Cancer Immunology, Immunotherapy (2023) 72:1365–1379
https://doi.org/10.1007/s00262-022-03349-4

REVIEW

Complete remissions following immunotherapy or immuno-oncology combinations in cancer patients: the MOUSEION-03 meta-analysis

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Received: 22 November 2022 / Accepted: 7 December 2022 / Published online: 12 January 2023

Abstract

Background Immunotherapy has determined unprecedented long-term responses in several hematological and solid tumors. In the MOUSEION-03 study, we conducted a meta-analysis to determine the possibility of achieving complete remissions (CR) with immunotherapy or immuno-oncology combinations in cancer patients.

Methods The primary endpoint was to assess the incidence of CR in cancer patients receiving immune checkpoint inhibitors (ICIs) alone or in combination with other agents versus control treatments. The pooled odds ratio (OR) and 95% confidence interval (CI) for CR rate were extracted.

Results A total of 12,130 potentially relevant trials were identified; 5 phase II and 80 phase III randomized studies (37 monotherapies and 48 combinations) and 49,425 cancer patients were included. The most frequent types of malignancies were non-small cell lung cancer ($n = 14{,}249$; 29%), urothelial cancer ($n = 6536$; 13%), renal cell carcinoma ($n = 5743$; 12%), and melanoma ($n = 2904$; 6%). In patients treated with immunotherapy (as monotherapy or in combination with other anticancer agents), the pooled OR was 1.67 (1.52–1.84). The highest OR was registered by immune-based combinations with two ICIs (3.56, 95% CI 1.28–9.90).

Conclusions To the best of the authors' knowledge, no comprehensive meta-analysis on the use of ICIs and ICI-based combinations in solid tumors to systematically investigate the probability to achieve CR has been published so far. Although CR is not a common event in several cancer patients receiving immunotherapy, the MOUSEION-03 suggests that the use of ICIs may significantly increase the chance of achieving CR in comparison with control treatments.

Keywords Pembrolizumab · Cancer · Complete response · Immuno-oncology combinations · Immunotherapy · Meta-analysis

Introduction

Immunotherapy has revolutionized the treatment scenario for hematological and solid tumors and has reported unprecedented clinical benefits in several settings. Multiple recent reports have supported the long-term benefit of immunotherapy, with even the possibility—in selected cases—to cure cancer patients [1, 2]. The current armamentarium of available immunotherapies for cancer patients encompasses several types of anticancer agents, including immune checkpoint inhibitors (ICIs) targeting cytotoxic T-lymphocyte antigen-4 (CTLA-4), programmed death 1 (PD-1) or its ligand [3, 4]; in addition, beyond immunomodulatory antibodies, several other agents and immune-based treatments have been assessed and are currently under evaluation, including adoptive cell transfer (ACT), oncolytic virus therapy, and vaccines. More recently, the possibility of combining immunotherapy with other systemic chemotherapies, antiangiogenic agents, or targeted therapies as well as other ICIs has emerged as a novel standard of care in a variety of tumors, including hepatocellular carcinoma, renal cell carcinoma (RCC), and non-small cell lung cancer (NSCLC) [5–7].

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According to RECIST 1.1 criteria [8], complete remission (CR) is defined as the disappearance of all target lesions in response to therapy, and achieving CR and maintaining it for more than 5 years is the "sine qua non" for considering a patient as potentially cured. Nowadays, the short median duration of the follow-up of cancer patients treated by immunotherapy or immuno-oncology combinations in clinical trials hardly allows estimating the rate of subjects who will maintain lifelong CR. At this regard, assessing the possibility to obtain CR results fundamental to enter in the second phase of the immunotherapy era, in which clinicians will finally not be afraid to tell a patient: "You have been definitively cured." Therefore, it is of pivotal importance to assess the probability of achieving CR with immunotherapy, and whether the use of ICIs would increase CR in cancer patients.

To the best of our knowledge, the MOUSEION-03 study is the first study aimed to systematically investigate the possibility of achieving CR in patients affected by solid tumors treated with immunotherapy or immuno-oncology combinations through a large up-to-date study-level meta-analysis of available randomized trials.

Materials and methods

Selection of studies and data extraction

Study selection was carried out according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement [9]. To identify relevant clinical trials, four authors (MS, FM, AR, and VM) reviewed citations from PubMed, MEDLINE, Embase, and Scopus from January 1966 to February 2022. The search was performed by combining the words "cancer" or "solid tumor" with the following words: "atezolizumab," "avelumab," "camrelizumab," "cemiplimab," "CTLA-4," "cytotoxic T-lymphocyte-associated protein-4," "durvalumab," "immune checkpoint inhibitor," "ipilimumab," "nivolumab," "PD-1," "PD-L1," "pembrolizumab," "programmed cell death receptor-1," "tislelizumab," and "tremelimumab." The search was limited to human studies and randomized clinical trials published in English that met the following criteria: (1) prospective randomized phase III trials of patients with solid tumors; (2) random assignment of participants to treatment with immunotherapy or control (active therapy) and (3) available data on outcome in males and females. When multiple publications of the same clinical trial were encountered, only the most recent or most complete reporting of that trial was included. Studies including ≥ 3 treatment arms were divided to compare each experimental arm with the control arm. Disagreements about trials were discussed and resolved by all investigators.

