

*David W Smith, John Mackenzie

School of Pathology and Laboratory Medicine, University of Western Australia, Nedlands, WA 6009, Australia (DWS); and Faculty of Health Science, Curtin University, Bentley, WA, Australia (JM)
david.smith@health.wa.gov.au

We declare no competing interests.

- 1 Enfissi A, Codrington J, Roosblad J, Kazanji M, Rousset D. Zika virus genome from the Americas. *Lancet* 2016; **387**: 227–28.
- 2 The Lancet. Zika virus: a new global threat for 2016. *Lancet* 2016; **387**: 96.
- 3 WHO. WHO statement on the first meeting of the International Health Regulations (2005) (IHR 2005). Emergency Committee on Zika virus and observed increase in neurological disorders and neonatal malformations. <http://www.who.int/mediacentre/news/statements/2016/1st-emergency-committee-zika/en/#> (accessed Feb 21, 2016).
- 4 Cao-Lormeau V-M, Blake A, Mons S, et al. Guillain-Barré Syndrome outbreak associated with Zika virus infection in French Polynesia: a case-control study. *Lancet* 2016; published online Feb 29. [http://dx.doi.org/10.1016/S0140-6736\(16\)00562-6](http://dx.doi.org/10.1016/S0140-6736(16)00562-6).

- 5 Yuki N, Hartung HP. Guillain-Barré syndrome. *N Engl J Med* 2012; **366**: 2294–304.
- 6 Carod-Artal FJ, Wichmann O, Farrar J, Gascón J. Neurological complications of dengue virus infection. *Lancet Neurol* 2013; **12**: 906–19.
- 7 Oehler E, Watrin L, Larre P, et al. Zika virus infection complicated by Guillain-Barré syndrome—case report, French Polynesia, December 2013. *Euro Surveill* 2014; **19**: pii=20720.
- 8 Gourinat AC, O'Connor O, Calvez E, Goarant C, Dupont-Rouzeyrol M. Detection of Zika virus in urine. *Emerg Infect Dis* 2015; **21**: 84–86.
- 9 Pan American Health Organization. Epidemiological update: neurological syndrome, congenital anomalies, and Zika virus infection. Jan 17, 2016. http://www.paho.org/hq/index.php?option=com_content&view=category&layout=blog&id=1218&Itemid=2291 (accessed Feb 21, 2016).
- 10 WHO. Guillain-Barré syndrome—Colombia and Venezuela. <http://www.who.int/csr/don/12-february-2016-gbs-colombia-venezuela/en/#> (accessed Feb 22, 2016).
- 11 Duffy MR, Chen TH, Hancock WT, et al. Zika virus outbreak on Yap Island, Federated States of Micronesia. *N Engl J Med* 2009; **360**: 2536–43.

Are we ready for immune checkpoint inhibitors for advanced non-small-cell lung cancer?

Published Online
December 19, 2015
[http://dx.doi.org/10.1016/S0140-6736\(15\)01308-2](http://dx.doi.org/10.1016/S0140-6736(15)01308-2)
See [Articles](#) page 1540

Are we ready to embrace the routine use of immune checkpoint inhibitors in patients with advanced stage non-small-cell lung cancer? In *The Lancet*, Roy Herbst and colleagues¹ report the results of KEYNOTE-010, a randomised phase 2/3 study in 202 academic medical centres in 24 countries that compared two doses of pembrolizumab (2 mg/kg and 10 mg/kg) with docetaxel (75 mg/m²) every 3 weeks in 1034 patients with previously treated, PD-L1-positive, advanced non-small-cell lung cancer. This biomarker-enriched study had two primary endpoints of overall survival and progression-free survival both in the total population and in the subgroup of patients with tumour proportion score of 50% or more, which is defined as the percentage of tumour cells expressing PD-L1 assessed by immunohistochemistry using antibody 22C3. In the total study population, there was significant improvement in overall survival with pembrolizumab compared with docetaxel for both pembrolizumab 2 mg/kg (n=344; hazard ratio [HR] 0.71, 95% CI 0.58–0.88; p=0.0008) and pembrolizumab 10 mg/kg (n=346; 0.61, 0.49–0.75; p<0.0001). Median progression-free survival was similar in all three groups (3.9 months with pembrolizumab 2 mg/kg, 4.0 months with pembrolizumab 10 mg/kg, and 4.0 months with docetaxel) and difference between both doses of pembrolizumab versus docetaxel did not meet the pre-specified threshold for statistical significance

