



Keytruda Treatment Costs In Mesothelioma Claims

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Introduction

In edition 167 of BC Disease News we reported on a new drug cancer treatment called Keytruda (also known as Pembrolizumab) which, according to its manufacturers Merck, has shown positive clinical outcomes in difficult to treat cancers such as lung cancer and mesothelioma.

We are now seeing private treatment costs of Keytruda in an increasing number of living mesothelioma claimants which are typically valued at around £70,000 or more. In this feature, we consider what Keytruda is and whether there is evidence that it is an effective treatment in mesothelioma claims.

This feature is abbreviated from a longer paper which also addresses the legal recoverability of such treatment costs-for a copy of the paper please email boris.cetnik@bc-legal.co.uk

What Is Keytruda?

Keytruda is a new immunotherapy drug treatment which 'wakes up' the body's own immune system to fight cancer cells.

Cancer cells can be very adept at evading detection by the body's immune defences and, in particular, our 'T-cells' which hunt down and kill foreign cells. The cancer cells disrupt certain signalling pathways of the immune system so that the T cells are effectively switched off and the cancer cells can proliferate.

Keytruda falls within a class of immunotherapy drugs known as 'checkpoint inhibitors' which work by making cancer tumours more visible to the immune system. PD-L1, or programmed death-ligand 1, is a protein that has been shown to play a role in suppressing the immune system and disguising the cancerous cells from the immune system defences. According to Merck, Keytruda blocks an interaction between a protein on the surface of T-cells, known as PD-1 and PD-L1 found on the surface of cancer cells so allowing activation of the T-cells to find and kill cancer cells.

Keytruda was originally developed for treating melanoma skin cancer that has spread around the body, and was approved by The National Institute for Health and Care Excellence (NICE) for use in England in

September 2015. When it was suggested that the treatment be used for non-small cell lung cancer (comprising around 87% of lung cancers in the UK)¹ patients, NICE rejected the proposal on the grounds that there was no robust data on its long term benefits and it was not cost-effective.² However, Merck then presented newer data and offered a discounted price for the drug. Since December 2016, it has been recommended for routine NHS use in non-small cell lung cancer patients displaying PD-L1³ and was placed on the Department of Health (UK) Cancer Drugs Fund List.⁴

In Europe, the European Medicines Agency (EMA) approved the use of Keytruda in melanoma and non-small cell lung cancer where the patient had been treated with at least one chemotherapy regime.⁵

Similarly, in October 2016, the Food and Drug Administration in the US approved Keytruda as a first-line treatment for non-small cell lung cancer that express PD-L1.⁶ (First-line treatments are those that are generally accepted by the medical establishment for initial treatment of a given type and stage of cancer).

Last month, Merck announced its intention to 'solidify its leading position' for Keytruda in lung cancer which it claims has the potential to become a foundational therapy for other cancers as well.⁷

Keytruda is now also being investigated and trialed as a potential treatment for mesothelioma. However, Keytruda is not a curative treatment. The purpose of the treatment is to limit tumour growth and increase remaining life expectancy.

So does Keytruda work in mesothelioma cases?

In April 2015 the preliminary results of a small clinical trial-known as the Phase IB Keynote-028 trial-involving treatment of 25 mesothelioma patients with Keytruda were announced at the American Association for Cancer Research Annual Meeting. The preliminary results were also published in a paper in Cancer Research.⁸ The trial is investigating safety, tolerability, and preliminary efficacy of Keytruda. Most of the 25 patients had received at least one prior course of chemotherapy, but had developed tumours that were continuing to grow. The patients all had PD-L1 expression in at least 1% of their tumour cells. The patients were given Keytruda doses of 10 mg/kg every 2 weeks for 6 months. Preliminary results indicated that the drug improved clinical outcomes for these patients.⁹ Six patients had a positive response in tumour size (24%), the cancer did not change in 13 patients (52%) and the cancer grew in 6 patients (24%). This suggests a disease control rate of 76%, representing the total of those whose cancers responded to treatment and those whose cancers did not grow. Tumour shrinkage in the responders was observed as early as 8 weeks after the first dose. The Keynote 28 trial is ongoing and should be complete by August 2017 with further results to be published after that.

