Efficacy of Immune Checkpoint Inhibitors in Rare Tumours: A Systematic Review

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Background: Rare cancers, as defined by the European Union, occur in fewer than 15 out of 100,000 people each year. The International Rare Cancer Consortium defines rare cancer incidence as less than six per 100,000 per year. There is a growing number of reports of the efficacy of immune checkpoint inhibitor (ICI) therapy in patients with rare tumours, and hence, we conducted a comprehensive review to summarise and analyse the available literature.

Methods: A literature search of PubMed was performed on January 31, 2021, using the following ICI names as keywords: ipilimumab, tremelimumab, cemiplimab, nivolumab, pembrolizumab, avelumab, atezolizumab, and durvalumab. Studies on patients with rare tumours who were being treated with ICIs were included. We plotted the overall response rate against the corresponding median survival across a variety of cancer types using linear regression.

Results: From 1,255 publications retrieved during the primary search, 62 publications were selected (with a total of 4,620 patients). Only four were randomised trials. A minority were first-line studies, while the remaining were studies in which ICIs were delivered as salvage therapy in pretreated patients. There was a good correlation between response rate and overall survival (Spearman R² >0.9) in skin cancers, mesothelioma, and sarcomas. Studies on patients with rare tumours who were being treated with ICIs were included. We plotted the overall response rate against the corresponding median survival across a variety of cancer types using linear regression.

Conclusions: Treatment of advanced-stage rare tumours with ICI therapy was found to be associated with significant activity in some orphan diseases (e.g., Merkel cell carcinoma) and hepatocellular carcinoma. Several ongoing prospective clinical trials will expand the knowledge on the safety and efficacy of ICI therapy in patients with these rare cancers.

Keywords: immunotherapy, rare tumours, systematic review, survival, anti-PD-(L)1 agents
INTRODUCTION

In the European Union (EU), rare cancers are defined as those with an incidence of less than six per 100,000 people per year. The Surveillance of Rare Cancers in Europe (RARECARE) project calculated that around four million people in the EU are affected by rare cancers and estimated the annual incidence rate of all rare cancers in Europe as about 108 per 100,000 people, corresponding to one-quarter of all malignancy diagnoses. A list of RARECARE cancers has been identified based on the above epidemiological criterion (1). The Information Network on Rare Cancers (RARECAREnet) project integrates any updated epidemiological information about rare cancers in the EU and provides indicators at the country level and time trends, studying to what extent treatment is centralised in Europe.

Rare cancers are a heterogeneous group of almost 200 cancers with a 5-year survival rate lower than that of more common cancers (49% versus 63%) (2). Beyond the influence of classical prognostic factors such as age, stage, or performance status, the prognosis of patients with rare malignancies is affected by additional factors. These include a lack of medical expertise or insufficient evidence-based guidelines in managing these diseases and difficulties in conducting clinical trials with sufficient statistical power due to the low number of patients affected (3).

Furthermore, rare cancers often display intrinsic biological characteristics that may differ from their “common” counterparts and are generally poorly studied. Therefore, rare cancers are also neglected in terms of pharmaceutical research, which translates into fewer therapeutic options for affected patients.

In the past few years, immune checkpoint inhibitors (ICIs) have revolutionised the therapeutic approach to different haematological and solid malignancies, and their efficacy has recently been explored in the rare cancer setting (4). However, the extent of the actual clinical benefit and the strength of the cumulative evidence are largely elusive or contradictory. This could result in misleading conclusions that immunotherapy is futile for some rare cancers and ultimately hamper the future development of immunotherapy trials and the identification of predictive factors in this setting.

Herein, we conducted and reported on a systematic review of the literature on the role of ICIs in patients with rare solid cancers.

MATERIALS AND METHODS

This systematic review was performed following the 2020 Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guideline. We performed a literature search using PubMed and Embase on January 31, 2021, with the following keywords to identify all studies that reported the efficacy of ICIs in patients affected by rare solid tumours: phase 2, phase 3, ipilimumab, tremelimumab, cemiplimab, nivolumab, pembrolizumab, avelumab, atezolizumab, and durvalumab. Four investigators from two different institutions (FP, AG, FC, and SG) independently screened published articles and meeting abstracts. The inclusion criterion was that the studies described patients with rare solid tumours treated with ICI therapy for advanced stage cancer. The exclusion criteria were haematological malignancies, phase 1 studies, conference abstracts, and a lack of evaluation of ICI therapy. Data extracted by the four authors were the type of disease, the number of patients, treatment, line of therapy, median follow-up, overall response rate (ORR), median progression-free survival (PFS), and overall survival (OS). For inclusion, rare cancers had to belong to the classification reported by RARECAREnet (http://rarecarenet.istitutotumori.mi.it/fact_sheets.php, last accessed December 12, 2020). OS was plotted against ORR, and a linear regression model was fitted. A Spearman correlation coefficient R² value of 0.70 or greater was considered a strong correlation, and an R² value between 0.50 and 0.70 was considered a moderate correlation.

