- Regardless of the expression of PD-L1 or the presence of a T-effector gene signature, the combination therapy proved beneficial.1
- The clinical benefits were observed in key subgroups of patients with EGFR and ALK genomic alterations and liver metastases.1
A number of phase III trials investigating immune checkpoint inhibitors have been published over the last few years and have provided hope in improving outcomes for patients diagnosed with advanced NSCLC.\textsuperscript{22,24,25,45}

IMpower150 has demonstrated that the addition of atezolizumab, a PD-L1 inhibitor, to bevacizumab, carboplatin and paclitaxel (BCP), as first line therapy, improved median OS by 4.5 months compared with BCP alone.\textsuperscript{1} Survival at 24 months was also 10% higher in the atezolizumab cohort despite nearly 40% of the BCP cohort subsequently receiving an ICI off trial.\textsuperscript{1} It provides another treatment option in the first line management of non-squamous NSCLC but what differentiates those who should receive a VEGF targeted therapy in combination with an ICI and chemotherapy from those who should receive ICI and chemotherapy alone?

The median OS of 19.2 months is similar to the 20 month median OS seen in PD-L1 high patients (PD-L1 expression (TPS ≥50%) receiving pembrolizumab monotherapy in the Keynote-042 trial).\textsuperscript{46} These results lead us to wonder if bevacizumab adds efficacy to the treatment regimen. A comparison of the ACP and ABCP arms would be helpful here and future publications of more mature data from IMpower150 are awaited. Survival data, to date, do not suggest that ICI monotherapy should be replaced as the first line treatment for PD-L1 high patients as it provides similar survival outcomes but less toxicity for patients, not only in the non-squamous setting but also in patients with squamous histology. Bevacizumab, of course, cannot be offered to patients with squamous cell carcinoma due to the high rates of pulmonary haemorrhage seen in earlier trials;\textsuperscript{6,47} It will be important to see more mature survival data from the ACP arm in this trial as well as from Keynote-189 which randomised patients with advanced squamous and non-squamous NSCLC to chemotherapy + pembrolizumab or placebo.\textsuperscript{10}

The improvement in median OS is also comparable to historic trials of single agent ICIs as second line therapy compared with docetaxel after treatment with a first line platinum doublet.\textsuperscript{22,24,25} Is combination therapy superior to sequential therapy in this population? Will combination first line therapy allow more patients to receive and benefit from immunotherapy as median survival after first line treatment is measured in a small number of months? Will immunotherapy drug combinations be more effective than chemotherapy in combination with an immunotherapy drug? Future trials will hopefully answer these questions.

Although PFS is an approved surrogate for clinical trials it has been acknowledged that it is not a predictor of improved OS in trial populations. In previously published ICI trials,\textsuperscript{22,24,25} there is either no difference in median PFS or the difference is small, as seen in IMpower150.\textsuperscript{1} The PFS rate, however, in the ABCP cohort in the ITT population was twice that of the BCP cohort at 12 months.\textsuperscript{1} It remains to be seen whether it is helpful to use these endpoints going forward as they do not appear to significantly influence funding for cancer treatments in publicly funded, resource constrained medical systems such as that seen in New Zealand.

The driver mutation results in IMpower150 provide important but hypothesis producing data as the numbers of patients recruited were small and so cohorts were not adequately powered to provide practice changing survival data.\textsuperscript{1} Further focused international, multicentre, clinical trials will hopefully answer the question of ICI efficacy, in both Asian and non-Asian patient populations, who have failed TKI therapy. They will have to compete with newer generations of TKI which have been engineered to target modes of resistance to earlier TKI therapy and appear to cause little toxicity.

Despite not being stratified at randomisation the populations of T eff high and T eff low were reasonably well balanced to provide data on outcomes.\textsuperscript{1} It will be interesting to see if T eff analysis predicts for survival benefit in patients receiving atezolizumab as it appears to have little bearing on the outcomes for patients not receiving an ICI. Will T eff analysis also predict for survival benefit with other ICIs? Will the T eff gene signature provide more information for our treatment approach in combination with PD-L1 expression and tumour mutation burden analyses?

Harmonisation of biomarker analyses will be important going forward to help standardise treatment approaches. To date, individual ICIs targeting PD-1/PD-L1 have been associated with different accompanying diagnostic assays for PD-L1 expression.\textsuperscript{48,49} From the Blueprint study the SP142 Ventana platform appeared to be an outlier compared with other assays.\textsuperscript{48} This was the assay used to assess tumour cell (TC) and immune cell (IC) PD-L1 expression in the IMpower150 trial.\textsuperscript{1} Different results may be seen with different assays. In Keynote-042, using the 22C3 Dako platform assay, 31% of the patients recruited were PD-L1 high\textsuperscript{46} whereas 20% of patients in IMpower150 were PD-L1 high.\textsuperscript{1}

In summary, IMpower150 has demonstrated that the addition of atezolizumab to BCP improves survival in advanced non-squamous lung cancer.\textsuperscript{1} It is a first line therapy option in this population, however, the employment of bevacizumab may not be essential for efficacy and would not be first choice therapy in PD-L1 high patients (defined as PD-L1 expression on at least 50% of TC or at least 10% of tumour-infiltrating IC in IMpower150).\textsuperscript{1} It will be important to await future results from this and other trials to help clarify appropriate treatment approaches that maximise efficacy and minimise toxicity in patients with advanced NSCLC.
Atezolizumab for first-line treatment of metastatic non-small NSCLC

Tecentriq® (atezolizumab) Abridged Prescribing Information

Tecentriq (atezolizumab), 1200 mg/2mL, concentration for solution for infusion is aPrescription Medicine for the treatment of the following:

Non-small cell lung cancer

Tecentriq, in combination with bevacizumab, paclitaxel and carboplatin, is indicated for the treatment of platinum- and paclitaxel-pretreated patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with programmed death-ligand 1 (PD-L1) expression (IMpower150): key subgroup analyses of patients with EGFR mutations or baseline liver metastases in a randomised, open-label phase 3 trial. Lancet Oncol 2019; 20:1449-59.

Tecentriq, in combination with bevacizumab, is indicated for the treatment of patients with locally advanced or metastatic triple-negative breast cancer (IMpower030).

Tecentriq, in combination with nab-paclitaxel, is indicated for the treatment of patients with unresectable locally advanced or metastatic triple-negative breast cancer (IMpower021), advanced or metastatic urothelial carcinoma (IMpower131), and small cell lung cancer (IMpower133).

Tecentriq, in combination with nab-paclitaxel, is indicated for the treatment of patients with unresectable locally advanced or metastatic non-small cell lung cancer (IMpower130) as first-line treatment in patients with programmed death-ligand 1 (PD-L1) expression.

Tecentriq, in combination with nab-paclitaxel, is indicated for the treatment of patients with unresectable locally advanced or metastatic non-small cell lung cancer (IMpower021).

Tecentriq, in combination with nab-paclitaxel, is indicated for the treatment of patients with locally advanced or metastatic triple-negative breast cancer (IMpower030).

Tecentriq, in combination with nab-paclitaxel, is indicated for the treatment of patients with unresectable locally advanced or metastatic non-small cell lung cancer (IMpower130) as first-line treatment in patients with programmed death-ligand 1 (PD-L1) expression.

Tecentriq, in combination with nab-paclitaxel, is indicated for the treatment of patients with locally advanced or metastatic triple-negative breast cancer (IMpower030).