The primary objective of this study was to assess the possibility, expressed as OR, of achieving CR in patients treated by immunotherapy alone or combined with other immuno-, chemo- or targeted therapies. Phase I, phase II, and randomized phase III trials including immunotherapy in both experimental and control arms were excluded, as well as studies with placebo as control arm. The meta-analysis was conducted according to PRISMA guidelines (Supplementary Material).

Statistical design

All statistical analyses were performed using RStudio.

Odds Ratios (ORs) were used to analyze dichotomous variables, including CR rate in cancer patients treated with immunotherapy versus control arms. Forest plots were used to assess ORs. Statistical heterogeneity between the included trials was examined using the chi-square test and the I^2 statistic; substantial heterogeneity was present when the I^2 value was greater than 50% or there was a low p value (<0.10) in the chi-square test. When no heterogeneity was noted, the fixed-effects model was used, while the random-effects model was applied in the presence of significant heterogeneity.

Results

Search results

A total of 12,130 potentially relevant studies investigating immunotherapy or immuno-oncology combinations in cancer patients were identified; 10,086 studies were excluded for at least one of the following reasons: observational and in vitro studies, review articles, meta-analyses, case reports, editorials, letters, or commentaries. Subsequently, among the 2044 selected clinical trials, 1959 studies were immediately excluded for at least one of the following reasons: phase I or phase II non-randomized studies, both control and treatment groups who received immunotherapy, non-active therapy as control arm or insufficient data on CR (Fig. 1). At the end of this review process, 77 papers [10 – 86] were considered to be of adequate quality and relevance for this analysis. Nine of them [15, 19, 29, 30, 37, 45, 63, 71, 81] were divided into 2 distinct studies for each one due to presence of 2 experimental arms and 1 control arm in each one, for a total of 85 randomized controlled trials (Fig. 1). The baseline characteristics of each trial are summarized in Table 1.

Population characteristics

A total of 49,425 patients were available for this meta-analysis, with 25,647 that were included in the experimental

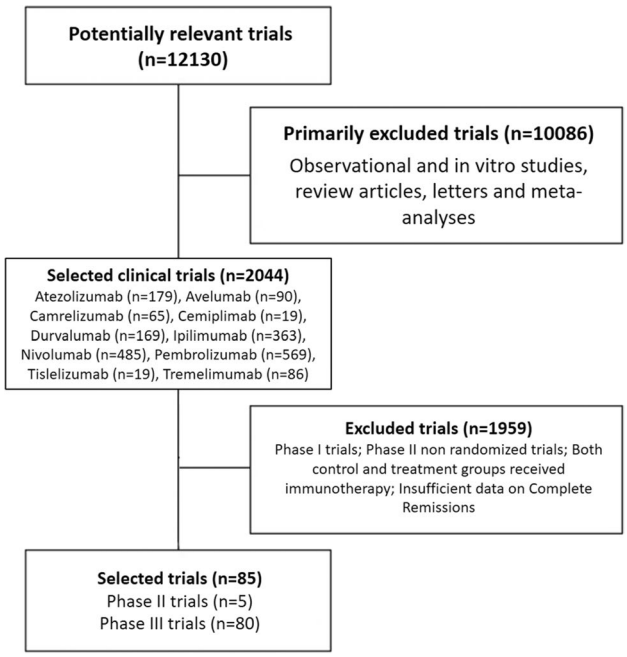

Fig. 1 Selection of randomized controlled trials (RCTs) included in the meta-analysis according to PRISMA statement

arms and 23,778 in the control arms; 14,249 (29%) of them presented a diagnosis of NSCLC [10, 12, 16, 22, 24, 32, 35, 40, 43, 44, 48, 50, 55, 56, 61–63, 67, 70, 79, 80, 85], 6536 (13%) urothelial cancer (UC) [13,19A,19B,26,37A,37B,65 ,76,82A,82B], 5743 (12%) RCC [17, 25, 45, 46, 59, 68, 69], 2904 (6%) melanoma [20, 38, 41, 42, 75, 86], and 2669 (5%) head and neck tumors (HNT) [28,34,64A,64B,66] (Table 1).