We used descriptive statistics to summarise the study findings. Statistical calculations were performed using Microsoft Excel.

RESULTS

From 1,255 publications retrieved during a primary search, 62 were selected for this study (including 4,620 patients: Figure 1) (1, 4–64). Patient characteristics are listed in Table 1. Papers were published between 2013 and 2021. The included studies focussed on the following conditions: skin cancers [n = 14; non-cutaneous melanoma, cutaneous squamous cell carcinoma (SCC) and Merkel cell carcinomas (MCC)], rare thoracic tumours (n = 13; mainly mesothelioma), endocrine malignancies (n = 11), hepatobiliary cancers (n = 10), sarcomas (n = 9), testicular cancers (n = 3), and salivary gland tumours (n = 2). All were phase 2 (single-arm) studies, except six that were randomised trials (n = 3 phase 2 and n = 3 phase 3) and two that were phase 1b or both phases 1b and 2 studies. One publication was a pooled analysis of various studies that included nivolumab. Most of the trial arms included single agents (n = 41); doublets of ICIs or ICIs + other agents were included in 21 trials. Only a minority were first-line studies, while the remaining were studies in which ICIs were delivered as salvage therapy in pretreated patients. None were biomarker-driven studies.

Skin Cancers

Most data on the use of ICIs in skin cancer were derived from studies on SCCs [n = 4 studies (5, 26, 29, 30)] and MCCs [n = 3 studies (19, 32, 53)]. The ORRs were >40% and 60%, respectively, when ICIs were used as first-line treatment in both cancers. Survival data were from the early stages, or median outcomes had not been reached. In these two settings, ICIs largely replaced the previous standard of care in locoregional or distant relapses (e.g., radiotherapy or cisplatin-based chemotherapy).

Immunotherapy was also explored in extracutaneous melanomas, such as mucosal or uveal melanomas (n = 7 studies). Data from a pooled analysis confirmed fair activity in
mucosal melanoma of nivolumab alone or with ipilimumab (ORR of 23% and 37%, respectively). Conversely, ICIs demonstrated limited activity in uveal melanoma, with a median PFS of a few months (61).

