Critical Reviews in Oncology/Hematology 98 (2016) 122–136

Contents lists available at ScienceDirect

Critical Reviews in Oncology/Hematology

journal homepage: www.elsevier.com/locate/critrevonc

# Meta-analysis of regression of advanced solid tumors in patients receiving placebo or no anti-cancer therapy in prospective trials

Pooja Ghatalia[a,1], Charity J. Morgan[b,1], Guru Sonpavde[c,*]

[a] Department of Internal Medicine, University of Alabama at Birmingham (UAB), AL, United States
[b] Department of Biostatistics, UAB School of Medicine, United States
[c] Department of Internal Medicine, Section of Medical Oncology, UAB Medical Center, United States

**Contents**



ARTICLE INFO

*Article history:*
Received 14 April 2015
Received in revised form 5 October 2015
Accepted 28 October 2015

*Keywords:*
Spontaneous regression
Placebo
Meta-analysis
Immune therapy

ABSTRACT

*Background:* A meta-analysis of prospective trials systematically investigated regression of advanced solid tumors in patients receiving placebo or no anticancer therapy to inform on spontaneous regressions.
*Patient and methods:* Arms of randomized controlled trials (RCTs) of metastatic solid tumors receiving placebo or no anti-cancer therapy were used. Statistical analyses were conducted to calculate the overall response rate (ORR) and to detect differentials based on histology, progression at baseline and prior therapies.
*Results:* A total of 7676 patients were evaluable from 61 RCTs evaluating 18 solid tumors. The ORR was 1.95% (95% CI: 1.52–2.48%). There was no significant effect of histology ($p = 0.110$), baseline progressive disease ($p > 0.20$) or the line of therapy ($p > 0.20$) on ORR.
*Conclusions:* Spontaneous regressions are seen across all advanced solid tumors. Some malignancies demonstrated higher rates of spontaneous regressions and may be relatively immunotherapy responsive.


## 1. Introduction

Spontaneous regression (SR) of malignancies is defined as the partial or complete disappearance of a tumor proven by microscopic examination, in the absence of any substantial treatment, or in the presence of therapy that is considered inadequate (Everson, 1967; Cole and Everson, 1966). Everson and Cole retrospec-

* Corresponding author at: UAB Comprehensive Cancer Center, 1802 6th Ave. S., NP2540B, Birmingham, AL 35294. United States. Fax: +1 205 975 3910.
*E-mail address:* gsonpavde@uabmc.edu (G. Sonpavde).
[1] Authors have equal contribution in this manuscript.

http://dx.doi.org/10.1016/j.critrevonc.2015.10.018
1040-8428/

tively observed reports of 176 patients, seen from 1908 to 1966, who exhibited SR. Renal cell carcinoma (RCC) and melanomas, immunotherapy-responsive malignancies, were most frequently associated with SR (Cole and Everson, 1966). Since then, there have been several retrospective case reports and series in the literature describing SR in a variety of cancers, including HPV-induced cervical intraepithelial neoplasia (Kadish et al., 2002), cholangiocarcinoma (Yoshimitsu et al., 1996), melanoma (Tran et al., 2013; Bramhall et al., 2014), hepatocellular carcinoma (Misawa et al., 1999; Harada et al., 2010; Meza-Junco et al., 2007; Oquiñena et al., 2009; Arakawa et al., 2008; Del Poggio et al., 2009; Lim et al., 2014), RCC (Crisci et al., 2008), esophageal carcinoma (Kubota et al., 2003), non-small cell lung cancer (NSCLC) (Hwang et al., 2013), merkel cell carcinoma (Brown et al., 1999; Torroni et al., 2007; Vesely et al., 2008; Karkos et al., 2010), small-cell lung cancer (Lee et al., 2008; Hirano et al., 2007; Horino et al., 2006; Gill et al., 2003; Zaheer et al., 1993; Nakano et al., 1988; Iwakami et al., 2013) and squamous cell lung cancer (Choi et al., 2013).

The incidence of SR of cancer is difficult to quantify, but is estimated to occur in 1 in 60,000–100,000 cancer patients (Everson, 1967). However, estimates of the rate vary widely, and many cases are probably not reported. Difficulties involved in establishing what criteria must be met in order for a specific case to constitute an instance of SR further complicate determining the true frequency of this phenomenon (Challis and Stam, 1990). We hypothesized that systematic prospectively collected information on response rates for a broad spectrum of malignancies receiving no anti-cancer therapy may essentially reflect and inform on SRs and selection of the most suitable tumors for trials of immunotherapy, i.e., tumors with the highest response rates when receiving no anti-cancer therapy may be biologically most prone to response to up-regulation of the immune system. Here we conducted a meta-analysis of response in control arms of available randomized clinical trials (RCT), which administered either placebo or no anti-cancer therapy, in adults with advanced solid tumors.

## 2. Methods

### 2.1. Selection of studies

An independent review of citations in the English language from PubMed/Medline from January 1980 to June 2014 was conducted. Keywords included in the search were "placebo"; "best supportive care" and "cancer". The "randomized controlled trial" option was selected to narrow the search. Abstracts and virtual meeting presentations from major conferences—American Society of Clinical Oncology (ASCO); European Society of Medical Oncology (ESMO); and American Association of Cancer Research (AACR); were also reviewed. Databases from clinicaltrials.gov were also searched. RCTs with at least one arm containing no anti-cancer therapeutic agent(s) (placebo; observation; supportive care) were selected. Trials not reporting tumor responses were excluded. Trials using either the Response Evaluation in Solid Tumors (RECIST 1.0 or 1.1) or World Health Organization (WHO) criteria were used (Therasse et al., 2000; World Health Organization, 1979; Eisenhauer et al., 2009). Trials containing chemotherapy in the best supportive treatment arm were excluded; however those containing palliative radiation therapy were included since, lesions in radiated fields are not considered evaluable for response. Study quality was assessed by using the Jadad ranking system (Jadad et al., 1996).

### 2.2. Data extraction and clinical end points

The variables extracted are shown in Table 1. We also captured the rates of complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD). Generally, radiographic monitoring was conducted every 6–12 weeks. The line of therapy was recorded, and prior therapy administered was recorded when the setting was ≥second line. Trials evaluating maintenance therapy following first-line therapy were classified as second-line trials. If some patients in a trial had received prior first line agents, whereas others had not, first-line therapy was recorded as administered to "some" patients. Whether patients were required to have PD at the time of trial entry was recorded; while most trials required PD at baseline, second-line maintenance trials required absence of PD at baseline. The version of the response criteria, RECIST (1.0 or 1.1) or WHO, used was also captured.

### 2.3. Statistical analysis

Statistical analyses were performed by using R statistical software, version 3.0 (Schwarzer, 2013; Viechtbauer, 2010). The proportion of evaluable patients with CR, PR, SD and PD were derived for each trial and used to calculate the overall response rate (ORR: CR + PR), which was the primary clinical endpoint, and the disease control rate (DCR: CR + PR + SD) as a secondary clinical endpoint. For studies reporting zero patients with either CR or PR, the classic half-integer correction was applied.

For the meta-analysis, both the fixed-effects model and the random-effects model were considered. The latter was calculated with the method of DerSimonian and Laird, which considers both inter and intra-trial variation (DerSimonian and Laird, 1986). Statistical heterogeneity among studies included in the meta-analysis was assessed using the Cochrane's $Q$ statistic, and inconsistency was quantified with the $I^2$ ($I$-squared) statistic, which is used to describe the percentage of total variation across studies that is due to heterogeneity rather than chance; a value of 0% indicates no observed heterogeneity, while larger values between 0% and 100% show increasing heterogeneity (Higgins et al., 2003). The assumption of homogeneity was considered invalid for $p$-values <0.1, and in this case, we reported summary estimates from the random-effects models.

We used meta-regression to determine whether the rates of ORR and DCR were significantly affected by the histological pattern. We also conducted a subgroup analysis to determine whether these rates were different for first-line studies as compared to ≥second-line studies, or for studies requiring PD vs. absence of PD at baseline. Trials in which some patients had received prior therapies whereas others did not, were excluded from the subgroup analysis examining ORR and DCR based on line of therapy. Finally, potential publication bias was evaluated through funnel plots with the Egger test using an arcsine transformation (Rucker et al., 2008). A two-tailed $p$-value of $p < 0.05$ was considered statistically significant.

## 3. Results

### 3.1. Search results

Our search yielded a total of 125 potentially relevant RCTs containing at least one arm with no anti-cancer therapy. Fig. 1 represents the selection process: 64 trials were excluded for not using the RECIST 1.0, RECIST 1.1 or WHO criteria to measure responses, or for not reporting response outcomes. The remaining 61 trials were considered highly relevant for the study (Table 1) (Demetri et al., 2013a,b, 2006; Grothey et al., 2013; Elisei et al., 2013; vanderGraaf et al., 2012; Sternberg et al., 2010; Ahn et al., 2013; Leboulleux et al., 2012; Lee et al., 2012a,b; Del Campo et al., 2011; Miller et al., 2012; Wu et al., 2013; Mulders et al., 2012; Van Cutsem et al., 2007; Shepherd et al., 2005; Thatcher et al., 2005; Ledermann et al., 2012; Gaafar et al., 2011; Goss et al., 2009; Zhang et al., 2012; Raymond