In the 37 trials exploring single immunotherapies, 11,100 patients were included in the experimental arms and 10,105 in the control arms; 4 trials had atezolizumab as experimental drug [10,13,15B,19B], 7 avelumab [23,24,26,27,29A,30A,30B], 1 camrelizumab [31], 1 cemiplimab [35], 1 durvalumab [37B], 11 nivolumab [41─45,47,49,50,51,53,57], 11 pembrolizumab [60,61,64A,65─67,72A,73,76,82B,84], and 1 tremelimumab [86] (Table 1).

In the 48 studies investigating immuno-oncology combinations, 14,547 patients were included in the experimental arms and 13,673 in the control arms; 30 trials explored the combination of chemo–immunotherapy [11,14,16,19A,21,22,28,29B,32–34,36,38–40,52,58,62,63, 64B,70,71,72B,74,77,79,80,82A,83,85], 4 immuno–immunotherapy [37A,46,48,54], 1 immuno–immuno–chemotherapy [55], 3 immuno-targeted therapy [15A,20,75], 7 immuno-antiangiogenetic drugs [17, 18, 25, 59, 68, 69, 78], and 3 immuno-targeted therapy–chemotherapy [12, 56, 81]. Eleven of these combinations included atezolizumab [11,12,14,15A,16–18,19A,20–22], 4 avelumab [25,28,29B,30B], 3 camrelizumab [32–34], 2 durvalumab [36,37A], 3 ipilimumab [38–40, 46, 48], 4 both ipilimumab and nivolumab [46, 48, 54, 55], 4 nivolumab [52, 56, 58, 59], 18 pembrolizumab [62–64,68-72B,74,75,77–83], and 1 tislelizumab [85] (Table 1).

Among the 25,647 patients included in the experimental arms with immunotherapy or immuno-combinations, 1474 CRs were reported. On the other hand, in the 23,778 patients treated in the control arms, we registered 855 CRs. The baseline characteristics of each trial are summarized in Table 1.

Immunotherapy versus control

Higher CR rate was reported in cancer patients treated with immunotherapy compared with control treatments (OR, 1.67; 95% CI, 1.52–1.84, Fig. 2). The analysis reported low heterogeneity (I^2 of 42%), and a fixed-effect model was used.

Similarly, CR rate was higher in patients receiving chemo–immunotherapy versus control treatments, with a OR of 1.60 (95% CI, 1.39–1.84, Supplimentary Fig. 2). A fixed-effect model was used due to low heterogeneity ($I^2 = 21\%$).

As for the 4 studies investigating immuno–immuno combinations (Supplimentary Fig. 3A), we observed the highest OR (3.56, 95% CI 1.28–9.90). In this case, a random-effects model was used due to high heterogeneity ($I^2 = 79\%$). On the other hand, the OR was 2.84 (95% CI 2.20–3.56) in the 7 studies comparing the combination of immunotherapy with antiangiogenetic agents versus controls (Supplimentary Fig. 3B); a fixed-effect model was used due to low heterogeneity ($I^2 = 0\%$).

Complete response rate according to primary tumor

We specifically focused our analyses on available data in terms of CR rate according to primary tumor (NSCLC, RCC, UC, and melanoma).

NSCLC

For 14,249 NSCLC patients treated with immunotherapy (ICI monotherapy or in combination with other anticancer agents) (n = 7794) versus control treatment (n = 6455), the pooled OR of CR rate was 2.0 (95% CI, 1.5–2.65, Supplimentary Fig. 4A). The analysis showed low heterogeneity (I^2 of 0), and thus, a fixed-effects model was used.

RCC

According to our analysis, for 5743 RCC patients receiving immune-based combinations (n = 2838) versus control treatment (n = 2905), CR rate was higher in the immunotherapy arm (OR, 2.4; 95% CI, 1.55–3.72, Spplimentary Fig. 4B). The analysis presented substantial heterogeneity ($I^2 = 59\%$), and a random-effects model was used.

Table 1 Baseline characteristics of randomized trials included in the meta-analysis

