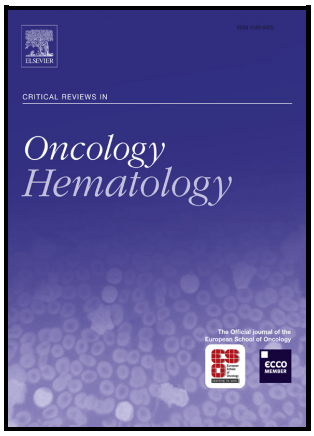

A systematic review and meta-analysis on the Optimal Treatment duration of cHEckpoint inhibitoRS in solid tumors: the OTHERS studyImmunotherapy duration in solid tumors

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Title: A systematic review and meta-analysis on the Optimal Treatment duration of cHEckpoint inhibitoRS in solid tumors: the OTHERS study

Running title: **Immunotherapy duration in solid tumors**

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List of abbreviations:

SoC, standard of care

ICIs, immune checkpoint inhibitors

NSCLC, non-small cell lung cancer

SCLC, small cell lung cancer

HNSCC, head & neck squamous cell carcinoma

RCC, renal cell carcinoma

UC, urinary tract cancer

HR, hazard ratio

CI, confidence interval

FDA, Food and Drug Administration

TKI, tyrosine-kinase inhibitor

PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses

GRADE, Grading of Recommendations Assessment, Development and Evaluation

Abstract

No clear evidence supports the advantage of fixed (up to two years (2yICI)) or continuous treatment (more than two years (prolonged ICI)) in cancer patients achieving stable disease or response on immune checkpoint inhibitors (ICIs). We performed a systematic review and meta-analysis of randomized controlled trials reporting the duration of ICIs (alone or in combination with standard of care (SoC)) across various solid tumors. Overall, we identified 28,417 records through database searching. Based on the eligibility criteria, 57 studies were identified for the quantitative synthesis, including 22,977 patients receiving ICIs (with or without SoC). Prolonged ICI correlated with better overall survival (OS) than 2yICI in patients with melanoma (HR:1.55; 95%CI: 1.22,1.98), while 2yICI-SoC led to better OS than prolonged ICI-SoC in patients with NSCLC (HR: 0.84; 95%CI: 0.68,0.89). Prospective randomized trials are needed to assess the most appropriate duration of ICIs.

Funding: The present study is supported by a research grant provided by AstraZeneca.

Keywords: Immunotherapy; duration; survival; solid tumors

Introduction

In recent years, immunotherapy has gained growing importance in oncology and, immune checkpoint inhibitors (ICIs), specifically, have become a crucial component of the treatment algorithms of several types of advanced solid tumors [3]. With more than 1,000 ongoing trials, immunotherapy is also the most promising area of cancer research [2].

Although the efficacy and safety profile of ICIs (alone or in combination with other agents) have been tested in several trials, some features related to ICIs use are still unclear. One of the most important unmet clinical needs is their duration of treatment. Early trials on immunotherapy suggested that ICIs should be continued until disease progression, evidence of clinical benefit, unacceptable toxicity (whichever came first), or up to two years [4, 5]. However, the optimal treatment duration for ICIs remains to be established. The commonly used two-year cut-off came from indirect comparison between the results of different early trials. Accumulating data question the role of fixed-duration immunotherapy in patients achieving a response to treatment [4-6]. However, the majority of studies comparing fixed (up to two years) or continuous immunotherapy (treatment allowed beyond two years) are based on retrospective experiences on a single tumor type, and suffer small sample sizes [4-6]. From the evidence so far, it is not possible to answer the question whether immunotherapy "should be continued *ad infinitum*" in patients who obtain a response or stabilization of the disease [7].

To assess the impact of immunotherapy duration on oncologic outcomes, we ran this systematic review and meta-analysis aiming to establish whether ICIs can be safely discontinued at completion of two years of active treatment across different types of solid tumors.

Material and Methods

This is a systematic review and meta-analysis. The project is registered in the International prospective register of systematic reviews (PROSPERO; ID: 296786). The framework of the PICO [8] is reported in Supplemental material 1.

The review followed the suggestions from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [9]. The main outcome measure was to assess whether treatment with ICIs can be discontinued on completion of two years (across different tumor types). We compared outcomes of patients receiving ICIs for up to two years and those receiving them for longer (until disease progression and/or unacceptable toxicity). Data were extracted from randomized controlled trials (RCT) evaluating fixed or continuous administration of ICIs.