(2 mg/kg 0.88, 0.74–1.05; p=0.070; 10 mg/kg HR 0.79, 95% CI 0.66–0.94; p=0.004). In patients with at least 50% of tumour cells expressing PD-L1, overall survival was significantly longer with pembrolizumab than with docetaxel (for 2 mg/kg median 14.9 months vs 8.2 months, HR 0.54, 95% CI 0.38–0.77, p=0.0002; and for 10 mg/kg 17.3 months vs 8.2 months, 0.50, 0.36–0.70, p<0.0001). Treatment-related adverse events were similar between the two doses of pembrolizumab but less common than with docetaxel.

The results of KEYNOTE-010 support the recent approval of pembrolizumab for the management of advanced non-small-cell lung cancer.² However, these findings need to be interpreted in light of two other randomised phase 3 studies of immune checkpoint inhibitors comparing second-line nivolumab with docetaxel, namely the CHECKMATE-017 and CHECKMATE-057 (table).^{3,4}

Amid the excitement of immuno-oncology, we must remain rational and address key questions related to the practical application of immune checkpoint inhibitors for advanced stage non-small-cell lung cancer. Namely, should immune checkpoint inhibitors be given as second-line or third-line therapy? Is the biomarker of PD-L1 expression according to tumour proportion score reliable and should all patients be tested before starting treatment? What is the optimum dose of pembrolizumab in advanced stage non-small-cell lung

cancer? More importantly, given the hefty costs of these drugs, are they considered cost effective?

We appreciate the investigators' intention to include patients whose disease had progressed after two lines of systemic therapy. 300 (29%) of 1034 patients in the trial¹ had had two or more lines of systemic therapy, compared with previous studies of nivolumab^{3,4} which enrolled patients with only one previous line. The positive findings from KEYNOTE-010 confirm that a treatment response is possible even in heavily pre-treated patients. This finding was first reported in the large KEYNOTE-001 phase 1 trial,⁵ which included patients with PD-L1-negative tumours and reported a response rate of 19.4%, median progression-free survival of 3.7 months, and a median overall survival of 12.0 months. More than 65% of the 495 patients enrolled in KEYNOTE-001 had received two or more lines of previous systemic chemotherapy.⁵ The findings of KEYNOTE-010¹ are thus consistent and confirm the efficacy of pembrolizumab as a second-line or third-line therapy.

Prospective collection of quality tumour samples is essential to the successful development of a biomarker. Herbst and colleagues painstakingly tested 2222 samples (including both archival and fresh samples) and found that 29% of patients had a tumour proportion score of more than 50%, 34% of patients had a score of 1–49%, and 34% of patients had a score of less than 1%. A similar distribution was noted in KEYNOTE-001,⁵ which helped establish the consistency and reliability of this biomarker. Although the greatest improvement in overall survival in KEYNOTE-010 was in patients with a tumour proportion score of 50% or greater (HR 0.53, 95% CI 0.40–0.70) for pembrolizumab compared with docetaxel, patients with a score of 1–49% also benefited (0.76, 0.60–0.96).¹

At present, there appear to be no solid data to support the routine application of PD-L1 expression as a predictive biomarker before the use of immune checkpoint inhibitors. Because patients with a tumour proportion score of less than 1% were excluded from this study, it is unclear whether such patients would have a different response to pembrolizumab compared with the 1–49% subgroup. On the basis of previous findings from the KEYNOTE-001 study,⁵ tumour response rate, median progression-free survival, and median overall survival might be similar in each subgroup. Given the data available, we caution about the use of a tumour

	KEYNOTE-010 (n=1034) ¹	Checkmate 057 (n=582) ⁴	Checkmate 017 (n=272) ³
Lines of previous chemotherapy allowed	One or more	One only	One only
Histology	Both non-squamous and squamous cell cancer	Non-squamous cell cancer	Squamous cell cancer
Biomarker (PD-L1 expression)	Prospective (44% archival, 56% new biopsy)	Retrospective	Retrospective
Drug dose	2 mg/kg every 3 weeks, 10 mg/kg every 3 weeks	3 mg/kg every 2 weeks	3 mg/kg every 2 weeks
Primary endpoints	Progression free survival, overall survival (in the total population and in patents with a tumour proportion score of ≥50%)	Overall survival (total population)	Overall survival (total population)

Table: Features of three phase 3 trials of immune checkpoint inhibitors for advanced non-small-cell lung cancer

proportion score of less than 1% as a negative predictive biomarker for this treatment.

