cervical cancer. The Article by Rodin and colleagues[4] is a welcome report and should be widely disseminated to policy makers and stakeholders for further consideration and successful implementation to treat patients with cervical cancer, especially in low-income and middle-income countries.

Umesh M Mahantshetty
Department of Radiation Oncology, Tata Memorial Hospital, Mumbai 400012, Maharashtra, India
mahantshettyum@tmc.gov.in

I declare no competing interests.

1 IARC, WHO. Cervical cancer fact sheet. International Agency for Research on Cancer, 2018. https://gco.iarc.fr/today/data/factsheets/cancers/23-Cervix-uteri-fact-sheet.pdf (accessed May 10, 2019).
2 Kamangar F, Dores GM, Anderson WF. Patterns of cancer incidence, mortality, and prevalence across five continents: defining priorities to reduce cancer disparities indifferent geographic regions of the world. *J Clin Oncol* 2006; **24:** 2137–50.
3 India State-Level Disease Burden Initiative Cancer Collaborators. The burden of cancers and their variations across the states of India: the Global Burden of Disease Study 1990–2016. *Lancet Oncol* 2018; **19:** 1289–306.
4 Rodin D, Burger EA, Atun R, et al. Scale-up of radiotherapy for cervical cancer in the era of human papillomavirus vaccination in 118 countries: a model-based analysis of need and economic impact. *Lancet Oncol* 2019; published online May 28. http://dx.doi.org/10.1016/S1470-2045(19)30308-0.
5 Pramesh CS, Badwe RA, Sinha RK. The national cancer grid of India. *Indian J Med Paediatr Oncol* 2014; **35:** 226–27.
6 Izewska J, Coffey M, Scalliet P, et al. Improving the quality of radiation oncology: 10 years' experience of QUATRO audits in the IAEA Europe. *Radiother Oncol* 2018; **126:** 183–90.
7 Grover S, Gudi S, Gandhi AK, et al. Radiation oncology in India: challenges and opportunities. *Semin Radiat Oncol* 2017; **27:** 158–63.
8 Grover S, Longo J, Einck J, et al. The unique issues with brachytherapy in low- and middle-income countries. *Semin Radiat Oncol* 2017; **27:** 136–142.

The second wave of checkpoint inhibitors with chemotherapy for advanced non-small-cell lung cancer

Published **Online** May 20, 2019 http://dx.doi.org/10.1016/S1470-2045(19)30148-2

See **Articles** page 924

On the basis of Allison and Honjo's Nobel Prize works, immunotherapy has greatly changed the treatment landscape of advanced non-small-cell lung cancer.[1] Within about 3 years, immune checkpoint blockade went from second-line to first-line therapy, from advanced to locally advanced non-small-cell lung cancer treatment, and from monotherapy to combination therapy. It has made the first-line treatment of advanced non-small-cell lung cancer a competitive battlefield of crucial importance (table).

The PD-1 inhibitor pembrolizumab took the lead on such checkpoint blockade therapy in non-small-cell lung cancer: it has been approved as monotherapy for treatment of non-small-cell lung cancer in patients with more than 50% expression of PD-L1 and as combination therapy with chemotherapy regardless of PD-L1 status.[2–4]

In *The Lancet Oncology*, Howard West and colleagues[5] reported the results of the phase 3, IMpower130 trial. The study compared atezolizumab plus chemotherapy (carboplatin plus nab-paclitaxel) with chemotherapy alone for first-line treatment of stage IV non-squamous non-small-cell lung cancer. There was a significant and clinically meaningful improvement in median overall survival (18·6 months [95% CI 16·0–21·2] in the atezolizumab plus chemotherapy group *vs* 13·9 months [12·0–18·7] in the chemotherapy group; stratified hazard ratio [HR] 0·79 [95% CI 0·64–0·98]; p=0·033) and a significant improvement in progression-free survival (7·0 months [95% CI 6·2–7·3] in the atezolizumab plus chemotherapy group *vs* 5·5 months [4·4–5·9] in the chemotherapy group; stratified HR 0·64 [95% CI 0·54–0·77; p<0·0001]). Overall, atezolizumab in combination with carboplatin plus nab-paclitaxel is an efficacious and a safe regimen and might be an additional treatment option for stage IV non-squamous non-small-cell lung cancer. Notably, these results are almost consistent with those of KEYNOTE-189, another phase 3 trial that published results in 2018. Both trials showed that PD-1 (KEYNOTE-189) or PD-L1 (IMpower130) blockade in combination with pemetrexed (KEYNOTE-189) or nab-paclitaxel (IMpower130) doublet chemotherapy improved overall survival and progression-free survival regardless of PD-L1 status, but patients with high PD-L1 expression (>50%) seemed to benefit more in terms of overall survival from these combinations than did patients with low or no PD-L1 expression.[4,5]