Study eligibility

We included patients with advanced and metastatic solid tumors treated with ICIs (anti-CTLA4, PD-1, and PD-L1 antibodies, as single agents or in combination). To reduce potential biases related to different types of treatment we evaluated separately patients treated with immunotherapy alone or immunotherapy combined with standard of care (SoC). SoC included conventional chemotherapy and tyrosine-kinase inhibitors (TKIs). We included only randomized controlled trials (RCT), written in English, published in the last ten years (since 1st January, 2020), and with more than ten patients. Studies focusing on outcomes beyond progression only, and the use of immunotherapy in neoadjuvant and adjuvant settings were excluded. We also excluded case reports, in vitro or cadaveric studies, technical notes, and disaster series, studies focusing on outcomes beyond progression only, and immunotherapy in neoadjuvant and adjuvant settings.

Literature search

The search was comprehensive, using several databases from each database's earliest inception to 21th September 2021. PubMed (MEDLINE), Embase, CENTRAL, Scopus, and Web of Science databases, as well as ClinicalTrials.gov were systematically searched and supplemented by secondary screening of the references of all studies included. We searched for abstracts and conference proceedings as well. The search strategy is reported in Supplemental material 2.

Selection of studies and data extraction

Two authors independently screened records retrieved through the search strategy from titles and abstracts. Potentially relevant studies were acquired in full text and assessed for final inclusion independently by two authors. Any disagreement was discussed with the other authors. Two review authors independently extracted the following information: study design and patients' characteristics, duration of immunotherapy, and data on OS and PFS. In case a study included several treatment arms, only those of interest were considered. Studies were grouped in two categories: (1) those assessing the efficacy of ICIs in combination with SoC, and (2) those assessing the efficacy of ICIs alone.

Risk of bias

Two authors independently assessed the risk of bias according to the criteria set out in the Cochrane Handbook for Systematic Reviews of Interventions [10]. The following criteria were considered: sequence

generation and allocation concealment (selection bias), blinding of participants and providers (performance bias), blinding of outcome assessors (detection bias), incomplete outcome data (attrition bias), and selective outcome reporting (reporting bias). Disagreement between reviewers was resolved by discussion.

Data synthesis

Analyses considered subgroups of type of cancer only. In view of the possible different responses of ICIs across solid tumors, we examined different tumor types separately. We calculated the hazard ratio (HR) of OS and PFS for each study, and their 95% confidence intervals (IC). We used the "O-E" and "V" method and fixed-effect model to estimate the pooled HR for each outcome [11]. Across the studies we measured the overall heterogeneity using the I^2 statistic, in which I^2 greater than 50% suggests high heterogeneity [12]. In studies that directly compared the interventions (immunotherapy vs. with SoC) up to two years or until disease progression, we estimated the difference of HR and its standard error (SE) for each subgroup. In studies without direct comparison, we estimated the differences between interventions (immunotherapy alone or with SoC) up to two years (2yICI or 2yICI-SoC) vs. until disease progression (prolonged ICI or prolonged ICI-SoC), using the inverse variance method and random-effect models [13]. We used Review Manager (RevMan v5.4, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) for statistical analysis.

Grading of Evidence

We assessed the overall certainty of the evidence for the primary outcomes using the five GRADE domains (study limitations, consistency of effect, imprecision, indirectness, and publication bias) according to the GRADE approach [14]. GRADE uses the following criteria to grade the evidence: High: we are very confident that the true effect lies close to that of the estimate of the effect. Moderate: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect. Very low: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect. The evidence was summarized in a "Synthesis of Findings" (SoF) table that provides key information about the magnitudes of relative and absolute effects of the interventions, the amount of evidence available and the certainty of that evidence [15].

Results

The database search identified 28,417 records. Based on study eligibility criteria, 57 studies were included for the quantitative synthesis. **Figure 1** shows the PRISMA flow chart. We found studies reporting data on duration of immunotherapy in melanoma (n=8) [16-23], non-small cell lung cancer (NSCLC) (n=28) [24-50], small cell lung cancer (SCLC) (n=4) [51-54], head & neck squamous cell carcinoma (HNSCC) (n=6) [55-60], renal cell cancer (RCC) (n=7) [61-67], and urinary tract cancer (UC) (n=5) [68-72]. Data of 22,977 patients with solid malignancies were examined. **Supplemental Material 3** reports the main characteristics and findings.