Further results, including some survival data, from Keynote 028 were reported at the International Association for the Study of Lung Cancer (IASLC) 17th World Conference on Lung Cancer in December 2016 by Dr. Evan Alley¹⁰. As of the 9th June 2016, median duration of follow-up was 18.7 months (range 1.5-24.6 months), and 4 patients were still receiving treatment. The response rate (proportion of patients with tumour shrinkage) was 28 % (7 of 25 patients) and 48 % of patients had stable disease, resulting in a disease control rate of 76 %. [Compared to the earlier published findings, there is now one more patient whose tumour shrank and one fewer with stable disease, giving the same rate of disease control]. It should be noted that the definition of 'stable' adopted within the Keynote-028 study includes those patients whose tumours have grown within 25%. This group may include patients with slow progression disease, which may be the natural course of the tumour and so the drug, in this instance, will not have given any benefit. The median duration of response (time for which the tumour remained shrunk) was 9.2 months (range 2.4 months to 20.5+ months). Median progression-free survival was 5.8 months and 6- and 12- month progression free survival rates were 50 % and 25 % respectively. Median overall

survival was 18.0 months, with 6- and 12- month overall survival rates of 83.5 % and 62.6 % respectively. However, no additional data, such as survival in patients being given a different treatment type, were reported for comparison. [The figures above are taken directly from the abstract of the conference report. Other sources, including Merck Newsroom, quote slightly different figures, such as the overall response rate of 20 %, 5 out of 25 patients]¹¹. In March 2017, Dr. Alley and colleagues published a paper in *The Lancet* in which preliminary results from 25 patients are outlined (this appears to be more up-to-date data from the 25 patients in the above report)¹². Five (20 %) patients had a partial response and 13 (52 %) had stable disease: no patient had a complete response. Although 2 additional patients had reduction in tumour size, meeting the criteria for partial response, they did not have subsequent imaging that confirmed partial response, and were not included in the confirmed objective response (this is probably why the earlier reports from this study were that 7 patients had tumour shrinkage). The median response duration was 12.0 months (confidence interval 3.7 to not reached) and two patients remained on treatment at the time of data cutoff. Median progression-free survival was 5.4 months and median overall survival was 18.0 months. The researchers comment that, “Pembrolizumab appears to elicit significant clinical activity with durable responses and a manageable safety and toxicity profile in patients with PD-L1-positive malignant pleural mesothelioma”.

KEYNOTE 158, a larger, phase 2 Keytruda trial¹ that includes mesothelioma patients¹³ is currently underway, and is still recruiting participants. It is estimated that there will be 1100 participants in total, though only some of these will be mesothelioma patients (mesothelioma is one of 11 types of tumour to be included). Primary data is expected to be collected by September 2017, with the study estimated to be completed by May 2019. There are not yet any publications of data from this trial.

Another phase 2 trial, KEYNOTE-139 (NCT02399371), by the University of Chicago and the National Cancer Institute, aims to investigate whether PD-L1 will predict the response of mesothelioma tumours (shrinking) to Keytruda^{14 15}. This study is currently recruiting participants, and is expected to include 65 mesothelioma patients. In part A of the study, the response rate (proportion of patients whose tumours respond) of Keytruda on all mesothelioma patients will be assessed. If a particular amount, or threshold, of PD-L1 presence on the tumour is identified as increasing the tumour response, part B of the trial will investigate the response rate among a PD-L1 positive population that meets this threshold. The study will last for 3 years, and will also investigate overall survival, progression-free survival and the disease control rate. Patients receive 200 mg of the drug intravenously over 30 minutes on day 1, and treatment is repeated every 21 days for up to 24 months in the absence of disease progression or unacceptable toxicity. After the completion of the study treatment, patients will be followed for up to 30 days (or 90 days for serious adverse effects), every 8 weeks until the patient’s disease progresses or they start a new anti-cancer treatment, and then every 12 weeks for 3 years. Some interim findings from this trial were announced at the 17th World Conference on Lung Cancer¹⁶. Of 34 patients enrolled in May/June 2016, the median progression-free survival was 6.2 months. Median overall survival is not yet reached. There were partial responses in 7 patients (21 %), stable disease in 19 (56 %), progression in 6 (18 %) and early death in 2 (6 %). These data give a disease control rate of 76 %. PD-L1 expression did not correlate with response. An optimal PD-L1 threshold for drug activity could not be established from this small sample. This appears to be the first report of PD-L1 properties of the tumour and response to Keytruda.