Author	Year	REF	Phase	Malignancy	Treatment arm	Control arm	N events (Treatment arm)	N of patients (Treatment arm)	N events (Control arm)	N of patients (Control arm)
Rittmeyer et al.	2017	10	3	NSCLC	Atezolizumab	Chemotherapy	6	425	1	425
Schmid et al.	2018	11	3	TNBC	Atezolizumab + nab-paclitaxel	Nab-paclitaxel	32	445	7	445
Socinski et al.	2018	12	3	Non-squamous NSCLC	Atezolizumab + bevacizumab + chemotherapy	Bevacizumab + chemotherapy	13	353	4	331
Powles et al.	2018	13	3	UC	Atezolizumab	Chemotherapy	16	467	16	464
Horn et al.	2018	14	3	SCLC	Atezolizumab + chemotherapy	Chemotherapy	5	201	2	202
Eng et al. (A)	2019	15A	3	CRC	Atezolizumab + cobimetinib	Regorafenib	0	183	0	90
Eng et al. (B)	2019	15B	3	CRC	Atezolizumab	Regorafenib	0	90	0	90
West et al.	2019	16	3	Non-squamous NSCLC	Atezolizumab plus chemotherapy	Chemotherapy	11	447	3	226
Rini et al.	2019	17	3	RCC	Atezolizumab + bevacizumab	Sunitinib	24	454	10	461
Finn et al.	2020	18	3	HCC	Atezolizumab + bevacizumab	Sorafenib	18	326	0	159
Galsky et al. (A)	2020	19A	3	UC	Atezolizumab + chemotherapy	Chemotherapy	56	447	27	397
Galsky et al. (B)	2020	19B	3	UC	Atezolizumab	Chemotherapy	22	359	27	397
Gutzmer et al.	2020	20	3	Melanoma	Atezolizumab + vemurafenib + cobimetinib	Vemurafenib + cobimetinib	40	256	44	258
Mittendorf et al.	2020	21	3	TNBC	Atezolizumab + chemotherapy	Chemotherapy	95	165	69	168
Jotte et al.	2020	22	3	Squamous NSCLC	Atezolizumab + carboplatin + nab-paclitaxel	Carboplatin + nab-paclitaxel	8	342	5	339
Bang et al.	2018	23	3	GC/GEJC	Avelumab	Chemotherapy	1	185	1	186
Barlesi et al.	2018	24	3	NSCLC	Avelumab	Docetaxel	5	396	2	396
Choueiri et al.	2020	25	3	RCC	Avelumab + axitinib	Sunitinib	17	442	9	444
Powles et al.	2020	26	3	UC	Avelumab	BSC	6	350	0	350
Moehler et al.	2021	27	3	GC/GEJC	Avelumab	Chemotherapy	8	249	5	250

Table 1 (continued)

Author	Year	REF	Phase	Malignancy	Treatment arm	Control arm	N events (Treatment arm)	N of patients (Treatment arm)	N events (Control arm)	N of patients (Control arm)
Lee et al.	2021	28	3	HNT	Avelumab + chemoradiotherapy	Chemoradiotherapy	167	350	177	347
Pujade-Lauraine et al.	2021	29A	3	Ovarian cancer	Avelumab	PLD	0	188	0	190
Pujade-Lauraine et al.	2021	29B	3	Ovarian cancer	Avelumab ± PLD	PLD	2	188	0	190
Monk et al.	2021	30A	3	Ovarian cancer	Chemotherapy—> mantainance avelumab	Chemotherapy—> observation	17	328	30	334
Monk et al.	2021	30B	3	Ovarian cancer	Chemotherapy + avelumab—> mantainance avelumab	Chemotherapy—> observation	20	329	30	334
Huang Jing et al.	2020	31	3	Oesophageal cancer	Camrelizumab	Chemotherapy	1	228	1	220
Zhu et al.	2020	32	3	NSCLC	Camrelizumab + chemotherapy	Chemotherapy	8	205	5	207
Luo et al.	2021	33	3	Oesophageal cancer	Camrelizumab + chemotherapy	Chemotherapy	7	298	5	298
Yang et al.	2021	34	3	Nasopharingeal carcinoma	Camrelizumab + chemotherapy	Chemotherapy	7	134	4	129
Sezer et al.	2021	35	3	NSCLC	Cemiplimab	Chemotherapy	6	283	3	280
Paz-Ares et al.	2019	36	3	SCLC	Durvalumab + carboplatin + etoposide	Carboplatin + etoposide	6	268	2	269
Powles et al. (A)	2020	37A	3	UC	Durvalumab + tremelimumab	Chemotherapy	27	342	22	344
Powles et al. (B)	2020	37B	3	UC	Durvalumab	chemotherapy	27	346	22	344
Robert et al.	2011	38	3	Melanoma	Ipilimumab + dacarbazine	dacarbazine	4	250	2	252
Reck et al.	2016	39	3	SCLC	Ipilimumab + platinum + etoposide	Platinum + etoposide	1	478	0	476
Govindan R et al	2017	40	3	Squamous NSCLC	Ipilimumab + carboplatin + paclitaxel	Carboplatin + paclitaxel	1	388	2	361
Robert et al.	2015	41	3	Melanoma	Nivolumab	Dacarbazine	16	210	2	208
Weber et al.	2015	42	3	Melanoma	Nivolumab	Chemotherapy	4	120	0	47
Borghaei et al.	2015	43	3	Non-squamous NSCLC	Nivolumab	Docetaxel	4	292	1	290

Table 1 (continued)