**Table 1**
Characteristics of randomized trials included in the final analysis.

| Author, year | Phase | Histology | No. of pts in trial | Treatment arms | No of pts evaluable for response in placebo arm | CR | PR | SD | PD | Overall response rate (ORR) | First line agent | Trial required disease progression | Prior therapies | RECIST version/WHO criteria used | Jadad score |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Urothelial/transitional cell cancer | | | | | | | | | | | | | | | |
| Bellmunt et al. (2009) | 3 | Urothelial tract transitional cell cancer | 370 | Vinfluline + BSC/BSC | 85 | 0 | | 23 (27.1%) | NR | ORR: 0%<br>DCR: 24.8% | No | Yes | Platinum-based chemo | 1.0 | 4 |
| Pancreatic cancer | | | | | | | | | | | | | | | |
| Negi et al. (2006) | NR | Pancreatic cancer | 46 | Flutamide/placebo | 23 | 0 | | NR | NR | 0% | Yes | Yes | None | WHO criteria | 4 |
| Ciuleanu et al. (2009a,b) | 3 | Pancreatic cancer | 303 | Glufosfamide + BSC/BSC | 155 | 1 (0.6%) | | 29 (19%) | NR | ORR: 0.6% | No | Yes | Gemcitabine | 1.0 | 5 |
| Prostate cancer | | | | | | | | | | | | | | | |
| Pili et al. (2011) | 2 | Prostate cancer | 201 | Tasquinimod/placebo | 39 | 0 | | 12 (31%) | 27 (69%) | ORR: 0% | Yes | Yes | None | 1.0 | 5 |
| Small-cell lung cancer | | | | | | | | | | | | | | | |
| O'Brien et al. (2006) | NR | SCLC | 141 | Topotectan + BSC/BSC | 70 | 0 | | 0 | NR | DCR: 0% | No | NR | NR | WHO | 4 |
| Ciuleanu (2010) | 3 | SCLC | 401 | Picoplatin + BSC/BSC | 84 | 0 | | 23 (27.4%) | NR | DCR: 27.4% | No | Yes | Platinum-based chemo | 1.0 | 3 |
| Gallbladder cancer | | | | | | | | | | | | | | | |
| Sharma et al. (2010) | NR | Gallbladder cancer | 82 | Fluorouracil/gemcitabine + oxaliplatin/BSC | 27 | 0 | 0 | 1 (3.7%) | 26 (96%) | ORR: 0%<br>DCR: 3.7% | NR | Yes | NR | 1.0 | 3 |
| Melanoma | | | | | | | | | | | | | | | |
| Eisen et al. (2010) | 02-Mar | Melanoma | 306 | Lenalidomide/placebo | 127 | 1 (0.6%) | 8 (5.2%) | 51 (33%) | 67 (43%) | ORR: 5.8%<br>DCR: 38.8% | No | Yes | Dacarbazine, IL2, INF-a, INF-b | 1.0 | 5 |
| HCC | | | | | | | | | | | | | | | |
| Cheng et al. (2009) | 3 | HCC | 224 | Sorafenib/placebo | 63 | 0 | 1 (1.3%) | 21 (27.6%) | 41 (54%) | ORR: 1.3%<br>DCR: 28.6% | Yes | Yes | None | 1.0 | 4 |
| Llovet et al. (2008) | 3 | HCC | 599 | Sorafenib/placebo | 302 | 0 | 2 (1%) | 202 (67%) | NR | ORR: m1%<br>DCR: 32% | Yes | Yes | None | 1.0 | 4 |
| Yuen et al. (2002) | NR | HCC | 70 | Octreotide/placebo | 35 | 0 | 1(2.8) | 2 (5.6%) | NR | ORR: 2.8% | Yes | Yes | None | WHO | 4 |
| Barbare et al. (2009) | 3 | HCC | 272 | Octreotide/placebo | 138 | 1 (0.7%) | 3 (2.1%) | NR | NR | ORR: 2.9% | Some | Yes | NR | 1.0 | 5 |
| Dollinger et al. (2010) | 3 | HCC | 135 | Thymostimmulin/placebo | 68 | 20 (29%) | | | NR | DCR: 29% | Some | Yes | PEI, TACE, hormone or chemo | 1.0 | 5 |
| Liu et al. (2000) | NR | HCC | 119 | Tamoxifen/Placebo | 58 | 0 | | 26 (44.8%) | NR | ORR: 0% | Yes | Yes | None | WHO | 4 |
| Castells et al. (1995) | NR | HCC | 120 | Tamoxifen/placebo | 62 | 1 (1.6%) | | NR | NR | ORR: 1.6% | Yes | Yes | None | WHO | 4 |
| Llovet et al. (2013) | 3 | HCC | 395 | Brivanib/placebo | 101 | 2 (2%) | | 51 (39%) | 48 (36%) | ORR: 2%<br>DCR: 40% | No | Yes | Sorafenib | 1.1 | 5 |
| Sarin et al. (2006) | NR | HCC | 42 | Vitamin K3/placebo | 19 | 0 | 1 (5.3%) | 2 (10.5%) | 16 (84.2%) | ORR: 5.3%<br>DCR: 15.8% | Yes | Yes | None | WHO | 4 |
| Hsu et al. (2012) | 2 | HCC | 67 | Vandetanib/placebo | 25 | 0 | 0 | 12 | 13 | ORR: 0%<br>DCR: NR | Yes | Yes | None | 1.0 | 4 |
| Santoro et al. (2013) | 2 | HCC | 71 | Tivantinib/placebo | 34 | 0 | 0 | 11 (31%) | 23 (64%) | ORR: 0% | No | Yes | Chemo type NR | 1.1 | 4 |
| Gastric/esophageal cancer | | | | | | | | | | | | | | | |
| Li et al. (2013) | 2 | Gastric cancer | 144 | Apatinib/placebo | 48 | 0 | | 5 | NR | ORR: 0%<br>DCR: 10.4% | No | Yes | Platinum, fluoropyrimidine | 1.0 | 4 |
| Ohtsu et al. (2013) | 3 | Gastric cancer | 656 | Everolimus/placebo | 161 | 0 | 4 (2%) | 38 (20%) | 119 (62%) | ORR: 2% | NO | Yes | Pyrimidine, platinum, taxanes | 1.0 | 5 |

| | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | DCR: 22% | | | | | |
| Fuchs et al. (2014) | 3 | Gastric or gastri-esophageal junction cancer | 355 | Ramucirumab/placebo | 90 | 0 | 3 (3%) | 24 (21%) | 63 (54%) | ORR: 3%<br>DCR: 23% | No | Yes | Platinum or fluoropyrimidine-containing | 1.0 | 5 |
| Colorectal cancer | | | | | | | | | | | | | | | |
| Yoshino et al. (2012) | 2 | Colorectal cancer | 169 | TAS-102/placebo | 55 | 0 | 6 (11%) | | NR | ORR: NR<br>DCR: 11% | No | Yes | Fluoropyrimidine, irinotecan, oxaliplatin | 1.0 | 5 |
| Rao et al. (2004) | 3 | Colorectal cancer | 368 | Tipifarnib/placebo | 124 | 0 | 0 | 17 (12.8%) | 107 (80.5%) | ORR: 0% | No | Yes | XRT, oxaliplatin, irinotectan | 1.0 | 4 |
| Grothey et al. (2013) | 3 | Colorectal cancer | 760 | Regorafenib/placebo | 242 | 0 | 1 (0.4%) | 37 (14.5%) | 204 (80%) | DCR: 15%<br>ORR: 0.4% | No | Yes | Fluoropyrimidine, bevacizumab, irinotecan, oxaliplatin, panitumumab, cetuxicmab | 1.1 | 5 |
| Jonker et al. (2007) | NR | Colorectal cancer | 572 | Cetuximab + BSC/BSC | 275 | 0 | 0 | 31 (10.9%) | NR | ORR: 0%<br>DCR: 10.9% | No | Yes | NR | 1.0 | 5 |
| Van Cutsem et al. (2007) | 3 | Colorectal cancer | 463 | Panitumumab/best supportive care[c] | 232 | 0 | 0 | 23 (10%) | NR | ORR: 0%<br>DCR: NR | No | Yes | 100% chemo type NR | 1.0 | 4 |
| Breast cancer | | | | | | | | | | | | | | | |
| Wildiers et al. (2010) | 2 | Breast cancer | 55 | Sunitinib/placebo | 19 | 0 | 0 | NR | NR | ORR: 0%<br>DCR: NR | No | No | Anthracycline, taxanes, hormone | 1.1 | 3 |
| PNET | | | | | | | | | | | | | | | |
| Raymond et al. (2011) | 3 | PNET | 171 | Sunitinib/placebo | 74 | 0 | 0 | 51 (60%) | 23 (27%) | ORR: 0%<br>DCR: NR | Some | Yes | XRT, TACE, PEI, ablation, anthracy-clines, fluropyrim-idines, streptozocin | 1.0 | 4 |
| Yao et al. (2011) | 3 | PNET | 410 | Everolimus/placebo | 180 | 0 | 4 (2%) | 97 (51%) | 79 (42%) | ORR: 2% | Some | Yes | NR chemo type (50% prior chemo) | 1.0 | 5 |
| GIST | | | | | | | | | | | | | | | |
| Demetri et al. (2013a,b) | 3 | GIST | 199 | Regorafenib/placebo | 66 | 0 | 1 (1.5%) | 22 (33.3%) | 43 (63.6%) | [a]DCR: 9.10%<br>ORR: 1.50% | No | Yes | Sunitinib, imatinib | 1.1 | 5 |
| Demetri et al. (2006) | 3 | GIST | 361 | Sunitinib/placebo | 94 | 0 | 0 | 50 (53%) | 44 (46.8%) | ORR: 0%<br>DCR: NR | No | Yes | Imatinib | 1.0 | 5 |
| Ovarian cancer | | | | | | | | | | | | | | | |
| Ledermann et al. (2012) | 2 | Ovarian cancer | 265 | Olaparib/placebo | 48 | 0 | 2 (4%) | NR | NR | ORR: 4%<br>DCR: 25% | No | Yes | NR | 1.0 | 5 |
| RCC | | | | | | | | | | | | | | | |
| Gleave et al. (1998) | NR | RCC | 197 | INF gamma1/placebo | 90 | 3 (3.3%) | 3 (3.3%) | 26 (29%) | 57 (64%) | ORR: 6.6% | Yes | Yes | None | WHO | 5 |

Table 1 (*Continued*)

| Author, year | Phase | Histology | No. of pts in trial | Treatment arms | No of pts evaluable for response in placebo arm | CR | PR | SD | PD | Overall response rate (ORR) | First line agent | Trial required disease progression | Prior therapies | RECIST version/WHO criteria used | Jadad score |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Motzer et al. (2008) | 3 | RCC | 410 | Everolimus/placebo | 107 | 0 | 0 | 44 (32%) | 63 (46%) | ORR: 0%<br>DCR: NR | No | Yes | INF, IL2, bevacizumab, chemo | 1.0 | 5 |
| Sternberg et al. (2010) | 3 | RCC | 435 | Pazopanib/placebo | 122 | 0 | 5 (3.4%) | 59 (40.6%) | 58 (40%) | ORR: 3.4%<br>DCR: NR | Some | Yes | Cytokine | 1.0 | 5 |
| Escudier et al. (2007) | 3 | RCC | 903 | Sorafenib/placebo | 414 | 0 | 8 (2%) | 239 (58%) | 167 (40.3)% | ORR: 2%<br>DCR: 37% | No | Yes | IL2, INF | 1.0 | 5 |
| Mulders et al. (2012) | 2 | RCC | 70 | Cediranib/placebo | 17 | 0 | 0 | 4 (22%) | 13 (72%) | ORR: 0%<br>DCR: 0% | Some | Yes | Immune, hormone therapy | 1.0 | 4 |
| Head and neck cancer | | | | | | | | | | | | | | | |
| Machiels et al. (2011) | 3 | Head and neck | 286 | Zalutumumab/placebo | 64 | 0 | 1 (1%) | 25 (26%) | 38 (40%) | ORR: 1.1%<br>DCR: 27% | No | Yes | XRT, chemo type NR | 1.0 | 5 |
| Del Campo et al. (2011) | 2 | Head and neck | 107 | Lapatinib/placebo | 16 | 0 | 0 | 12 (75%) | 4 (25%) | ORR: 0%<br>DCR: NR | Yes | Yes | None | 1.0 | 4 |
| NSCLC | | | | | | | | | | | | | | | |
| Lee et al. (2012a,b) | 3 | NSCLC | 647 | Erlotinib/placebo | 320 | 7 (2%) | | NR | NR | ORR: 2%<br>DCR: NR | Yes | Yes | None | 1.0 | 5 |
| Wu et al. (2013) | 3 | NSCLC | 125 | Erlotinib/placebo | 65 | 3 (4.8%) | | NR | NR | ORR: 4.8%<br>DCR: 34.9% | No | No | 100% chemo type NR | 1.0 | 5 |
| Mubarak et al. (2012) | 2 | NSCLC | 106 | Pemetrexed + BSC/BSC | 27 | 0 | | 12 (44.4%) | NR | ORR: 0%<br>DCR: 44.4% | No | Yes | Induction chemotherapy: Pemetrexed + cisplatin | 1.0 | 4 |
| Cappuzzo et al. (2010) | 3 | NSCLC | 889 | Erlotinib/placebo | 444 | 24 (5.24%) | | 98 (22%) | NR | ORR: 5.4%<br>DCR: 27.4% | No | No | Platinum-based chemo | 1.0 | 5 |
| Ciuleanu et al. (2009a,b) | 3 | NSCLC | 663 | Pemetrexed + BSC/placebo + BSC | 194 | 1 (0.5%) | | 55 (28.3%) | NR | ORR: 0.5%<br>DCR: 29% | No | No | Platinum-based chemo | 1.0 | 5 |
| Cellerino et al. (1991) | NR | NSCLC | 128 | Chemotherapy/BSC | 57 | 0 | | 27 (47%) | 30 (53%) | ORR: 0%<br>DCR: 47% | Yes | Yes | None | WHO | 4 |
| Zhang et al. (2012) | 3 | NSCLC | 296 | Gefitinib/placebo | 148 | 1 (0.7%) | | NR | NR | ORR: 0.7%<br>DCR: NR | No | No | Platinum, taxanes | 1.0 | 5 |
| Paz-Ares et al. (2012) | 3 | Non-squamous NSCLC | 539 | Pemetrexed and BSC/placebo and BSC | 154 | 0 | 1 (0.6%) | 92 (59%) | 61 (39%) | ORR: 0.6%<br>DCR: 60% | Yes | No | None | 1.0 | 5 |

| | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Parikh et al. (2011) | 2 | NSCLC | 100 | Talactoferrin alfa/placebo | 43 | 0 | 1 (2%) | 11 (21%) | NR | ORR: 2%<br>DCR: 28% | No | Yes | Platinum, gemcitabine, taxanes, pemetrexed, etoposide, gefitinib | 1.0 | 4 |
| Goss et al. (2009) | 2 | NSCLC | 201 | Gefitinib + BSC/ placebo + BSC | 101 | 0 | 1 (1%) | 22 (22%) | NR | ORR: 1%<br>DCR: 22.8% | Yes | Yes | None | 1.0 | 5 |
| Ramalingam et al. (2013) | 3 | NSCLC | 742 | Talactoferrin alfa/placebo | 203 | 0 | 3 (1.2%) | 91 (37.1%) | 109 (44.5%) | ORR: 1.2%<br>DCR: NR | No | Yes | Chemo, EGFR TKI, bevacizumab, XRT | 1.0 | 5 |
| Gaafar et al. (2011) | 3 | NSCLC | 173 | Gefitinib/placebo | 85 | 0 | 1 (1.1%) | 56 (66%) | 28 (33%) | ORR: 1.1%<br>DCR: 66% | No | No | Platinum | 1.0 | 5 |
| Thatcher et al. (2005) | 3 | NSCLC | 1129 | Gefitinib/placebo | 386 | 0 | 6 (1%) | 148 (31%) | 232 (48%) | ORR: 1%<br>DCR: NR | No | Yes | Platinum, docetaxel | 1.0 | 5 |
| Shepherd et al. (2005) | 3 | NSCLC | 731 | Erlotinib/placebo | 211 | 0 | 2 (<1%) | NR | NR | ORR: <1%<br>DCR: NR | No | Yes | Platinum | 1.0 | 5 |
| Lee et al. (2012a,b) | 3 | NSCLC | 922 | Vandetanib/placebo | 285 | 0 | 2 (0.7%) | NR | NR | ORR: 0.7%<br>DCR: NR | No | Yes | Chemo, targeted therapy | 1.0 | 4 |
| Miller et al. (2012) | 2b/3 | NSCLC | 697 | Afatinib + BSC/ placebo + BSC | 195 | 0 | 1 (<1%) | 41 (21%) | NR | ORR: <1%<br>DCR: 18% | No | Yes | Platinum, erlotinib, gefitinib | 1.0 | 5 |
| Ahn et al. (2013) | 2 | NSCLC | 117 | Vandetanib/placebo | 42 | 0 | 1 (2.4%) | NR | NR | ORR: 2.4%<br>DCR: NR | No | No | VEGFR TKI or mTROi | 1.0 | 4 |
| Sarcoma | | | | | | | | | | | | | | | |
| Demetri et al. (2013a,b) | 3 | Sarcoma | 711 | Ridaforolimus/placebo | 364 | 18 (28.6%) | | | NR | ORR: NR<br>DCR: 28.6% | No | No | Yes, but not mentioned | 1.0 | 5 |
| VanderGraaf et al. (2012) | 3 | Metastatic soft-tissue sarcoma | 369 | Pazopanib/placebo | 117 | 0 | 0 | 47 (38%) | 70 (57%) | ORR: 0%<br>DCR: 38% | No | Yes | 62% chemo type NR | 1.0 | 5 |
| Thyroid cancer | | | | | | | | | | | | | | | |
| Elisei et al. (2013) | 3 | Medullary thyroid cancer | 323 | Cabozantinib/placebo | 109 | 0 | 0 | NR | NR | ORR: 0%<br>DCR: NR | Some | Yes | Chemo type NR, VEGFR TKI | 1.0 | 5 |
| Leboulleux et al. (2012) | 2 | Papillary and follicular thyroid cancer | 145 | Vandetanib/placebo | 73 | 0 | 4 (5%) | 22 (30%) | NR | ORR: 5%<br>DCR: 36% | Some | Yes | Gemcitabine, cisplatin | 1.0 | 4 |
| Total | 02-March | | 20173 | | 7685 | | | | | | | | | | |

BSC: best supportive care; CR: complete response; DCR: disease control rate; IL2: interleukin 2, INF: interferon; GIST: gastrointestinal stromal tumor; HCC: hepatocellular carcinoma; NSCLC: non-small cell lung cancer; NR: not reported; ORR: overall response rate; PR: partial response; PD: progressive disease; PEI: percutaneous ethanol injection; RCC: renal cell carcinoma; RECIST: response evaluation criteria in solid tumors; SD: stable disease; TACE: transarterial chemoembolization; WHO: World Health Organization criteria; XRT: radiation therapy.

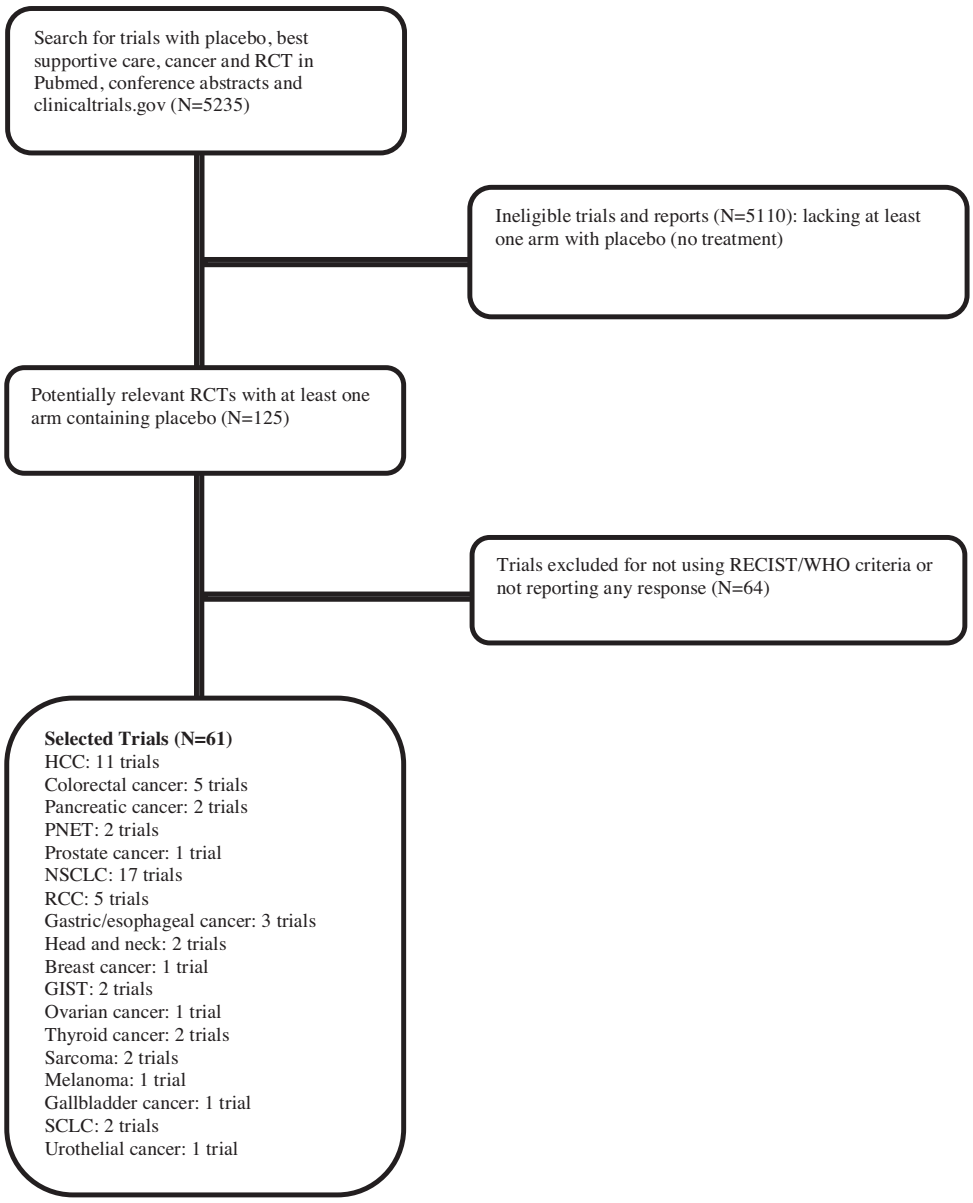


**Fig. 1.** Selection process for trials included in the meta-analysis.
GIST: gastrointestinal stromal tumor; HCC: hepatocellular carcinoma; NSCLC: non-small cell lung cancer; PNET: pancreatic neuroendocrine tumor; RCC: renal cell carcinoma; SCC: small cell lung cancer.

et al., 2011; Wildiers et al., 2010; Llovet et al., 2008, 2013; Cheng et al., 2009; Escudier et al., 2007; Yao et al., 2011; Scher et al., 2012; Ramalingam et al., 2013; Paz-Ares et al., 2012; Machiels et al., 2011; Parikh et al., 2011; Ohtsu et al., 2013; Jonker et al., 2007; Fuchs et al., 2014; Motzer et al., 2008; Gleave et al., 1998; Santoro et al., 2013; Hsu et al., 2012; Sarin et al., 2006; Rao et al., 2004; Barbare et al., 2009; Yuen et al., 2002; Dollinger et al., 2010; Cappuzzo et al., 2010; Pili et al., 2011; Negi et al., 2006; Liu et al., 2000; Bellmunt et al., 2009; Ciuleanu et al., 2009a,b; Ciuleanu et al., 2010; Sharma et al., 2010; Eisen et al., 2010; Castells et al., 1995; Li et al., 2013; Yoshino et al., 2012; Mubarak et al., 2012; Cellerino et al., 1991; O'Brien et al., 2006). The trials enrolled patients with urothelial cancer ($n=1$), pancreatic cancer ($n=2$), prostate cancer ($n=1$), small cell lung cancer ($n=2$), gallbladder cancer ($n=1$), melanoma ($n=1$), HCC ($n=11$), gastro-esophageal cancer ($n=3$), colorectal cancer ($n=5$), breast cancer ($n=1$), pancreatic neuroendocrine tumor ($n=2$), gastrointestinal stromal tumor ($n=2$), ovarian cancer ($n=1$), RCC ($n=5$), head and neck cancer ($n=2$), NSCLC ($n=17$), sarcoma ($n=2$) and thyroid cancer ($n=2$). A total of 21,073 patients were enrolled in these trials, of whom, 7676 patients were evaluable for response in the arms not containing anti-cancer therapy. The drugs used in the cancer-therapy arm/arms are listed in Table 1. Fifteen trials were conducted in the first-line setting, 37 trials in the ≥second-line setting, and 8 trials had combination of patients receiving first line and second line agents. In one of the trials, it was unclear if patients had received prior therapies. A total of 52 trials required PD at baseline, 8 trials did not, and one trial (O'Brien et al., 2006) did not provide data on whether disease was progressive at baseline. Follow-up time was adequate in these trials. The majority of trials were of high quality according to the Jadad score (3–5).

