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PII: S0959-8049(22)01327-2

DOI: https://doi.org/10.1016/j.ejca.2022.10.024

Reference: EJC 12700

To appear in: *European Journal of Cancer*

Received Date: 7 October 2022

Accepted Date: 24 October 2022

Please cite this article as: Bouche G, Langley R, Rush H, Parmar M, Gilbert DC, Testing alternative schedules of adjuvant Immune checkpoint Blockers – the need for well-designed clinical trials, *European Journal of Cancer*, https://doi.org/10.1016/j.ejca.2022.10.024.

Testing alternative schedules of adjuvant Immune checkpoint Blockers – the need for well-designed clinical trials

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Running head:

Optimising Adjuvant Use of Immune checkpoint Blockers

Word count (excluding abstract, table & references):

994

Dear Editor,

Immune checkpoint Blockers (ICB) have transformed the treatment landscape of many advanced cancers, and attention naturally shifts to the adjuvant setting. FDA and EMA have approved 4 anti-PD-(L)1 antibodies (atezolizumab, durvalumab, nivolumab and pembrolizumab) in a total of 9 adjuvant indications, as of October 2022 (Table). The cost of these drugs is in excess of $150,000 a year for all ICI listed (e.g. US list price of 200mg pembrolizumab is $20,948).

Table: List of approved Immune checkpoint Blockers as (neo-)adjuvant treatment as of October 2022

Drug	**Cancer**	**FDA approval**	**EMA approval**	**Dose and schedule on the drug's label (number of administration)**	
				First schedule	**Other schedule(s)**
Pembrolizumab	Melanoma	Yes	Yes	200mg Q3W (18)	400mg Q6W (9)
Pembrolizumab	TNBC	Yes	Yes	200mg Q3W (8[a]+9)	400mg Q6W (4[a]+4)
Pembrolizumab	RCC	Yes	Yes	200mg Q3W (18)	400mg Q6W (9)
Nivolumab	Melanoma	Yes	Yes	240mg Q2W (26)	480mg Q4W (13)
Nivolumab	Urothelial	Yes	Yes	240mg Q2W (26)	480Mg Q4W (13)
Nivolumab	Oesophageal	Yes	Yes	240mg Q2W (26)	480mg Q4W (13)
Nivolumab	NSCLC	Yes	Yes	360mg Q3W (3[a])	/
Atezolizumab	NSCLC	Yes	Yes	840mg Q2W (26)	1200mg Q3W(17) or 1680mg Q4W(13)
Durvalumab	NSCLC	Yes	Yes	10 mg/kg Q2W (26)	1500 mg Q4W (13)

[a] neoadjuvant; NSCLC: non-small cell lung cancer, RCC; renal-cell carcinoma, TNBC: triple-negative breast cancer

In most indications, adjuvant ICI are recommended for a year at one of the approved schedules (Table). Other schedules were approved mainly based on the results of exposure-response modelling and simulation studies.[1] The dose and frequency of adjuvant ICI tested in the adjuvant trials were the same as those used in trials in the advanced and metastatic setting, whereas the choice of a 12-month duration seems empirical. There is a strong interest from clinicians, healthcare systems and patients alike to test alternatives to this standard regimen. Trials testing alternative regimens or stopping strategies are

ongoing in the metastatic setting [2] where duration varies greatly between patients, depending mainly on response duration and tolerability.

In the adjuvant setting, there is now a pressing need for trials to reduce toxicity, to spare patients who may not need adjuvant ICI at all or for a full year, and to reduce costs. Potential long-term toxicity of ICI [3] become a central concern in the adjuvant setting as a substantial proportion of patients are cured. Importantly, improving techniques and knowledge identifying biomarkers of need and response (e.g. cell free DNA and minimal residual disease [4]) will also allow better targeting of treatment and should be included in all future studies. Despite the clinical and health-economic benefits such trials might bring, research focused on reducing the dose, frequency or duration of treatment is of little interest to pharmaceutical companies and not required by medicines agencies.

The most important questions to be addressed in future trials may be cancer specific and/or drug specific. For example, in triple negative breast cancer (TNBC), the results of KEYNOTE-522 (NCT03036488) raise the question of continuing pembrolizumab after surgery in patients who achieved a pathological complete response (pCR) after 4 cycles of pembrolizumab given every 3 weeks with paclitaxel and carboplatin.[5] For nivolumab, clinical evidence and pharmacological results from the early phase trials (reviewed in [6]) support testing lower doses of adjuvant nivolumab. However, in cancers with a more dismal prognosis despite adjuvant ICI, such as NSCLC, giving less drug may not be the most pressing question as patients and clinicians may want to prioritize ‘more’ over ‘less’ treatment questions.

Optimisation questions usually require non-inferiority trials which, particularly for mortality outcomes, may be leading to too much uncertainty to give a satisfactory answer.[7] For instance, despite the clinically convincing results from the IDEA consortium in 12,800 patients [8], debate continues about the non-

inferiority of 3 vs 6 months of adjuvant chemotherapy for stage III colorectal cancer, in part due to the statistical considerations around non-inferiority. Specific designs – such as the DURATIONS design [9] – can overcome some of the limitations of standard non-inferiority trials. The DURATIONS design randomises patients to a number of duration (or interval) arms with the objective to identify the shortest acceptable treatment duration (or the longest acceptable interval). This design is used for the REFINE trial (NCT04913025), a trial aiming at identifying the longest acceptable interval between two ICI infusions in patients with advanced or metastatic cancers.