Results from a phase II study of Nivolumab (Opdivo), another PD-L1/PD-1 inhibitor, treatment for mesothelioma patients were also announced at the conference¹⁷. Using data from 29 patients, a clear

¹ [A phase 1 trial has an emphasis on safety and investigates what the most frequent and serious adverse effects from the drug are, and may also investigate how the drug is metabolized and excreted. A phase 2 trial gathers preliminary data on effectiveness of the drug. Participants receiving the drug may be compared to similar participants receiving a different drug treatment or a placebo.]

correlation between PD-L1 expression and response was observed, whereby patients with greater PD-L1 expression were more likely to respond. Conversely, a study published in 2015 reported that expression of PD-L1 was not predictive of benefit in squamous-cell non-small-cell lung cancer (NSCLC) patients treated with nivolumab¹⁸.

The Canadian Cancer Trials Group also has a phase 2 trial that is recruiting participants¹⁹. The study will primarily investigate the progression free survival time, which is the time from when the patient is allocated a treatment type (Keytruda alone, Keytruda with other drugs, or other drugs) until disease relapses or progresses. The time frame of the trial is 32 months and 126 patients are expected to be enrolled. The study is estimated to be completed in December 2019.

There are no phase 3 trials of Keytruda for mesothelioma at this stage, though data from phase 3 trials for non-small cell lung cancer is available²⁰ and phase 3 trials of other immunotherapy treatments for mesothelioma are underway²¹.

The current data published from studies of Keytruda and mesothelioma relates to overall survival time and to progression free survival. Publications have not included details of the patients' symptoms and quality of life, though some patients who responded to treatment have posted articles online describing symptom improvement²². In addition, there does not appear to be any available data that indicates the effectiveness of treatment for different sub-groups of patients, broken down by age or disease severity, for example.

One area of ongoing investigation is Keytruda's mechanism of acting as a PD-1 inhibitor and whether it can be effective in mesothelioma tumours that do not show a positive PD-L1 expression. If there is no PD-L1 involvement from the tumour, how can Keytruda act?

Is PD-L1 expression required?

An article discussing the preliminary results of the 028 trial²³ identified there might not be a correlation between PD-L1 expression and positive responses and '*further research is needed to identify the patients most likely to benefit from the drug. PD-L1 expression in tumour cells may be a potential biomarker, but whether it truly predicts therapeutic benefit or is merely prognostic – providing information on disease outcome independent of therapy – remains to be established*²⁴.

Another study, of a different PD-L1/PD-1 inhibitor, found a clear correlation between PD-L1 expression and response, using data from 29 patients. However, the numbers of patients with the greatest amount of PD-L1 expression were small (3 patients). Data from larger study groups is needed. If the data suggests that the response to Keytruda does not depend on the amount of PD-L1 expression, further studies will be required to determine which features of the tumours are associated with response to Keytruda, so that those patients that will benefit may be identified.

A 2012 study found a relationship between PD-L1 expression on tumour cells and objective response to an anti-PD-1 antibody among patients with advanced melanoma, non-small-cell lung cancer, castration-resistant prostate cancer, or renal-cell or colorectal cancer²⁵. Of 27 patients with PD-L1-negative tumours, none had an objective response; 9 of 25 patients (36 %) with PD-L1-positive tumours had an objective response.