### 3.2. Overall response and disease control rates

Fifty-eight trials provided sufficient information for calculating ORR. The ORR was 1.95% (95% CI: 1.52–2.48%). There was significant evidence of heterogeneity in the rates of regression for the trials:

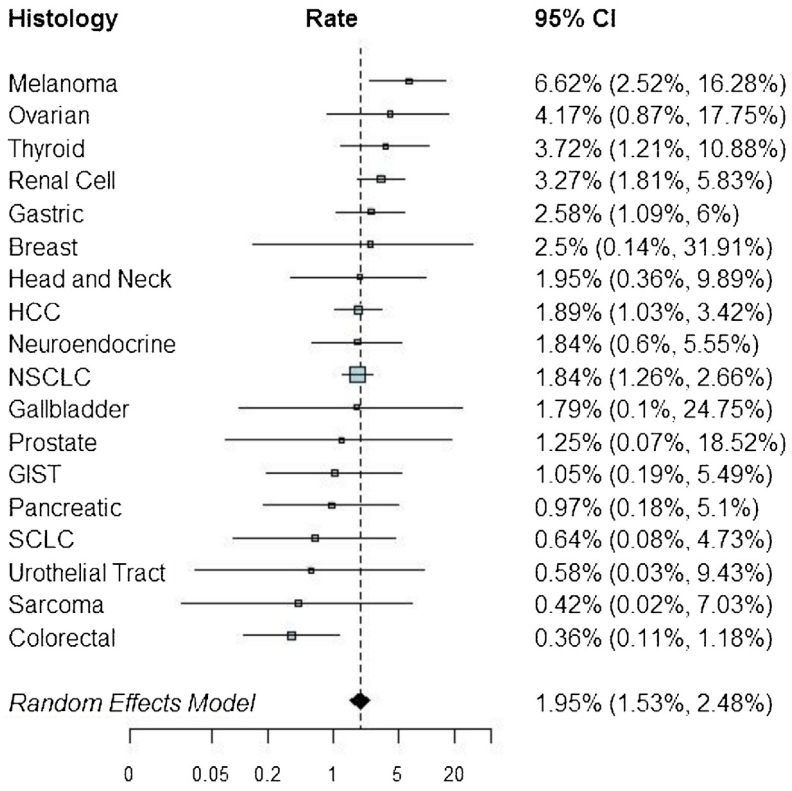


**Fig. 2.** Overall response rate by histology.

$I^2$ = 31.2%, $Q$ = 85.5, $p$ = 0.011. The DCR calculation was feasible in 49 trials. The pooled estimate of DCR was 32.4% (95% CI: 27.3–38.0%). As with the previous analysis, there was significant evidence of heterogeneity: $I^2$ = 94.0%, $Q$ = 805.6, $p$ < 0.001.

### 3.3. Subgroup analysis of response and disease control by histology, baseline progressive disease and line of therapy

There was no significant effect of histology on ORR ($p$ = 0.110). The rates of regression by histology are shown in Fig. 2. As an exploratory analysis, we divided the histologies into quartiles using their estimated rates of regression. We then compared the quartile that had the highest ORR (melanoma, gastro-esophageal cancer, ovarian, RCC, thyroid) to the quartile with the lowest rate of regression (urothelial, pancreatic, SCLC, colorectal, sarcoma). The rate of regression was 0.5% (95% CI: 0.2–1.2%) for the quartile with the lowest ORR and 3.8% (2.8–5.1%) for the quartile with the highest ORR. This difference in ORR was statistically significant ($p$ < 0.001). Whether the disease was progressive or not before the trial had no effect on ORR in 60 evaluable trials ($p$ > 0.20). There was no significant effect of the line of treatment on ORR ($p$ > 0.20) (Fig. 4).

There was a significant effect of histology on DCR ($p$ < 0.001), with the rates ranging from 3.70% (for gallbladder cancers) to 62.4% (neuroendocrine cancers) (Fig. 3). We also divided the histologies into quartiles and compared histologies with the highest rates of DCR (melanoma, neuroendocrine, GIST, head and neck) to those with the lowest rates of DCR (SCLC, gallbladder, colorectal, sarcoma). As with ORR, the difference in DCR for these quartiles was statistically significant ($p$ < 0.001), with the first quartile having a DCR rate of 13.1% (95% CI: 8.6–19.4%) and the fourth quartile having a rate of 52.4% (39.4–65.1%). The presence or absence of PD prior to the trial had no significant effect on DCR ($p$ > 0.20). For first line trials, the rate of DCR was 40.3% (95% CI: 29.2–52.4%); for ≥second-line trials, the rate was 28.3% (95% CI: 22.6–34.8%). This difference showed a trend towards statistical significance ($p$ = 0.068) (Fig. 4).

### 3.4. Publication bias

Although the funnel plot for the overall response rate (Fig. 5) showed some evidence of asymmetry; the Egger test was not statistically significant ($p$ = 0.083). The funnel plot for disease control rate is shown in Fig. 6. There was no evidence of funnel plot asymmetry ($p$ > 0.20).

## 4. Discussion

The phenomenon of SR of cancer was reported by Everson and Cole in 1974 and updated by Challis and Stamm. In these retrospective studies, RCC, melanoma, low-grade non-Hodgkins's lymphoma (NHL), chronic lymphocytic leukemia (CLL) and neuroblastoma appeared to more frequently display SRs compared to other malignancies (Challis and Stam, 1990; Avinoach and Aflalo, 1992). In our large pooled meta-analysis of 7676 evaluable patients receiving no anti-cancer therapy from 61 RCTs evaluating 18 solid tumors, the primary endpoint, ORR, was 1.95% (95% CI: 1.52–2.48%). We then performed a hypothesis-generating analysis by distributing malignancies in quartiles based on the ORR in order to identify tumors with the highest and lowest ORRs. The quartile of histologic tumor types with the highest ORR demonstrated a significantly higher ORR compared to the quartile with the lowest ORR: 3.8% (95% CI: 2.8–5.1%) vs. 0.5% (95% CI: 0.2–1.2%), $p$ < 0.001. In our study, the quartile with the highest ORR included cancers recognized to be responsive to immunotherapy, i.e., melanoma and RCC. Indeed, a cytotoxic T-lymphocyte (CTLA)-4 inhibitor, ipilimumab, extends survival in melanoma (Hodi et al., 2010). High dose interleukin (IL)-2 is known to induce durable remissions in ~5% of patients with clear cell RCC (Fyfe et al., 1995). Pro-

