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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

Table 1
Patient characteristics.

Characteristics	First treatment (n = 13)	Rechallenging (n = 8)
Age (years)	49	
Range	32–79	
Gender		
Male	8	4
Female	5	4
RMH score		
0	5	6
1	5	1
2	3	1
GRIm-score		
0	7	6
1	5	2
2	1	
Tumour type		
Colorectal MSI-high genotype	5	2
Urothelial carcinoma	3	2
Melanoma	1	1
Uveal melanoma	1	1
Squamous NSCLC	1	
Non-squamous NSCLC	1	1
Triple-negative breast cancer	1	1
Number of previous systemic therapies		
1	5	
2	3	
3	3	
4	2	

RMH, Royal Marsden Hospital; GRIm-score, Gustave Roussy Immune score; MSI-high, microsatellite instability–high genotype; NSCLC, Non–small-cell lung cancer.

2–3 months by computed tomography scan and in cases of progression could be reinduced by the same anti-PD(L)1 therapy. The patients' characteristics are described in Table 1.

3.1. First induction by anti-PD(L)1

After a median time of anti-PD(L)1 treatment of 12 months (range 10.6–12.0), patients achieved 1 (8%) CR, 10 (77%) PR and 2 (15%) SD. Two pseudoprogressions were observed among patients with colorectal microsatellite instability (MSI)–high cancer at the first evaluation. The nadir of response was achieved after treatment discontinuation for nine patients (69%). For these nine patients, the nadir of response was obtained after 7.9 months (range 0.3–29.7) of anti PD-(L)1 therapy period completion.

3.2. Observation period

Once anti PD-(L)1 was stopped, eight (61.5%) patients progressed after a median delay of 11.7 months (range 5.1–39.7). Among them, four patients had progressive disease (PD) characterised by new lesions (lymph nodes for three patients and visceral for one patient), and four patients experienced PD in the same initial tumour lesions. After a median follow-up of 35 months (range 16.3–65.8), median PFS1 was 24.4 months (range 15.8–49.0), and median TFT was 12.6 months (range 4.0–39.7).

3.3. Rechallenge by anti-PD(L)1

All patients who progressed were rechallenged by the same anti-PD(L)1. For the rechallenge period, patients were retreated by anti-PD(L)1 until progression or unacceptable toxicity. Among the eight patients who progressed and were rechallenged, two patients (25%) achieved a PR and six patients (75%) an SD. The median PFS2 was 12.9 months (range 5.0–35.4). Following the C1′D1′, patients stopped treatment because of disease progression (n = 2); one patient underwent surgery after a PR (n = 1) and as per protocol (n = 1). Patients who experienced progressive disease were treated for a triple-negative breast cancer and a uveal melanoma. None of the patients had grade 3–4 toxicity neither during first course nor during rechallenge. The median PFS2 was 12.9 months (range 5.1–35.4) with a PFS2/PFS1 ratio of 0.5. An overview of the duration of the responses is represented in Fig. 1 and Table 2.

Regarding the five patients still responding without needing rechallenge, three patients had an MSI-high colorectal cancer, one patient had a squamous lung cancer and one had a urothelial carcinoma.

4. Discussion and conclusion

The optimal duration of treatment in long-term responders to anti PD-(L)1 remains unclear. Indeed, as PDL-1 blockade restores the function of T cells, it has been hypothesised that some patients might develop an immune adaptive endogenous memory which might lead to durable effects even after stopping treatment [6,13,14]. These observations have been supported by sustained responses in patients who discontinued ICIs because of immune-related toxicities [15,16]. Moreover, fixed treatment in responding patients could be an alternative taking to account patient's quality of life or a prolonged exposure to adverse events in addition to the cost-effectiveness.

As some protocols planned a specified duration of treatment, the Food and Drug Administration and European Medicines Agency (EMA) recommended for particular tumour types to continue immunotherapy until disease progression or up to 24 months in patients without disease progression [17,18]. However, in the phase III CheckMate-153, better outcomes were observed with nivolumab in NSCLC patients with prolonged exposure as compared with 12-month therapy [19]. Continuous treatment significantly improved PFS with a hazard ratio (HR) of 0.43 (95% CI 0.25–0.76), and there was a trend towards improved overall survival (OS) in the continuous arm with a median OS not reached in the continuous arm compared with 23.2

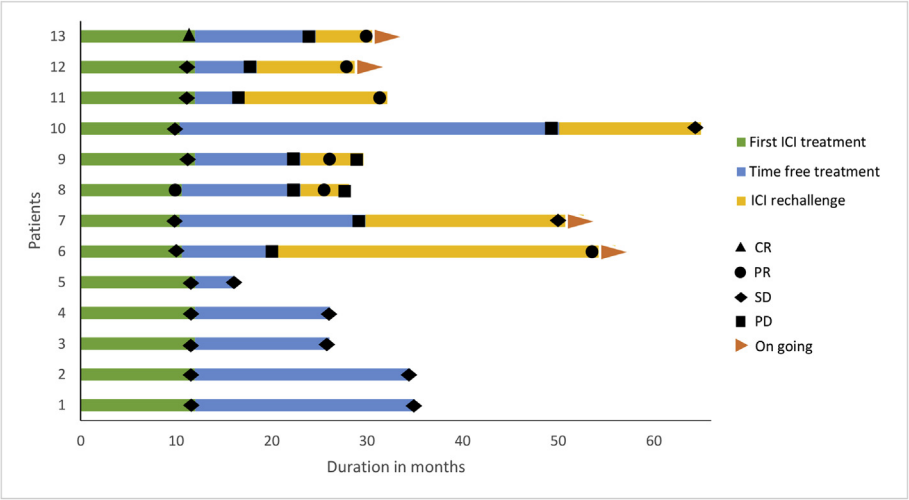

Fig. 1. Swimmer plot representing best response during the first ICI treatment, during follow-up and during rechallenge for each 13 patients. CR, complete response; PR, partial response; SD, stable disease; PD, progression disease; ICI, immune checkpoint inhibitor.

Table 2
Outcomes of patients during anti-PD(L)1 courses.

Patient number	Tumour type	First ICI duration (months)	Best response to first ICI	TFT (months)	Progression characteristics	PFS1 (months)	Best response after rechallenge	Outcome after rechallenge	PFS2 (months)
1	NSCLC	12	PR	23	0	35	–	–	
2	Colorectal cancer	11.9	PR after PP	22.6	0	34.5	–	–	
3	Colorectal cancer	12	PR after PP	14.1	0	26.1	–	–	
4	Colorectal cancer	12	PR	14.1	0	26.1	–	–	
5	Urothelial carcinoma	12	PR	4.1	0	16.1	–	–	
6	NSCLC	10.6	PR	10	NL (adenopathy)	19.9	SD	Ongoing	35.4
7	Urothelial carcinoma	10.4	PR	19.5	TL (adenopathy)	28.5	PR	Ongoing	22.8
8	Uveal melanoma	10.6	SD	12.4	NL (visceral, bone)	21.3	SD	PD	5.1
9	Breast cancer	12	PR	11.1	NTL (adenopathy)	22.9	SD	PD	6.6
10	Melanoma	10.4	PR	39.7	NL (adenopathy)	49	PR	PR	14.8
11	Colorectal cancer	12	PR	5.1	NL (adenopathy)	15.8	SD	Cessation per protocol in SD	15
12	Urothelial carcinoma	12	PR	6.5	NTL (adenopathy)	17.8	SD	Ongoing	11.1
13	Colorectal cancer	12	CR	12.6	NTL (adenopathy)	24.4	SD	Ongoing	6
Median		11.7		12.6		24.4			12.9

PR, partial response; CR, complete response; PP, pseudoprogression; SD, stable disease; NL, new lesion; TL, target lesion; NTL, non–target lesion; ICI, immune checkpoint inhibitor; PFS, progression-free survival.

months in the 1-year treatment arm (HR 0.63 [95% CI 0.33–1.20]).

Furthermore, we not yet have substantial evidence of effective treatment to propose to patients who progressed after responding and stopping anti PD-(L)1. Most of the case series excluding melanoma reported in the literature explore the efficacy of rechallenging with the same or different anti PD(L)-1 among patients who discontinued anti PD-(L)1 because of disease progression ([20–22]).

We report here a small series of patients that stopped therapy while deriving benefit from anti PD-(L)1 per phase I protocol with a long-term follow-up. Interestingly, patients treated for MSI-high colorectal carcinoma and urothelial carcinoma had similar long-term responses. The best response rate was observed after treatment completion for nine patients, revealing a prolonged systemic immune response. The two patients obtained PRs after rechallenge plaid for the potentiality of restoring anti-tumour immunity even in patients treated with the same immunotherapy.

Although patient numbers are too small to draw definitive conclusions, the rechallenge of anti–PDL-1 in patients after treatment completion with the same immunotherapy appears to be associated with lower response rates and shorter responses compare with the first induction phase. However, with 25% of PR, our data suggest that anti-PD(L)1 therapy should be resumed if progression occurs after a planned anti–PDL-1 interruption. Larger prospective studies are required to further investigate the rechallenge efficacy after anti PD-(L)1 completion.

Conflict of interest statement

S.P.-V. received honoraria from AstraZeneca. A.H. received honoraria from Merck Serono, had an advisory role for Amgen and Lilly and received travel and accommodation expenses from Amgen and Servier. A.M. received honoraria/consultancy fees from MedImmune, Lilly, Amgen, BMS, Merck Serono, Sanofi Genzyme, Janssen, Astellas, Genentech, Orion and Ipsen. J.-C.S. is full time employed in MedImmune since September 2017 and received consultancy fees from AstraZeneca, Astex, Clovis, GSK, GamaMabs, Lilly, MSD, Mission Therapeutics, Merus, Pfizer, PharmaMar, Pierre Fabre, Roche-Genentech, Sanofi, Servier, Symphogen and Takeda in the last 2 years. C.M. received honoraria/consultancy fees from Sanofi Genzyme, Janssen, Astellas, Genentech, Orion, MedImmune and Ipsen. The other authors have no conflicts of interest to disclose.

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References

[1] Hodi FS, Kluger HM, Sznol M, Carvajal RD, Lawrence DP, Atkins MB, et al. CT001 Durable, long-term survival in previously treated patients with advanced melanoma who received nivolumab monotherapy in a phase I trial. Cancer Res July 22 2016;76(14 Suppl). https://doi.org/10.1158/1538-7445.AM2016-CT001. CT001-CT001.

[2] Gettinger S, Horn L, Jackman D, Spigel D, Antonia S, Hellmann M, et al. Five-year follow-up of nivolumab in previously treated advanced non-small-cell lung cancer: results from the CA209-003 study. J Clin Oncol Off J Am Soc Clin Oncol 2018. https://doi.org/10.1200/JCO.2017.77.0412. JCO2017770412.

[3] Gettinger SN, Horn L, Gandhi L, Spigel DR, Antonia SJ, Rizvi NA, et al. Overall survival and long-term safety of nivolumab (Anti–Programmed Death 1 Antibody, BMS-936558, ONO-4538) in patients with previously treated advanced non–small-cell lung cancer. J Clin Oncol Off J Am Soc Clin Oncol 2015;33:2004–12. https://doi.org/10.1200/JCO.2014.58.3708.

[4] Robert C, Long GV, Schachter J, Arance A, Grob JJ, Mortier L, et al. Long-term outcomes in patients (pts) with ipilimumab (ipi)-naive advanced melanoma in the phase 3 KEYNOTE-006 study who completed pembrolizumab (pembro) treatment. J Clin Oncol Off J Am Soc Clin Oncol 2017;35. https://doi.org/10.1200/JCO.2017.35.15_suppl.9504. 9504–9504.

[5] Lebbe C, Weber JS, Maio M, Neyns B, Harmankaya K, Hamid O, et al. Survival follow-up and ipilimumab retreatment of patients with advanced melanoma who received ipilimumab in prior phase II studies. Ann Oncol 2014;25:2277–84. https://doi.org/10.1093/annonc/mdu441.

[6] Lipson EJ, Sharfman WH, Drake CG, Wollner I, Taube JM, Anders RA, et al. Durable cancer regression off-treatment and effective reinduction therapy with an anti-PD-1 antibody. Clin Cancer Res 2013;19:462–8. https://doi.org/10.1158/1078-0432.CCR-12-2625.

[7] Blasig H, Bender C, Hassel JC, Eigentler TK, Sachse MM, Hiernickel J, et al. Reinduction of PD1-inhibitor therapy: first experience in eight patients with metastatic melanoma. Melanoma Res 2017;27:321–5. https://doi.org/10.1097/CMR.0000000000000341.

[8] Nomura M, Otsuka A, Kondo T, Nagai H, Nonomura Y, Kaku Y, et al. Cancer Chemother Pharmacol 2017. https://doi.org/10.1007/s00280-017-3444-0.

[9] Robert C, Ribas A, Hamid O, Daud A, Wolchok JD, Joshua AM, et al. Durable complete response after discontinuation of pembrolizumab in patients with metastatic melanoma. J Clin Oncol 2017. https://doi.org/10.1200/JCO.2017.75.6270. JCO.2017.75.627.

[10] Chiou VL, Burotto M. Pseudoprogression and immune-related response in solid tumors. J Clin Oncol 2015;33:3541–3. https://doi.org/10.1200/JCO.2015.61.6870.

[11] Arkenau H-T, Olmos D, Ang JE, de Bono J, Judson I, Kaye S. Clinical outcome and prognostic factors for patients treated within the context of a phase I study: the Royal Marsden Hospital experience. Br J Cancer 2008;98:1029–33. https://doi.org/10.1038/sj.bjc.6604218.

[12] Bigot F, Castanon E, Baldini C, Hollebecque A, Carmona A, Postel-Vinay S, et al. Prospective validation of a prognostic score for patients in immunotherapy phase I trials: the Gustave Roussy Immune Score (GRIm-Score). Eur J Cancer 2017;84:212–8. https://doi.org/10.1016/j.ejca.2017.07.027.

[13] Kim JM, Chen DS. Immune escape to PD-L1/PD-1 blockade: seven steps to success (or failure). Ann Oncol 2016;27:1492–504. https://doi.org/10.1093/annonc/mdw217.

[14] Cogdill AP, Andrews MC, Wargo JA. Hallmarks of response to immune checkpoint blockade. Br J Cancer 2017;117:1–7. https://doi.org/10.1038/bjc.2017.136.

[15] Michot JM, Bigenwald C, Champiat S, Collins M, Carbonnel F, Postel-Vinay S, et al. Immune-related adverse events with immune checkpoint blockade: a comprehensive review. Eur J Cancer Oxf Engl 1990 2016;54:139–48. https://doi.org/10.1016/j.ejca.2015.11.016.

[16] Schadendorf D, Wolchok JD, Hodi FS, Chiarion-Sileni V, Gonzalez R, Rutkowski P, et al. Efficacy and safety outcomes in patients with advanced melanoma who discontinued treatment with nivolumab and ipilimumab because of adverse events: a pooled analysis of randomized phase II and III trials. J Clin Oncol Off J Am Soc Clin Oncol 2017;35:3807–14. https://doi.org/10.1200/JCO.2017.73.2289.

[17] https://www.nice.org.uk/guidance/ta428/resources/pembrolizumab-for-treating-pdl1positive-nonsmallcell-lung-cancer-after-chemotherapy-pdf-82604670410437.

[18] https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/125514s016lbl.pdf.

[19] Spigel DR, McLeod M, Hussein MA, Waterhouse DM, Einhorn L, Horn L, et al. 1297O Randomized results of fixed-duration (1-yr) vs continuous nivolumab in patients (pts) with advanced non-small cell lung cancer (NSCLC). Ann Oncol 2017;28. https://doi.org/10.1093/annonc/mdx380.002.

[20] Fujita K, Uchida N, Kanai O, Okamura M, Nakatani K, Mio T. Retreatment with pembrolizumab in advanced non-small cell lung cancer patients previously treated with nivolumab: emerging reports of 12 cases. Cancer Chemother Pharmacol 2018. https://doi.org/10.1007/s00280-018-3585-9.

[21] Hakozaki T, Okuma Y, Kashima J. Re-challenging immune checkpoint inhibitor in a patient with advanced non-small cell lung cancer: a case report. BMC Cancer 2018;18. https://doi.org/10.1186/s12885-018-4212-1.

[22] Martini DJ, Lalani A-KA, Bossé D, Steinharter JA, Harshman LC, Hodi FS, et al. Response to single agent PD-1 inhibitor after progression on previous PD-1/PD-L1 inhibitors: a case series. J Immunother Cancer 2017;5:66. https://doi.org/10.1186/s40425-017-0273-y.