**Hepatobiliary Cancers**

Hepatocellular carcinoma (HCC) has been a popular target for ICI therapy investigations over the last years. At least four phase 2 studies explored pembrolizumab and nivolumab after first-line failure (sorafenib), with a mean ORR, median PFS, and OS of about 20% (range, 18–22%), 4.5 months (range, 3–6.9), and 12.2 months (range, 8.2–13.9), respectively (10, 39, 42, 49). A phase 3 study also established atezolizumab + bevacizumab, the new standard first-line therapy in advanced HCC (11). Biliary tract cancers (BTCs) were also included in phase 2 studies investigating ICIs; however, preliminary data were unsatisfactory, with few response rates and median PFS and OS not reported (9, 17, 21, 22).
| Author/year       | Type of tumor                          | Type of study/median follow up (months) | Treatment | Line of therapy | No. of patients | ORR (%) | Median PFS (months; 95%CI) | Median OS (months; 95%CI) | Main AEs (>5%) |
|-------------------|----------------------------------------|----------------------------------------|-----------|----------------|----------------|----------|--------------------------|--------------------------|----------------|----------------|
| Highly responsive tumours (response rate >20%; median PFS >6 months; median OS > 12–24 months) |
| **skin cancers and non-cutaneous melanoma** |
| D’Angelo/2018 (54) | Merkel cell carcinoma                  | Phase 2/5.1                             | AVE       | 1st            | 39             | 62.1     | 9.1 (–)                 | –                        | NR             |
| D’Angelo/2017 (52) | Mucosal melanoma                       | Pooled analysis/157                     | NIVO/NIVO + IPI/IPI | Various       | 157            | 23.3 vs. 37.1 vs. 8.3 (2.8–5.4) vs. 2.7 (2.6–2.8) | –                        | Fatigue, diarrhoea, rash |
| Johnson/2019 (15)  | Uveal melanoma                         | Phase 2/11.1                            | PEMBRO    | Advanced       | 5              | 20       | 11.0 (–)                | –                        | nR             |
| Joshua/2015 (16)   | Uveal melanoma                         | Phase 2/11                              | TREME     | Advanced       | 11             | 0        | 2.9 (2.8–3.0)           | 12.8 (3.8–19.7)          | Nausea, diarrhoea, pain |
| Kaufman/2018 (19)  | Merkel cell carcinoma                  | Phase 2/16.4                            | AVE       | Pretreated     | 88             | 33       | 2.7 (1.4–6.9)           | 12.9 (7.5–nr)            | NR             |
| Maubec/2020 (26)   | SCC                                     | Phase 2/22.4                            | PEMBRO    | 1st            | 39             | 41       | 6.7 (–)                 | 25.3 (14.2–ne)           | Fatigue, diarrhoea, hypothyroidism |
| Migden/2018 (30)   | SCC                                     | Phase 2/7.9                             | CEMI      | Advanced       | 59             | 47       | –                        | –                        | –              |
| Migden/2020 (29)   | SCC                                     | Phase 2/9.3                             | CEMI      | Advanced       | 78             | 44       | –                        | –                        | –              |
| Naing/2020 (5)     | Mucosal, acral and uveal melanoma      | Phase 2                                 | NIVO      | Pretreated     | 221            | –        | –                        | 11.5 (6.4–15.0; mucosal) | Fatigue, rash, hypothyroidism, diarrhoea |
| Nghiem/2019 (32)   | Merkel cell carcinoma                  | Phase 2/14.9                            | PEMBRO    | 1st            | 50             | 56       | 18.8 (4.6–ne)           | 12.0 (3.5–nr)            | Hypothyroidism, pneumonia |
| Nomura/2020 (33)   | Mucosal melanoma                       | Phase 2/18                              | NIVO      | Advanced       | 20             | 23.5    | 1.4 (1.2–2.6)           | 11.5 (6.4–15.0; mucosal) | Pruritus, rash |
| Schadendorf/2019   | Mucosal, acral and uveal melanoma      | Phase 2/14.3                            | NIVO      | Pretreated     | 221            | –        | –                        | 25.8 (15.1–30.6; mucosal) | Skin endocrine and gastrointestinal |
| Zimmer/2015 (50)   | Uveal melanoma                         | Phase 2/–                               | IPI       | Advanced       | 34             | 0        | 2.8 (2.5–2.9)           | 6.8 (3.7–8.1)            | Diarrhoea, AST, ALT |
| **Gastrointestinal cancers** |
| El-Khoueiry/2017 (63) | HCC                                  | Phase 2/–                               | NIVO      | 1st–2nd        | 113^            | 23 & 22 | 5.4 (3.9–8.5) & 4.0 (2.6–6.7) | 8.5 (5.0–12.5)            | Rash, AST increase, pruritus |
| Feng/2020 (9)      | Biliary                                | Phase 2/12.8                            | CDDP + GEM + NIVO | 1st–2nd       | 32             | 55.6    | 6.1 (3.4–8.2)           | 13.0 (7.0–nr)            | Nausea, neutropenia, fatigue |
| Feun/2019 (10)     | HCC                                    | Phase 2/17                              | PEMBRO    | 1st–2nd        | 29             | 32       | 4.5 (2.0–7.0)           | 13.0 (7.0–nr)            | Rash, fatigue, ALT and bilirubin |
| Finn/2020 (1)      | HCC                                    | Phase 3/13.8                            | PEMBRO    | Pretreated     | 413            | 18.3 vs. 4.4 | 3.0 (2.8–4.1) vs. 2.8 (2.5–4.1) | 13.9 (11.6–16) | Hyperthension, fatigue and proteinuria |
| Finn/2020 (11)     | HCC                                    | Phase 3/8.8                             | ATEZ + BEV vs. sorafenib | 1st         | 501            | 27.3 vs. 11.9 | 6.8 (5.7–8.3) vs. 4.3 (4.0–6.8) | 13.2 (10.4–nr) | Colitis, fever, abdominal pain |
| Boileve/2020 (17)  | Biliary                                | Phase 2/9.8                             | DURVA + TREME ± pacitinaxel | NIVO       | Pretreated     | 20             | 5        | –                        | –                        | Alkaline phosphatase |
| Kim/2020 (20)      | Biliary                                | Phase 2/12.4                            | NIVO      | Pretreated     | 54             | 11°      | 3.6 (2.3–5.6)           | –                        | –              |