Author	Year	REF	Phase	Malignancy	Treatment arm	Control arm	N events (Treatment arm)	N of patients (Treatment arm)	N events (Control arm)	N of patients (Control arm)
Brahmer et al.	2015	44	3	Squamous NSCLC	Nivolumab	Docetaxel	1	135	0	137
Motzer et al.	2015	45	3	RCC	Nivolumab	Everolimus	4	410	2	411
Motzer et al.	2018	46	3	RCC	Nivolumab + ipilimumab	Sunitinib	40	425	5	422
Gillison	2018	47	3	HNT	Nivolumab	Chemotherapy	6	240	1	121
Hellmann MD et al.	2019	48	3	NSCLC	Nivolumab + ipilimumab	Chemotherapy	33	576	10	570
Kato et al.	2019	49	3	Oesophageal cancer	Nivolumab	Chemotherapy	1	171	2	158
Wu et al.	2019	50	3	NSCLC	Nivolumab	Docetaxel	1	338	0	166
Reardon et al.	2020	51	3	Glioblastoma	Nivolumab	Bevacizumab	2	184	4	185
Tsujikawa et al.	2020	52	2	Pancreatic	Cyclophosphamide/Nivo/GVAX + Nivo/CRS-207	Cyclophosphamide/GVAX + CRS-207	0	51	0	42
Hamanishi et al.	2021	53	3	Ovarian cancer	Nivolumab	Chemotherapy	2	119	2	114
Baas et al.	2021	54	3	MPM	Nivolumab + ipilimumab	Chemotherapy	5	303	0	302
Reck et al.	2021	55	3	NSCLC	Nivolumab + ipilimumab + chemotherapy	Chemotherapy	12	361	4	358
Sugawara et al.	2021	56	3	NSCLC	Nivolumab + CHT/Beva	Placebo + CHT/Beva	14	275	8	275
Spigel et. al.	2021	57	3	SCLC	Nivolumab	chemotherapy (topotecan or amrubicin)	1	284	1	285
Janjigian et al.	2021	58	3	Gastric/G-O junction	Nivolumab + chemotherapy	Chemotherapy	59	603	39	608
Choueiri et al.	2021	59	3	RCC	Nivolumab + cabozantinib	Sunitinib	26	323	15	328
Ribas et al.	2015	60	2	Melanoma	Pembrolizumab	Chemotherapy	9	357	0	171
Herbst et al.	2016	61	2/3	NSCLC	Pembrolizumab	Docetaxel	0	682	0	309
Paz-Ares et al.	2018	62	3	Squamous NSCLC	Pembrolizumab + chemotherapy	Chemotherapy	4	278	6	281
Gandhi et al.	2018	63	3	NSCLC	Pembrolizumab + chemotherapy	Chemotherapy	2	410	1	206

Table 1 (continued)

Author	Year	REF	Phase	Malignancy	Treatment arm	Control arm	N events (Treatment arm)	N of patients (Treatment arm)	N events (Control arm)	N of patients (Control arm)
Burtness et al. (A)	2019	64A	3	HNT	Pembrolizumab	Cetuximab + chemotherapy	6	300	3	287
Burtness et al. (B)	2019	64B	3	HNT	Pembrolizumab + chemotherapy	Cetuximab + chemotherapy	9	278	1	266
Fradet et al.	2019	65	3	UC	Pembrolizumab	Chemotherapy	25	270	8	272
Cohen et al.	2019	66	3	HNT	Pembrolizumab	Chemotherapy	1	246	0	234
Mok et al.	2019	67	3	NSCLC	Pembrolizumab	Chemotherapy	3	637	3	637
Rini et al.	2019	68	3	RCC	Pembrolizumab + axitinib	Sunitinib	25	432	8	429
Powles et al.	2020	69	3	ccRCC	Pembrolizumab + axitinib	Sunitinib	38	429	13	425
Paz-Ares et al.	2020	70	3	Squamous NSCLC	Pembrolizumab + chemotherapy	Placebo + chemotherapy	6	278	9	281
Schmid et al.	2020	71	3	TNBC	Pembrolizumab + chemotherapy	Chemotherapy	260	401	103	201
Shitara et al.	2020	72A	3	GC/GEJC	Pembrolizumab	Chemotherapy	9	256	14	250
Shitara et al.	2020	72B	3	GC/GEJC	Pembrolizumab + chemotherapy	Chemotherapy	24	257	14	250
André et al.	2020	73	3	CCR	Pembrolizumab	Chemotherapy	17	153	6	154
Rudin et al.	2020	74	3	SCLC	Pembrolizumab + chemotherapy	Placebo + chemotherapy	4	228	2	225
Ferrucci et al.	2020	75	2	Melanoma	Pembrolizumab + dabrafenib + trametinib	Placebo + dabrafenib + trametinib	12	60	9	60
Nishiyama et al.	2020	76	3	UC	Pembrolizumab	Chemotherapy	3	30	1	22
Tolaney et al.	2020	77	2	Breast cancer	Pembrolizumab + eribulina	Eribulina	0	44	0	44
Motzer et al.	2021	78	3	RCC	Pembrolizumab + lenvatinib	Everolimus + lenvatinib / sunitinib	57	355	35 (E + L) / 15 (S)	357 (E + L) / 357 (S)
Rodriguéz-Abreu et al.	2021	79	3	Non-squamous NSCLC	Pembrolizumab + pemetrexed + platinum	Platinum + pemetrexed + placebo	5	410	1	206