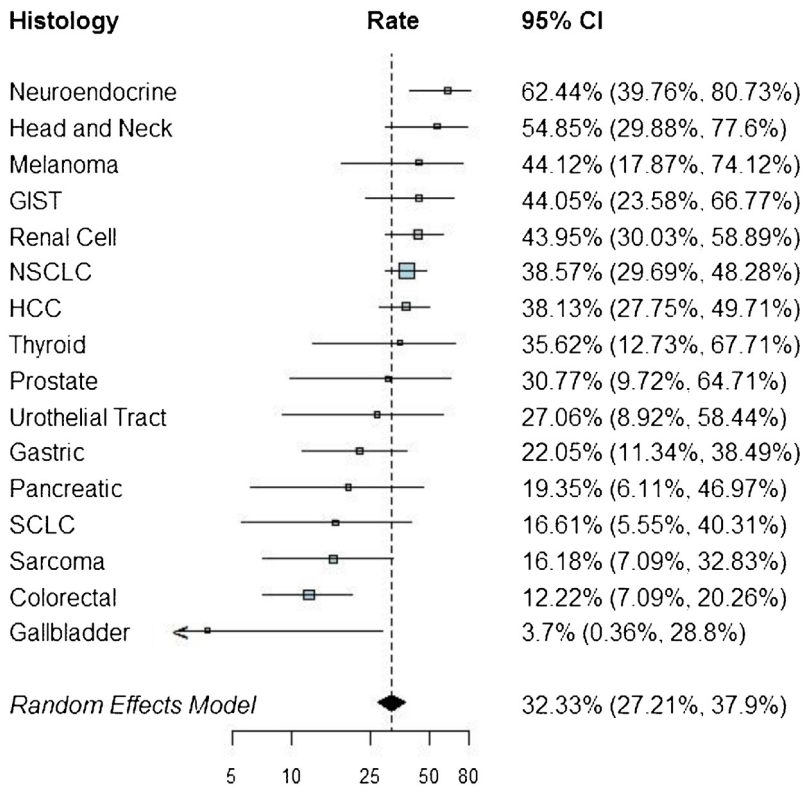


**Fig. 3.** Disease control rate by histology.

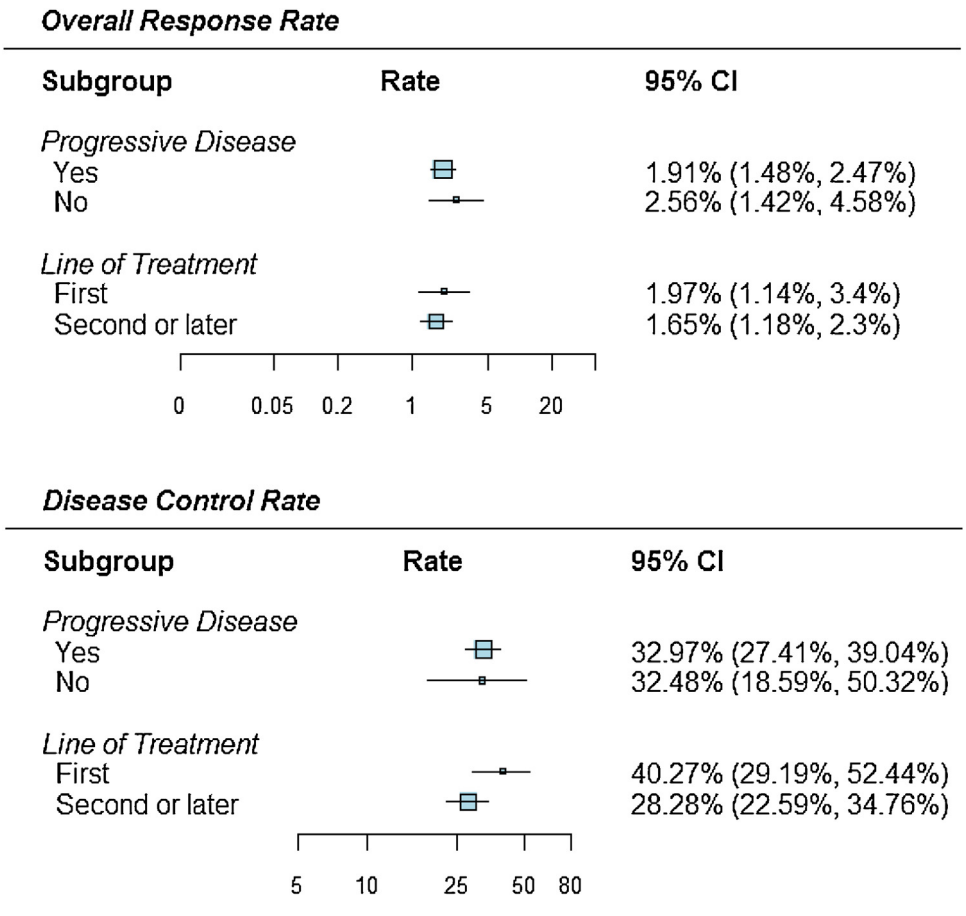


**Fig. 4.** Overall response rate and disease control rate based on baseline progression and line of therapy.

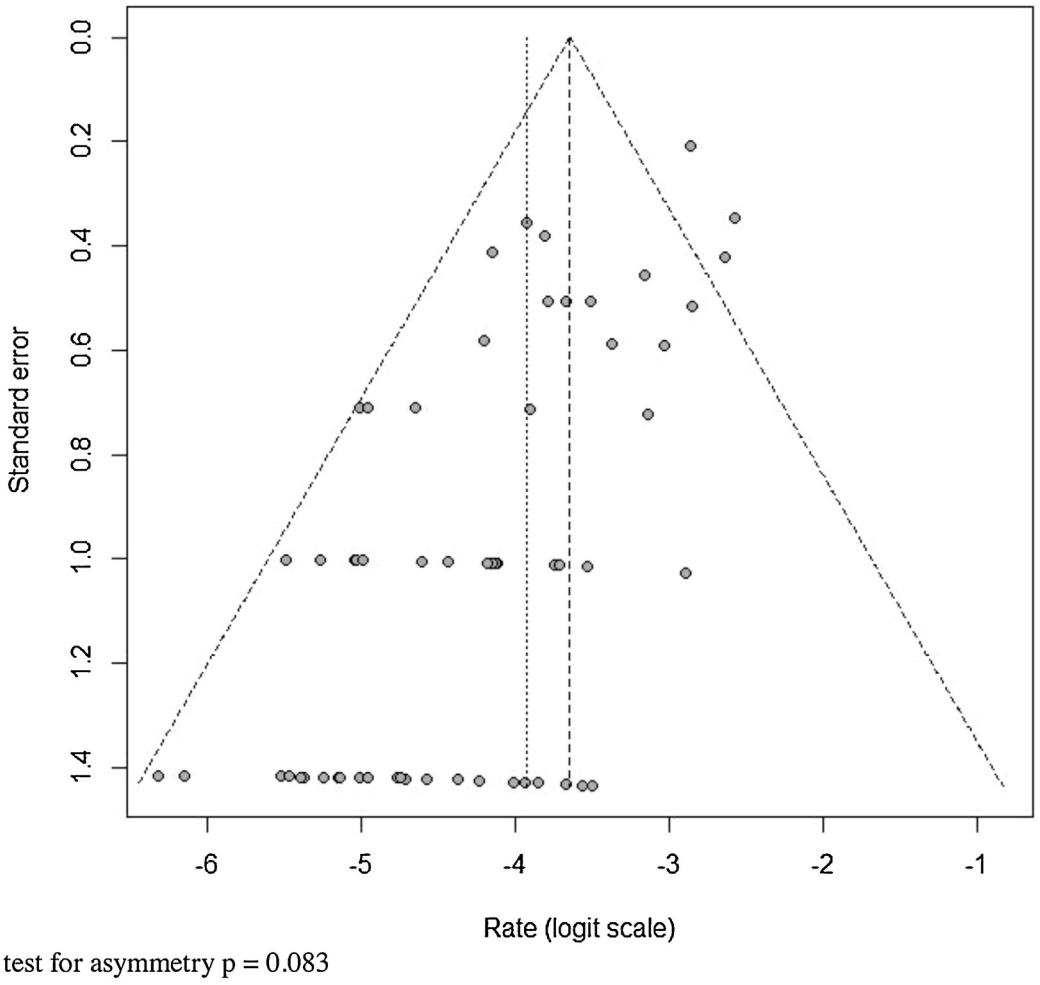


**Fig. 5.** Funnel plot showing publication bias for overall response rate*. *Egger test for asymmetry $p = 0.083$.

grammed death (PD)-1 pathway inhibitors have significant activity in melanomas and clear-cell RCC (Hamid et al., 2013; Brahmer et al., 2012; Topalian et al., 2012). Other malignancies not readily recognized to be immunotherapy-responsive were in the highest ORR quartile: gastro-esophageal cancer, ovarian cancer and thyroid cancers. Intriguingly, a recent presentation suggests promising activity for PD-1 inhibitors, pembrolizumab for salvage therapy in gastric cancer, and nivolumab, in the platinum-resistant ovarian cancer (Muro et al., 2014; Hamanishi et al., 2014). Conversely, the quartile with the lowest ORR included some of the most aggressive solid tumors, i.e., urothelial, pancreatic, small-cell lung and colorectal carcinomas and sarcomas. Malignancies not belonging to the highest or lowest ORR quartiles may be hypothesized to have intermediate sensitivity to immunotherapy.

Recent data suggest that immunotherapy employing PD-1 inhibitors have substantial activity in advanced urothelial carcinoma and non-small cell lung cancer (NSCLC), although these malignancies were not in the quartile exhibiting the highest ORR (Powles et al., 2014; Brahmer et al., 2015; Garon et al., 2015). However, urothelial carcinoma was represented by a single trial in our pooled analysis and SR rates observed may not be representative of the true SR. Intriguingly, both urothelial carcinoma and NSCLC are characterized by a high mutation burden, which may enable an immunotherapeutic agent to yield efficacy despite a suboptimal innate host immune response (Creighton et al., 2013; Collisson et al., 2014; Lawrence et al., 2013). Gastric and esophageal cancers figure in our highest ORR quartile and also have one of the highest mutation burdens (Lawrence et al., 2013). Conversely, thyroid cancer has one of the lowest mutation burdens, but was in our highest ORR quartile. Specific tumor tissue markers are probably yet another predictive assay, e.g., PD-ligand (L)-1 expression to predict better activity of inhibitors of the PD-1 pathway (Topalian et al., 2012). Thus, all of these parameters may complement each other in selecting certain malignancies in general and patients in specific for the development of immunotherapy.

Potentially, some cases of SR may be caused by delayed response to prior anti-cancer therapy or immunotherapy even after initial radiographic progression or pseudoprogression. However, only 4 trials in our analysis included patients that had documented evidence of receipt of previous immunotherapy, where delayed responses even after initial pseudoprogression has been reported (Wolchok et al., 2009). However, the cohort not exposed to prior anticancer therapy did not seem to have a different regression rate compared to pre-treated patients suggesting that the delayed response phenomenon after previous psudoprogression is unlikely to account for most of the responses observed in our analysis. Nevertheless, we cannot discount the possibility that some of the regressions may have been from delayed immune responses following prior chemotherapy or other non-immunotherapy classes of agents. We do not make any definite conclusions about the immune responsiveness of tumors based on this study. However, in this study we hoped to revisit the phenomenon of SR and its possible association with an immune mediated mechanism, especially given the surge of immunotherapeutic agents for cancer treatment.

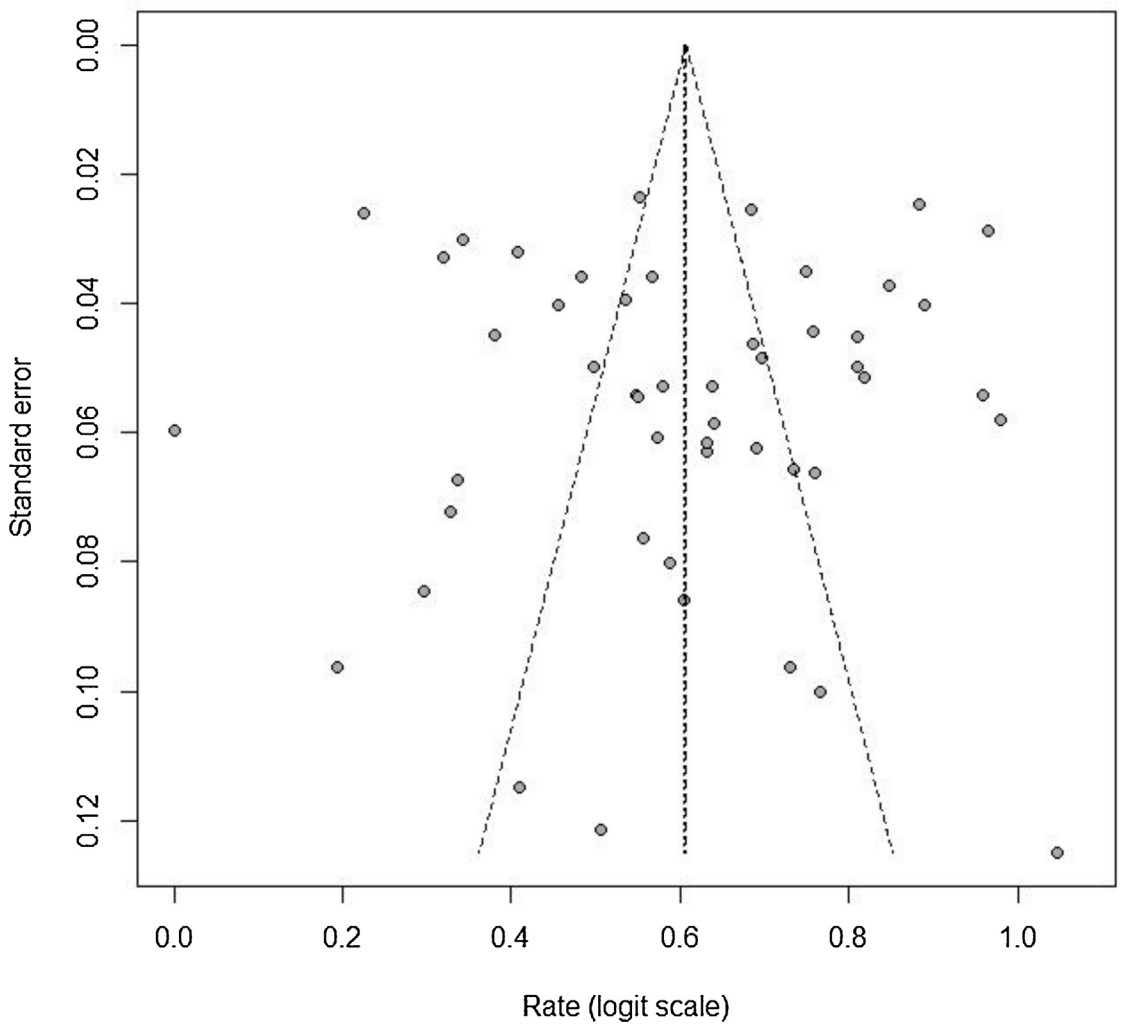


**Fig. 6.** Funnel plot showing publication bias for disease control rate*. *Egger test for asymmetry $p > 0.20$.

The mechanisms of SR are still largely unknown, although host immune response against neoantigens expressed by tumors has been most often implicated. Indeed, a recent study presented a tumor neoantigen landscape that may be associated with response to CTLA-4 blockade (Snyder et al., 2014). A robust febrile reaction from a natural or induced acute infection has been reported as a symptom associated with tumor regression (Thomas and Badini, 2011). The florid immune infiltrate reported at the site of the tumor regression in patients with malignant melanoma strongly suggests the role of antitumor immune response in tumor elimination (Kappauf et al., 1997). Mechanisms other than immune response may also be operative in inducing SRs, such as removal of carcinogenic substances, infection, induction of apoptosis, action of antibodies, anti-angiogenic mechanisms of maturation, natural killer activity, endocrine system activity, tumor inhibition by growth factors and/or cytokines, induction of cell differentiation, tumor necrosis, and/or inhibition of angiogenesis (Challis and Stam, 1990; Kappauf et al., 1997). Indeed, many reports of SRs have implicated surgery or operative trauma as an element that can increase immunological resistance to tumor growth and the removal of a portion of the tumor (e.g., cytoreductive nephrectomy in patients with metastatic clear cell RCC) might facilitate the destruction of the remaining neoplasm by the host immune system (Challis and Stam, 1990).

We also studied DCR to identify any consistent signals compared to ORR. DCR may be hypothesized to be more influenced by innate tumor cell biology rather than the influence of host related factors or therapeutic interventions. Notably, melanoma was again found to belong in the quartile with the highest DCR. However, the other malignancies in the quartile with the highest DCR probably reflect an indolent pace of growth, i.e., neuroendocrine tumors. Nevertheless, the indolent growth of certain tumors may potentially also reflect an innate immune-state-responsiveness. Interestingly, subgroup analyses identified no significant differences in ORR based on line of therapy or disease progression at baseline. These data suggest that even patients with disease progression in the salvage line setting may demonstrate a small SR rate. Indeed, 45 of the 61 trials pooled in our analysis were conducted in a setting beyond first-line therapy.