To our knowledge, IMpower 130 is the first study to show that PD-L1 blockade combined with chemotherapy works as first-line treatment of advanced non-small-cell lung cancer. Although the regimen tested in IMpower150 (table) was also approved for non-squamous non-small-cell lung cancer, it added antiangiogenic therapy to the checkpoint inhibitor chemotherapy combination. Second, IMpower130 showed that PD-L1 blockade

	KEYNOTE-189 (NCT02578680)	KEYNOTE-407 (NCT02775435)	IMpower131 (NCT02367794)*	IMpower130 (NCT02367781)	IMpower132 (NCT02657434)*	IMpower150 (NCT02366143)
Therapy	Pembrolizumab plus pemetrexed plus cisplatin or carboplatin *vs* pemetrexed plus cisplatin or carboplatin	Pembrolizumab plus nab-paclitaxel or paclitaxel plus carboplatin *vs* nab-paclitaxel or paclitaxel plus carboplatin	Atezolizumab plus nab-paclitaxel or paclitaxel plus carboplatin *vs* nab-paclitaxel or paclitaxel plus carboplatin	Atezolizumab plus nab-paclitaxel plus carboplatin *vs* nab-paclitaxel plus carboplatin	Atezolizumab plus pemetrexed plus cisplatin or carboplatin *vs* pemetrexed plus cisplatin or carboplatin	Atezolizumab plus bevacizumab plus paclitaxel plus carboplatin *vs* paclitaxel plus carboplatin plus bevacizumab
Histology	Non-squamous	Squamous	Squamous	Non-squamous	Non-squamous	Non-squamous
Objective response	47·6% (95% CI 42·6–52·5) *vs* 18·9% (13·8–25·0)	57·9% (95% CI 51·9–63·8) *vs* 38·4% (32·7–44·4)	49·0% *vs* 41·0%	49·2% (95% CI 44·5–54·0) *vs* 31·9% (25·8–38·4)	47·0% *vs* 32·0%	63·5% (95% CI 58·2–68·5) *vs* 48·0% (42·5–53·6)
Median progression-free survival, months	8·8 (95% CI 7·6–9·2) *vs* 4·9 (4·7–5·5)	6·4 (95% CI 6·2–8·3) *vs* 4·8 (4·3–5·7)	6·3 (95% CI 5·7–7·1) *vs* 5·6 (5·5–5·7)	7·0 (95% CI 6·2–7·3) *vs* 5·5 (4·4–5·9)	7·6 (95% CI 6·8–8·5) *vs* 5·2 (4·3–5·6)	8·3 (95% CI 7·7–9·8) *vs* 6·8 (6·0–7·1)
Median overall survival, months	Not reached *vs* 11·3 (95% CI 8·7–15·1); p<0·01	15·9 (95% CI 13·2 to not reached) *vs* 11·3 (9·5–14·8); p<0·001	14·0 (95% CI 12·0–17·0) *vs* 13·9 (12·3–16·4); p=0·69	18·6 (95% CI 16·0–21·2) *vs* 13·9 (12·0–18·7); p=0·033	18·1 (95% CI 13·0 to not reached) *vs* 13·6 (11·4–15·5); p=0·080	19·2 (95% CI 17·0–23·8) *vs* 14·7 (13·3–16·9); p=0·0164
US FDA or EMA approval	Yes	Yes	No	No	No	Yes

FDA=Food and Drug Administration. EMA=European Medicines Agency. *95% CI for objective response not reported.