Table 1 (continued)

Author	Year	REF	Phase	Malignancy	Treatment arm	Control arm	N events (Treatment arm)	N of patients (Treatment arm)	N events (Control arm)	N of patients (Control arm)
Awad et al.	2021	80	2	Non-Squamous NSCLC	Pembrolizumab + chemotherapy	Chemotherapy	5	60	2	63
Colombo et al.	2021	81	3	Cervical cancer	Pembrolizumab + chemotharapy + bevacizumab	Placabo + chemotherapy + bevacizumab	2	307	1	309
Powles et al.	2021	82A	3	UC	A) Pembrolizumab + chemotherapy B) pembrolizumab	Chemotherapy	3	347	1	342
Powles et al.	2021	82B	3	UC	A) Pembrolizumab + chemotherapy B) pembrolizumab	Chemotherapy	2	304	1	342
Sun et al.	2021	83	3	Oesophageal cancer	Pembrolizumab + chemotherapy	Placebo + chemotherapy	0	370	1	370
Winer et al.	2021	84	3	TNBC	Pembrolizumab	Chemotherapy	11	312	5	310
Lu et al.	2021	85	3	NSCLC	Tislelizumab + chemotherapy	Chemotherapy	6	223	1	111
Ribas et al.	2013	86	3	Melanoma	Tremelimumab	Chemotherapy	11	328	8	327

