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

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. Optimized 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 have shown 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^{-1} every 3 weeks or higher[1], and there were no differences in response rates between 2 and 10 mg kg^{-1} (ref. [2]). Trials of nivolumab did not report differences in response, survival or target-binding using doses between 0.1 and 10 mg kg^{-1} 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^{-1}. The recommended phase 2 dose was 3 mg kg^{-1} 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) when compared with patients receiving standard-of-care dosing. Single-arm studies showed that reducing the number of cycles of nivolumab and ipilimumab combination treatment (by stopping ipilimumab after two cycles and continuing nivolumab) in responding patients with metastatic melanoma led to similar PFS and OS rates to those expected with combination immunotherapy[5]. Caution with early cessation is needed, as a real-world cohort study reported outcomes from patients with advanced melanoma who electively discontinued treatment in the absence of progressive disease or toxicity[6]. A complete response was achieved in 63% of patients, but patients receiving fewer than 6 months of treatment had a higher risk of relapse. Similarly, the CheckMate 153 phase 3b/4 study included a cohort of patients diagnosed with NSCLC who were randomized 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 randomized trials are evaluating dose optimization of immunotherapy drugs, broadly testing early cessation, extended interval administration or reduced doses (Table 1). The multi-center DANTE (ISRCTN15837212) trial in the UK is evaluating the overall duration of immune checkpoint inhibitors in metastatic melanoma, randomizing patients that respond after 12 months of treatment between stopping (with the option of re-starting on progression) and continuation, with a primary endpoint of PFS. Other trials in patients with melanoma include STOP-GAP in Canada (NCT02821013), SAFE STOP in The Netherlands (NL7293/NTR7502) and PET-STOP in the USA (NCT04462406), which are testing the safety of discontinuing treatment after maximal responses, complete responses and metabolic complete responses, respectively. The SAVE (JCOG1701) trial in Japan is randomizing patients with NSCLC that respond to treatment after one year to stop or continue treatment, with OS as the primary outcome. DIAL (NCT05255302) in France 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-armed approach to investigate extending the interval between the administration of immune checkpoint inhibitors. In the UK, the multistage REFINE (NCT04913025) basket trial includes patients with advanced-stage cancer treated with immune checkpoint inhibitors who show a response or stable disease at 3 months. The initial stage randomizes patients to continue standard-of-care treatment or extend treatment at double the interval, with a primary outcome measure of PFS and a planned subsequent expansion to five arms with increasing treatment intervals. This design is used in the parallel phase 3 UK study REFINE-Lung, which is enrolling patients who respond to standard treatment for NSCLC after 6 months.

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

The above treatment optimization trials should be supported enthusiastically to reduce costs and, potentially, toxicity; late toxicity of immune checkpoint inhibitors is increasingly recognized 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 that compared 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, if 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 optimized 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

Table 1 | Current clinical trials to optimize immune checkpoint inhibitors in advanced cancer

Type	Trial	Indication	Design	Planned *n*	Country	Registration number
Early cessation	DANTE	Melanoma	Randomized between stop at 1 year vs continue to 2 years in responding patients	1,208	UK	ISRCTN15837212
	STOP-GAP	Melanoma	Randomized between stop at response (restart at progression) vs continuous treatment to 2 years	614	Canada	NCT02821013
	SAFE STOP	Melanoma	Stop on complete response, single-arm cohort, PFS at 2 years	200	The Netherlands	NL7293 (NTR7502)
	PET-STOP	Melanoma	Stop on PET-CR, single-arm cohort, PFS	150	USA	NCT04462406
	SAVE	NSCLC	ICI after chemotherapy randomized to stop at 1 year vs continuation	216	Japan	JCOG1701
	STOP	Renal cell carcinoma	ICI responding at 1 year randomized to stop at 1 year vs continuation	216	Japan	JCOG1905
	DIAL	NSCLC	Randomized between 6 months and 2 years of pembrolizumab after chemotherapy	114	France	NCT05255302
	OPTIMICE-pCR	TNBC	Observation vs adjuvant ICI after chemo-immunotherapy combination	1,295	USA	TBC
Extended interval	NCT04295863	Any	1x vs 2x SOC interval	264	USA	NCT04295863
	REFINE	Basket (renal)	MAMS initially 1x vs 2x SOC 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	1,750	UK	NCT05085028
	NCT04032418	NSCLC	Pembrolizumab 3 vs 12 weeks after combination chemotherapy	152	USA	NCT04032418
	PULSE	NSCLC	Pembrolizumab 3 vs 6 weeks after combination chemotherapy	1,100	France	TBC
Low dose	NVALT-30 Dedication	NSCLC	Randomized between pembrolizumab and pembrolizumab 25% dose reduction	750	The Netherlands	EudraCT 2020-000493-15
	CTRI-DELLI	HNSCC	Low-dose nivolumab (20 mg twice weekly) vs chemotherapy	TBC	India	CTRI/2020/02/023441

ICI, immune checkpoint inhibitors; MAMS, multi-arm, multi-stage; SOC, standard of care; TBC, to be confirmed.

administration carry substantial burden for patients in time, as well as cost.

New trial designs and concepts of near equivalence[10], which emphasize 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 learned from. Patients must also be involved in any decision about acceptable risks to take in clinical trials as well as favored approaches to optimization, both of which will be crucial for trial recruitment and subsequent incorporation into clinical guidelines, in which convincing payers, physicians and patients alike will be required to gain acceptance. Establishing optimized immune checkpoint inhibitor protocols will be challenging, but is a necessary step toward global access.

Major efforts to optimize 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.

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Competing interests

The authors declare no competing interests.