(Continued)
### TABLE 1 | Continued

| Author/year | Type of tumor | Type of study/median follow up (months) | Treatment | Line of therapy | No. of patients | ORR (%) | Median PFS (months; 95% CI) | Median OS (months; 95% CI) | Main AEs (>5%) |
|-------------|--------------|----------------------------------------|-----------|-----------------|-----------------|---------|-----------------------------|-----------------------------|------------------|
| Klein/2020  | Biliary      | Phase 2/–                              | NIVO + IPI → NIVO TREME | Pretreated      | 39              | 23                  | 2.9 (2.2–4.6)               | 5.7 (2.7–11.9)   | lymphopenia, AST ↑, fatigue NR |
| Sangro/2013 | HCC          | Phase 2/–                              | NIVO      | Pretreated      | 17              | 17.6                | 6.4 (3.9–9.1) TTP            | 8.2 (4.6–21.3)   | Rash, fatigue, anorexia |
| Zhu/2018    | HCC          | Phase 2/12.3                           | PEMBRO    | 2nd             | 104             | 17                  | 4.9 (3.4–7.2)               | 12.9 (9.7–15.5)  | Fatigue, pruritus, diarrhoea |
| **Thoracic cancers** |             |                                       |           |                 |                 |                     |                             |                             |                  |
| BaaS/2021   | Mesothelioma (pleural) | Phase 3/29.7                        | NIVO + IPI vs. CT | 1st line      | 713             | 40 vs. 43           | 6.8 (5.6–7.4) vs. 7.2 (6.9–8) | 18.1 (16.8–21.4) vs. 14.1 (12.4–16.2) | NR |
| Calabrò/2015| Mesothelioma (pleural) | Phase 2/21.3                       | TREME    | Pretreated      | 29              | 3.4                  | 6.2 (5.7–6.7)               | 11.3 (9.4–19.2)   | NR |
| Calabrò/2018| Mesothelioma (pleural) | Phase 2/19.2                       | TREME + DURVA PEMBRO | 1st–2nd line | 40              | 25                   | 5.7 (1.7–9.7)               | 16.6 (13.1–20.1) | Skin, gastrointestinal, Hepatitis, myocardiitis, myasthenia gravis |
| Cho/2018    | Thymic carcinoma/thymoma | Phase 2/14.9                      | PEMBRO    | Pretreated      | 33              | 21                   | 6.1 (5.3–6.9)               | 14.9 (–) *         | Infusion reactions, fatigue, skin disorders |
| Disselhorst/2019 | Mesothelioma (pleural) | Phase 2/14.3                       | NIVO + IPI | Pretreated      | 36              | 29                   | 6.2 (4.1–nr)               | nr                 |                  |
| Giaconne/2018| Thymic carcinoma | Phase 2/20                       | PEMBRO    | Pretreated      | 40              | 22.5                | 4.2 (2.9–10.3)              | 24.9 (15.5–nr)    | Fatigue, AST and ALT ↑ |
| Katsuyla/2019| Thymic carcinoma | Phase 2/14.1                      | NIVO      | Pretreated      | 15              | 0                    | 3.8 (1.9–7.0)               | 14.1 (11.1–nr)    | Hypoalbuminemia, anemia |
| Kim/2020    | NSCLC (sarcomatoid) | Phase 2/12                        | DURVA + TREME | Pretreated (61%) | 18             | 26.7                 | 5.9 (1.9–11.9)              | 15.4 (11.1–nr)    | Rash, pruritus, pneumonitis |
| Maio/2018   | Mesothelioma (pleural 95%) | Phase 2b/–                       | DURVA + TREME | Pretreated (61%) | 382            | 4.5                  | –                              | 7.7 (8.8–9.9)     | Diarrhoea, dyspnoea, anorexia |
| Nowak/2020  | Mesothelioma (pleural) | Phase 2/28.2                     | CDDP + PEME + DURVA NIVO | 1st–3rd line | 54             | 48                   | 7.0 (5.7–9.0)               | 18.4 (13.1–24.8) | Constipation, fatigue, nausea |
| Okada/2019  | Mesothelioma (pleural) | Phase 2/16.8                      | NIVO      | 2nd–3rd line    | 34              | 29                   | 6.1 (2.9–9.9)               | 17.3 (11.5–nr)    | Infection, weight increase |
| Quispel–Janssen/2018 | Mesothelioma (pleural) | Phase 2/27.5                      | NIVO      | Pretreated      | 34              | 24                   | 2.6 (2.2–5.4)               | 11.8 (9.7–15.7)  | NR |
| Scherpereel/2019 | Mesothelioma (pleural) | Random phase 2/20.1              | NIVO vs. NIVO + IPI | Pretreated      | 125             | 19 vs. 28            | 4.0 (2.8–5.7) vs. 5.6 (3.1–8.3) | 11.9 (6.7–17.7) vs. 15.9 (10.7–nr) | Stomatitis, artritis, AST, ALT ↑ |
| **Moderately-poorly responsive tumors (response rate <20%; median PFS <3–6 months; median OS <12–24 months)** | | | | | | | | | |
| Rodriguez/2020 | Salivary gland | Phase 2/13.1                      | PEMBRO + vorinostat PEMBRO ± RT | Advanced | 25         | 16                   | 6.9 (4.1–nr)               | 14.0 (8.5–nr)    | Creatinine ↑, fatigue |
| Mahmood/2021 | Salivary gland | Phase 2/19.8                      | PEMBRO PEbrO | Advanced | 20         | 0                    | 4.5 (2.4–20.6) vs. 6.6 (2.4–13.1) | nr vs. 27.2 (22.9–nr) | NR |
| **Sarcomas** | | | | | | | | | |
| Ben-Hami/2017 | Sarcoma (uterine) | Phase 2/–                         | NIVO      | Pretreated      | 12              | 0                    | 1.8 (0.8–nr)               | nr                 | Reported only rare SAEs |
| D’Angelo/2018 | STS          | Random phase 2/13.6              | NIVO vs. NIVO + IPI PEMBRO + T-VEO | Pretreated | 85             | 5 vs. 16             | 1.7 (1.4–4.3) vs. 4.1 (2.6–4.7) | 10.7 (5.5–15.4) vs. 14.3 (9.6–nr) | Anorexia, fatigue, dyspnoea |
| Kelly/2020   | STS          | Phase 2/14                       | PEMBRO + T-VEO | Pretreated | 20            | 30                   | 4.1 (3.0–nr)               | 18.6 (12.2–nr)    | NR |
| Le Cesne/2019 | Osteosarcoma | Phase 2/18.9                     | PEMBRO + mCTX IPI | Pretreated | 17           | 6.7                  | 1.4 (1.0–1.4)              | 5.6 (2.1–12.1)   | Nausea, anaemia, fatigue |
| Maki/2013    | Synoval sarcoma | Phase 2/–                        | NIVO      | Pretreated      | 6              | 0                    | 1.8 (0.4–2.1) TTP          | 8.7 (0.7–19.7)   | Alkaline phosphatase, bilirubin ↑ |