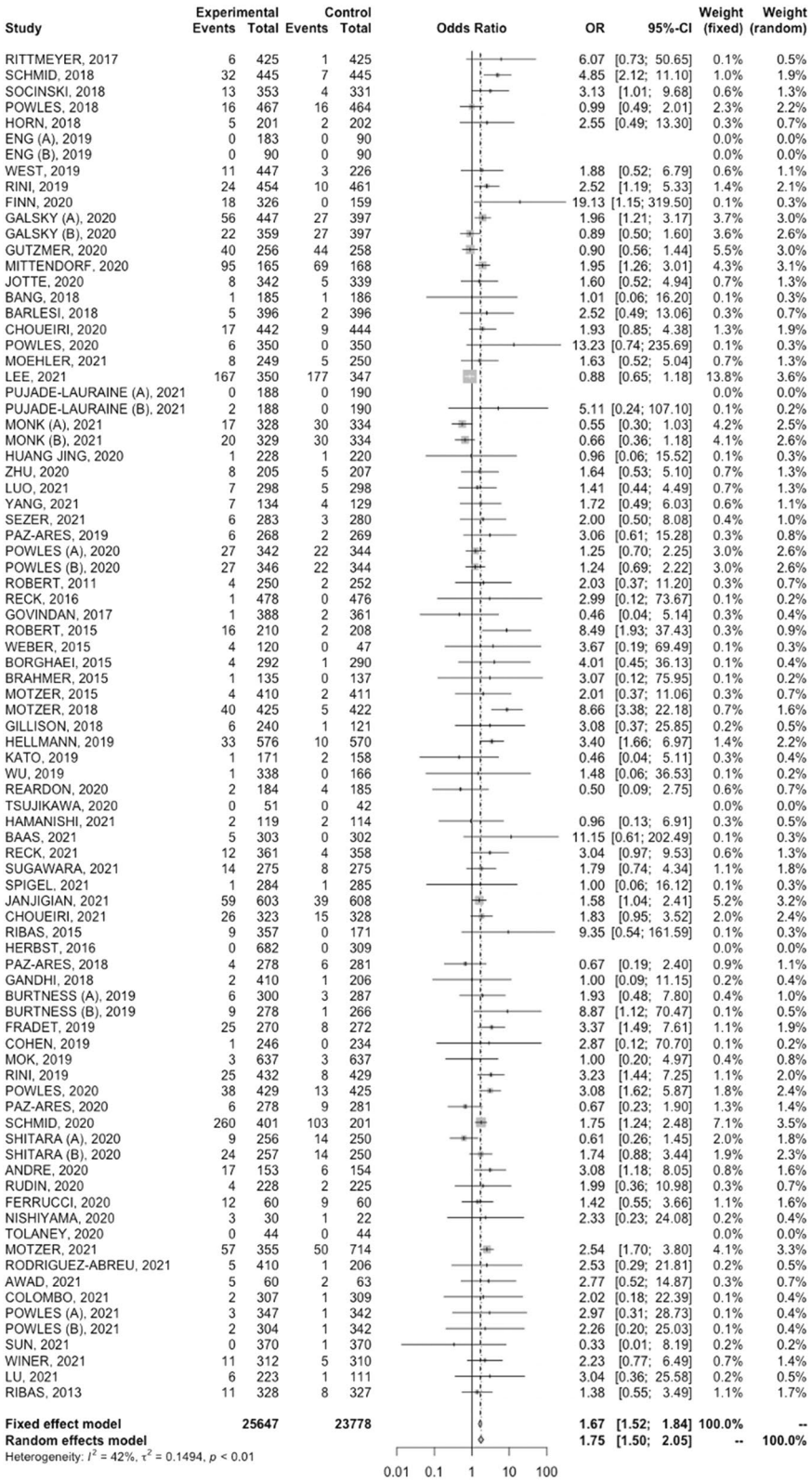

Fig. 2 Forest plot of comparison between immunotherapy alone and immuno-combinations versus control arms in cancer patients; the outcome (Effect Size) was odds ratio (OR) of complete response (CR) rate. *Abbreviations: CI: confidence interval; OR: odds ratio*

UC

For 6536 UC patients receiving ICIs (n = 3262) versus control treatment (n = 3274), the pooled OR for CR rate was 1.51 (95% CI, 1.19–1.91). The analysis was conducted according to fixed-effect model, due to low heterogeneity observed ($I^2 = 30\%$).

Melanoma

Higher CR rate was reported in melanoma patients treated with immunotherapy (n = 1581) compared with control (n = 1323) treatments (OR, 1.45; 95% CI, 1.03–2.03). A fixed-effect model was used due to heterogeneity lower than 50% (I^2 of 48%).

Discussion

The introduction of ICIs and ICI-based combination therapies into clinical practice has been an undoubted breakthrough in the treatment of cancer patients [87–89]. In particular, ICIs have been suggested to induce durable and robust anticancer responses in an important proportion of patients, and even CR, in selected cases [90–92]. Of note, although several case reports have been published in recent years, the likelihood of achieving a CR in cancer patients treated with immunotherapy has not been systematically determined [93–95].

Achieving the cure is the Holy Grail of anticancer treatment for metastatic disease, and CR is independently associated with improved survival in several solid tumors. Therefore, it is fundamental to assess the probability of achieving CR with ICIs, and whether the use of immunotherapy would increase CRs in cancer patients. At the same time, several questions regarding modern immunotherapy remain unanswered. Among these, ICIs present a specific set of treatment-related toxicities, which are commonly called as immune-related adverse events (irAEs) and are due to the erroneous activation of the immune system against self-antigens [96, 97]. Several organ systems may be affected by irAEs, with the incidence and severity of irAEs depending on multiple factors, including the type of ICI, the tumor type, and the disease setting, and some studies have also associated irAEs with anticancer response, and even CR [98]. On the other side, patients achieving CR could stop therapy without compromising clinical outcomes and, in this way, by minimizing toxicities and treatment-related costs. However, few clinical trials have specifically addressed this crucial point, and available data are limited on potential predictors of CR and patient disposition after ICIs discontinuation following CR; the mechanisms underlying durable CR certainly require further investigation. Another fundamental issue in current and future cancer immunotherapy is the identification of reliable biomarkers of response or resistance. In fact, despite ICIs seem to have found their role in several tumors in monotherapy or as part of combinatorial strategies, the lack of validated biomarkers of response represents an important issue since only a proportion of cancer patients benefit from immunotherapy [99–101]. Based on these premises, a greater understanding of the role of potential biomarkers including programmed death ligand 1 (PD-L1) expression, tumor mutational burden (TMB), microsatellite instability (MSI) status, gut microbiota, concomitant medications, and several others, and their association with CR, is of great importance [102–104]. In addition, clinical trials on cancer immunotherapy frequently differ in terms of drugs, patients, designs, and inconsistent clinical outcomes, including CR rate.

To the best of the authors' knowledge, our study represents the first study-level meta-analysis in the literature to systematically assess the probability to achieve CR in cancer patients receiving ICIs. In MOUSEION-03, 49,425 patients from 85 clinical trials were included in the analysis. Higher CR rate was reported in cancer patients treated with immunotherapy compared with control treatments as well as in those receiving chemo–immunotherapy versus control treatments. Of note, the highest CR rate was observed with the dual checkpoint blockade through the combination of two ICIs (OR 3.56, 95% CI 1.28–9.90).

