Optimising the dose and schedule of immune checkpoint inhibitors in cancer to allow global access

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To the Editor - Immune checkpoint inhibitors such as pembrolizumab or nivolumab, which inhibit PD-1, have greatly improved survival for many patients with cancer but are prohibitively expensive and unattainable for most of the global cancer population. Optimised dosing, with a reduced unit dose, less frequent schedule and/or shorter duration of treatment could reduce costs and potentially toxicity, thereby improving global access to effective cancer therapy.

In phase 1 studies, immune checkpoint inhibitors showed efficacy at lower doses than those approved, with no evidence of a dose-response relationship, while also showing prolonged bioavailability and target binding. Pembrolizumab showed full target engagement at doses of 1 mg/kg every 3 weeks or higher[1], and there were no differences in response rates between 2 or 10 mg/kg [2]. Trials of nivolumab did not find differences in response, survival, or target-binding using doses between 0.1 and 10 mg/kg every 2 weeks. Although the half-life of nivolumab is 2-3 weeks, pharmacodynamic studies showed target occupancy for at least 2 months and saturation of T-cells at levels of 0.3 mg/kg. The recommended phase 2 dose was 3 mg/kg every 3 weeks despite this representing at least 15 times the minimal effective dose[3].

Retrospective data from patients with non-small cell lung cancer (NSCLC) treated with low-dose nivolumab[4] did not show statistically significant differences in either progression-free survival (PFS) or overall survival (OS) as compared with patients receiving standard of care dosing. Single arm studies showed that reducing the number of cycles of combination nivolumab and ipilimumab (by stopping the ipilimumab after 2 cycles and continuing nivolumab) in responding patients diagnosed with metastatic melanoma, led to similar PFS and OS to those expected with combination immunotherapy[5]. Caution with early cessation is needed, as a real-world cohort study reported outcomes from advanced melanoma patients who electively discontinued treatment in the absence of progressive disease or toxicity[6]. A complete response (CR) was achieved in 63%, but patients receiving <6 months of treatment had a higher risk of relapse. Similarly, the Checkmate 153 phase IIIb/IV study included a cohort of patients diagnosed with NSCLC and who were randomised to continue or discontinue nivolumab after 1 year[7]. Median PFS was longer with continuous treatment, and although not formally powered, median OS was also longer in the continuous arm. However, this trial included patients who were already receiving nivolumab beyond progression before random assignment to any arm.

Many randomised trials are evaluating dose optimisation of immunotherapy drugs, broadly testing early cessation, extended interval administration or reduced dose (Table 1). DANTE (ISRCTN15837212) is evaluating overall duration of immune checkpoint inhibitors in metastatic melanoma, randomising patients responding after 12 months treatment between stopping (with the option of re-start on progression) versus continuation, with a primary endpoint of PFS. Also, in melanoma, STOP-GAP in Canada (NCT02821013), SAFE STOP in the Netherlands (NL7293 (NTR7502) and PET-STOP in the US (NCT04462406) are testing the safety of discontinuing treatment after maximal response, complete response, or metabolic complete response, respectively. SAVE (JCOG1701) is randomizing NSCLC patients who respond at 1 year to stop or continue, with OS as the primary outcome. DIAL (NCT05255302) is evaluating the efficacy of pembrolizumab versus observation in patients with NSCLC who respond to a six-month induction treatment.

Several French and US studies are using a two-arm approach to investigate extending the interval between administration of immune checkpoint inhibitors. In the UK, the multistage

basket trial REFINE (NCT04913025) includes patients with advanced disease treated with immune checkpoint inhibitors who show response or stable disease at 3 months. The initial stage randomises patients to continue standard of care versus extended treatment at double the interval, with a primary outcome measure of PFS and with a planned subsequent expansion to 5 arms with increasing treatment intervals. This design is used in the parallel phase III study, REFINE-Lung, that is enrolling patients who respond to their initial 6 months treatment for NSCLC.

The impact of reducing doses is also being explored with the DEDICATION-1/NVALT30 (EudraCT 2020-000493-15) trial, a Dutch non-inferiority study comparing pembrolizumab 300mg versus the usual 400mg every 6 weeks in advanced NSCLC - an innovative example of a self-funding trial. The DELLI (CTRI/2020/02/023441) trial is enrolling patients in India with recurrent/relapsed solid tumours that progress after first line systemic therapy and who are eligible for second line treatment. Patients will be randomised to standard of care chemotherapy versus low dose nivolumab, with OS as the primary outcome.