We performed four direct analyses for PFS or OS for each type of tumor. These analyses compared: (i) prolonged ICI vs. SoC, (ii) prolonged ICI-SoC vs. SoC, (iii) 2yICI vs. SoC, and (iv) 2yICI-SoC vs. SoC. The analyses focusing on PFS are reported in **Supplemental Material 4, 5, 6, and 7**, and the pooled analyses focusing on OS are reported in **Supplemental material 8, 9, 10, and 11**. The SoF of these comparisons are reported in **Supplemental material 12, 13, 14, and 15**. Risk of bias is summarized in **Supplemental material 16**. Using the data from these direct comparisons, we calculated an indirect comparison of PFS and OS in patients treated with 2yICI vs. prolonged ICI (**Figure 2**), and 2yICI-SoC vs. prolonged ICI-SoC (**Figure 3**).

Concerning PFS, pooled results suggested that in case of disease response, 2yICI correlated with better PFS than prolonged ICI, in patients with metastatic melanoma (HR 0.70; 95%CI 0.51,0.95), while, the duration of immunotherapy had no impact on PFS of patients with NSCLC and H&N. Differently, patients receiving 2yICI-SoC achieved better PFS than prolonged ICI-SoC in patients with NSCLC (HR 0.85; 95%CI 0.76, 0.96), and RCC (HR 0.79; 95%CI 0.66,0.94). The duration of immunotherapy plus SoC had no impact on PFS of patients with melanoma and SCLC.

In terms of OS, prolonged ICI correlated with better survival than 2yICI in patients with melanoma (HR 1.55; 95%CI 1.22,1.98). A trend toward better OS was observed for patients with UC receiving 2yICI compared to prolonged ICI (HR 0.79; 95%CI 0.62,1.00). The duration of immunotherapy had no impact on OS for patients with NSCLC and HNSCC. However, patients with NSCLC receiving 2yICI-SoC had better OS than those treated with prolonged ICI-SoC (HR 0.84; 95%CI 0.68,0.89). The duration of immunotherapy plus SoC did not affect the OS of patients with melanoma, RCC, UC, and SCLC. SoF reporting data of 2yICI vs. prolonged ICI and 2yICI-SoC vs. prolonged ICI-SoC are reported in **Tables 1 and 2**, respectively.

Discussion

The optimal duration of immunotherapy for the management of advanced solid tumors is still debated and several investigations have led to discordant results [4-6]. Evidence is based on indirect comparisons between trials testing continuous or fixed-duration immunotherapy.

An exploratory analysis of the Phase IIIb/IV CheckMate153 trial suggested that continuing nivolumab beyond one year vs. stopping at one year was associated with better outcomes in patients with previously treated NSCLC [76]. No clear data are available to assess the best duration of ICIs beyond two years. In clinical practice, anyway, patients achieving durable complete or partial responses could be the most suitable candidates for a suspension of the treatment [77].

To our knowledge, the present systematic review and meta-analysis is the first to examine the duration of treatment with ICIs in different types of advanced solid tumors. We included 57 clinical trials with almost 23,000 patients affected either by NSCLC, melanoma, RCC, HNSCC, UC, or SCLC. Our findings were: (1) among patients with NSCLC, 2yICI-SoC correlated with better PFS and OS compared to prolonged treatments, while no differences were found with ICIs alone; (2) RCC patients given 2yICI-SoC experienced better PFS than patients treated with prolonged ICI-SoC, but similar OS; (3) among patients with melanoma, 2yICI gave better PFS, but prolonged ICI correlated with better OS; (4) treatment duration did not seem to have any impact on outcomes among patients with HNSCC,UC and SCLC.