The effectiveness of anticancer treatment depends on a plethora of elements, including the indication for which a specific agent is used, as well as the biology of the disease itself, the setting and line of treatment. According to our results, ICI-based treatment was associated with a higher likelihood of achieving CR in patients affected by the most common malignancies included in the current study. In NSCLC patients OR was 2.0 (95% CI, 1.5–2.65), in RCC 2.4 (95% CI, 1.55–3.72), in UC 1.51 (95% CI, 1.19–1.91), and in melanoma 1.45 (95% CI, 1.03–2.03). Our results are consistent with the observations which have been previously reported by several authors, including those highlighted by Li and colleagues, who assessed the chance of obtaining CR in 4803 NSCLC patients enrolled in 9 randomized controlled trials [105]. Compared to systemic chemotherapy, ICI-based treatment was associated with higher possibility of archiving CR in this study (RR 2.89, 95% CI: 1.44–5.81, P = 0.003) [105].

Our analysis presents some strengths, including the quality of statistical analysis and the selection of the most updated results of clinical trials including a large sample size (49,425 cancer patients treated with ICIs—immunotherapy = 25,647; control = 23,778). However, some limitations should be acknowledged. First, this is a study-level meta-analysis based on pooled data, and thus, the potential presence of confounding factors and single-patient variables

(e.g., patient age, comorbidities, concomitant medications, etc.) was not included. In addition, despite random-effects modeling was performed to address heterogeneity among clinical trials, some analyses were associated to substantial heterogeneities. This issue is particularly relevant for analyses regarding RCC, UC, and melanoma (59%, 30%, and 48%, respectively), and I^2 was used to test heterogeneity. Of note, all statistical tests to assess heterogeneity are weak—including I^2 —and the clinical implications of this issue are considerable and should be examined on a case-by-case basis; in particular, the perception of statistical heterogeneity as well as homogeneity is often involved in influencing clinicians in important decision. In fact, at the same time, lack of evidence of heterogeneity is not evidence of homogeneity and putting too much trust in homogeneity of effects itself may give a false sense of reassuring the "one fits all." Thus, our results must be interpreted cautiously. Lastly, most of the included studies were industry funded, and thus, were prone to reporting bias; all the immunotherapeutic agents present different and not superimposable features, and thus, this element may have introduced some bias. In addition, not all studies included central response assessment.

Conclusions

In recent years, immunotherapy has shown outstanding efficacy in pan-tumors, and an impressive number of clinical trials of ICIs has been published. In the MOUSEION-03, we conducted an updated and comprehensive meta-analysis enrolling a large sample size with the aim of assessing CR rate in cancer patients receiving immunotherapy versus control treatment. We obtained data from 85 identified international trials and almost 50.000 patients were included in our analysis, which showed that immunotherapy may confer therapeutic advantages in several settings and varying on multiple factors, including primary tumor site as well as the use of ICIs as monotherapy or as part of combinatorial strategies.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00262-022-03349-4.

Acknowledgements Fernando Sabino Marques Monteiro has received research support from Janssen, Merck Sharp and Dhome and honoraria from Janssen, Ipsen, Bristol Myers Squibb and Merck Sharp and Dhome. All unrelated to the present paper. Andrey Soares has received honoraria: Janssen, Pfizer, Bayer, Novartis, AstraZeneca, Astellas Pharma, Pierre Fabre, Merck Serono, Sanofi,Roche, Ipsen, Zodiac. Consulting or Advisory Role: Astellas Pharma, Janssen, Roche, Bayer, Lilly, AstraZeneca, Novartis, MSD, Bristol Myers Squibb, Zodiac, Amgem, Ipsen, United, Zodiac. Research Funding: Bristol Myers Squibb (Inst), Astellas (Inst), AstraZeneca (Inst). Travel, Accommodations, Expenses: AstraZeneca,Pfizer, AstellasPharma, Bristol Myers Squibb, Bayer, Roche, Janssen, Merck Serono, Sanofi, Ipsen, Zodiac. Enrique Grande has received honoraria for speaker engagements, advisory roles or funding of continuous medical education from Adacap, AMGEN, Angelini, Astellas, Astra Zeneca, Bayer, Blueprint, Bristol Myers Squibb, Caris Life Sciences, Celgene, Clovis-Oncology, Eisai, Eusa Pharma, Genetracer, Guardant Health, HRA-Pharma, IPSEN, ITM-Radiopharma, Janssen, Lexicon, Lilly, Merck KGaA, MSD, Nanostring Technologies, Natera, Novartis, ONCODNA (Biosequence), Palex, Pharmamar, Pierre Fabre, Pfizer, Roche, Sanofi-Genzyme, Servier, Taiho, and Thermo Fisher Scientific. EG has received research grants from Pfizer, Astra Zeneca, Astellas, and Lexicon Pharmaceuticals. Francesco Massari reports personal fees from Astellas, BMS, Janssen, Ipsen, MSD, and Pfizer outside the submitted work.

Author contributions M.S, A.R. and F.M. wrote the main manuscript text. All authors reviewed the manuscript

Funding None to declare.

Declarations

Conflict of interest The authors declare no competing interests.

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