A review paper by Elly Marcq of the Centre for Oncological Research in Antwerp²⁶, considers studies up to September 2015 which looked at PD-L1 expression in mesothelioma. The results were as follows:

Table 2

Summary of PD-L1 expression in mesothelioma reported by five different groups using immunohistochemistry. E, epithelioid subtype; S, sarcomatoid subtype; B, biphasic subtype; NE, non-epithelioid subtype.

Refs.	Method	Antibody clone	Sample size	Cut off (%)	% PD-L1+
Mansfield et al. [106]	Immunohistochemistry	5H1-A3	106	≥5	40% (E 21%, S 94%, B 57%)
Cedres et al. [108]	Immunohistochemistry	E1L3N	119	>1	20% (E 13%, NE 38%)
Kindler et al. [125] (and personal communication)	Immunohistochemistry	5H1-A3	45	≥50	27% (E 17%, B 7%)
Cowan et al. [109]	Immunohistochemistry	5H1-A3	33	≥5	70%
Alley et al. (data presented at the 16th World Conference on Lung Cancer in Denver, USA)	Immunohistochemistry	22C3	80	>1	45.2%

It can be seen that the percentage of patients who were found to have a positive PD-L1 expression ranged from 20-70 %. Marcq stated on the available evidence that PD-L1 expression '*can vary over time...and that it is so far unknown if it is a conclusive biomarker for PD-1 and/or PD-L1 targeting immunology*'.²⁷

The study by Cedres on the list above found that, among the 119 patients reviewed, there was a significant relationship between PD-L1 expression and tumour cell type: PD-L1 expression was more common in non-epithelioid tumours (37.5 % in non-epithelioid and 13.2 % in epithelioid)²⁸

A research group from the University of Chicago has published plans for a study that aims to investigate the mechanism of action of Keytruda, by comparing treated and untreated samples of pleura, and to identify features of the tumour that may predict benefit or resistance to Keytruda²⁹. An article on the proposed study begins by noting that, '*Although PD-1 inhibitors have demonstrated significant activity in MPM, not all patients benefit*'. This study will include 15 patients, and the primary data is expected to be collected by March 2018³⁰.

At the IASLC 17th World Conference on Lung Cancer in December 2016, there was a 50-minute debate entitled 'Immunotherapy Does NOT Work in Mesothelioma'³¹, which suggests that there is doubt among some researchers and a lack of consensus regarding whether immunotherapy is effective for mesothelioma. The Program for the conference is shown below:

08:00 - 11:00: Mesothelioma Workshop (WS04) (Ticketed Session €25,00)

Room: Stolz 2

Chair: Michele Carbone, USA

- **08:00 - Debate - Extrapleural Pneumonectomies Should NOT be Performed for Pleural Mesothelioma**
David Jablons, USA, Raja Flores, USA & Isabelle Schmitt-Opitz, Switzerland
- **08:50 - Q&A**
- **09:00 - Debate - Immunotherapy Does NOT Work in Mesothelioma**
Hedy Kindler, USA, Luciano Mutti, UK, Paul Bass, The Netherlands & Daniel Sterman, USA
- **09:50 - Q&A**
- **10:00 - Debate - Induction Chemotherapy is Better than Postoperative Adjuvant Therapy for Early Stage Pleural Mesothelioma**
Anne Tsao, USA, Walter Weder, Switzerland, Marc de Perrot, Canada, Wickii Vigneswaran, USA
- **10:50 - Q&A**

Thus, at this stage, it could be argued that there is insufficient information to conclude that PD-L1 is a safe biomarker of mesothelioma and it is therefore questionable whether PD-L1 immunotherapy would assist in the treatment of mesothelioma. Furthermore, testing for the PD-L1 protein is carried out by immunohistochemistry staining and it is rare for mesothelioma patients to be tested in this way. As such, in most cases, defendants will be unable to determine if an individual tested positive for PD-L1.