Before this study, the optimum dose of pembrolizumab for treatment of non-small-cell lung cancer was unclear. The five-fold dose range in KEYNOTE-001 and KEYNOTE-010 was supported by pharmacological models.^{6,7} The KEYNOTE-010 study is the first and only study that shows a dose of 2 mg/kg to be equally efficacious as 10 mg/kg. Instead of establishing the recommended dose near the maximum tolerated dose, the investigators have aimed for a minimum effective dose. We are satisfied to endorse 2 mg/kg as the optimum dose but cannot resist wondering if similar treatment outcomes could be achieved with a dose lower than 2 mg/kg. A standard dose of nivolumab for the treatment of malignant melanoma is 3 mg/kg every 2 weeks, but at 1.0 mg/kg, eight (30%) of 27 patients responded in one study.⁸ Establishing a lower minimum effective dose of pembrolizumab has clinical implications because it is available in preparations of 100 mg per vial only. A lower minimum effective dose could halve treatment costs for patients with low bodyweight if only one instead of two vials were needed per dose.

The cost-effectiveness of immune checkpoint inhibitors is particularly difficult to evaluate. The drugs are expensive and only some patients may benefit. Ideally, cost-effectiveness can be established if a robust biomarker for response is identified, thus limiting the use of treatment to patients who would benefit most. For example, the presence of an *EGFR* mutation is a strong predictive biomarker of response⁹ and is routinely used for the cost-effective prescription of *EGFR* tyrosine-kinase inhibitors.¹⁰ We hope that eventually

the cost-effectiveness of pembrolizumab treatment will be demonstrable, at least in patients with a tumour proportion score of 50% or greater, especially if costs can be reduced and waste avoided by enforcing the manufacture of preparations with smaller doses. This study has clearly taken us one big step closer to being ready for the routine use of immune checkpoint inhibitors for advanced stage non-small-cell lung cancer.

*Tony S K Mok, Herbert H Loong

Department of Clinical Oncology, Faculty of Medicine, State Key Laboratory in Oncology in South China, The Chinese University of Hong Kong, Hong Kong Special Administrative Region, China
tony@cuhk.edu.hk

TSKM has received honoraria from Boehringer Ingelheim, BioMarin Pharmaceuticals, AstraZeneca, Roche/Genentech, Pfizer, Eli Lilly, Merck Serono, Merck Sharp & Dohme, Janssen, Clovis Oncology, GlaxoSmithKline, Novartis, SFJ Pharmaceutical, ACEA Biosciences, Vertex Pharmaceuticals, Bristol-Myers Squibb, AVEO & Biodesix, Prime Oncology, and Amgen; speakers fees from AstraZeneca, Roche/Genentech, Pfizer, Eli Lilly, Boehringer Ingelheim, Merck Sharp & Dohme, Amgen, Janssen, Clovis Oncology, GlaxoSmithKline, Novartis, Bristol-Myers Squibb, and Prime Oncology; advisory board fees from AstraZeneca, Roche/Genentech, Pfizer, Eli Lilly, Boehringer Ingelheim, Merck Serono, Merck Sharp & Dohme, Janssen, Clovis Oncology, BioMarin, GlaxoSmithKline, Novartis, SFJ Pharmaceutical, ACEA Biosciences, Vertex Pharmaceuticals, AVEO & Biodesix, and Bristol-Myers Squibb; and is a shareholder in Sanomic. HHL has received honoraria from Celgene, Novartis, and Roche; research funding from Merck Sharp & Dohme; advisory board fees from Celgene, Novartis, and Roche; and travel grants from Bayer, Bristol-Myers Squibb, Merck Sharp & Dohme, Novartis, and Roche.