(Continued)
| Author/year | Type of tumor | Type of study/median follow up (months) | Treatment | Line of therapy | No. of patients | ORR (%) | Median PFS (months; 95% CI) | Median OS (months; 95% CI) | Main AEs (>5%) |
|------------|--------------|----------------------------------------|-----------|----------------|----------------|---------|-----------------------------|-----------------------------|----------------|
| Tamura/2019 (4) | STS | Phase 2/10.2 | NIVO | Pretreated | 21 | 0 | 1.4 (1.4–2.8) | ne (10.8–ne) | Pruritus, hypothyroidism, AST, ALT ↑ |
| Tawbi/2017 (44) | STS | Bone sarcoma | PEMBRO | Pretreated | 80 | 18 | 4.5 (2.0–5.2) vs. 2.0 (1.7–2.2) | 12.2 (8.5–18.2) vs. 13.0 (10.0–18.0) | Only rare SAE reported |
| Toulmonde/2018 (45) | STS (various) | Phase 2/6.8 | PEMBRO + mCTX | Advanced | 50 | 2 | 1.4 (1.1–4.0) vs. 1.4 (0.9–4.0) vs. 1.4 (0.9–5.3)** | 9.2 (2.4–15.9) vs. 5.6 (3.2–16.1) vs. 7.1 (2.0–16.3) vs. nr** | NR |
| Wilky/2019 (47) | STS | Phase 2/14.7 | PEMBRO + axitinib | Pretreated | 33 | 25 | 4.7 (3.0–9.4) | 18.7 (12.0–nr) | Fatigue, mucositis, thyroid dysfunction |
| **Male urological cancers** | | | | | | | | | |
| Adra/2018 (6) | Germ-cell | Phase 2/ | PEMBRO | Pretreated | 12 | 0 | – | – | Fatigue, nausea, vomiting |
| Mego/2019 (27) | Germ-cell | Phase 2/2.6 | AVE | Pretreated | 8 | 0 | 0.9 (0.5–1.9) | 2.7 (1.0–3.3) | NR |
| Necchi/2019 (31) | Germ-cell | Phase 2/7.5 | DURVA vs. DURVA + TREME | Advanced | 22 | 9.1 | – | – | NR |
| **Endocrine and neuroendocrine tumors** | | | | | | | | | |
| Capdevila/2020 (58) | Thyroid (anaplastic) | Phase 2/ | SPARTA | Advanced | 42 | 19 | 1.7 (1.2–1.9) | 5.9 (2.4–nr) | Diarrhoea, pruritus, fatigue |
| Carneiro/2019 (55) | Adrenocortical carcinoma | Phase 2/ | NIVO | Pretreated | 10 | 10 | 1.8 (0.1–4.3) | 21.2 (0.1→25.6) | Rash, fatigue |
| Chintakuntlawar/2019 (48) | Thyroid (anaplastic) | Phase 2/ | CTRT + PEMBRO | 1st | 3 | – | – | 2.7 (∼) | Pneumonitis |
| Habra/2019 (13) | Adrenocortical carcinoma | Phase 2/ | PEMBRO | Pretreated | 14 | 14 | – | – | Fatigue, rash, hypothyroidism |
| Klein/2020 (56) | NET | Phase 2/ | IPI + NIVO | Pretreated | 29 | 24 | 4.8 (2.7–10.5) | 14.8 (4.1–21.3) | Diarrhoea, fatigue, pruritus |
| LeTourneau/2018 (65) | Adrenocortical carcinoma | Phase 2/ | AVE | Pretreated | 50 | 6 | 2.6 (1.4–4.0) | 10.6 (7.4–15) | Nausea, fatigue, fever |
| Mehnert/2019 (59) | Thyroid (papillary/follicular) | Phase 1b/31 | PEMBRO | Pretreated | 21 | 9 | 7.0 (2.0–14.0) | nr (22.0–nr) | Diarrhoea, fatigue, pruritus, rash, AST, ALT and alkaline |
| Jimenez/2020 (14) | Adrenocortical carcinoma | Phase 2/ | PEMBRO | Pretreated | 15 | 15 | – | – | NR |
| Naing/2020 (5) | Pheochromocytomas/paragangliomas | Phase 2/ | PEMBRO | Pretreated | 9 | 0 | – | – | Phosphatase ↑ |
| Patel/2020 (36) | Non-pancreatic NET | Phase 2/ | IPI + NIVO | Pretreated | 32 | 25 | 4.0 (3.0–6.0) | 11.0 (6.0–nr) | Fatigue, nausea, vomiting |
| Rai/2019 (40) | Adrenocortical carcinoma | Phase 2/17.8 | PEMBRO | Advanced | 39 | 23 | 2.1 (2.0–10.7) | 24.9 (4.2–nr) | AST, ALT ↑, fatigue |
| Vijayvergia/2020 (46) | NET | Phase 2/ | NIVO | Pretreated | 29 | 3.4 | 2.2 (1.5–2.3) | 5.1 (3.2–ne) | AST, alkaline phosphatase ↑, fatigue |