An article in the Journal of Lung Cancer from January this year notes that, *'Despite the significant interest in immunotherapy for MPM, the failure of another immune checkpoint strategy, the low response rate to a PD-L1 inhibitor, and the low mutational burden of MPM have diminished expectations for immunotherapy for this disease'*³². It is pointed out that the assumption that PD-L1 expression should be predictive of a response to the drug is challenged by some results from small cell lung cancer studies. In addition, the author notes that there are important differences between the 2 trials (Keynote 028 and NCT02399371) from which data relating to the action of Keytruda on mesothelioma patients has been published, such as the dosing, the frequency of imaging examinations, and the definitions used to define tumour growth. The article also notes that, in the phase 2 trial, over half of the patients did not have detectable PD-L1 expression, and responses were seen regardless. There is also a need for trials to consider other factors for survival when selecting participants; for example, it has been suggested that a particular mutation may increase long-term survival in mesothelioma patients³³. Thus, trials that have greater proportions of such patients may report increased disease control rates and survival times.

Whilst it is unarguable Keytruda has shown promise in treating several cancer types, at this stage there is very limited evidence regarding its potential treatment for mesothelioma. Keytruda should be regarded as an experimental therapy for mesothelioma, rather than a standard treatment, but that in itself is unlikely to be an effective defence to claims for private cost of treatment.

Use in other countries

In the USA, mesothelioma patients at several cancer centres can receive the drug through Merck's special Patients Access Program³⁴. Towards the end of 2016, the FDA approved its use for metastatic non-small cell lung cancer, but it is not yet approved for mesothelioma.

In Australia, Keytruda is available cheaply for melanoma, but costs thousands of dollars when used for mesothelioma. It is available to those who participate in a trial or can afford to pay for the treatment, including travel costs. There are currently several small trials underway in Australia, which are necessary to get Keytruda approved on the Pharmaceutical Benefits Scheme for mesothelioma patients (it is approved for melanoma). Merck subsidises about 30 % of the cost of Keytruda, so a typical dose costs a patient \$5,888. In New South Wales, if a patient is entitled to reparation from the Workers' Compensation Dust Diseases Authority (DDA), the DDA is willing to pay for Keytruda treatment in cases where the consulting oncologist conforms that the patient has exhausted all other treatment options and Keytruda could be beneficial. Payment is only made to those who were exposed to asbestos whilst working as an employee in NSW³⁵.

The European Medicines Agency lists Keytruda as being a treatment for melanoma and NSCLC that has spread, and being specific for lung tumours that produce PD-L1³⁶.

Conclusion

Will Keytruda prove to be an effective treatment in claimants identified as having no PD-L1 present? Arguably, based on Keytruda's mechanism of acting, the treatment will serve no clinical benefit and, as such, the cost of this treatment would be unreasonable - although in time it may be shown to have a different mechanism of acting and still an effective treatment.

Even where claimants do have PD-L1 present will Keytruda always be a suitable treatment?

The participants in the Keynote 28 study, were selected based upon an ECOG performance level of 0/1. ECOG is a grading system which describes a patient's level of functioning in terms of their ability to care for themselves, daily activity, and physical ability (walking, working, etc). The full ECOG scale can be seen in the table below:³⁷

ECOG Performance Status

Developed by the Eastern Cooperative Oncology Group, Robert L. Comis, MD, Group Chair.*

GRADE	ECOG PERFORMANCE STATUS
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Dead

Will the successful preliminary outcomes seen in the Keynote 28 study, in relation to extending life, apply to patients further progressed in the disease with higher ECOG performance status?

At this stage and until we have the results of further clinical trials we cannot answer these questions.

Keytruda is an experimental therapy and only in the early stages of clinical trials to determine whether it is a potentially effective treatment for mesothelioma.

The coming few years are set to see major developments in mesothelioma treatment-not just Keytruda-which have the potential to significantly increase the cost of claims. The results of ongoing clinical trials will hopefully answer many of the questions raised in this feature and bring some clarity as to where and what treatments might be effective and whether costs are reasonably recoverable. We will continue to update in this area on a regular basis.