Table: **Comparison of trials investigating PD-1 or PD-L1 inhibitors plus chemotherapy in advanced non-small-cell lung cancer**

plus chemotherapy can be used without pemetrexed and corticosteroids, which might weaken the efficacy of immunotherapy in advanced non-small-cell lung cancer.[7] Third, IMpower130 provided further evidence that patients with advanced non-small-cell lung cancer with *EGFR* or *ALK* aberrations could not obtain benefit from checkpoint blockade.

IMpower130 and KEYNOTE-189 seem to have established the new standard care of first-line treatment for advanced non-squamous non-small-cell lung cancer. However, several issues need to be addressed. One major issue is whether the antitumour effects of all PD-1 or PD-L1 inhibitors are similar. On the basis of published data (table), the answer is no because the overall survival was different. As checkpoint inhibitors in combination with chemotherapy are now the standard treatment for advanced non-small-cell lung cancer, all new trials in the first-line setting should choose the combination regimen as the control group. This will be a great challenge for development of new drugs, which need to be directly compared with each other, in this field. The second point is how to select the target population more precisely. PD-L1 can be used as a biomarker to predict responses to immunotherapies; however, it is increasingly becoming clear that PD-L1 expression in tumour cells is not a straightforward indicative biomarker,[7,8] and could not predict response to PD-1 or PD-L1 inhibitors in KEYNOTE-189 and IMpower130. Whether circulating soluble PD-L1 can be used to guide clinical decisions on choice of immunotherapeutic agents should be considered in the further trials.[7] Tumour mutation burden, especially tumour mutation burden measured in circulating tumour cells, seems to be a prognostic factor but not a predictive biomarker.[9] Therefore, identification of a comprehensive biomarker is crucial in this setting. The third point is how to select a treatment regimen in clinical practice. So far, we have no evidence to guide selection among the few regimens available. Perhaps new head-to-head trials of different anti-PD-1 or anti-PD-L1 agents are needed, even though they might not be commercially driven. Last, should we need to explore different chemotherapy regimens with PD-1 or PD-L1 inhibitors? On the basis of the evidence from ECOG1594 and CTONG 1002, third-generation chemotherapy drugs had similar efficacy.[10]

We thank the contribution of IMpower130 to add a novel first-line treatment option for advanced non-squamous non-small-cell lung cancer. However, there might be more efficacious immunotherapy combinations to test for lung cancer.

*Yangqiu Li, *Yi-Long Wu*
Institute of Hematology, School of Medicine, and Key Laboratory for Regenerative Medicine of Ministry of Education, Jinan University, Guangzhou, 510632, China (YL); Guangdong Lung Cancer Institute, Guangdong Provincial People's Hospital & Guangdong Academy of Medical Sciences, Guangzhou, China (Y-LW)
syylwu@live.cn

Y-LW reports personal fees from AstraZeneca, Eli Lilly, Roche, Pfizer, Bristol-Myers Squibb, Merck, and Boehringer Ingelheim; consulting or advisory role with AstraZeneca, Roche, Merck, and Boehringer Ingelheim; and research funding to Guangdong Lung Cancer Institute from Boehringer Ingelheim, AstraZeneca, and Roche. YL declares no competing interests.