In this large meta-analysis, we performed an accurate assessment of the risk of bias. Anyway, we acknowledge several limitations of our work. The principal weaknesses are (i) The present meta-analysis included RCTs comparing 2yICI vs. prolonged ICI. In those studies, patients were included, irrespective on the fact that they reached the 2 years threshold. Although in both groups patients might stop the treatment before 2 years (e.g., patients progressing and eventually dying), this might influence data interpretation (ii) We have to stressed that no data regarding number of patients discontinuing the treatment was not available, We acknowledged this as another important limitation of our study. (iii) The fact that, across all tumor types, there is only a minority of patients who continue with ICI-based therapy for two years and beyond, while in the majority of cases such therapies are discontinued because of either progressive disease, death, or toxicity. As a consequence, only a small fraction of the 23,000 patients is determining our results.With such limitations, our analysis suggested that two-year fixed treatment was associated with shorter OS, but longer PFS in patients with melanoma. Such counterintuitive results could be biased by the assessment schedule adopted during the follow up after 2 years of treatment (detection bias). For example, in Keynote-006 radiologic imaging was requested only for the first 2 years after the end of treatment (every 3

months for the first year and every 6 months through year two). In view of this, similar PFS were reported for patients who discontinued treatment with complete response after 6 months vs. two years, being assessed with the same timetable of radiologic follow up [78].

The following points regarding prolonged immunotherapy need to be addressed: (i) the role of immune-related adverse events among patients achieving a response have to be carefully weighed up and examined, also considering the possibility of long-term toxicity, its impact on the patients' quality of life, but also on oncologic outcomes [80]; (ii) similarly, further prospective evidence is needed to assess the impact of this treatment on patients' quality of life; (iii) the burden for the healthcare system, and cost-effectiveness need to be addressed as well; (iv) although we investigated the duration of immunotherapy in several types of solid tumor (melanoma, NSCLC, SCLC, HNSCC, RCC, and UC) we did not find sufficient data (see Supplemental material 2) for assessing this correlation in patients with other malignancies (e.g., gynecological cancer, hepatocellular carcinoma, sarcoma); (v) although we did two separate analyses (immunotherapy alone, and immunotherapy plus SoC), we could not estimate the effects of prolonged administration of SoC (e.g., TKIs) in patients receiving continuous treatment; and (vi) our investigation could not correct the results for several variables, such as sex, obesity, concurrent medications, that might interfere with the results of immunotherapy [79, 80].

The main weaknesses of the present analysis include the inherent limits related to the heterogeneity of the studies included, in terms of line of treatments and the different types of ICI (i.e. anti-CTLA4, anti-PD-1, and anti-PD-L1 antibodies). Additionally, other limitations included: several confounding factors might influence the interpretation of our results (e.g., shorter ICI treatment may signify a selection of patients with exceptional responses); the availability of efficacious post-ICI treatment strategies vary between tumors and may influence OS.

The main strengths are: (i) the inclusion of RCTs; (ii) the evaluation of different solid tumors (melanoma, NSCLC, SCLC, HNSCC, RCC, and UC); and (iii) the two separate analyses (the first for immunotherapy alone and the second for immunotherapy with SoC). This latter point is important to reduce possible limitations related to the effects of therapies other than ICI.

In conclusion, the present systematic review and meta-analysis suggests that the outcomes of patients with advanced solid tumors are not enhanced by prolonged immunotherapy. In fact, patients with NSCLC receiving immunotherapy plus SoC for up to two years experienced better PFS and OS than patients continuing the immune agents until disease progression. For other types of solid tumors, the optimal duration

of immunotherapy remains an open question. Further direct prospective randomized trials are needed to assess the most appropriate duration of immunotherapy in cancer patients.

Founding: None

Author's contributions:

Conceptualization: PG; Methodology: MC, NT; Data collection: All authors; Analyses: MC, NT, MM; Project administration: GB, PG.; Supervision: GB, PG.; writing – original draft: GB, PG, MB; writing – review & editing: All authors

All named authors approved the final version of the paper.