- 1 Herbst RS, Baas P, Kim D-W, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. *Lancet* 2015; published online Dec 19. [http://dx.doi.org/10.1016/S0140-6736\(15\)01281-7](http://dx.doi.org/10.1016/S0140-6736(15)01281-7).
- 2 US Food and Drug Administration. FDA approves Keytruda for advanced non-small cell lung cancer. Oct 2, 2015. <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm465444.htm> (accessed Dec 16, 2015).
- 3 Brahmer J, Reckamp KL, Baas P, et al. Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. *N Engl J Med* 2015; **373**: 123–35.
- 4 Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. *N Engl J Med* 2015; **373**: 1627–39.
- 5 Garon EB, Rizvi NA, Hui R, et al. Pembrolizumab for the treatment of non-small-cell lung cancer. *N Engl J Med* 2015; **372**: 2018–28.
- 6 Lindauer A, Valiathan C, Mehta K, et al. Translational pharmacokinetic/ pharmacodynamic model of tumor growth inhibition by the new anti-PD1 monoclonal antibody MK-3475. Annual Meeting of the Population Approach Group in Europe; June 10–13, 2014; Alicante, Spain; abstract 3214.
- 7 Ahamadi M, Prohn M, Rossenu S, et al. Population pharmacokinetics of MK-3475, a human anti-PD-1 monoclonal antibody in patients with progressive locally advanced or metastatic carcinoma, melanoma, and non-small cell lung carcinoma. Annual Meeting of the Population Approach Group in Europe; June 10–13, 2014; Alicante, Spain; abstract 3229.
- 8 Topalian SL, Hodi FS, Brahmer JR, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. *N Engl J Med* 2012; **366**: 2443–54.
- 9 Mok TS, Wu YL, Thongprasert S, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. *N Engl J Med* 2009; **361**: 947–57.
- 10 de Lima Lopes G Jr, Segel JE, Tan DS, Do YK, Mok T, Finkelstein EA. Cost-effectiveness of epidermal growth factor receptor mutation testing and first-line treatment with gefitinib for patients with advanced adenocarcinoma of the lung. *Cancer* 2012; **118**: 1032–39.

Daratumumab in multiple myeloma

Published Online

January 6, 2016

[http://dx.doi.org/10.1016/S0140-6736\(15\)01226-X](http://dx.doi.org/10.1016/S0140-6736(15)01226-X)

See [Articles](#) page 1551

It is easy to be overwhelmed by hype in cancer research, with promising new discoveries often portrayed as so-called game changers.¹ Most new treatments for cancer are far from being transformative, but daratumumab is possibly a rare exception. It targets CD38, an antigen that is uniformly expressed in myeloma cells.² As the most anticipated new drug in multiple myeloma in more than a decade, daratumumab has all the features that are necessary to make a substantive difference in a devastating cancer, which—despite many advances—manages to outwit all available treatments over time: a novel mechanism of action, single-agent activity, non-cross resistance, and safety.

In *The Lancet*, Sagar Lonial and colleagues³ provide the results of a phase 2 clinical trial that led to accelerated approval of daratumumab in the USA for patients with multiple myeloma who have received at least three previous treatments. The trial enrolled 106 patients with relapsed and refractory multiple myeloma with

daratumumab administered at the approved dose as a single agent. These patients had exhausted available treatment options. Almost all patients had failed therapy with an immunomodulatory agent as well as a proteasome inhibitor, and most were refractory to alkylating agents and new drugs such as pomalidomide, carfilzomib, or both. 80% had relapsed after previous autologous stem-cell transplantation. At a median of 5 years from diagnosis, and five failed treatments, one could say that hope was in short supply for these patients.

In this setting, Lonial and colleagues showed that roughly 30% of patients achieved a partial response ($\geq 50\%$ reduction in tumour burden) with daratumumab, and had an overall survival outcome that was better than that expected from historical cohorts (overall response noted in 31 patients; response rate 29.2%, 95% CI 20.8–38.9).^{3,4} Several aspects of these findings are striking. First, this level of single-agent activity is higher than that reported in refractory myeloma with