The above treatment optimisation trials should be supported enthusiastically in order to reduce costs and, potentially, toxicity; late toxicity of immune checkpoint inhibitors is increasingly recognised and may be in part due to treatment exposure[8]. Reduced treatment costs could be used to fund clinical trials through innovative funding models.[9]: A clinical trial comparing the approved dose and schedule of pembrolizumab with a 50% de-escalation, would save approximately US$37,500 per patient for each year of treatment. The magnitude of savings should such trials meet their primary outcome measures with a consequent change in clinical practice are self-evident. Initial industry opposition to such approaches might be expected, but ultimately an optimised schedule should be more attractive to health-care systems as it could lead to an increase in overall usage. The prolonged schedules of high frequency administration carry substantial burden for patients in time, as well as cost.

Novel trial designs and concepts of near equivalence[10] - emphasizing outcomes over cost while including analysis of pharmacokinetic and pharmacodynamic data for support- are required so that prohibitively large conventional non-inferiority trials are not needed for each indication.

Patients must be involved in the design and conduct of these trials. Many patients had to adapt their treatment during the COVID-19 pandemic, experiences that can be learnt from. Patients must also be involved in any decision about acceptable risks to take in clinical trials as well as favoured approaches to optimisation, both of which will be crucial for trial recruitment and subsequent incorporation into clinical guidelines, where convincing payers, physicians and patients alike will be required to gain acceptance. Establishing optimised immune checkpoint inhibitor protocols will be challenging, but it is a necessary step towards global access.

Major efforts to optimise treatments for patients with advanced cancer are underway and should serve as a blueprint for reassessing comparable strategies across a range of indications. This strategy must involve patients from the outset and should be supported by industry, health care systems and oncologists alike.

Competing interests: None to disclose.

Table 1: Ongoing clinical trials to optimise immune checkpoint inhibitors in advanced cancer.

Type	Trial	Indication	Design	Planned N	Country	Registration number
Early cessation	DANTE	Melanoma	Randomised between stop at 1 year vs continue to 2 years in responding patients	1208	UK	ISRCTN15837212
	STOP-GAP	Melanoma	Randomised between stop at response (restart at progression) vs continuous treatment to 2 years	614	Canada	NCT02821013
	SAFE STOP	Melanoma	Stop on complete response (CR), single arm cohort, PFS at 2 years	200	Netherlands	NL7293 (NTR7502)
	PET-STOP	Melanoma	Stop on PET-CR, single arm cohort, PFS	150	US	NCT04462406
	SAVE	NSCLC	ICI following chemotherapy randomised to stop at 1 year vs continuation	216	Japan	JCOG1701
	STOP	Renal Cell Carcinoma	ICI responding at 1 year randomised to stop at 1 year vs continuation	216	Japan	JCOG1905
	DIAL	NSCLC	Randomised between 6/12 months vs 2 years of pembrolizumab after chemotherapy	114	France	NCT05255302
	OPTIMICE-pCR	TNBC	Observation vs adjuvant ICI after chemo-IO combination	1295	US	TBA
Extended interval	NCT04295863	Any	1x vs 2xSOC interval	264	US	NCT04295863
	REFINE	Basket (Renal)	Multi-Arm, Multi-Stage (MAMS) initially 1x vs 2xSOC interval expanding to 3x	160	UK	NCT04913025
	MOIO	Any	SOC vs 12 weeks	656	France	NCT05078047
	REFINE-Lung	NSCLC	MAMS initially Pembrolizumab 6 vs 12 weeks	1750	UK	NCT05085028

	NCT04032418	NSCLC	Pembrolizumab 3 vs 12 weeks after combination chemotherapy	152	US	NCT04032418
	PULSE	NSCLC	Pembrolizumab 3 vs 6 weeks after combination chemotherapy	1100	France	TBA
Low dose	NVALT-30 Dedication	NSCLC	Randomised between Pembrolizumab and Pembrolizumab 25% dose reduction	750	Netherlands	EudraCT 2020-000493-15
	CTRI-DELLI	HNSCC	Low dose Nivolumab (20mg 2-weekly) vs chemotherapy	TBA	India	CTRI/2020/02/023441

References

1. Patnaik, A. et al. Clinical Cancer Research 21, 4286–4293 (2015).
2. Lindauer, A. et al. CPT Pharmacometrics Syst Pharmacol 6, 11–20 (2017).
3. Agrawal, S., et al. J Immunother Cancer 4, (2016).
4. Yoo, S. H. et al. ESMO Open 3, (2018).
5. Postow, M. A. et al. Journal of Clinical Oncology 40, 1059–1067 (2021).
6. Jansen, Y. J. L. et al. Annals of Oncology 30, 1154–1161 (2019).
7. Waterhouse, D. M. et al. Journal of Clinical Oncology 38, 3863–3873 (2020).
8. Johnson, D. B., et al. Nat Rev Clin Oncol 19, 254–267 (2022).
9. van Ommen-Nijhof, A. et al. Annals of Oncology 32, 1212–1215 (2021).
10. Tannock, I. F. et al. Journal of Clinical Oncology 39, 950–955 (2021).