Our approach is unique as we study response rates in placebo arms of RCTs that utilize the well-established RECIST/WHO criteria, where ORR can be used to quantify SR. Using this method has several advantages: It helps to establish consistency across all

trials reporting response rates, making analysis reliable. Additionally, uncertainties in reporting of SR related to misdiagnosis, lack of histological confirmation or incorrect interpretation of simultaneous changes in the patients' condition can usually be eliminated in RCTs. However, there are several caveats in our study that should be mentioned. First, we do acknowledge that SR, defined as ORR in the placebo arm of RCTs is not identical to SR as defined by Everson and Cole. However, using a standardized definition of tumor response as defined by the RECIST/WHO criteria helped us simplify the analysis. Second, only 15 of the 61 trials in our study included patients who had not received any prior therapy. However, it is interesting to note that the ORR was not different in patients in the placebo arm who had received no prior therapy compared to those that had received prior lines of therapy. These findings suggest that although immunotherapy is traditionally delivered as an early line of therapy, its benefits may extend to the salvage setting. Conversely, our study may underestimate the SR rate in untreated patients, given the smaller sample size of this group. Third, we only included trials using RECIST (1.0 or 1.1) or WHO criteria to monitor response. Indeed, this is a major strength of our study, since these trials prospectively collected data and objectively captured tumor measurements at regular intervals of generally every 6–12 weeks. This led to elimination of RCTs where other markers may have been used to monitor tumor response. We could not control the time point at which tumor responses were measured in each of the trials, although most trials performed radiographic imaging every 6–12 weeks, and earlier if clinically warranted. We chose to focus on adults with advanced solid tumors and did not investigate hematologic malignancies (including lymphomas) or pediatric malignancies (e.g., neuroblastomas), which have been reported to undergo spontaneous remissions (Challis and Stam, 1990; Diede, 2014). In the case of neuroblastomas, in addition to an immune mechanism, a delay in developmental time-switch for apoptosis has been postulated as the mechanism (Pritchard and Hickman, 1994). Finally, we could only capture size changes as CR, PR, SD and PD, and could not capture SRs that did not attain the level of PR at least.

We found some evidence of funnel plot asymmetry for ORR, which could potentially indicate publication bias. This bias, when it occurs, can be a sign that non-significant results are less likely to be published. Here, a possible source of this bias could be studies that had high placebo response rates (making it more difficult to detect a significant difference between the treatment and placebo arms) are being underreported. If this were the case, we would actually be underestimating the placebo response rate. As a sensitivity analysis, the trim and fill method (Duval and Tweedie, 2000a,b) may be used to try to correct for publication bias. The corrected estimated ORR is 3.1% (95% CI: 2.4–4.0%), compared to the uncorrected ORR of 1.95% (95% CI: 1.52–2.48%). Results from the trim and fill method must be interpreted carefully however, particularly when there is evidence of between-study heterogeneity (Peters et al., 2007).

This is the first ever conducted systematic study analyzing SR in arms of RCTs receiving placebo or no anti-cancer therapy. Our study sheds light on the fact that this phenomenon is not uncommon and is widely observed across all cancer types. We hypothesize that malignancies with higher SR rates may be particularly responsive to immunotherapy, which may guide the selection of appropriate malignancies for the investigation of immunotherapeutic agents. SR rates may complement tumor mutation burden to select malignancies in general, and patient-specific predictive biomarkers may assist in selecting patients in specific for the development of immunotherapy.

## Role of funding source

None.

## Relevant disclosures

None.

## Author contributions

Sonpavde involved in study concept and design.

Ghatalia involved in acquisition of data.

Ghatalia, Morgan and Sonpavde involved in analysis and interpretation of data.

Ghatalia, Morgan and Sonpavde involved in drafting of the manuscript.

Ghatalia, Morgan and Sonpavde involved in critical revision of the manuscript for intellectual content.

Morgan involved in statistical analysis.

Sonpavde involved in study supervision.

## References

Ahn, J.S., Lee, K.H., Sun, J.M., Park, K., Kang, E.S., Cho, E.K., et al., 2013. A randomized, phase II study of vandetanib maintenance for advanced or metastatic non-small-cell lung cancer following first-line platinum-doublet chemotherapy. Lung Cancer 82, 455–460.

Arakawa, Y., Mori, H., Ikegami, T., Hanaoka, J., Kanamoto, M., Kanemura, H., et al., 2008. Hepatocellular carcinoma with spontaneous regression: report of the rare case. Hepatogastroenterology 55, 1770–1772.

Avinoach, I., Aflalo, E., 1992. Human melanoma cell lines established from metastases of a patient with a completely regressed primary site. Cancer 69, 113–122.

Barbare, J.C., Bouché, O., Bonnetain, F., Dahan, L., Lombard-Bohas, C., Faroux, R., et al., 2009. Treatment of advanced hepatocellular carcinoma with long-acting octreotide: a phase III multicentre, randomised, double blind placebo-controlled study. Eur. J. Cancer 45, 1788–1797.

Bellmunt, J., Theodore, C., Demkov, T., Komyakov, B., Sengelov, L., Daugaard, G., et al., 2009. Phase III. trial of vinflunine plus best supportive care compared with best supportive care alone after a platinum-containing regimen in patients with advanced transitional cell carcinoma of the urothelial tract. J. Clin. Oncol. 27, 4454–4461.

Brahmer, J.R., Tykodi, S.S., Chow, L.Q., Hwu, W.J., Topalian, S.L., Hwu, P., et al., 2012. Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. N. Engl. J. Med. 366, 2455–2465.

Brahmer, J., Reckamp, K.L., Baas, P., Crino, L., Eberhardt, W.E., Poddubskaya, E., et al., 2015. Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. N. Engl. J. Med. 373, 123–135.

Bramhall, R.J., Mahady, K., Peach, A.H., 2014. Spontaneous regression of metastatic melanoma—clinical evidence of the abscopal effect. Eur. J. Surg. Oncol. 40, 34–41.

Brown, T.J., Jackson, B.A., Macfarlane, D.F., Goldberg, L.H., 1999. Merkel cell carcinoma: spontaneous resolution and management of metastatic disease. Dermatol. Surg. 25, 23–25.

Cappuzzo, F., Ciuleanu, T., Stelmakh, L., Cicenas, S., Szczésna, A., Juhász, E., et al., 2010. Erlotinib as maintenance treatment in advanced non-small-cell lung cancer: a multicentre, randomised, placebo-controlled phase 3 study. Lancet Oncol. 11, 521–529.

Castells, A., Brúix, J., Brú, C., Ayuso, C., Roca, M., Boix, L., et al., 1995. Treatment of hepatocellular carcinoma with tamoxifen: a double-blind placebo-controlled trial in 120 patients. Gastroenterology 109, 917–922.

Cellerino, R., Tummarello, D., Guidi, F., Isidori, P., Raspugli, M., Biscottini, B., et al., 1991. A randomized trial of alternating chemotherapy versus best supportive care in advanced non-small-cell lung cancer. J. Clin. Oncol. 9, 1453–1461.

Challis, G.B., Stam, H.J., 1990. The spontaneous regression of cancer: a review of cases from 1900 to 1987. Acta Oncol. 29, 545–550.

Cheng, A.L., Kang, Y.K., Chen, Z., Tsao, C.J., Qin, S., Kim, J.S., et al., 2009. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. Lancet Oncol. 10, 25–34.

Choi, S.M., Go, H., Chung, D.H., Yim, J.J., 2013. Spontaneous regression of squamous cell lung cancer. Am. J. Respir. Crit. Care Med. 188, e5–e6.

Ciuleanu, T.E., Pavlovsky, A.V., Bodoky, G., Garin, A.M., Langmuir, V.K., Kroll, S., et al., 2009a. A randomised phase III trial of glufosfamide compared with best supportive care in metastatic pancreatic adenocarcinoma previously treated with gemcitabine. Eur. J. Cancer 45, 1589–1596.

Ciuleanu, T., Brodowicz, T., Zielinski, C., Kim, J.H., Krzakowski, M., Laack, E., et al., 2009b. Maintenance pemetrexed plus best supportive care versus placebo plus