We anticipate 3 main challenges of conducting trials optimising the use of adjuvant ICI. First, many optimisation options exist and choosing the best one(s) is not trivial. With 3 main optimisation parameters (dose, treatment interval and duration), one alternative choice for each parameter (*eg* 50% of the dose, doubling of the intervals and 50% reduction of the total duration) would lead to 8 possible combinations. And other optimisation approaches are worth considering in the design of clinical trials, such as initiating ICI before surgery (with the option to adapt the adjuvant ICI based on the pathological response like in TNBC) or using pharmacological guidance or liquid biopsy to adapt treatment. Second, a methodological challenge in the adjuvant setting is the lack of an early readout to guide decision-making during the course of the trial, particularly to close arms early when necessary. Third, patients may decline participation for the fear of being undertreated if randomised to the experimental arm(s). But they also may opt in looking at the potential benefit of having fewer visits and a better quality of life. Involving patients in co-developing and running these trials is key together with measuring toxicity and patient-reported outcomes in a comprehensive manner to capture fully the patient perspective.

Funders, in particular if they also are payers, should be interested in funding these trials as they offer a chance to reduce the overall cost of expensive ICI without compromising efficacy. Trials may be self-

funding as the savings made from giving less drug in the experimental arm(s) may recoup the cost of conducting the trial.[10] For instance, in the UK REFINE trial, the first stage of the RCC cohort will save the NHS £5,010,000 in treatment cost, an amount that greatly exceeds the budget needed for running the first stage of the RCC cohort. Randomised multi-arm multi-stage trials running as one protocol across a number of cancer type cohorts would be a very efficient way to address these questions.

Optimising the use of adjuvant ICI represents a unique opportunity to reduce the burden on both patients and healthcare systems and to improve access to adjuvant ICI globally. Once protocols addressing the issues of dose, frequency or duration have been developed, these trials could be conducted at the European or international level, assuming sufficient funding is made available. We believe that payers – with the Netherlands leading by example [10] – should identify funding for these trials as they may end up with results that will save them billions of €/£/$ in the long term for a trial that pays for itself.

Funding: None

References

[1] Gilbar PJ, Davis MR. Dosing of PD-1 and PD-L1 inhibitors: Cost saving initiatives for significantly decreasing associated expenditure. J Oncol Pharm Pract 2021;27:199–204. https://doi.org/10.1177/1078155220974077.

[2] Hirsch I, Goldstein DA, Tannock IF, Butler MO, Gilbert DC. Optimizing the dose and schedule of immune checkpoint inhibitors in cancer to allow global access. Nat Med 2022. https://doi.org/10.1038/s41591-022-02029-1.

[3] Johnson DB, Nebhan CA, Moslehi JJ, Balko JM. Immune-checkpoint inhibitors: long-term implications of toxicity. Nat Rev Clin Oncol 2022;0123456789. https://doi.org/10.1038/s41571-022-00600-w.

[4] Montagut C, Vidal J. Liquid Biopsy for Precision Adjuvant Chemotherapy in Colon Cancer. N Engl J Med 2022. https://doi.org/10.1056/NEJMe2204625.

[5] Schmid P, Cortes J, Dent R, Pusztai L, McArthur H, Kümmel S, et al. Event-free Survival with Pembrolizumab in Early Triple-Negative Breast Cancer. N Engl J Med 2022;386:556–67. https://doi.org/10.1056/NEJMoa2112651.

[6] Maritaz C, Broutin S, Chaput N, Marabelle A, Paci A. Immune checkpoint-targeted antibodies: a room for dose and schedule optimization? J Hematol Oncol 2022;15:1–16. https://doi.org/10.1186/s13045-021-01182-3.

[7] Pong S, Urner M, Fowler RA, Mitsakakis N, Seto W, Hutchison JS, et al. Testing for non-inferior mortality: a systematic review of non-inferiority margin sizes and trial characteristics. BMJ Open 2021;11:e044480. https://doi.org/10.1136/bmjopen-2020-044480.

[8] André T, Meyerhardt J, Iveson T, Sobrero A, Yoshino T, Souglakos I, et al. Effect of duration of adjuvant chemotherapy for patients with stage III colon cancer (IDEA collaboration): final results

from a prospective, pooled analysis of six randomised, phase 3 trials. Lancet Oncol 2020;21:1620–9. https://doi.org/10.1016/S1470-2045(20)30527-1.

[9] Quartagno M, Carpenter JR, Walker AS, Clements M, Parmar MKB. The DURATIONS randomised trial design: Estimation targets, analysis methods and operating characteristics. Clin Trials 2020;17:644–53. https://doi.org/10.1177/1740774520944377.

[10] van Ommen-Nijhof A, Retèl VP, van den Heuvel M, Jager A, van Harten WH, Sonke GS. A revolving research fund to study efficient use of expensive drugs: big wheels keep on turning. Ann Oncol 2021;32:1212–5. https://doi.org/10.1016/j.annonc.2021.08.1747.

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: