Outcomes of patients with advanced solid tumors who discontinued immune-checkpoint inhibitors: a systematic review and meta-analysis

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Summary

Background The outcome of patients with metastatic tumors who discontinued immune checkpoint inhibitors (ICIs) not for progressive disease (PD) has been poorly explored. We performed a meta-analysis of all studies reporting the clinical outcome of patients who discontinued ICIs for reasons other than PD.

Methods We searched PubMed, Embase and Scopus databases, from the inception of each database to December 2023, for clinical trials (randomized or not) and observational studies assessing PD-(L)1 and CTLA-4 inhibitors in patients with metastatic solid tumors who discontinued treatment for reasons other than PD. Each study had to provide swimmer plots or Kaplan–Meier survival curves enabling the reconstruction of individual patient-level data on progression-free survival (PFS) following the discontinuation of immunotherapy. The primary endpoint was PFS from the date of treatment discontinuation overall and according to tumor histotype, type of treatment and reason of discontinuation. The Combersure's method was used to estimate meta-analytical non-parametric summary survival curves assuming random effects at study level.

Findings Thirty-six studies (2180 patients) were included. The pooled median PFS (mPFS) was 24.7 months (95% CI, 18.8–30.6) and the PFS-rate at 12, 24, and 36 months was respectively 69.8% (95% CI, 63.1–77.3), 51.0% (95% CI, 43.4–59.8) and 34.0% (95% CI, 27.0–42.9). Univariable analysis showed that the mPFS was significantly longer for patients with melanoma (43.0 months), as compared with non-small cell lung cancer (NSCLC, 13.5 months) and renal cell carcinoma (RCC, 10.0 months; between-strata comparison test p-value < 0.001); for patients treated with anti-PD-(L)1 + anti-CTLA-4 as compared with anti-PD-(L)1 monotherapy (44.6 versus 19.9 months; p-value < 0.001), and in NSCLC when the reason of treatment discontinuation was elective as compared with toxicity onset (19.6 versus 4.8 months; p-value = 0.003). The multivariable analysis confirmed these differences.

Interpretation The long-term outcome of patients who stopped ICIs for reasons other than PD was substantially affected by clinicopathological features: PFS after treatment discontinuation was longer in patients with melanoma, and/or treated with anti-PD-(L)1 + anti-CTLA-4, and shorter in patients with RCC or in those patients with NSCLC who stopped treatment for toxicity onset.

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Keywords: Immune-checkpoint inhibitors; Discontinuation; Meta-analysis melanoma; NSCLC

Research in context

Evidence before this study

Immune checkpoint inhibitors (ICIs) are widely used for treatment of several solid tumors. Several retrospective studies reported outcomes of patients who discontinued ICIs for reasons other than progressive disease, with not conclusive results.

We searched PubMed, Embase and Scopus and other databases with no language restrictions, from the inception of each database to December 2023, to identify studies (including clinical trial, randomized or not, and observational studies) that reported the outcomes of patients who discontinued ICI for reasons other than progression of disease. We included studies assessing PD-(L)1 and CTLA-4 inhibitors administered either as monotherapy or in combination with another ICI and/or other anti-cancer drugs in patients with advanced or metastatic solid tumors.

Added value of this study

Our study provides evidence that patients with melanoma, and patients treated with the combination of anti-PD1 with antiCTLA4, who stop treatment with ICIs for reason other than PD have favorable outcomes, while patients with RCC or NSCLC, especially if interrupted treatment for toxicity, have shorter progression free survival.

Implications of all the available evidence

The long-term outcome of patients who stopped ICIs for reasons other than PD was substantially affected by clinicopathological features including type of cancer and immunotherapy administered and reason of discontinuation. The findings of our study could help physicians select patients who can discontinue immunotherapy.

Introduction

Immune checkpoint inhibitors (ICIs), such as anti-PD-(L)1 and anti-CTLA-4, administered as monotherapy or in combination with other drugs, have dramatically improved the survival of patients with several advanced solid tumors.[1]

Compared with other treatments, like standard chemotherapy, ICIs lead to long-lasting tumor response in a higher percentage of patients.[2] However, the optimal duration of ICI treatment remains inconsistently investigated in randomized clinical trials (RCTs).[3–6] In some trials, patients continued receiving ICIs until disease progression (PD), while in others, treatment was concluded after a maximum of two years in the absence of PD.[3] Additionally, during trials some patients discontinue treatment for reasons, such as unacceptable toxicity or personal decision, unrelated to PD or the achievement of the end of therapy planned by protocol.[4]

In the past few years, retrospective evidence from many observational studies and RCTs has been published, reporting contrasting results on the long-term clinical outcome of patients who discontinued ICIs for reasons unrelated to PD.[3–6]

To provide reliable evidence on this relevant clinical issue, we conducted a comprehensive and methodologically rigorous systematic review and meta-analysis of all the available studies on this topic. Our aims were to assess the outcome (i.e., progression-free survival, PFS, from the date of treatment discontinuation) of patients who discontinued ICIs for reasons other than PD, and to explore heterogeneity of patients' outcome according to the tumor histotype, to the type of immunotherapy received (i.e., ICIs given as monotherapy, ICIs combined with another ICI or ICIs combined with other drugs), and to the reason of treatment discontinuation (i.e., elective reason - achievement of the maximum duration of treatment defined by protocol or patients' or physicians' decision - versus toxicity onset).

Methods

Search strategy, selection criteria and data extraction

We followed PRISMA guidelines to perform this systematic review and meta-analysis.[7]

We searched PubMed, Embase and Scopus databases to identify studies (including clinical trial, randomized or not, and observational studies) that reported the outcomes of patients who discontinued ICI for reasons other than PD. The search spanned from the inception of each database to December 31, 2023.

Two investigators (LP and FC) independently searched the databases. The search terms were "immunotherapy", "discontinuation", "CTLA-4", "cytotoxic T-lymphocyte-associated protein 4", "PD-1", "PD-L1", "programmed death receptor 1", "programmed death receptor ligand 1" and "immune checkpoint inhibitor".

We included studies assessing PD-(L)1 and CTLA-4 inhibitors administered either as monotherapy or in combination with another ICI and/or other anti-cancer drugs in patients with advanced or metastatic solid tumors.

To be considered eligible, a study had to provide information enabling the reconstruction of individual patient-level PFS data following the discontinuation of immunotherapy, for all patients considered in the study or for a subset of them.

Titles, abstracts, and full-text articles were reviewed independently by two authors (LP, FC). Inconsistencies were discussed to reach consensus. Reference lists of articles included in the final selection were reviewed to identify additional relevant papers.

Based on a predefined form, we extracted data on the following variables: study's name, first author and year of publication, study design, trial phase (for RCTs), underlying malignancy, treatment administered, line of therapy.

Individual patient-level data reconstruction

Pseudo individual patient-level data (IPD) on PFS following the discontinuation of immunotherapy for reasons other than PD were primarily reconstructed through published swimmer plots or Kaplan–Meier (KM) survival curves. In three cases, we relied on a published table that directly presented individual-patient data on PFS.

To extract pseudo IPDs from published swimmer plots, we used a validated web-based tool called WebPlotDigitizer.[8] For each patient represented in the swimmer plot not presenting PD before discontinuation of immunotherapy, we extracted the time of discontinuation of immunotherapy, as well as the time of progression, death, or last follow-up (whichever occurred first) from the digitized plot. This process allowed us to directly derive the individual time to progression after treatment discontinuation and the corresponding event indicator.

The same validated tool was used to extract data coordinates of time points and survival probabilities from digitized KM PFS curves presenting survival data from the time of ICI discontinuation. Subsequently, the validated algorithm proposed by Guyot et al. was applied to reconstruct the pseudo IPDs.[9]

A comprehensive description of IPD reconstruction was included in the Supplementary Material.

The reason of treatment discontinuation at patient level, when available, was extracted from study description, swimmer plots, or survival curves. The reported reasons were classified into two categories: elective interruption (such as completion of the prescribed therapy duration as per protocol, usually two years, or voluntary discontinuation of treatment due to reasons unrelated to PD or toxicity) and interruption of treatment due to unacceptable toxicity.

The duration of ICI exposure before discontinuation at patient-level was extracted from the swimmer plots or from other information reported in the publication.

Quality assessment of studies

To ascertain risk of bias, we assessed the methodological quality of each trial using the Cochrane Risk of bias tool (version 5.1.0) for randomized clinical trials.

Responses in each domain (random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data and selective outcome reporting) were assessed as having a 'low', 'unclear' or 'high' risk of bias.

The Newcastle–Ottawa scale has been used for non-randomized clinical studies. It contains 8 items categorized into three dimensions: selection, comparability, and outcome or exposure. The total maximum score of these three dimensions is 9. A study with score from 7 to 9 has high quality, 4–6 means high risk, and 0–3 very high risk of bias.[10]

To assess the adequacy of follow-up duration in cohort studies, we decided to rate studies that reported a median follow-up of at least 12 months as having a low risk of bias, because it is a reasonable time to observe a PFS event.

Statistics

Once pseudo IPDs have been generated, PFS function was reconstructed for all studies applying the KM estimation method. Meta-analytical non-parametric summary survival curves assuming random effects were estimated using the approach proposed by Combescure et al.[10] Briefly, summary survival probabilities were derived using a product-limit estimator, without making any assumption on the shape of the survival curve. To account for the between-study heterogeneity in the estimation of the pooled conditional survival probabilities, an extension of DerSimonian and Laird's methodology for multiple outcomes was applied.[11]

Summary survival curves were estimated overall and according to tumor histotype, type of treatment administered and reason of treatment discontinuation. To compare summary survival curves a between-strata statistical test was also performed according to Combescure et al.[11]

Additionally, univariable and multivariable Cox proportional hazards regression models with random effects at study level were used to compare PFS according to tumor histotype, type of treatment administered, reason of treatment discontinuation, and duration of ICI exposure before discontinuation. Hazard ratios (HR) and 95% confidence intervals (CI) were reported.

Finally, as exploratory analysis, we compared the outcome of our cohort of patients who discontinued ICI for reasons other than PD (case-cohort) with that of patients who continued treatment until progression or censoring (control-cohort). We matched each case with a similar control (matching ratio 1:1) derived from an external dataset of 25 RCTs testing the efficacy of ICI in patients with advanced melanoma, non-small cell lung cancer (NSCLC) or renal cell carcinoma (RCC). Matching variables included tumor histotype and type of treatment (i.e., anti-PD-(L)1 alone, anti-PD-(L)1 + anti-CTLA-4, or anti-PD-(L)1 + other treatment). To avoid the immortal time bias, we ensured that the control patient had a PFS time at least as long as the case's treatment

duration. The analysis used the time of treatment discontinuation for the case as the starting point. For the matching control, the starting time was not their treatment initiation but rather the discontinuation time of their matched case. This method ensures a fair comparison of time to progression between the two groups. Cox proportional hazards regression model was used to compare PFS of cases and matched controls. Additional details for this analysis were reported in the Supplementary Material.

All analyses were performed with SAS software v. 9.4 (SAS Institute, Cary, North Carolina, USA) and R software (version 3.6.3).

Role of funding source
The funder of the study had no role in study design, data collection, data analysis, interpretation, or writing of the report. All authors had full access to the data and had final responsibility for the decision to submit for publication.

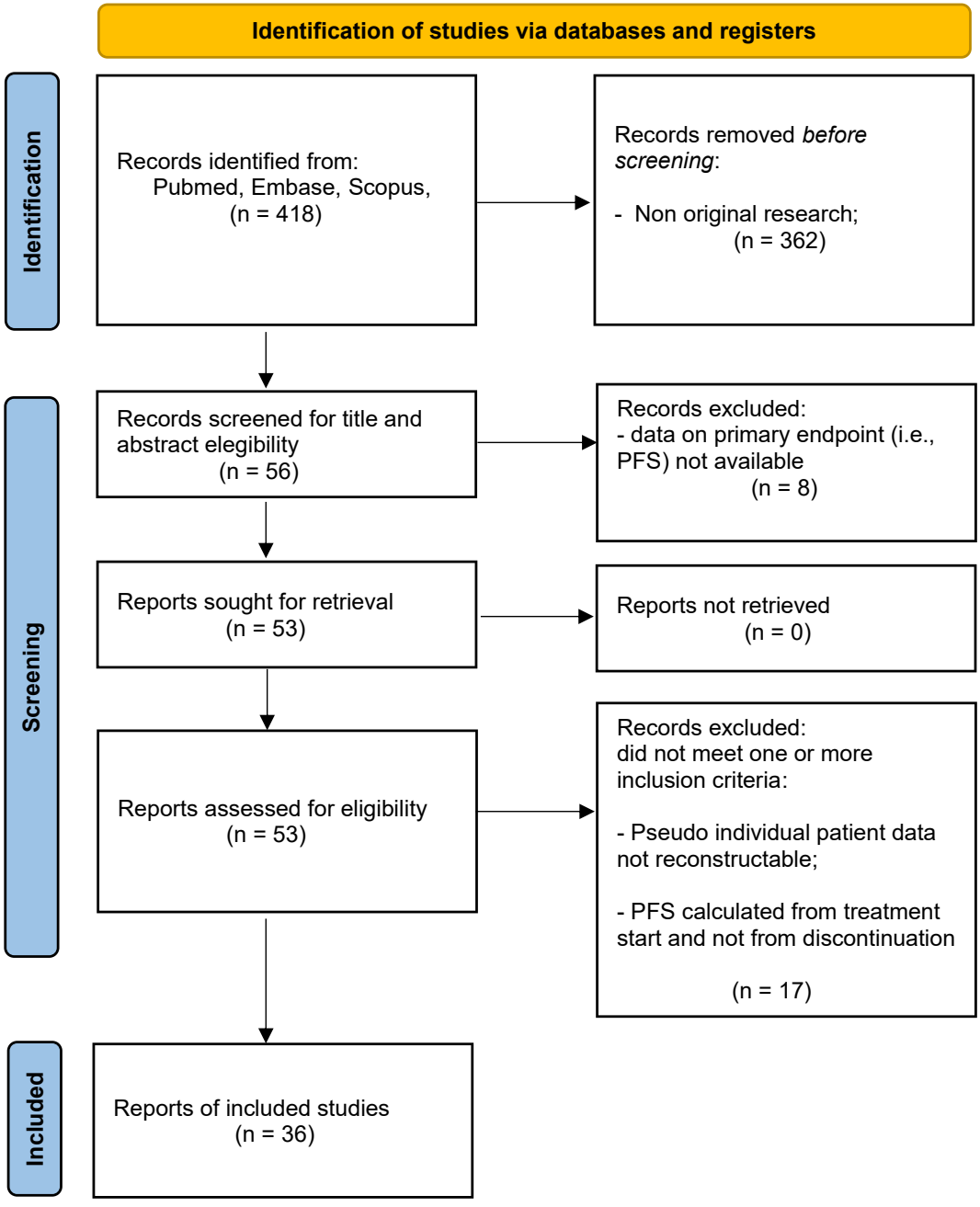

Fig. 1: **PRISMA flow chart.** Figure shows the process of studies' selection.

Results

Thirty-six studies[2,12–46] for a total of 2180 patients were included in the analysis (Fig. 1, Table 1 and Supplementary Table S1).

Six were RCTs while 30 were non-randomized prospective trials or observational studies.

Fourteen studies included patients with melanoma (1389 patients, 63.7%), 8 with NSCLC (414, 19.0%), 10 with RCC (198, 9.1%), 1 with colorectal cancer (64, 2.9%) and 3 had patients with mixed tumor histotypes (115, 5.3%).

In twenty-three studies (63.9%) patients received ICIs as monotherapy, in 10 studies (27.8%) ICIs were combined with other ICIs (i.e., anti-PD-(L)1 in combination with anti-CTLA-4), and in 3 studies (8.3%) ICIs were combined with other drugs (i.e., anti-angiogenic drugs). The ipilimumab dosage was specified only in 3 out of 10 studies, being 1 mg/kg in one study and 1 or 3 mg/kg in the other two.

In the majority of patients (1409, 64.6%) the reason for ICIs discontinuation was elective, in 15.8% (345) of cases was due to toxicity onset and in the remaining patients (426, 19.5%) the specific reason for treatment discontinuation in absence of progressive disease was not specified.

The median time of treatment duration before ICI discontinuation was 11.6 months (IQR 5.1–21.2) in the whole patients' population, and respectively 14.0 (IQR 9.1–22.0) in patients with melanoma, 10.3 (IQR 2.5–23.9) for NSCLC, and 8.1 (IQR 5.1–11.0) for RCC.

The median follow-up period after discontinuation showed considerable variation across studies, spanning from less than one month to 44 months. The median value was 12.2 months.

Supplementary Table S2 reports the quality assessment of trials included in the analysis. Overall, the quality of RCTs was high, as the risks of selection, attrition, reporting and other forms of bias for all the trials included in the analysis were low. The only potential biases affecting trials were performance and detection bias, since none of the RCTs had a double blinding design.

Also the overall quality of non-randomized studies is reported in Supplementary Table S2. All but 5 studies received a high-quality score.

In the whole patients' population, the pooled median PFS (mPFS) was 24.7 months (95% CI, 18.8–30.6) and the PFS-rate at 12, 24 and 36 months was respectively 69.8% (95% CI, 63.1–77.3), 51.0% (95% CI, 43.4–59.8) and 34.0% (95% CI, 27.0–42.9; Table 2 and Fig. 2).

The patients' PFS was significantly different according to different tumor histotypes (between-strata comparison test p-value < 0.001; Table 2 and Fig. 3).

In patients with advanced melanoma, the pooled mPFS was 43.0 months (95% CI, 36.8–47.8), and the PFS-rate at 12, 24 and 36 months was respectively 88.1% (95% CI, 82.4–94.1), 75.4% (95% CI, 67.6–83.9) and 61.1% (95% CI, 53.3–70.0).

	N of studies (%) N = 36	N of patients (%) = 2180
Year of publication		
2016–2020	21 (58.3)	886 (40.6)
2021–2024	15 (41.7)	1294 (59.4)
Study type		
Prospective observational studies	22 (61.1)	1634 (75.0)
Not randomized clinical trial	8 (22.2)	150 (6.9)
Randomized controlled trial (RCT)	6 (16.7)	396 (18.2)
Trial phase	*(n = 14)*	*(n = 546)*
I or Ib or Ib/II or II or II/III	10 (71.4)	287 (52.6)
III or IIIb/IV	4 (28.6)	259 (47.4)
Line of therapy		
I	5 (13.9)	421 (19.3)
>I	6 (16.7)	163 (7.5)
Any	25 (69.4)	1596 (73.2)
Tumor histotype		
Melanoma	14 (38.9)	1389 (63.7)
Non-small cell lung cancer (NSCLC)	8 (22.2)	414 (19.0)
Renal cell carcinoma (RCC)	10 (27.8)	198 (9.1)
Colorectal cancer	1 (2.8)	64 (2.9)
Mixed histotypes	3 (8.4)	115 (5.3)
Treatment type		
Anti-PD-(L)1 alone	23 (63.9)	1648 (75.6)
Anti-PD-(L)1 + anti-CTLA-4	10 (27.8)	468 (21.5)
Anti-PD-(L)1 + other treatment	3 (8.3)	64 (2.9)
Reason of treatment discontinuation		
Elective		1409 (64.6)
Toxicity		345 (15.8)
Unknown		426 (19.5)
Treatment duration before ICI discontinuation (months)		
≤6		129 (5.9)
(6–12]		242 (11.1)
(12–24]		312 (14.3)
>24		171 (7.8)
Unknown or not available at patient-level		1326 (60.8)

Table 1: **Main features of included studies.**

In patients with advanced NSCLC, the pooled mPFS was 13.5 months (95% CI, 6.5–21.5) and the PFS-rate at 12, 24 and 36 months was respectively 53.1% (95% CI, 38.6–73.0), 33.1% (95% CI, 21.2–51.8), and 15.8% (95% CI, 7.7–32.4).

In patients with advanced RCC, the pooled mPFS was 10.0 months (95% CI, 4.5–16.4) and the PFS-rate at 12, 24 and 36 months was respectively 44.8% (95% CI, 30.4–66.0), 21.1% (95% CI, 10.3–43.3) and 10.5% (95% CI, 3.5–31.2).

Results did not materially change in a sensitivity analysis including only patients treated with anti-PD-(L)1 monotherapy (Supplementary Fig. S1).

The patients' PFS was significantly different according to different type of treatments received

	N of studies	N of patients	N of PFS events	Median FUP (min–max) -months	12-months PFS (95% CI)	24-months PFS (95% CI)	36-months PFS (95% CI)	48-months PFS (95% CI)	Pooled median PFS (95% CI) - months	p-value
Overall	36	2180	636	12.2 (0.8–44.0)	69.8 (63.1–77.3)	51.0 (43.4–59.8)	34.0 (27.0–42.9)	19.2 (13.7–26.8)	24.7 (18.8–30.6)	
Tumor histotype										<0.001
Melanoma	14	1389	319	21.6 (12.1–44.0)	88.1 (82.4–94.1)	75.4 (67.6–83.9)	61.1 (53.3–70.0)	43.0 (34.9–53.1)	43.0 (36.8–47.8)	
Non-small cell lung cancer (NSCLC)	8	414	155	6.9 (3.1–15.2)	53.1 (38.6–73.0)	33.1 (21.2–51.8)	15.8 (7.7–32.4)	n.e.	13.5 (6.5–21.5)	
Renal cell carcinoma (RCC)	10	198	94	5.5 (0.8–30.5)	44.8 (30.4–66.0)	21.1 (10.3–43.3)	10.5 (3.5–31.2)	4.3 (0.9–20.1)	10.0 (4.5–16.4)	
Treatment type										<0.001
Anti-PD-(L)1 alone	23	1648	522	12.0 (1.0–27.1)	64.7 (52.6–79.7)	43.4 (30.9–60.9)	24.9 (15.2–40.8)	8.1 (3.3–20.2)	19.9 (12.4–29.3)	
Anti-PD-(L)1 + anti-CTLA-4	10	468	77	28.1 (4.5–44.0)	85.8 (78.8–93.4)	72.5 (62.8–83.6)	60.0 (50.6–71.1)	44.9 (36.7–54.9)	44.6 (34.0–48.2)	
Anti-PD-(L)1 + other treatment	3	64	37	1.9 (0.8–2.1)	22.9 (11.4–45.8)	3.7 (0.7–20.7)	1.0 (0.1–9.8)	0.3 (0.02–4.2)	4.8 (n.e.)	
Tumor histotype and reason of treatment discontinuation										
Melanoma										1.00
Elective		1049	209	20.5 (13.3–44.5)	87.5 (81.7–93.7)	73.6 (65.2–83.1)	56.4 (46.6–68.1)	36.1 (26.4–49.5)	39.6 (32.8–43.8)	
Toxicity		292	98	25.9 (11.6–44.4)	80.1 (68.9–93.1)	62.8 (49.7–79.3)	45.9 (33.1–63.7)	28.6 (17.7–46.0)	33.2 (21.5–39.8)	
NSCLC										0.003
Elective		266	90	8.0 (6.7–12.0)	68.4 (51.4–90.9)	41.7 (29.8–58.5)	16.4 (7.0–38.9)	n.e.	19.6 (10.4–23.6)	
Toxicity		49	36	3.9 (3.1–4.8)	17.9 (6.1–52.7)	6.9 (1.1–44.7)	3.0 (0.4–24.3)	n.e.	4.8 (n.e.)	
RCC										
Elective		57	13	8.0 (1.0–39.5)	58.6 (39.1–87.8)	30.3 (11.6–79.5)	16.9 (3.6–79.5)	10.8 (1.8–65.1)	16.1 (4.9–26.4)	

PFS, progression free survival; FUP, follow-up; CI, confidence intervals; n.e., not estimable.

Table 2: **Progression-free survival (PFS).**

(between-strata comparison test p-value < 0.001; Table 2 and Fig. 4).

The pooled mPFS was 19.9 months (95% CI, 12.4–29.3) for patients treated with anti-PD-(L)1 monotherapy; 44.6 months (95% CI, 34.0–48.2) for patients treated with anti-PD-(L)1 + anti-CTLA-4; and 4.8 months (95% CI, not estimable) for patients treated with anti-PD-(L)1 in combination with other drugs.

Considering the outcome of patients according to the reason of treatment discontinuation, there was no significative difference between patients with advanced melanoma who discontinued ICIs for elective reasons (n = 1049) versus toxicity onset (n = 292): the pooled mPFS was respectively 39.6 months (95% CI, 32.8–43.8) and 33.2 months (95% CI, 21.5–39.8; p-value = 1.0; Table 2 and Fig. 5).

On the contrary, patients with advanced NSCLC who discontinued treatment for elective reasons (n = 266) had significantly longer PFS as compared with toxicity onset (n = 49): the pooled mPFS was respectively 19.6 months (95% CI, 10.4–23.6) versus 4.8 months (95% CI, not estimable; p-value = 0.003; Table 2 and Fig. 5). All patients with advanced RCC included in the analysis discontinued ICI for elective or unknown reasons.

We performed Cox proportional hazards regression models with random effects according to tumor histotype, type of treatment administered, reason of discontinuation, and duration of ICI exposure before discontinuation (Supplementary Table S3). Results obtained in the multivariable model confirmed those of univariable analyses, showing significantly poorer outcome for patients with NSCLC (HR-PFS: 2.95, 95% CI 1.13–7.68) or RCC (HR-PFS: 3.42, 95% CI 1.27–9.23), as compared with patients with melanoma; better outcome for patients treated with anti-PD-(L)1 + anti-CTLA-4 as compared with anti-PD-(L)1 monotherapy (HR-PFS: 0.43, 95% CI 0.16–1.12); poorer outcome when the reason of treatment discontinuation was toxicity onset as compared with elective reasons (HR-PFS: 2.68, 95% CI 1.33–5.40); and better outcome for longer duration of treatment before discontinuation (HR-PFS: 0.87, 95% CI 0.79–0.97).

Finally, as exploratory analysis, starting from 740 patients in the case-cohort and 7452 patients in the control-cohort (additional details are reported in Supplementary Materials), we successfully matched 543 cases with 543 controls. Among them, 234 patients had melanoma, 534 NSCLC and 318 RCC; 840 were treated with anti-PD-(L)1 alone, 124 with anti-PD-(L)1 + anti-CTLA-4, and 122 with anti-PD-(L)1 + other treatment. The PFS of the case-cohort was not significantly different compared to that of the matched control-cohort: HR-PFS 0.86, 95% CI 0.71–1.05 (Supplementary Fig. S2).

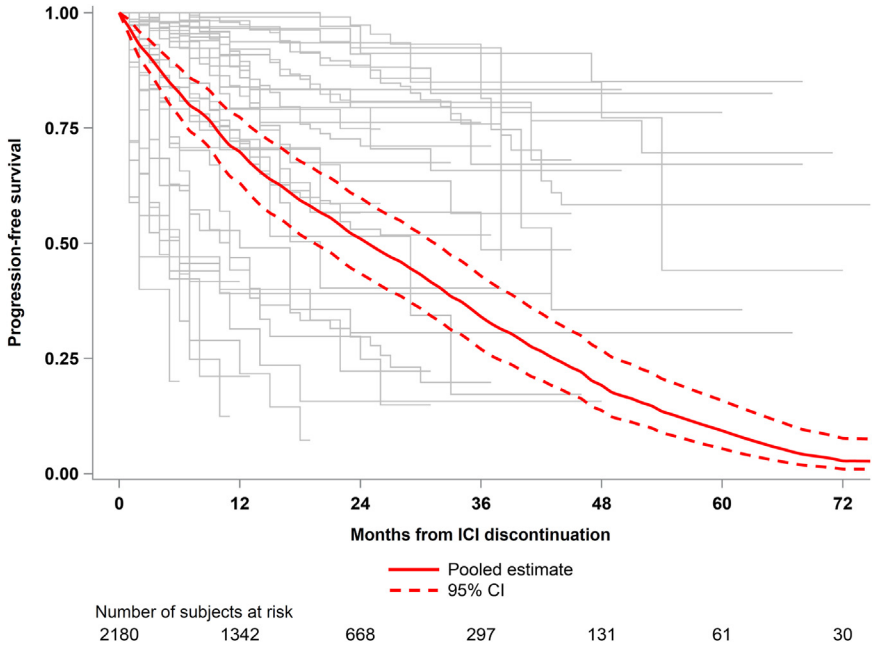

Fig. 2: **Progression-free survival (PFS) in the whole patients' population.** Figure shows the Kaplan–Meier PFS curves in all patients included in the analysis. The solid red line showed the pooled PFS and dotted red lines the 95% confidence interval (CI), while gray lines showed PFS reported in each single study.

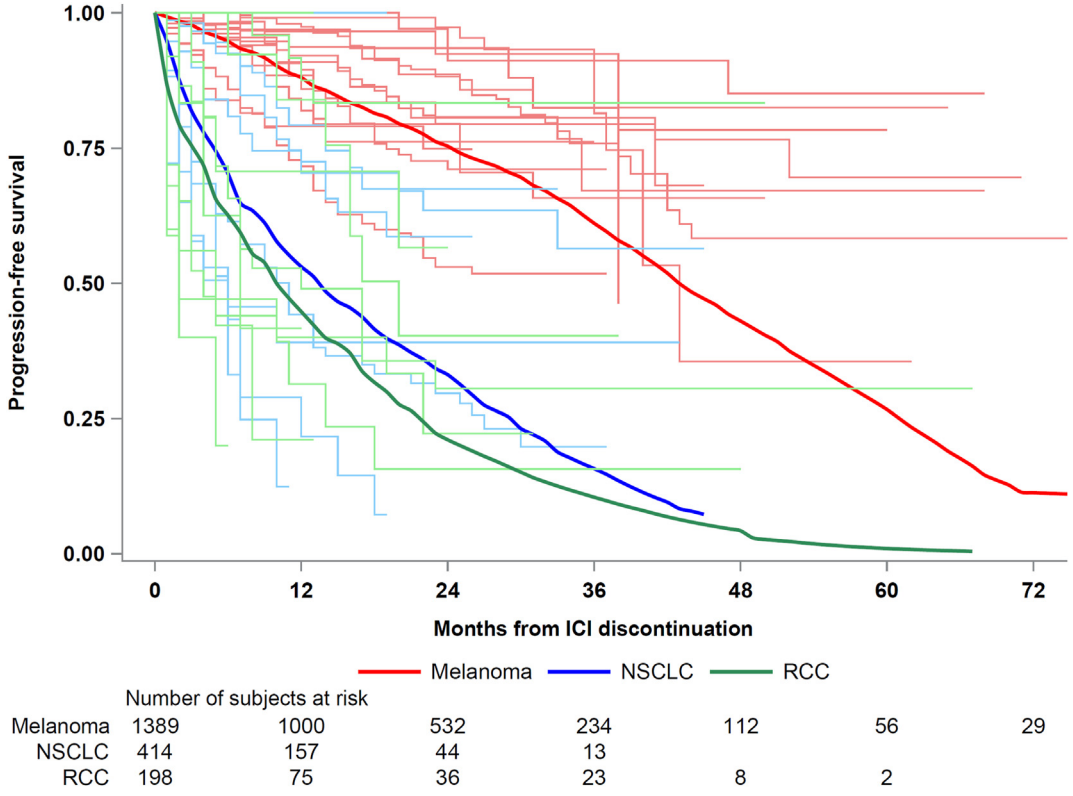

Fig. 3: **Progression-free survival (PFS) according to tumor histotype.** Figure shows the Kaplan–Meier PFS curves according to tumor histotype. Thick lines showed the pooled PFS while thin lines showed PFS reported in each single study. Colors indicate tumor histotype: red for melanoma, blue for non-small cell lung cancer (NSCLC), and green for renal cell carcinoma (RCC).

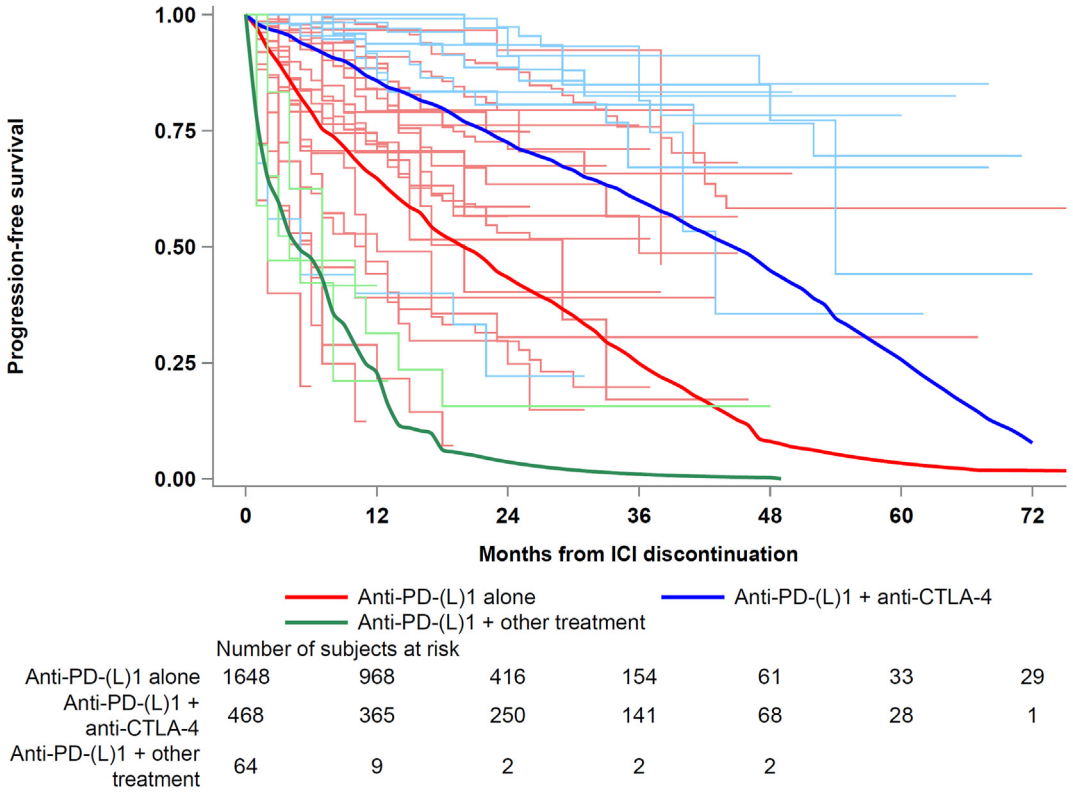

***Fig. 4:* Progression-free survival (PFS) according to treatment type.** Figure shows the Kaplan–Meier PFS curves according to treatment type. Thick lines showed the pooled PFS while thin lines showed PFS reported in each single study. Colors indicate treatment type: red for anti-PD-(L)1 as monotherapy, blue for anti-PD-(L)1 + anti-CTLA-4, and green for anti-PD-(L)1 + other drugs.

Discussion

It has been hypothesized that given their particular mechanisms of action, is it possible that after the induction or reinvigoration of a robust anticancer immune response, ICIs can be safely discontinued maintaining a long-lasting tumor control exerted by the immune system of the patient.[47–50]

Our results showed that the outcome of patients who stopped ICIs for reasons other than PD was substantially affected by several clinicopathological features including tumor histotype, type of treatment received and cause of discontinuation. The statistically significant and clinically meaningful heterogeneity of results observed across such subgroups, supports the need to draw separate conclusions for each specific context.

The factor that mainly affects patients' outcome was the tumor histotype. The relative risk of progression or death after immunotherapy discontinuation was respectively 3 and 4 times higher in patients with NSCLC and RCC as compared with melanoma. This translated into meaningful absolute differences: only 12% of patients with melanoma experienced disease progression before 12 months from treatment interruption, as compared with almost 50% of those with NSCLC and RCC.

Several biological reasons can be put forward to explain such observation.

Melanoma has long been recognized as one of the most immunogenic tumors, as revealed by spontaneous tumor regression described for both primary and metastatic disease.[51,52]

Both primary tumors and metastases often have a brisk infiltration by T-cells able to recognize highly immunogenic tumor antigens such as melanocyte differentiation antigens, including gp100, tyrosinase and MART-1/MELAN-A, and also cancer-testis genes, such as MAGE and NY-eso-1.[53–63] Moreover, melanoma is one of the solid tumors harboring the highest tumor mutational burden.[64,65]

Differences in the presence and significance of other leukocyte populations in the tumor microenvironment, such as tumor-associated macrophages endowed with immunosuppressive properties may also contribute the durability of ICI-elicited immunity and clinical benefit.[66]

All this not only translates in higher response rate in patients with advanced melanoma treated with ICIs as compared with other tumors, but also sustains the

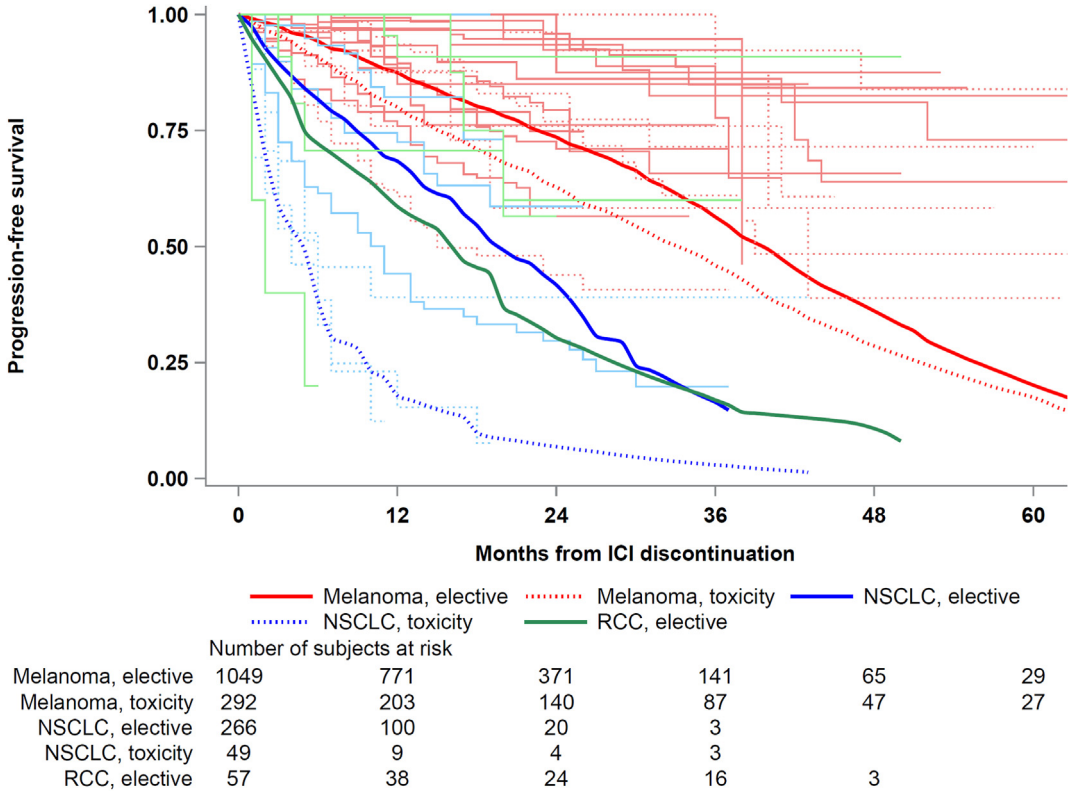

Fig. 5: **Progression-free survival (PFS) according to reason of treatment discontinuation and tumor histotype.** Figure shows the Kaplan–Meier PFS curves according to reasons of treatment discontinuation and tumor histotype. Thick lines showed the pooled PFS while thin lines showed PFS reported in each single study. Line type indicates reasons for treatment discontinuation: solid lines indicate elective reasons and dotted lines indicates toxicity reasons; colors indicate tumor histotype: red for melanoma, blue non-small cell lung cancer (NSCLC), and green for renal cell carcinoma (RCC).

generation of long-lived tumor-specific memory T-cells - particularly tissue-resident memory (TRM) CD8+ T cells - that likely exert long-lasting protective immunity beyond ICIs interruption. Indeed, several reports have described tumor-specific TRM T-cells and effector memory T-cells persisting in skin and blood samples of long-term survivors with advanced melanoma treated with immunotherapy up to nine years after treatment discontinuation.[67,68]

Similarly, the risk of progression after ICIs discontinuation substantially changed according to type of treatment received by patients. In particular, patients who received the combination of anti-PD-(L)1 + anti-CTLA-4 drugs had the best outcome, being more than 50% of them without PD after 36 months from treatment interruption.