¹ Cancer Research UK. Types of lung cancer. (2015). Available at: <http://www.cancerresearchuk.org/about-cancer/type/lung-cancer/about/types-of-lung-cancer>. (Accessed: 8th December 2016)

² McKee, S. NICE rejects MSD's Keytruda for lung cancer. (2016). Available at: http://www.pharmatimes.com/news/nice_rejects_msds_keytruda_for_lung_cancer_1153495. (Accessed: 8th December 2016)

³ NICE recommends new lung cancer drug pembrolizumab | News and features | News | NICE. Available at: <https://www.nice.org.uk/news/article/nice-recommends-new-lung-cancer-drug-pembrolizumab>. (Accessed: 10th December 2016)

⁴ National Cancer Drugs Fund (CDF) List < <https://www.england.nhs.uk/wp-content/uploads/2017/01/national-cdf-list-v1-19.pdf>> accessed 7 February 2017.

⁵ European Medicines Agency, 'EPAR Summary for the Public' < http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Summary_for_the_public/human/003820/WC500190993.pdf> accessed 7 February 2017.

⁶ U.S. Food & Drug Administration, 'Pembrolizumab (KEYTRUDA) Checkpoint Inhibitor' (Approved Drugs October 24 2016) < <http://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm526430.htm>> accessed 7 February 2017.

⁷ Bill Berkrot, 'Merck 2017 Forecast Reassuring; Full-Speed Ahead With Keytruda' (Reuters 2 February 2017) < <http://uk.reuters.com/article/us-merck-co-results-idUKKBN15H19N>> accessed 7 February 2017.

⁸ Alley, E. W. et al. Abstract CT103: Clinical safety and efficacy of pembrolizumab (MK-3475) in patients with malignant pleural mesothelioma: Preliminary results from KEYNOTE-028. *Cancer Res* 75, CT103–CT103 (2015).

⁹ Potential Immune Therapy for Mesothelioma. American Association for Cancer Research: *Cancer Discov* (2015). doi:10.1158/2159-8290.CD-NB2015-067

¹⁰ Alley, E. et al. OA13.03 Long-Term Overall Survival for Patients with Malignant Pleural Mesothelioma on Pembrolizumab Enrolled in KEYNOTE-028. *Journal of Thoracic Oncology* 12, S294 (2017). Available at [http://www.jto.org/article/S1556-0864\(16\)31543-X/fulltext](http://www.jto.org/article/S1556-0864(16)31543-X/fulltext) (Accessed 19 February 2017)

¹¹ Merck newsroom, Updated Keytruda (pembrolizumab) Data in Small Cell Lung Cancer and Mesothelioma Presented at 17th World Conference on Lung Cancer, December 6, 2016 <http://www.mercknewsroom.com/news-release/oncology-newsroom/updated-keytruda-pembrolizumab-data-small-cell-lung-cancer-and-mesoth> (Accessed 20 February 2017)

¹² Alley, E. W. et al. Clinical safety and activity of pembrolizumab in patients with malignant pleural mesothelioma (KEYNOTE-028): preliminary results from a non-randomised, open-label, phase 1b trial. *The Lancet Oncology* 0, (2017).

¹³ Study of Pembrolizumab (MK-3475) in Participants With Advanced Solid Tumors (MK-3475-158/KEYNOTE-158) - Full Text View - ClinicalTrials.gov. Available at: <https://clinicaltrials.gov/ct2/show/NCT02628067>. (Accessed: 10th December 2016)

¹⁴ Pembrolizumab in Treating Patients With Malignant Mesothelioma <https://clinicaltrials.gov/ct2/show/NCT02399371> (Accessed: 19th February 2017)

¹⁵ Mesothelioma Cancer Alliance, <https://www.mesothelioma.com/treatment/clinical-trials/NCT02399371/> (Accessed: 19th February 2017)

¹⁶ Kindler, H. et al. OA13.02 Phase II Trial of Pembrolizumab in Patients with Malignant Mesothelioma (MM): Interim Analysis. *Journal of Thoracic Oncology* 12, S293–S294 (2017).