ORR, overall response rate; PFS, progression-free survival; TTP, time to progression; OS, overall survival; CI, confidence interval; SCC, cutaneous squamous cell carcinoma; HCC, hepatocellular carcinoma; NSCLC, non-small-cell lung cancer; STS, soft-tissue sarcoma; NET, neuroendocrine tumor; AVE, avelumab; NIVO, nivolumab; IPI, ipilimumab; PEMBRO, pembrolizumab; TREME, tremelimumab; CEMI, cemiplimab; ATEZO, atezolizumab; DURVA, durvalumab; SPARTA, spartalizumab; BEV, bevacizumab; CTRT, chemoradiotherapy; CDOP, cisplatin + GEM, gemcitabine; PEME, pemtrexed; mCTX, metronomic cyclophosphamide; T-VEC, talimogene laherparepvec; RT, radiotherapy; BSC, best supportive care; nr, not reached; ne, not estimable; –, not reported.

*Thymic carcinoma.
**Three different sarcoma subgroups
*By central review assessment.
*Noninfected patients.
↑Increase the other: followed by.

**Thoracic Cancers**
Eight phase 2 trials (n = 734 patients) evaluated ICIs in pleural mesothelioma (MPM) (8, 24, 28, 34, 35, 37, 38, 43). Only two studies included ICIs as a first-line strategy. Two appropriate therapeutic options have shown promising activity in MPM: the anti-programmed cell death protein 1 (PD-1) antibodies pembrolizumab and nivolumab as single agents, and nivolumab with ipilimumab. The Food and Drug Administration (FDA) has approved nivolumab + ipilimumab for unresectable mesothelioma; the ORR was 29% with nivolumab and ipilimumab. As a first-line approach, a combination of
ICIs (anti-PD1 and anti-CTLA4) was associated with a median OS of 16.6 months. The combination of durvalumab plus cisplatin and pemetrexed demonstrated an ORR of 48% and an OS of 18.4 months. A confirmatory phase 3 study established the combination of nivolumab + ipilimumab as a potential new standard of care for previously untreated patients with MPM (63).

The role of ICIs was also explored in pretreated thymic epithelial tumours. Pembrolizumab showed fair activity, with an ORR of about 20% (12, 51), while no apparent activity was associated with nivolumab (18).

