European Journal of Cancer 115 (2019) 24–26

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Letter to the Editor

Comment on 'Randomised phase 2 study of pembrolizumab plus CC-486 versus pembrolizumab plus placebo in patients with previously treated advanced non-small cell lung cancer'—No support for de-escalation of immunotherapy

Alexandros Georgiou*, Anna Minchom, Mary O'Brien

The Royal Marsden Hospital Foundation Trust, UK

Received 4 April 2019; accepted 6 April 2019
Available online 10 May 2019

Dear Editor,

We read with great interest the randomised phase 2 trial by Levy et al., which evaluated the efficacy of 3-weekly pembrolizumab 2 mg/kg with placebo or with the addition of epigenetic agent CC-486 in patients with previously treated advanced non–small cell lung cancer (NSCLC) [1]. Overall, there was no significant difference in progression-free survival (PFS) and overall survival (OS) between the two arms. However, it is worth noting that numerically the experimental arm had a lower median PFS (2.9 versus 4.0 months; P = 0.1789) and median OS (11.9 months versus not estimable; P = 0.2968).

As the authors discussed, this may have been due to an antagonistic effect of the combination, with CC-486 potentially upregulating immune checkpoints. However, there is no experimental data to support this, and instead prior preliminary clinical evidence in NSCLC supports the combination of pembrolizumab and epigenetic agents [2]. Therefore, it is worth considering the possibility that the inferior outcomes of the CC-486 group were secondary to the decreased exposure to pembrolizumab. The CC-486 combination arm had a shorter duration of treatment (median 15.0 weeks [3.5 months] versus 24.1 weeks [5.6 months]) and a lower number of treatment cycles (median, 5 versus 7 cycles), likely due to higher toxicity leading to treatment discontinuation (39.2% versus16.3%).

Uncertainties exist over the optimal dosing and treatment duration of immune checkpoint inhibitors and the impact that dose intensity has on tumour response. There is limited trial data addressing this question.

KEYNOTE-01 and KEYNOTE-10 provided us with some clinical data relating to the optimal pembrolizumab dosing per cycle. KEYNOTE-10 showed that there were no statistically significant differences in efficacy between the 10 mg/kg arm and the 2 mg/kg arm, when administered 3-weekly [3]. Significantly, the two pembrolizumab arms had the same median duration of treatment (3.5 months) and similar adverse event discontinuation rate of 4–5%. Similarly, KEYNOTE-01 found no significant differences in efficacy or side-effect

DOI of original article: https://doi.org/10.1016/j.ejca.2018.11.028.
* *Corresponding author*:
E-mail address: a.georgiou@nhs.net (A. Georgiou).

https://doi.org/10.1016/j.ejca.2019.04.011

Table 1
Median doses administered and median treatment duration of anti-PD1 and anti-PDL1 inhibitors in NSCLC second line and beyond trials.

Trial	Agent	Median number of doses	Median treatment duration (months)
KEYNOTE-010 [3]	Pembrolizumab	5[a]	3.5
CHECKMATE-057 [9]	Nivolumab	6	3.0
CHECKMATE-017 [10]	Nivolumab	8	3.7[b]
OAK [11]	Atezolizumab	5[a]	3.4
BIRCH [12]	Atezolizumab	7	4.2
Levy *et al.* [1]	Pembrolizumab + CC-486	5	3.5
	Pembrolizumab + placebo	7	5.6

NSCLC, non–small cell lung cancer.
[a] Extrapolated from median months duration as number of doses not reported.
[b] Extrapolated from median number of doses as treatment duration not reported.

profile between patients who were treated with 10 mg/kg every 2 weeks and those receiving the same dose every 3 weeks [4]. These results suggest that in the context of equal duration of exposure, a dose higher than 2 mg/kg per cycle did not seem to impact on treatment outcomes. This was in fact correctly predicted by the first in human phase 1 trial of pembrolizumab which based on pharmacokinetic and pharmacodynamic profiling, suggested that the lowest dose with full potential for antitumour activity was 2 mg/kg every 3 weeks [5].

Further evidence in support of the significance of pharmacokinetic-based dosing was also provided by Basak et al. They showed that amongst 76 NSCLC patients who were all treated with the nivolumab 3 mg/kg 2-weekly, patients with higher trough concentration (at 2, 4 and 10 weeks) had higher response rates and longer OS ($p < 0.001$), at all the time points measured [6]. Therefore, though limited by the small number of patients, this trial suggested a clear exposure-response relationship.

We have less evidence to guide our practice with regards to duration immunotherapy for advanced NSCLC. Preliminary long-term survival data from KEYNOTE-010 suggested that the 79/690 (11%) patients who completed 2 years of pembrolizumab had a durable response with a 36-month OS rate of 98.7%. As per trial protocol, after stopping at 35 cycles or 2 years of pembrolizumab, 25/79 (32%) patients had subsequent progressive disease [7]. In the CHECKMATE-153, trial patients with advanced NSCLC who had ≥1 prior systemic therapy were treated with nivolumab 3 mg/kg IV 2-weekly. The patients who remained on nivolumab at 1-year were randomised to continue until disease progression or to stop nivolumab. Those who were treated continuously had better PFS than those who stopped (HR 0.453; 96% confidence interval 0.25–0.76). There was a trend towards better OS in those continuing at 1-year, although the trial was small, and updated survival is awaited to confirm this [8]. Therefore, current evidence, though limited, supports the notion that in patients tolerating immunotherapy, the most evidence-based approach is to treat for as long as possible.