1 Liu SY, Wu YL. An immunological storm for cancer therapy: 2018 Nobel Prize in Physiology or Medicine. *Sci Bull* 2018; **63:** 1608–70.
2 Wu YL, Planchard D, Lu S, et al. Pan-Asian adapted Clinical Practice Guidelines for the management of patients with metastatic non-small-cell lung cancer: a CSCO–ESMO initiative endorsed by JSMO, KSMO, MOS, SSO and TOS. *Ann Oncol* 2019; **30:** 171–210.
3 Reck M, Rodríguez-Abreu D, Robinson AG, et al. Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. *N Engl J Med* 2016; **375:** 1823–33.
4 Gandhi L, Rodríguez-Abreu D, Gadgeel S, et al. Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. *N Engl J Med* 2018; **378:** 2078–92.
5 West H, McCleod M, Hussein M, et al. Atezolizumab in combination with carboplatin plus nab-paclitaxel chemotherapy compared with chemotherapy alone as first-line treatment for metastatic non-squamous non-small-cell lung cancer (IMpower130): a multicentre, randomised, open-label, phase 3 trial. *Lancet Oncol* 2019; published online May 20. http://dx.doi.org/10.1016/S1470-2045(19)30167-6.
6 Arbour KC, Mezquita L, Long N, et al. Impact of baseline steroids on efficacy of programmed cell death 1 and programmed death ligand 1 blockade in patients with non-small-cell lung cancer. *J Clin Oncol* 2018; **36:** 2872–78.
7 Liu D, Wang S, Bindeman W. Clinical applications of PD-L1 bioassays for cancer immunotherapy. *J Hematol Oncol* 2017; **10:** 110.
8 Doroshow DB, Sanmamed MF, Hastings K, et al. Immunotherapy in non-small cell lung cancer: facts and hopes. *Clin Cancer Res* 2019; published online Mar 1. DOI:10.1158/1078-0432.CCR-18-1538.
9 Wang Z, Duan J, Cai S, et al. Assessment of blood tumor mutational burden as a potential biomarker for immunotherapy in patients with non-small cell lung cancer with use of a next-generation sequencing cancer gene panel. *JAMA Oncol* 2019; published online Feb 28. DOI:10.1001/jamaoncol.2018.7098.
10 Wang Z, Huang C, Yang JJ, et al. A randomised phase II clinical trial of nab-paclitaxel and carboplatin compared with gemcitabine and carboplatin as first-line therapy in advanced squamous cell lung carcinoma (C-TONG1002). *Eur J Cancer* 2019; **109:** 183–91.

Machine versus man in skin cancer diagnosis

Skin examinations for diagnosis of skin cancer are facilitated by the use of dermatoscopy, a non-invasive skin imaging technique that amplifies features of pigmented skin lesions that are not easily discernable when examined by the naked eye. Since its introduction in the late 1980s, dermatoscopy has substantially increased diagnostic accuracy in the identification of melanoma. However, interpretation of dermatoscopic criteria remains a subjective procedure that requires specific and dedicated training. Several strategies based on artificial intelligence and machine learning, including deep learning networks, have been developed as aids for less experienced dermatologists or other physicians to classify dermatoscopic images into benign and malignant skin tumours, as well as more specific diagnostic categories,[1–4] which in the long-term could revolutionise dermatology practice.

In *The Lancet Oncology*, Philipp Tschandl and colleagues[5] compared the accuracy of diagnoses produced by human readers with that of machine-learning algorithms for dermatoscopic images of pigmented skin lesions. Most outcome measures were outperformed by the machine-learning algorithms with respect to human readers. The best machine-learning algorithms achieved a mean of 7·94 (95% CI 7·76–8·12; p<0·0001) more correct diagnoses than the average human reader, and a mean of 6·65 (6·06–7·25; p<0·0001) more correct diagnoses than expert human readers with more than 10 years of experience.[5] This robustly powered study provides a timely contribution to an increasingly exciting debate in the field of dermatology and focuses on the more general issue of artificial intelligence use in diagnostic medicine. Tschandl and colleagues have aggregated a hugely balanced amount of information across patient populations from different geographical areas and human readers with varying experience from a large variety of geographically, ethnically, and culturally diverse countries. Sets of images representative of various types of disease (benign and malignant) were analysed and coupled with a robust statistical model, resulting in sound acceptability. The comparison of a large series of different machine-learning algorithms, which were developed by 77 laboratories that participated in the International Skin Imaging Collaboration Forum 2018 challenge,[6] is also novel.

Despite a marked effort to control for the intrinsic drawbacks of overfitting in machine learning, the authors underline that training too hard causes the predictive models to be too specific to the training set used.[5] Overfitting emerges as a problem with models that fit to the training data too closely, thus limiting the generalisability of the model and leading to poor success for data that might seem similar, but are actually different. The training set in an overfitted model might generate a very high performance, which


skvalval/Shutterstock.com

Published **Online** June 11, 2019 http://dx.doi.org/10.1016/S1470-2045(19)30391-2

See **Articles** page 938

For more on the **ISIC 2018 challenge** see https://challenge2018.isic-archive.com