**Sarcomas**

Nine phase 2 studies evaluated ICIs in 324 patients with advanced pretreated sarcomas (including uterine sarcomas and bone sarcomas) (4, 7, 23, 25, 44, 47, 53, 60). ORRs were rare overall, and the median PFS was approximately 1–2 months; however, three trials reported an ORR >10% and a median PFS of more than 3 months. Among the latter, in a combination trial of pembrolizumab and axitinib (n = 33 patients), the ORR was 25% and median PFS and OS were 4.7 (range, 3.0–9.4) and 18.7 [range, 12.0 to not reached (NR)] months, respectively (47). In another trial of pembrolizumab and T-VEC (n = 20 patients), the ORR was 30%, and median PFS and OS were 4.1 (3.0 to NR) and 18.6 (12.2 to NR) months, respectively (60).

**Endocrine Cancers**

Eleven trials evaluated ICIs in 215 patients with endocrine malignancies, including adrenocortical carcinomas (ACC, n = 5), neuroendocrine tumours (NETs, n = 3), thyroid carcinoma (n = 2), and pheochromocytomas/paragangliomas (PCPG, n = 1) (5, 36, 40, 46, 48, 55, 56, 58, 59).

In the ACC setting, three ICI agents (i.e., avelumab, nivolumab, and pembrolizumab) were evaluated in pretreated patients. ORR ranged from 6% to 23%. Median PFS was below 3 months, and OS ranged from 21 to 24 months. Nine patients with pheochromocytomas/paragangliomas were treated as a subcohort in one trial with pembrolizumab. No responses were observed, and the median PFS and OS were 5.9 and 17 months, respectively.

Three studies explored the role of ICIs in 90 patients with NETs. Anti-PD1 monotherapy with pembrolizumab was associated with lower ORRs than combo-immunotherapy with nivolumab-ipilimumab (3.4% versus 25%).

Only three patients with anaplastic carcinoma of the thyroid were included in a phase 2 trial of chemo-immunotherapy with pembrolizumab. No responses were observed, and the median OS was <3 months.

**Other Cancer Types**

Salivary gland carcinomas are putative targets for ICIs (41). In a phase 2 trial, pembrolizumab + vorinostat was associated with a median OS of 14 months (ORR of 16%). No activity was reported with ICIs in anaplastic or differentiated thyroid cancer or with pembrolizumab + radiotherapy in adenoid cystic carcinoma.

**Correlation of ORR With OS**

A significant and good linear correlation was observed between the ORR and OS (Figure 2). The Spearman correlation coefficient was 0.69, indicating that about 70% of outcomes could be driven by tumour response. According to the calculations for various diseases, this correlation was very high for skin cancers (R^2 = 0.98), mesotheliomas (R^2 = 0.97), and sarcomas (R^2 = 0.93), moderate for endocrine neoplasm (R^2 = 0.65) and poor (R^2 = −0.14) for hepatobiliary cancers. This correlation was similar both in highly responsive disease (e.g., skin cancers) and in hard-to-treat cancers (e.g., sarcomas, head and neck or endocrine neoplasm) where R^2 were 0.7 and 0.66, respectively. This means that disease shrinkage may be useful when drug are screened for rare tumours clinical trials.

**DISCUSSION**

In this study, we conducted a systematic review of published studies with full-text outcome data that explored the efficacy of ICIs in rare solid tumours.

More than 60 trials with different ICIs in rare cancers were conducted over 7 years between 2013 and 2021, with most trials published in the last 3 years (2018–2021). Our search identified 17 groups of rare neoplasms treated in most cases in patients with advanced and pretreated diseases. Our principal objective was to determine the objective response rate in this setting rather than the survival endpoints that are influenced by several variables for each neoplasm. It is worth noting that most of the studies included here were small phase 2 trials in which OS was not reached or the primary endpoint.

A first observation from our analysis is that the ORR varied widely, from 0% to 60%, with a slightly lower median rate of 20% among all groups of rare cancers. This indicates that the ORR obtained with ICIs in rare cancers does not significantly differ from that of more common neoplasms. Among the rare cancer types that displayed response rates higher than 25% were MCC, SCC of the skin, mesothelioma, BTCs, and some NETs.

The analysis of survival endpoints was not as informative as that of ORR. This was partly because these data were not based on the primary endpoints of the corresponding trials or were not reported. In general, PFS did not significantly exceed 6 months in all trials and all groups (except two trials in MCC), with the poorest PFS rates observed in patients with sarcomas, germ cell tumours, and adrenal neoplasms, in which median PFS was below 3 months. Rates of PFS and OS were found to be aligned with those of each neoplasm in the corresponding setting and, therefore, reflect/represent more the intrinsic clinical course of each disease than definitive immune resistance. Regression of the ORR with OS showed a modest correlation, demonstrating that cancer shrinkage is not a prerequisite for longer survival.