best supportive care for non-small-cell lung cancer: a randomised, double-blind, phase 3 study. Lancet 374, 1432–1440.
Ciuleanu, T., Samarzjia, M., Demidchik, Y., Beliakouski, V., Rancic, M., Bentsion, D.L., Orlov, S.V., Schaeffler, B.A., De Jager, R.L., Breitz, H.B., 2010. Randomized phase III study (SPEAR) of picoplatin plus best supportive care (BSC) or BSC alone in patients (pts) with SCLC refractory or progressive within 6 months after first-line platinum-based chemotherapy. J. Clin. Oncol.
Cole, W.H., Everson, T.C., 1966. Spontaneous Regression of Cancer, 1st ed. W.B. Saunders, Philadelphia, PA.
Collisson, E.A., Campbell, J.D., Brooks, A.N., et al., 2014. Cancer Genome Atlas Research N, Cancer Genome Atlas Research N., 2014. Comprehensive molecular profiling of lung adenocarcinoma. Nature 511, 543–550.
Creighton, C.J., Morgan, M., Gunaratne, P.H., et al., 2013. Comprehensive molecular characterization of clear cell renal cell carcinoma. Nature 499, 43–49.
Crisci, A., Corsale, I., Abrami, F., Politi, L., Andreani, M., Borgianni, S., et al., 2008. Spontaneous regression of lung metastases from renal cell carcinoma: the importance of immunogenetic factors and a review of the literature. Minerva Urol. Nefrol. 60, 123–135.
Del Campo, J.M., Hitt, R., Sebastian, P., Carracedo, C., Lokanatha, D., Bourhis, J., et al., 2011. Effects of lapatinib monotherapy: results of a randomised phase II study in therapy-naive patients with locally advanced squamous cell carcinoma of the head and neck. Br. J. Cancer 105, 618–627.
Del Poggio, P., Mattiello, M., Gilardoni, L., Jamoletti, C., Colombo, S., Zabbialini, G., 2009. The mysterious case of spontaneous disappearance of hepatocellular carcinoma. Dig. Liver Dis. 41, e21–e25.
Demetri, G.D., van Oosterom, A.T., Garrett, C.R., Blackstein, M.E., Shah, M.H., Verweij, J., et al., 2006. Efficacy and safety of sunitinib in patients with advanced gastrointestinal stromal tumour after failure of imatinib: a randomised controlled trial. Lancet 368, 1329–1338.
Demetri, G.D., Reichardt, P., Kang, Y.K., Blay, J.Y., Rutkowski, P., Gelderblom, H., et al., 2013a. Efficacy and safety of regorafenib for advanced gastrointestinal stromal tumours after failure of imatinib and sunitinib (GRID): an international, multicentre, randomised, placebo-controlled, phase 3 trial. Lancet 381, 295–302.
Demetri, G.D., Chawla, S.P., Ray-Coquard, I., Le Cesne, A., Staddon, A.P., Milhem, M.M., et al., 2013b. Results of an international randomized phase III trial of the mammalian target of rapamycin inhibitor ridaforolimus versus placebo to control metastatic sarcomas in patients after benefit from prior chemotherapy. J. Clin. Oncol. 31, 2485–2492.
DerSimonian, R., Laird, N., 1986. Meta-analysis in clinical trials. Control Clin. Trials 7, 177–188.
Diede, S.J., 2014. Spontaneous regression of metastatic cancer: learning from neuroblastoma. Nat. Rev. Cancer 14, 71–72.
Dollinger, M.M., Lautenschlaeger, C., Lesske, J., Tannapfel, A., Wagner, A.D., Schoppmeyer, K., et al., 2010. Thymostimulin versus placebo for palliative treatment of locally advanced or metastasised hepatocellular carcinoma: a phase III clinical trial. BMC Cancer 10, 457.
Duval, S., Tweedie, R., 2000a. Trim and fill: a simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. Biometrics 56, 455–463.
Duval, S., Tweedie, R.L., 2000b. A nonparametric trim and fill method of accounting for publication bias in meta-analysis. J. Am. Stat. Assoc. 95, 89–98.
Eisen, T., Trefzer, U., Hamilton, A., Hersey, P., Millward, M., Knight, R.D., et al., 2010. Results of a multicenter, randomized, double-blind phase 2/3 study of lenalidomide in the treatment of pretreated relapsed or refractory metastatic malignant melanoma. Cancer 116, 146–154.
Eisenhauer, E.A., Therasse, P., Bogaerts, J., Schwartz, L.H., Sargent, D., Ford, R., et al., 2009. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur. J. Cancer 45, 228–247.
Elisei, R.S., Muller, S.P., Schoffski, P., Brose, M., Shah, Manisha, et al., Cabozantinib in Progressive Medullary Thyroid Cancer. p. 3639–46.
Escudier, B., Eisen, T., Stadler, W.M., Szczylik, C., Oudard, S., Siebels, M., et al., 2007. Sorafenib in advanced clear-cell renal-cell carcinoma. N. Engl. J. Med. 356, 125–134.
Everson, T.C., 1967. Spontaneous regression of cancer. Prog. Clin. Cancer 3, 79–95.
Fuchs, C.S., Tomasek, J., Yong, C.J., Dumitru, F., Passalacqua, R., Goswami, C., et al., 2014. Ramucirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (REGARD): an international, randomised, multicentre, placebo-controlled, phase 3 trial. Lancet 383, 31–39.
Fyfe, G., Fisher, R.I., Rosenberg, S.A., Sznol, M., Parkinson, D.R., Louie, A.C., 1995. Results of treatment of 255 patients with metastatic renal cell carcinoma who received high-dose recombinant interleukin-2 therapy. J. Clin. Oncol. 13, 688–696.
Gaafar, R.M., Surmont, V.F., Scagliotti, G.V., van Klaveren, R.J., Papamichael, D., Welch, J.J., et al., 2011. A double-blind, randomised, placebo-controlled phase III intergroup study of gefitinib in patients with advanced NSCLC, non-progressing after first line platinum-based chemotherapy (EORTC 08021/ILCP 01/03). Eur. J. Cancer 47, 2331–2340.
Garon, E.B., Rizvi, N.A., Hui, R., Leighl, N., Balmanoukian, A.S., Eder, J.P., et al., 2015. Pembrolizumab for the treatment of non-small-cell lung cancer. N. Engl. J. Med. 372, 2018–2028.
Gill, S., Murray, N., Dalmau, J., Thiessen, B., 2003. Paraneoplastic sensory neuronopathy and spontaneous regression of small cell lung cancer. Can. J. Neurol. Sci. 30, 269–271.
Gleave, M.E., Elhilali, M., Fradet, Y., Davis, I., Venner, P., Saad, F., et al., 1998. Interferon gamma-1b compared with placebo in metastatic renal-cell carcinoma. Canadian Urologic Oncology Group. N. Engl. J. Med. 338, 1265–1271.
Goss, G., Ferry, D., Wierzbicki, R., Laurie, S.A., Thompson, J., Biesma, B., et al., 2009. Randomized phase II study of gefitinib compared with placebo in chemotherapy-naive patients with advanced non-small-cell lung cancer and poor performance status. J. Clin. Oncol. 27, 2253–2260.
Grothey, A., Van Cutsem, E., Sobrero, A., Siena, S., Falcone, A., Ychou, M., et al., 2013. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. Lancet 381, 303–312.
Hamanishi, J., Mandai, M., Ikeda, T., et al., 2014. Efficacy and safety of anti-PD-1 antibody (Nivolumab: BMS-936558, ONO-4538) in patients with platinum-resistant ovarian cancer. J. Clin. Oncol. 32 (Suppl. (5s)) (abstr 5511).
Hamid, O., Robert, C., Daud, A., Hodi, F.S., Hwu, W.J., Kefford, R., et al., 2013. Safety and tumor responses with lambrolizumab (anti-PD-1) in melanoma. N. Engl. J. Med. 369, 134–144.
Harada, T., Sakaguchi, T., Inaba, K., Nakamura, T., Kurachi, K., Fukazawa, A., et al., 2010. Spontaneous regression of hepatocellular carcinomas. Nihon Shokakibyo Gakkai Zasshi 107, 432–441.
Higgins, J.P., Thompson, S.G., Deeks, J.J., Altman, D.G., 2003. Measuring inconsistency in meta-analyses. BMJ 327, 557–560.
Hirano, S., Nakajima, Y., Morino, E., Fujikura, Y., Mochizuki, M., Takeda, Y., et al., 2007. A case of spontaneous regression of small cell lung cancer with progression of paraneoplastic sensory neuropathy. Lung Cancer 58, 291–295.
Hodi, F.S., O'Day, S.J., McDermott, D.F., Weber, R.W., Sosman, J.A., Haanen, J.B., et al., 2010. Improved survival with ipilimumab in patients with metastatic melanoma. N. Engl. J. Med. 363, 711–723.
Horino, T., Takao, T., Yamamoto, M., Geshi, T., Hashimoto, K., 2006. Spontaneous remission of small cell lung cancer: a case report and review in the literature. Lung Cancer 53, 249–252.
Hsu, C., Yang, T.S., Huo, T.I., Hsieh, R.K., Yu, C.W., Hwang, W.S., et al., 2012. Vandetanib in patients with inoperable hepatocellular carcinoma: a phase II, randomized, double-blind, placebo-controlled study. J. Hepatol. 56, 1097–1103.
Hwang, E.D., Kim, Y.J., Leem, A.Y., Ji, A.Y., Choi, Y., Jung, J.Y., et al., 2013. Spontaneous regression of non-small cell lung cancer in a patient with idiopathic pulmonary fibrosis: a case report. Tuberc. Respir. Dis. (Seoul) 75, 214–217.
Iwakami, S., Fujii, M., Ishiwata, T., Iwakami, N., Hara, M., Ihara, H., et al., 2013. Small-cell lung cancer exhibiting spontaneous regression. Intern. Med. 52, 2249–2252.
Jadad, A.R., Moore, R.A., Carroll, D., Jenkinson, C., Reynolds, D.J., Gavaghan, D.J., et al., 1996. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin. Trials 17, 1–12.
Jonker, D.J., O'Callaghan, C.J., Karapetis, C.S., Zalcberg, J.R., Tu, D., Au, H.J., et al., 2007. Cetuximab for the treatment of colorectal cancer. N. Engl. J. Med. 357, 2040–2048.
Kadish, A.S., Timmins, P., Wang, Y., Ho, G.Y., Burk, R.D., Ketz, J., et al., 2002. Regression of cervical intraepithelial neoplasia and loss of human papillomavirus (HPV) infection is associated with cell-mediated immune responses to an HPV type 16 E7 peptide. Cancer Epidemiol. Biomark. Prev. 11, 483–488.
Kappauf, H., Gallmeier, W.M., Wünsch, P.H., Mittelmeier, H.O., Birkmann, J., Büschel, G., et al., 1997. Complete spontaneous remission in a patient with metastatic non-small-cell lung cancer. Case report, review of the literature, and discussion of possible biological pathways involved. Ann. Oncol. 8, 1031–1039.
Karkos, P.D., Sastry, A., Hampal, S., Al-Jafari, M., 2010. Spontaneous regression of Merkel cell carcinoma of the nose. Head Neck 32, 411–414.
Kubota, M., Sueyoshi, S., Fujita, H., Fujii, T., Yamana, H., Shirouzu, K., 2003. Spontaneous regression in small cell esophageal carcinoma. Jpn. J. Thorac. Cardiovasc. Surg. 51, 660–664.
Lawrence, M.S., Stojanov, P., Polak, P., Kryukov, G.V., Cibulskis, K., Sivachenko, A., et al., 2013. Mutational heterogeneity in cancer and the search for new cancer-associated genes. Nature 499, 214–218.
Leboulleux, S., Bastholt, L., Krause, T., de la Fouchardiere, C., Tennvall, J., Awada, A., et al., 2012. Vandetanib in locally advanced or metastatic differentiated thyroid cancer: a randomised, double-blind, phase 2 trial. Lancet Oncol. 13, 897–905.
Ledermann, J., Harter, P., Gourley, C., Friedlander, M., Vergote, I., Rustin, G., et al., 2012. Olaparib maintenance therapy in platinum-sensitive relapsed ovarian cancer. N. Engl. J. Med. 366, 1382–1392.
Lee, Y.S., Kang, H.M., Jang, P.S., Jung, S.S., Kim, J.M., Kim, J.O., et al., 2008. Spontaneous regression of small cell lung cancer. Respirology 13, 615–618.
Lee, J.S., Hirsh, V., Park, K., Qin, S., Blajman, C.R., Perng, R.P., et al., 2012a. Vandetanib versus placebo in patients with advanced non-small-cell lung cancer after prior therapy with an epidermal growth factor receptor tyrosine kinase inhibitor: a randomized, double-blind phase III trial (ZEPHYR). J. Clin. Oncol. 30, 1114–1121.
Lee, S.M., Khan, I., Upadhyay, S., Lewanski, C., Falk, S., Skailes, G., et al., 2012b. First-line erlotinib in patients with advanced non-small-cell lung cancer unsuitable for chemotherapy (TOPICAL): a double-blind, placebo-controlled, phase 3 trial. Lancet Oncol. 13, 1161–1170.
Li, J., Qin, S., Xu, J., Guo, W., Xiong, J., Bai, Y., et al., 2013. Apatinib for chemotherapy-refractory advanced metastatic gastric cancer: results from a randomized, placebo-controlled, parallel-arm, phase II trial. J. Clin. Oncol. 31, 3219–3225.