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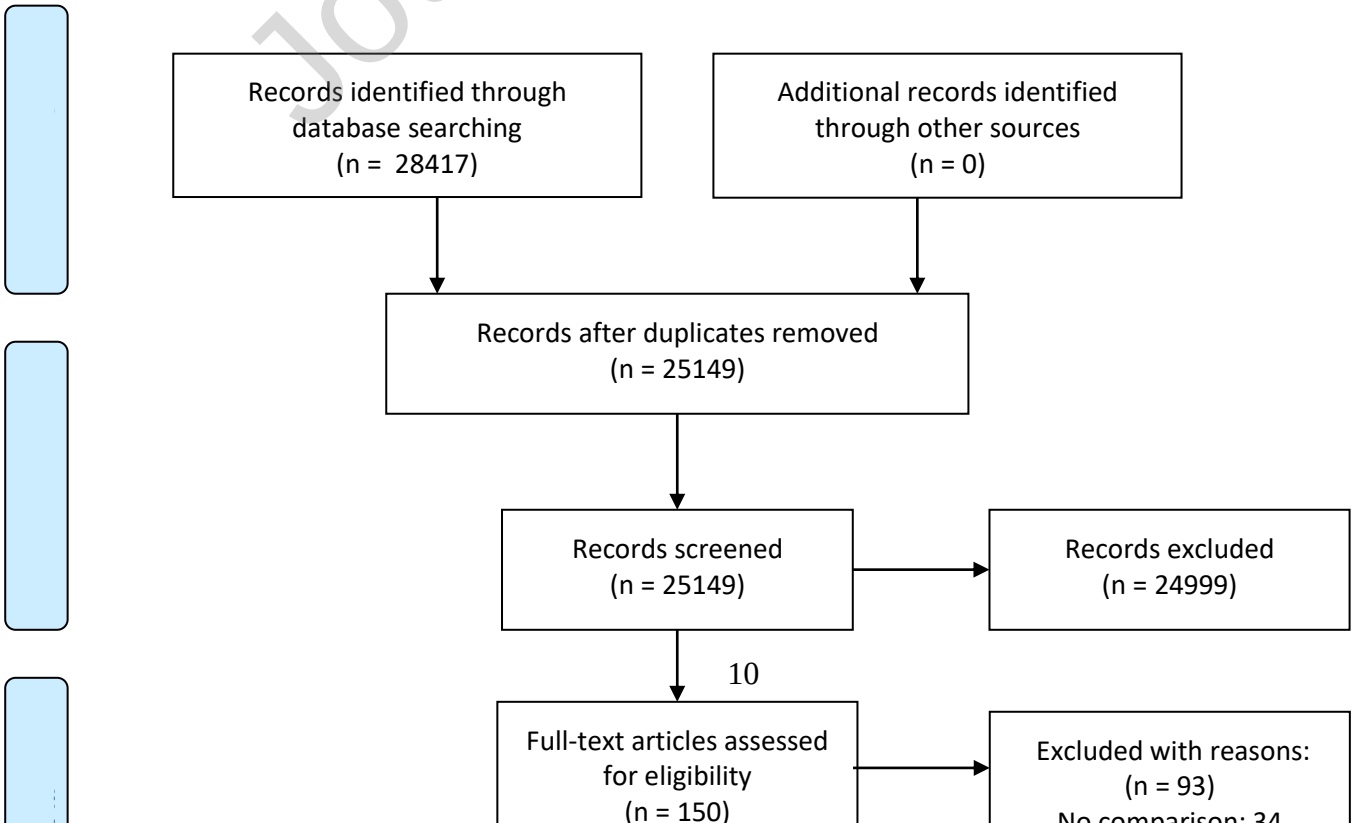
Legend to Figure

PRISMA 2009 Flow Diagram:



Studies included in qualitative synthesis (n = 57)

Figure 1: PRISMA flow diaphragm

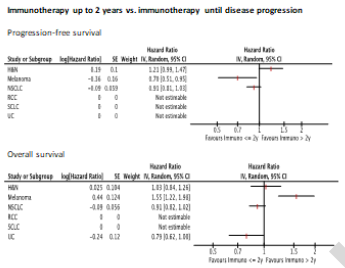


Figure 2: Progression-free and overall survival for immunotherapy up to two years vs. immunotherapy until disease progression

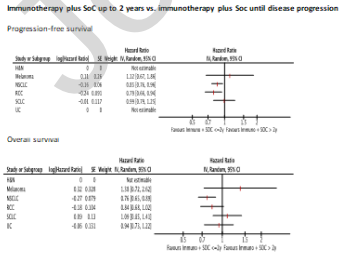


Figure 3: Progression-free and overall survival for immunotherapy plus SoC up to two years vs. immunotherapy plus SoC until disease progression

Conflicts of interest:

The authors indicate no financial relationship

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Short biography:

Giorgio Bogani was born in Italy in 1982. He graduated from the Faculty of Medicine in 2007, and he completed his residency in Gynecology and Obstetrics in 2013. In 2016, he obtained a Ph.D. in Oncology and Experimental Medicine. In 2013 he received his research fellowship at the Gynecologic Unit of the Mayo Clinic (Rochester, MN). Since April 2014, Dr. Bogani works in the department of Gynecologic Surgery at the Fondazione IRCCS Istituto Nazionale dei Tumori di

Milano, Milan (Italy). He has more than 250 publications in peer-reviewed journals. In 2021 Dr Bogani achieve the title of associate professor from the University "La Sapienza" of Rome. He has been honored with awards for his academic excellence by several societies, including the *European Society of Gynaecological Oncology (ESGO), European Society for Gynaecological Endoscopy (ESGE), and International Society of Gynecological Endocrinology (ISGE)*. Professor Bogani is a member of the EORTC and a member of the Cancer Core Europe. He performed more than 5,000 surgical procedures, mostly performed with minimally invasive techniques. His areas of interest include gynecologic oncology, precision medicine, targeted therapies as well as the treatment of frail and elderly patients.

Table 1 Synthesis of findigs:Immunotherapy up to 2 years vs. immunotherapy until disease progression in patients with advanced/metastatic solid tumors

Individuals: patients with advanced / metastatic solid tumors
Setting: inpatients
Intervention: Immunotherapy + SoC up to 2 years
Comparator: immunotherapy + SoC until diisease progression

Findings	**Anticipated effect*** (95% CI)		Relative effects (95% CI)	Number of partecipants (studies)	Level of evidence (GRADE)	Comments
	Risk for immunotherapy until progression	**Risk for immunotherapy for up to 2 years**				
Overall survival- H&N	77 /100	**78 / 100** (70 to 84)	**HR 1.03** (0.84 to 1.26)	1025 (4 RCT)	⊕⊕◯◯ Low[a,b]	No correlation
Overall survival - Melanoma	65 /100	**80 / 100** (72 to 88)	**HR 1.55** (1.22 to 1.98)	576 (1 RCT)	⊕⊕⊕◯ Moderate[b]	Improved overall survival for patients having treatment until disease progression in comparison to patients having treatment for up to 2 years
Overall survival - NSCLC	55 /100	**52 / 100** (48 to 56)	**HR 0.91** (0.82 to 1.02)	4609 (14 RCT)	⊕⊕◯◯ Low[b,c]	No correlation
Overall survival - RCC – not reported	-	-	-	-	-	Not estimable
Overall survival - SCLC – not reported	-	-	-	-	-	Not estimable
Overall survival- UC	66 /100	**58 / 100** (49 to 66)	**HR 0.79** (0.62 to 1.00)	1437 (4 RCT)	⊕⊕◯◯ Low[b,c]	No correlation
Progression free survival - H&N	77 /100	**83 / 100** (76 to 88)	**HR 1.21** (0.99 to 1.47)	1025 (4 RCT)	⊕◯◯◯ Very low[b,d,e]	No correlation
Progression free survival- Melanoma	26 /100	**19 / 100** (14 to 25)	**HR 0.70** (0.51 to 0.95)	1038 (3 RCT)	⊕⊕◯◯ Low[b,f]	Improved progression-free survival for patients having treatment for up to 2 years in comparison to patients having treatment until disease progression

Individuals: patients with advanced / metastatic solid tumors
Setting: inpatients
Intervention: Immunotherapy + SoC up to 2 years
Comparator: immunotherapy + SoC until diisease progression

Findings	**Anticipated effect*** (95% CI)		Relative effects (95% CI)	Number of partecipants (studies)	Level of evidence (GRADE)	Comments
	Risk for immunotherapy until progression	**Risk for immunotherapy for up to 2 years**				
Progression free survival -NSCLC	68 /100	**64 / 100** (60 to 69)	**HR 0.91** (0.81 to 1.03)	3749 (12 RCT)	⊕◯◯◯ Very low[b,e,g]	No correlation
Progression free survival - RCC – not reported	-	-	-	-	-	Not estimable
Progression free survival - SCLC - not reported	-	-	-	-	-	Not estimable
Progression free survival - UC - not reported	-	-	-	-	-	Not estimable

* The risk in the interventional group (and its 95% confidence interval (CI)) is based in the risk of the control group and on the effect of the intervention (and its 95%CI)

SoC, standard of care; CI: Confidence interval; HR: Hazard Ratio; NSCLC, non small cell lung cancer; SCLC; small cell lung cancer; H&N, head&neack tumor; RCC, renal cell carcinoma; UC, urinary tract cancer.