¹⁷ Quispel-Janssen, J. et al. OA13.01 A Phase II Study of Nivolumab in Malignant Pleural Mesothelioma (NivoMes): with Translational Research (TR) Biopies. *Journal of Thoracic Oncology* 12, S292–S293 (2017).

¹⁸ Brahmer, J. et al. Nivolumab versus Docetaxel in Advanced Squamous-Cell Non–Small-Cell Lung Cancer. *New England Journal of Medicine* 373, 123–135 (2015).

¹⁹ Pembrolizumab in Patients With Advance Malignant Pleural Mesothelioma <https://clinicaltrials.gov/ct2/show/record/NCT02784171> (Accessed 20 February 2017)

²⁰ Reck, M. et al. Pembrolizumab versus Chemotherapy for PD-L1–Positive Non–Small-Cell Lung Cancer. *New England Journal of Medicine* 375, 1823–1833 (2016).

²¹ A mesothelioma journal, Phase 3 mesothelioma trial due in the US in 2017 <https://ajandray.wordpress.com/category/mesothelioma-treatments/research-into-new-treatments/> (Accessed 20 February 2017)

²² Mesothelioma survivor praises Keytruda for fresh optimism, September 9, 2016 <https://www.asbestos.com/blog/2016/09/09/mesothelioma-survivor-praises-keytruda-optimism/>

²³ Published in *Cancer Discovery*, D. Ross Camidge, MD, PhD, Director of the University of Colorado Comprehensive Cancer Centre’s thoracic oncology clinical program

²⁴ Ibid

²⁵ Topalian, S. L. et al. Safety, Activity, and Immune Correlates of Anti–PD-1 Antibody in Cancer. *New England Journal of Medicine* 366, 2443–2454 (2012).

²⁶ E. Marcq et al, Targeting Immune Checkpoints: New Opportunity for Mesothelioma Treatment? *Cancer Treatment Review* (2014) 41 914 – 924.

²⁷ Ibid.

²⁸ Cedrés, S. et al. Analysis of Expression of Programmed Cell Death 1 Ligand 1 (PD-L1) in Malignant Pleural Mesothelioma (MPM). *PLOS ONE* 10, e0121071 (2015).

²⁹ Kindler, H. et al. P2.06-029 Pilot Window-Of-Opportunity Study of Pembrolizumab in Patients with Resectable Malignant Pleural Mesothelioma (MPM). *Journal of Thoracic Oncology* 12, S1089 (2017).

³⁰ A Pilot Window of Opportunity Study of the Anti-PD-1 Antibody Pembrolizumab in Patients with Resectable Malignant Pleural Mesothelioma <https://clinicaltrials.gov/ct2/show/NCT02707666> (Accessed: 20 February 2017)

³¹ IASLC, <http://wclc2016.iaslc.org/wp-content/uploads/2016/11/WCLC-2016-Scientific-Program.pdf> see page 6 (Accessed 20 February 2017)

³² Mansfield, A. S. Immune checkpoint inhibition in malignant mesothelioma: Does it have a future? *Lung Cancer* doi:10.1016/j.lungcan.2017.01.004

³³ Baumann, F. et al. Mesothelioma patients with germline BAP1 mutations have 7-fold improved long-term survival., Mesothelioma patients with germline BAP1 mutations have 7-fold improved long-term survival. *Carcinogenesis* 36, 36, 76, 76–81 (2015).

³⁴ Asbestos.com, Using Keytruda for Mesothelioma May Become a Reality, November 2, 2016 <https://www.asbestos.com/news/2016/11/02/keytruda-for-mesothelioma-reality/> (Accessed: 20 February 2017)

³⁵ Key facts you should know about Keytruda. Available at: <https://www.slatergordon.com.au/blog/key-facts-you-should-know-about-keytruda>. (Accessed: 20th February 2017)

³⁶ European Medicines Agency - Find medicine - Keytruda. Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/003820/human_med_001886.jsp&mid=WC0b01ac058001d124. (Accessed: 20th February 2017)

³⁷ Oken M, Creech R, Tormey D, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol*. 1982;5:649-655.