The biological mechanism underpinning such clinical observation could be the fact that different immunotherapy strategies can have quantitative and qualitative different effects on the dynamics of T-cells response.[69]

Notably, very recent evidence showed that anti-CTLA-4 and anti-PD-(L)1 have different effects on memory T-cell response. Using murine tumor models, Allison et al. traced and profiled tumor-antigen specific CD8 T-cells throughout all phases of anticancer immune-response (i.e., priming, expansion, memory phase, and antigen re-challenge), showing that anti-CTLA-4 generates a more robust memory antitumor response than anti-PD-(L)1. In particular, the memory responses generated by anti-CTLA-4 and anti-PD-(L)1 drugs diverged at priming, where anti-CTLA-4 generates more memory-like T-cells than anti-PD-(L)1. Furthermore, relevant differences remained throughout all other phases of anticancer immune-response, including antigens re-challenge, where the memory T-cells generated by anti-CTLA-4 expanded in greater frequency, have greater cytokine production and antitumor activity, and more frequently differentiate into effector CD8 T-cells than those generated by anti-PD-(L)1 treatment.[70]

Finally, we found that the impact of the reason of treatment interruption on patient's outcome seems to be context dependent. Indeed, patients with advanced melanoma had very favorable PFS independently if ICIs were stopped for toxicity-onset or elective reasons. On the contrary, patients with advanced NSCLC who

interrupted treatment for toxicity had poorer outcome, with only 18% of them without PD after 12 months from treatment interruption.

Notably, results of the multivariable analysis confirmed that each of these three clinicopathological factors were significantly and independently associated with patients' long-term outcome after ICIs discontinuation, even when comparisons were adjusted for the length of treatment duration before its interruption.

Our analysis has several strengths. The first one is the sizeable number of studies and patients evaluated. Notably, whilst there have been several reports on this issue, according to our knowledge, this is the first meta-analysis reported, providing the largest, most comprehensive, and robust evidence available.

For each study included in the analysis, we reconstructed pseudo individual patient-level data using robust and validated algorithms, that substantially improved the quality of analyses presented as compared with a meta-analysis based on aggregate data. Moreover, it made possible to explore heterogeneity of results according to relevant clinical factors, that allowed for the first time to identify statistically significant and clinically meaningful differences, confirmed in the context of a multivariable analysis.[11,71] The main limit of our analysis is the retrospective nature of some included studied, and therefore results obtained required further validation by prospective trials.

Furthermore, among the 10 studies testing ipilimumab included in our analysis only 3 reported the dosage administered, and thus conclusion on the impact of ipilimumab dosage on the outcome of patients cannot be drawn.

Finally, we acknowledge that the results of the matched analysis should be approached with caution due to the heterogeneous nature of the data involved. Matching patients across different trials, rather than within a single RCT, introduces a degree of variability and bias that may influence the outcomes.

In conclusion, we demonstrated a large and clinically meaningful heterogeneity in the outcome of patients who stopped ICIs for reasons other than PD according to the tumor histotype, type of treatment received and reasons of treatment discontinuation: while patients with melanoma, and/or treated with the combination of anti-PD(L)1 + anti-CTLA4 had very encouraging long-term outcome, on the other hand the PFS was substantially shorter for patients with RCC or those patients with NSCLC who stopped treatment for toxicity onset.

Such new findings should be taken into account in daily clinical practice and should inform the design of future clinical trials. Indeed, in the absence of conclusive evidence from RCTs that establish the optimal duration of ICI treatment, our results could serve as an informative resource for physicians to counsel patients regarding the risk-benefit ratio associated with immunotherapy discontinuation. Moreover, our findings highlight the need for future prospective studies to evaluate the impact of ICI discontinuation on patients' prognosis in a context-specific manner. This necessitates to take into account pertinent clinicopathological factors, including tumor histotype, specific immunotherapy administered, and reason of treatment interruption.

Contributors

Laura Pala, Eleonora Pagan, Vincenzo Bagnardi, Fabio Conforti contributed to study design, data collection, data interpretation, data verification, writing of the manuscript.

Eleonora Pagan, Isabella Sala, Vincenzo Bagnardi contributed to statistical data analysis.

Alberto Mantovani, Giuseppe Viale, Richard D. Gelber provided key scientific inputs and contributed to data interpretation.

Laura Pala, Eleonora Pagan, Isabella Sala, Chiara Oriecuia, Matteo Oliari, Tommaso De Pas, Claudia Specchia, Emilia Cocorocchio, Emma Zattarin, Giovanna Rossi, Chiara Catania, Giovanni Luca Ceresoli, Daniele Laszlo, Jacopo Canzian, Elena Valenzi, Giuseppe Viale, Richard D. Gelber, Alberto Mantovani, Vincenzo Bagnardi, Fabio Conforti contributed to the revision of the manuscript.

All authors had full access, verified all the underlying data in the study and had final responsibility for the decision to submit for publication.

All authors read and approved the final version of the manuscript.

Data sharing statement

Data collection form and extracted data can be made available upon request to the authors.

Declaration of interests

LP declares speaker engagements with Pierre Fabre.

TDP declares Advisory board/Consultations roles with GSK Boehringer Ingelheim and trial support from Pfizer Blueprint Medicines Gilead Amgen Merck.

CC declares travel supports from Astra Zeneca and Roche.

GLC declares advisory roles and speaker engagements with Novocure, Bristol-Myers Squibb, Astrazeneca, Novartis, Merck Sharp & Dohme, Bayer, and Astellas.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2024.102681.

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