Since the early observation that approximately 20% of patients with cancer respond to immunotherapy with ICIs (67), the prediction of each neoplasm’s responsiveness and each individual patients’ physiology have become central issues in immune oncology. Research initially focused on investigating single biomarkers or pathways potentially involved in response to ICIs, particularly the PD-1-programmed death-ligand 1 (PD-L1) axis, and the extent to which tumour-infiltrating lymphocytes (TILs) are present within cancer tissue (68–70). In the case of PD-L1, such an...
approach led regulatory authorities to approve the clinical use of ICIs in selected cancers (e.g., non-small cell lung cancer) under conditional expression of PD-L1 at different cutoff levels. By contrast, in other neoplasms (e.g., head and neck squamous cell carcinomas), approval was granted regardless of PD-L1 expression, indicating that clinical benefit could be obtained independently of PD-L1 expression or TIL infiltration grade (71).

Second-generation studies focused on tumour mutation burden (TMB) as a measure of the neoantigen load and, therefore, tumour foreignness within the immune system (72). Reclassification of tumours from the The Cancer Genome Atlas (TCGA) datasets did prove a clear relationship between TMB levels and the ORR obtained using ICIs (73). On this basis, new ICIs received approval in an agnostic way for TMB-high tumours (e.g., small cell lung cancer). However, very recent evidence calls for more caution in using high TMB as a universal predictive biomarker for all ICIs and in all cancers (74).

The above-cited studies offer a framework for analysing the results of the ICI immunotherapy trials in rare neoplasms cited in this systematic review. With the highest multiparameter TIG scores are cancers such as MCC and cutaneous SCC—all neoplasms with response rates higher than 30% and up to 62%. At the opposite end of the scale, with the lowest TIG scores, are some rare neoplasms, including ACC, PCPG, soft tissue sarcomas, uveal melanoma, germ cell tumours, and low-grade gliomas. These tumours come from anatomical sites that are considered “immune-privileged” and were all characterised by response rates well below 30% (and down to 0% in many cases) in several different trials. More common cancers, such as prostate and breast carcinomas, also segregate into this subgroup. The intermediate TIG score group includes rare neoplasms, such as BTCs, HCC, mesothelioma, and thymic carcinoma, and other more common neoplasms (e.g., lung, head and neck and renal cell cancers). In our analysis, the ORR of these neoplasms was in the range of 20–45%. This portrait is confirmed by our attempt to link OS with ORR, attaining a strong correlation in skin cancers, mesothelioma, and sarcomas. In these cancers, despite data about OS and ORR being available in only 43 studies, more than 90% of observed...
outcomes may be explained by a durable tumour response as observed in non-melanoma skin cancers and mesothelioma.

There are several limitations associated with our systematic review. First, only a few randomised studies that compared ICIs with standard treatments are available, and a direct comparison was not possible. Second, many confirmatory phase 3 studies are ongoing and were not included in the present review. Third, there was a lack of information regarding predictive biomarkers in many trials, so further knowledge is awaited from ongoing correlative studies.

Based on the present systematic review results and in the absence of final approval for most of these indications, the present data suggest that for some conditions (e.g., HCC, non-melanoma skin cancers and MCC), treatment with ICIs offers significant clinical benefit. In particular, for non-melanoma skin cancers, the activity of ICIs is outstanding, and cemiplimab was recently approved for advanced squamous cell histology in both the US and European countries. In other rare tumours, the efficacy of ICI therapy cannot be fully ascertained because of the small sample sizes and non-randomised design of clinical trials (78, 79).

In conclusion, these considerations raise some final questions: Is the prediction of response to ICIs in rare cancers different from that of common cancers? What are the minimum immunological predictive factors for selecting patients with different responses to ICI therapy in rare cancers? What kind of data should be collected from future trials of immunotherapy in rare solid cancers? At present, we can only attempt to address a limited number of points. First, mechanisms that regulate immune responses are universal and do not differ among rare and common cancers. However, the immunological environment in which specific cancers develop can be specific and diverse, regardless of their rarity (80, 81). For example, in ACC, several drivers of intrinsic immunoresistance have been identified, including alteration of the WNT/beta-catenin pathway, TP53 mutations, cortisol hypersecretion, and PD-L1 downregulation (82, 83). These elements derive from the specific genomic landscape of ACC and cannot be generalised to other cancers. Second, beyond clinical trials, the on-label prescription of immunotherapy is currently granted for a few rare cancers. In these limited cases, clinicians are asked to provide minimum predictive factors of immunoresponse, such as PD-L1 expression, TMB, or MSI status. New immunological markers require more validation and are not yet ready for routine implementation. Multiparameter analysis of biomarkers that are predictive of the potential activity of ICIs in rare cancers and in common cancers will open new avenues for better selection of patients who may benefit from immunotherapy.

**DATA AVAILABILITY STATEMENT**

The original contributions presented in the study are included in the article. Further inquiries can be directed to the corresponding author.

**AUTHOR CONTRIBUTIONS**

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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