The quality of evidence was evaluated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methods [11].

Legend

a. The certainty of evidence was downgraded by selective reporting and sponsor bias
b. The certainty of evidence was downgraded because the result was performed through indirect comparison
c. The certainty of evidence was downgraded by sponsor bias
d. The certainty of evidence was downgraded by performance and sponsor bias
e. The certainty of evidence was downgraded by heterogeneity among the studies
f. The certainty of evidence was downgraded by performance bias
g. The certainty of evidence was downgraded by performance, detection and sponsor bias

Table 2 Synthesis of findigs: Immunotherapy + SoC up to 2 years vs. immunotherapy + SoC until disease progression in patients with advanced/metastatic solid tumors

Individuals: patients with advanced / metastatic solid tumors
Setting: inpatients
Intervention: Immunotherapy + SoC up to 2 years
Comparator: immunotherapy + SoC until diisease progression

Findings	**Anticipated effect*** (95% CI)		Relative effects (95% CI)	Number of partecipants (studies)	Level of evidence (GRADE)	Comments
	Risk for immunotherapy + SoC until progression	**Risk for immunotherapy + SoC for up to 2 years**				

Individuals: patients with advanced / metastatic solid tumors
Setting: inpatients
Intervention: Immunotherapy + SoC up to 2 years
Comparator: immunotherapy + SoC until diisease progression

Findings	Anticipated effect* (95% CI)		Relative effects (95% CI)	Number of partecipants (studies)	Level of evidence (GRADE)	Comments
	Risk for immunotherapy + SoC until progression	**Risk for immunotherapy + SoC for up to 2 years**				
Overall survival- H&N – not reported	-	-	-	-	-	Not estimable
Overall survival- Melanoma	46 / 100	**57 / 100** (35 to 80)	**HR 1.38** (0.72 a 2.62)	468 (3 RCT)	⊕◯◯◯ Very low[b,c]	No correlation
Overall survival- NSCLC	48 / 100	**39 / 100** (35 to 44)	**HR 0.76** (0.65 a 0.89)	2884 (10 RCT)	⊕⊕◯◯ Low[b,d,e]	Improved overall survival for patients having treatment for up to 2 years in comparison to patients having treatment until disease progression
Overall survival- RCC	39 / 100	**34 / 100** (29 to 40)	**HR 0.84** (0.68 a 1.02)	2201 (5 RCT)	⊕⊕◯◯ Low[b,d]	No correlation
Overall survival- SCLC	55 / 100	**58 / 100** (49 to 68)	**HR 1.09** (0.85 a 1.41)	758 (4 RCT)	⊕⊕◯◯ Low[a,b,e]	No correlation
Overall survival- UC	52 / 100	**50 / 100** (42 to 59)	**HR 0.94** (0.73 a 1.22)	802 (2 RCT)	⊕⊕◯◯ Low[b,d]	No correlation
Progression free survival- H&N – not reported	-	-	-	-	-	Not estimable
Progression free survival- Melanoma	38 / 100	**41 / 100** (27 to 59)	**HR 1.12** (0.67 a 1.86)	849 (5 RCT)	⊕◯◯◯ Very low[a,b,c]	No correlation
Progression free survival- NSCLC	50 / 100	**45 / 100** (41 to 49)	**HR 0.85** (0.76 a 0.96)	3009 (12 RCT)	⊕⊕◯◯ Low[b,d,e,f]	Improved progression-free survival for patients having treatment for up to 2 years in comparison to patients having treatment until disease progression
Progression free survival- RCC	49 / 100	**41 / 100** (36 to 47)	**HR 0.79** (0.66 a 0.94)	1850 (5 RCT)	⊕⊕◯◯ Low[b,d,g]	Improved progression-free survival for patients having treatment for up to 2 years in comparison to patients having treatment until disease progression
Progression free survival- SCLC	42 / 100	**42 / 100** (35 to 50)	**HR 0.99** (0.79 a 1.25)	758 (4 RCT)	⊕⊕◯◯ Low[b,h]	No correlation

* The risk in the interventional group (and its 95% confidence interval (CI)) is based in the risk of the control group and on the effect of the intervention (and its 95%CI)

SoC, standard of care; CI: Confidence interval; HR: Hazard Ratio; NSCLC, non small cell lung cancer; SCLC; small cell lung cancer; H&N, head&neack tumor; RCC, renal cell carcinoma; UC, urinary tract cancer.

