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Original Research

Outcomes of long-term responders to anti-programmed death 1 and anti-programmed death ligand 1 when being rechallenged with the same anti-programmed death 1 and anti-programmed death ligand 1 at progression

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Abstract ***Background:*** Long-term responders have been observed with anti-programmed death 1 and anti-programmed death ligand 1 (anti-PD(L)1). Optimal duration of therapy in responding and stable disease (SD) patients is unclear with various attitudes encompassing treatment until progression disease, stopping therapy after a defined timeframe.
Patients and methods: We report the experience of 13 patients who discontinued immune checkpoint inhibitor in phase I trials as per protocol while experiencing a tumour-controlled disease. According to protocols, patients could restart the same immunotherapy if radiological or clinical progression occurred.
Results: Patients were treated for colorectal microsatellite instability–high genotype (n = 5), urothelial carcinoma (n = 3), melanoma (n = 2), non–small-cell lung cancer (n = 2) and triple-negative breast cancer (n = 1) for a median time of 12 months (range 10.6–12). Patients achieved 1 (8%) complete response, 10 (77%) partial response (PR) and 2 (15%) SD. The median progression-free survival 1 (PFS1) defined as the time from the first infusion until progression was 24.4 months (range 15.8–49). The median time free-treatment after

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discontinuation was 12.6 months (range 4–39.7). Eight patients experienced disease progression and were retreated. Best responses observed after rechallenging were 2 PR (25%) and 6 SD (75%). Median PFS2 defined from the first day of retreatment until disease progression or the last news was 12.9 months (range 5–35.4). No grade 3/4 events occurred during the study period.

Conclusion: Our data suggest that anti–PD(L)1 therapy should be resumed if progression occurs after a planned anti–PD(L)1 interruption. Further prospective studies are needed to confirm these results.

1. Background

Immune checkpoint inhibitors (ICIs) are a new cornerstone of cancer treatment and have demonstrated a great efficacy in various tumour types. By restoring anti-tumour immunity, long-term responses have been observed in patients across several tumour types. In the phase I trial of nivolumab, the 5-year survival rate was 34% for melanoma patients [1] and 16% in previously treated patients with advanced non–small-cell lung cancer (NSCLC) [2]. Interestingly, in the NSCLC cohort, among the 18 responders who discontinued treatment without disease progression, 50% were still responding after 9 months of treatment interruption [3]. Similarly, in the phase III trial comparing pembrolizumab versus ipilimumab in advanced melanoma, among 19% (104/556) of patients who completed pembrolizumab with a median exposure of 24 months, 98% were still alive after a 9-month follow-up [4].

Data about the outcomes of the long-term responders after anti-programmed death 1 and anti-programmed death ligand 1 (anti-PD(L)1) completion and the efficacy of the rechallenge with the same immunotherapy remain scarce. For now, our experience in treating these long-term responders was based on trials enrolling melanoma patients. First, with ipilimumab, the phase II CA184-025 evaluated the response and safety of retreating patients with an advanced melanoma with ipilimumab. Among the 122 patients included in the study, retreatment with ipilimumab showed an objective response rate of 23% (confidence interval [CI] 95% 15.8–31.4) [5]. Regarding anti–PD-(L)1 therapies, only small case studies have been reported [6–8]. Recently, in a phase III study comparing pembrolizumab and ipilimumab in patients with ipilimumab-naive advanced melanoma, among 68 complete responders who stopped pembrolizumab to undergo observation, four patients experiencing a progressive disease were retreated with pembrolizumab [9]. One patient achieved partial response (PR), whereas three experienced a progressive disease. The efficacy and safety of rechallenging with the same anti PD-(L)1 remain unclear in other tumour types.

We report here the outcomes of patients who discontinued anti PD-(L)1 per protocol in phase I trials and who were rechallenged with the same immunotherapy.

2. Patients and methods

This observational case series included patients enrolled from May 2012 to October 2017 in phase I trials with anti–PD-(L)1 in the Drug Development Department, Gustave Roussy, Villejuif, France, who stopped immunotherapy according to the protocol recommendations and even though the tumour disease was controlled (complete response [CR], PR or stable disease [SD]). Response was assessed using Response Evaluation Criteria in Solid Tumours, version 1.1, and immune-related response criteria by investigator's review. Pseudoprogression was defined by an increase $\geq$20% of tumour burden or new lesions followed by tumour shrinkage or SD assessed by a 1-month later scan [10]. According to protocols, patients could restart the same immunotherapy if radiological or clinical progression occurred. Clinical and biological characteristics were reported at C1D1 and at retreatment C1′D1′ prospectively by the trial investigators. The Royal Marsden Hospital [11] score and the Gustave Roussy Immune Score (GRIm-score) were collected. The GRIm-score is based on albumin, lactate dehydrogenase and neutrophil-to-lymphocyte ratio, known as a significant prognostic variable [12]. Progression-free survival 1 (PFS1) was defined from C1D1 of protocol until progressive disease; time free-treatment (TFT) was the period from the last infusion of anti PD-(L)1 until the C1′D1′ of retreatment and PFS2 was from C1′D1′ of rechallenge to progression or the last news. PFS were calculated according to the Kaplan–Meier method. The main objective was to define median PFS1, TFT and PFS2 after the rechallenge with the same anti PD-(L)1.

3. Results

From May 2012 through May 2016, 13 patients derived benefit from anti PD-(L)1 and stopped immunotherapy as per protocol without progression. Beyond the anti-PD(L)1 cessation, these patients were followed up every