It is worth noting that the median duration of therapy in second-line clinical trials, regardless of the anti-PD1 or anti-PDL1 investigated, has been consistently fairly short (Table 1). We also investigated our own practice and found similar rates with median number of pembrolizumab cycles administered in 88 patients being equal to four (range 1–27). These results suggest that the long-term data provided by KEYNOTE-10 and CHECKMATE-153 are actually less relevant to most patients who tend to receive a shorter duration of treatment. Hence, the trial by Levy et al. provide us with useful data as it may suggest that a reduced duration of exposure to pembrolizumab may impact on efficacy adversely, in the context of a median treatment duration that was fairly consistent with that of previous trials and our 'real life' practice.

These results raise important issues as we are moving to an era of combination strategies with immunotherapy for advanced lung cancer, with greater toxicity and an ongoing discussion about the safety of de-escalation. While the optimal duration of anti-PD1 or anti-PDL1 remains unknown, there is evidence to suggest that treatment duration matters. Therefore, increased toxicity from the addition of another agent or indeed a negative interaction with immune targets may compromise the exposure to anti-PD1 and PDL1 therapy and could impact adversely on outcomes. Rather than de-escalation perhaps we should be considering long-term treatment, with robust pharmacokinetic-response assessments incorporated in trial design, while awaiting for better predictive biomarkers to guide patient selection.

Conflicts of interest statement

Alexandros Georgiou and Anna Minchom declare no conflicts of interest.

Mary O'Brien received Honoraria from Merck, Merck Serono, AbbVie, Bristol-Myers Squibb, Roche and Pierre Fabre. Consulting or advisory role for

Merck. Travel and accommodations, expenses from Bristol-Myers Squibb.

Acknowledgement

The authors thank Dr Wing San Mak for audit data.

References

[1] Levy BP, Giaccone G, Besse B, Felip E, Garassino MC, Domine Gomez M, et al. Randomised phase 2 study of pembrolizumab plus CC-486 versus pembrolizumab plus placebo in patients with previously treated advanced non-small cell lung cancer. Eur J Cancer 2019;108:120–8.

[2] Hellmann M, Jänne P, Opyrchal M, Hafez N, Raez L, Gabrilovich D, et al. Efficacy/safety of entinostat (ENT) and pembrolizumab (PEMBRO) in NSCLC patients previously treated with anti-PD-(L)1 therapy. Presented at: the IASLC 19th world conference on lung cancer; September 23-26; Toronto, Canada. Abstract OA05.01.

[3] Herbst RS, Baas P, Kim DW, Felip E, Perez-Gracia JL, Han JY, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. Lancet 2016;387(10027):1540–50.

[4] Garon EB, Rizvi NA, Hui R, Leighl N, Balmanoukian AS, Eder JP, et al. Pembrolizumab for the treatment of non-small-cell lung cancer. N Engl J Med 2015;372(21):2018–28.

[5] Patnaik A, Kang SP, Rasco D, Papadopoulos KP, Elassaiss-Schaap J, Beeram M, et al. Phase I Study of pembrolizumab (MK-3475; anti-PD-1 monoclonal antibody) in Patients with advanced solid tumors. Clin Cancer Res 2015;21(19):4286–93.

[6] Basak EA, Koolen SLW, Hurkmans DP, Schreurs MWJ, Bins S, Oomen-de Hoop E, et al. Correlation between nivolumab exposure and treatment outcomes in non-small-cell lung cancer. Eur J Cancer 2019;109:12–20.

[7] Herbst RS, Garon EB, Kim D, Chul Cho B, Pérez Gracia JL, Han J, et al. Ann Oncol 2018;29(suppl 5). Abstr LBA63.

[8] Spigel D, McLeod M, Hussein MA, Waterhouse DM, Einhom L, Horn L, et al. Randomized results of fixed-duration (1-yr) vs continuous nivolumab in patients (pts) with advanced non-small cell lung cancer (NSCLC). In: ESMO 2017 National Congress; 2017. Madrid, Spain.

[9] Borghaei H, Paz-Ares L, Horn L, Spigel DR, Steins M, Ready NE, et al. Nivolumab versus Docetaxel in advanced non-squamous non-small-cell lung cancer. N Engl J Med 2015;373(17):1627–39.

[10] Brahmer J, Reckamp KL, Baas P, Crino L, Eberhardt WE, Poddubskaya E, et al. Nivolumab versus Docetaxel in advanced squamous-cell non-small-cell lung cancer. N Engl J Med 2015;373(2):123–35.

[11] Rittmeyer A, Barlesi F, Waterkamp D, Park K, Ciardiello F, von Pawel J, et al. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. Lancet 2017;389(10066):255–65.

[12] Peters S, Gettinger S, Johnson ML, Janne PA, Garassino MC, Christoph D, et al. Phase II Trial of atezolizumab as first-Line or subsequent Therapy for patients with programmed death-ligand 1-selected advanced non-small-cell lung cancer (BIRCH). J Clin Oncol 2017;35(24):2781–9.