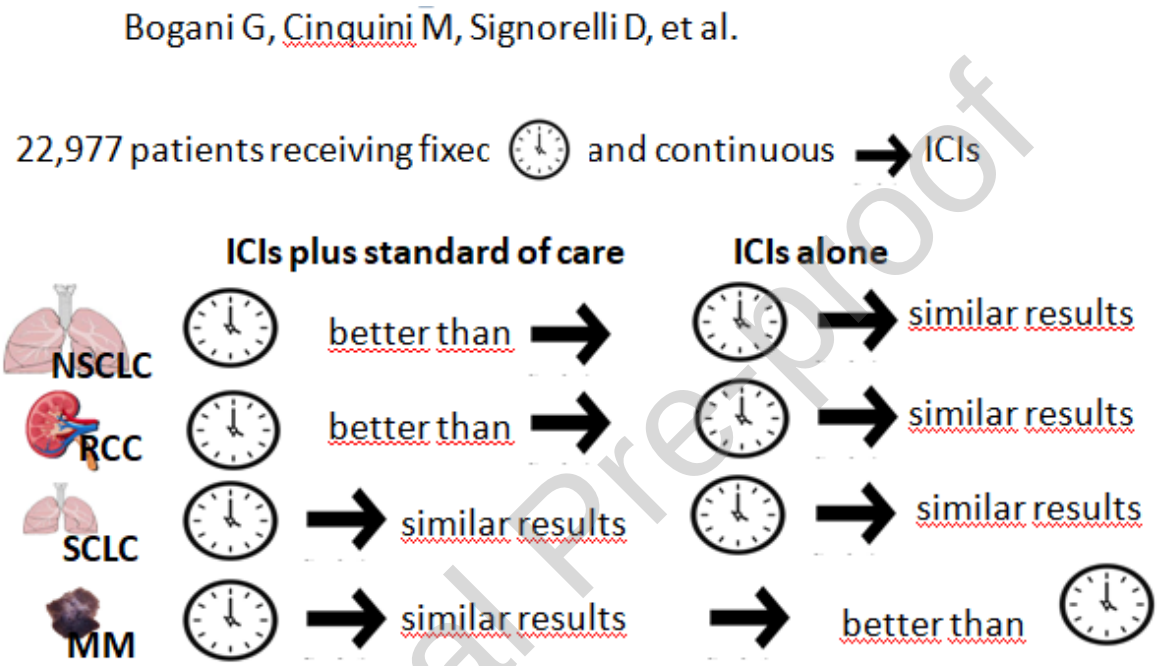
The quality of evidence was evaluated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methods [11].

Legend

a. The certainty of the evidence was downgraded by selective reporting bias
b. The certainty of evidence was downgraded because the result was performed through indirect comparison

c. The certainty of evidence was downgraded by the low number of events
d. The majority of RCTs included in this analysis came from abstracts
e. The certainty of evidence was downgraded by sponsor bias
f. The certainty of evidence was downgraded by performance, detection and sponsor bias
g. The certainty of evidence was downgraded by performance and sponsor bias
h. The certainty of the evidence was downgraded by performance and detection bias

Graphical abstract



Objective: No clear evidence supports the advantage of fixed (up to two years (2yICI)) or continuous treatment (more than two years (prolonged ICI)) in cancer patients achieving stable disease or response on immune checkpoint inhibitors (ICIs). Here, we assessed the optimal treatment duration for ICIs in solid tumors.

Conclusions: Prolonged ICIs administration does not seem to improve the outcomes of patients with NSCLC an RCC.

Conflict of interest: None

Highlights

- The optimal duration of immune checkpoint inhibitors (ICI) is still unclear
- This meta-analysis compared prolonged ICI vs. 2-year schedule
- Prolonged ICIs seems beneficial in patients with melanoma
- In other solid tumor prolonged ICI does not correlated with improved survival