Lim, D.H., Park, K.W., Lee, S.I., 2014. Spontaneous complete regression of multiple metastases of hepatocellular carcinoma: a case report. Oncol. Lett. 7, 1225–1228.
Liu, C.L., Fan, S.T., Ng, I.O., Lo, C.M., Poon, R.T., Wong, J., 2000. Treatment of advanced hepatocellular carcinoma with tamoxifen and the correlation with expression of hormone receptors: a prospective randomized study. Am. J. Gastroenterol. 95, 218–222.
Llovet, J.M., Ricci, S., Mazzaferro, V., Hilgard, P., Gane, E., Blanc, J.F., et al., 2008. Sorafenib in advanced hepatocellular carcinoma. N. Engl. J. Med. 359, 378–390.
Llovet, J.M., Decaens, T., Raoul, J.L., Boucher, E., Kudo, M., Chang, C., et al., 2013. Brivanib in patients with advanced hepatocellular carcinoma who were intolerant to sorafenib or for whom sorafenib failed: results from the randomized phase III BRISK-PS study. J. Clin. Oncol. 31, 3509–3516.
Machiels, J.P., Subramanian, S., Ruzsa, A., Repassy, G., Lifirenko, I., Flygare, A., et al., 2011. Zalutumumab plus best supportive care versus best supportive care alone in patients with recurrent or metastatic squamous-cell carcinoma of the head and neck after failure of platinum-based chemotherapy: an open-label, randomised phase 3 trial. Lancet Oncol. 12, 333–343.
Meza-Junco, J., Montaño-Loza, A.J., Martinez-Benítez, B., Cabrera-Aleksandrova, T., 2007. Spontaneous partial regression of hepatocellular carcinoma in a cirrhotic patient. Ann. Hepatol. 6, 66–69.
Miller, V.A., Hirsh, V., Cadranel, J., Chen, Y.M., Park, K., Kim, S.W., et al., 2012. Afatinib versus placebo for patients with advanced, metastatic non-small-cell lung cancer after failure of erlotinib, gefitinib, or both, and one or two lines of chemotherapy (LUX-lung 1): a phase 2b/3 randomised trial. Lancet Oncol. 13, 528–538.
Misawa, K., Hata, Y., Manabe, K., Matsuoka, S., Saito, M., Takada, J., et al., 1999. Spontaneous regression of hepatocellular carcinoma. J. Gastroenterol. 34, 410–414.
Motzer, R.J., Escudier, B., Oudard, S., Hutson, T.E., Porta, C., Bracarda, S., et al., 2008. Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomised, placebo-controlled phase III trial. Lancet 372, 449–456.
Mubarak, N., Gaafar, R., Shehata, S., Hashem, T., Abigeres, D., Azim, H.A., et al., 2012. A randomized, phase 2 study comparing pemetrexed plus best supportive care versus best supportive care as maintenance therapy after first-line treatment with pemetrexed and cisplatin for advanced, non-squamous, non-small cell lung cancer. BMC Cancer 12, 423.
Mulders, P., Hawkins, R., Nathan, P., de Jong, I., Osanto, S., Porfiri, E., et al., 2012. Cediranib monotherapy in patients with advanced renal cell carcinoma: results of a randomised phase II study. Eur. J. Cancer 48, 527–537.
Muro, K., Bang, Y., Shankaran, V., et al., 2014. A phase 1b study of pembrolizumab (Pembro; MK-3475) in patients with advanced gastric cancer. ESMO Congr., LBA15.
Nakano, T., Tamura, S., Higashino, K., 1988. Hepatocellular carcinoma after spontaneous regression of extensive small cell lung cancer. Am. J. Med. 84, 178–179.
Negi, S.S., Agarwal, A., Chaudhary, A., 2006. Flutamide in unresectable pancreatic adenocarcinoma: a randomized, double-blind, placebo-controlled trial. Invest. New Drugs 24, 189–194.
O'Brien, M.E., Ciuleanu, T.E., Tsekov, H., Shparyk, Y., Cucevia, B., Juhasz, G., et al., 2006. Phase III. trial comparing supportive care alone with supportive care with oral topotecan in patients with relapsed small-cell lung cancer. J. Clin. Oncol. 24, 5441–5447.
Ohtsu, A., Ajani, J.A., Bai, Y.X., Bang, Y.J., Chung, H.C., Pan, H.M., et al., 2013. Everolimus for previously treated advanced gastric cancer: results of the randomized, double-blind, phase III GRANITE-1 study. J. Clin. Oncol. 31, 3935–3943.
Oquiñena, S., Guillen-Grima, F., Iñarrairaegui, M., Zozaya, J.M., Sangro, B., 2009. Spontaneous regression of hepatocellular carcinoma: a systematic review. Eur. J. Gastroenterol. Hepatol. 21, 254–257.
Parikh, P.M., Vaid, A., Advani, S.H., Digumarti, R., Madhavan, J., Nag, S., et al., 2011. Randomized, double-blind, placebo-controlled phase II study of single-agent oral talactoferrin in patients with locally advanced or metastatic non-small-cell lung cancer that progressed after chemotherapy. J. Clin. Oncol. 29, 4129–4136.
Paz-Ares, L., de Marinis, F., Dediu, M., Thomas, M., Pujol, J.L., Bidoli, P., et al., 2012. Maintenance therapy with pemetrexed plus best supportive care versus placebo plus best supportive care after induction therapy with pemetrexed plus cisplatin for advanced non-squamous non-small-cell lung cancer (PARAMOUNT): a double-blind, phase 3, randomised controlled trial. Lancet Oncol. 13, 247–255.
Peters, J.L., Sutton, A.J., Jones, D.R., Abrams, K.R., Rushton, L., 2007. Performance of the trim and fill method in the presence of publication bias and between-study heterogeneity. Stat. Med. 26, 4544–4562, I>.
Pili, R., Häggman, M., Stadler, W.M., Gingrich, J.R., Assikis, V.J., Björk, A., et al., 2011. Phase II randomized, double-blind, placebo-controlled study of tasquinimod in men with minimally symptomatic metastatic castrate-resistant prostate cancer. J. Clin. Oncol. 29, 4022–4028.
Powles, T., Eder, J.P., Fine, G.D., Braiteh, F.S., Loriot, Y., Cruz, C., et al., 2014. MPDL3280A (anti-PD-L1) treatment leads to clinical activity in metastatic bladder cancer. Nature 515, 558–562.
Pritchard, J., Hickman, J.A., 1994. Why does stage 4s neuroblastoma regress spontaneously? Lancet 344, 869–870.
Ramalingam, S., Crawford, J., Chang, A., Manegold, C., Perez-Soler, R., Douillard, J.Y., et al., 2013. Talactoferrin alfa versus placebo in patients with refractory advanced non-small-cell lung cancer (FORTIS-M trial). Ann. Oncol. 24, 2875–2880.
Rao, S., Cunningham, D., de Gramont, A., Scheithauer, W., Smakal, M., Humblet, Y., et al., 2004. Phase III. double-blind placebo-controlled study of farnesyl transferase inhibitor R115777 in patients with refractory advanced colorectal cancer. J. Clin. Oncol. 22, 3950–3957.
Raymond, E., Dahan, L., Raoul, J.L., Bang, Y.J., Borbath, I., Lombard-Bohas, C., et al., 2011. Sunitinib malate for the treatment of pancreatic neuroendocrine tumors. N. Engl. J. Med. 364, 501–513.
Rucker, G., Schwarzer, G., Carpenter, J., 2008. Arcsine test for publication bias in meta-analyses with binary outcomes. Stat. Med. 27, 746–763.
Santoro, A., Rimassa, L., Borbath, I., Daniele, B., Salvagni, S., van Laethem, J.L., et al., 2013. Tivantinib for second-line treatment of advanced hepatocellular carcinoma: a randomised, placebo-controlled phase 2 study. Lancet Oncol. 14, 55–63.
Sarin, S.K., Kumar, M., Garg, S., Hissar, S., Pandey, C., Sharma, B.C., 2006. High dose vitamin K3 infusion in advanced hepatocellular carcinoma. J. Gastroenterol. Hepatol. 21, 1478–1482.
Scher, H.I., Fizazi, K., Saad, F., Taplin, M.E., Sternberg, C.N., Miller, K., et al., 2012. Increased survival with enzalutamide in prostate cancer after chemotherapy. N. Engl. J. Med. 367, 1187–1197.
Schwarzer G., 2013. Meta-Analysis with R.R package version 2.3-0. http://CRANR-projectorg/package=meta.
Sharma, A., Dwary, A.D., Mohanti, B.K., Deo, S.V., Pal, S., Sreenivas, V., et al., 2010. Best supportive care compared with chemotherapy for unresectable gall bladder cancer: a randomized controlled study. J. Clin. Oncol. 28, 4581–4586.
Shepherd, F.A., Rodrigues Pereira, J., Ciuleanu, T., Tan, E.H., Hirsh, V., Thongprasert, S., et al., 2005. Erlotinib in previously treated non-small-cell lung cancer. N. Engl. J. Med. 353, 123–132.
Snyder, A., Makarov, V., Merghoub, T., Yuan, J., Zaretsky, J.M., Desrichard, A., et al., 2014. Genetic basis for clinical response to CTLA-4 blockade in melanoma. N. Engl. J. Med. 371, 2189–2199.
Sternberg, C.N., Davis, I.D., Mardiak, J., Szczylik, C., Lee, E., Wagstaff, J., et al., 2010. Pazopanib in locally advanced or metastatic renal cell carcinoma: results of a randomized phase III trial. J. Clin. Oncol. 28, 1061–1068.
Thatcher, N., Chang, A., Parikh, P., Rodrigues Pereira, J., Ciuleanu, T., von Pawel, J., et al., 2005. Gefitinib plus best supportive care in previously treated patients with refractory advanced non-small-cell lung cancer: results from a randomised, placebo-controlled, multicentre study (iressa survival evaluation in lung cancer). Lancet 366, 1527–1537.
Therasse, P., Arbuck, S.G., Eisenhauer, E.A., Wanders, J., Kaplan, R.S., Rubinstein, L., et al., 2000. New guidelines to evaluate the response to treatment in solid tumors European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J. Natl. Cancer Inst. 92, 205–216.
Thomas, J.A., Badini, M., 2011. The role of innate immunity in spontaneous regression of cancer. Indian J. Cancer 48, 246–251.
Topalian, S.L., Hodi, F.S., Brahmer, J.R., Gettinger, S.N., Smith, D.C., McDermott, D.F., et al., 2012. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. N. Engl. J. Med. 366, 2443–2454.
Torroni, A., Loré, B., Iannetti, G., 2007. The importance of the head and neck region in regression of advanced MCC: a clinical report. J. Craniofac. Surg. 18, 1173–1176.
Tran, T., Burt, D., Eapen, L., Keller, O.R., 2013. Spontaneous regression of metastatic melanoma after inoculation with tetanus-diphtheria-pertussis vaccine. Curr. Oncol. 20, e270–3.
vanderGraaf, W.T., Blay, J.Y., Chawla, S.P., Kim, D.W., Bui-Nguyen, B., Casali, P.G., et al., 2012. Pazopanib for metastatic soft-tissue sarcoma (PALETTE): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet 379, 1879–1886.
Van Cutsem, E., Peeters, M., Siena, S., Humblet, Y., Hendlisz, A., Neyns, B., et al., 2007. Open-label phase III trial of panitumumab plus best supportive care compared with best supportive care alone in patients with chemotherapy-refractory metastatic colorectal cancer. J. Clin. Oncol. 25, 1658–1664.
Vesely, M.J., Murray, D.J., Neligan, P.C., Novak, C.B., Gullane, P.J., Ghazarian, D., 2008. Complete spontaneous regression in Merkel cell carcinoma. J. Plast. Reconstr. Aesthet. Surg. 61, 165–171.
Viechtbauer, W., 2010. Conducting meta-analyses in R with the metafor package. J. Stat. Softw. 36 (3), 1–48.
Wildiers, H., Fontaine, C., Vuylsteke, P., Martens, M., Canon, J.L., Wynendaele, W., et al., 2010. Multicenter phase II randomized trial evaluating antiangiogenic therapy with sunitinib as consolidation after objective response to taxane chemotherapy in women with HER2-negative metastatic breast cancer. Breast Cancer Res. Treat. 123, 463–469.
Wolchok, J.D., Hoos, A., O'Day, S., Weber, J.S., Hamid, O., Lebbe, C., et al., 2009. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. Clin. Cancer Res. 15, 7412–7420.
World Health Organization Handbook for Reporting Results of Cancer Treatment. Geneva, Switzerland 1979.
Wu, Y.L., Zhou, C., Cheng, Y., Lu, S., Chen, G.Y., Huang, C., et al., 2013. Erlotinib as second-line treatment in patients with advanced non-small-cell lung cancer and asymptomatic brain metastases: a phase II study (CTONG-0803). Ann. Oncol. 24, 993–999.
Yao, J.C., Shah, M.H., Ito, T., Bohas, C.L., Wolin, E.M., van Cutsem, E., et al., 2011. Everolimus for advanced pancreatic neuroendocrine tumors. N. Engl. J. Med. 364, 514–523.

Yoshimitsu, K., Honda, H., Kaneko, K., Fukuya, T., Irie, H., Aibe, H., et al., 1996. Temporary spontaneous regression of intrahepatic cholangiocarcinoma. Comput. Med. Imaging Graph. 20, 115–118.
Yoshino, T., Mizunuma, N., Yamazaki, K., Nishina, T., Komatsu, Y., Baba, H., et al., 2012. TAS-102 monotherapy for pretreated metastatic colorectal cancer: a double-blind, randomised, placebo-controlled phase 2 trial. Lancet Oncol. 13, 993–1001.
Yuen, M.F., Poon, R.T., Lai, C.L., Fan, S.T., Lo, C.M., Wong, K.W., et al., 2002. A randomized placebo-controlled study of long-acting octreotide for the treatment of advanced hepatocellular carcinoma. Hepatology 36, 687–691.
Zaheer, W., Friedland, M.L., Cooper, E.B., DoRosario, A., Burd, R.M., Gagliardi, J., et al., 1993. Spontaneous regression of small cell carcinoma of lung associated with severe neuropathy. Cancer Invest. 11, 306–309.
Zhang, L., Ma, S., Song, X., Han, B., Cheng, Y., Huang, C., et al., 2012. Gefitinib versus placebo as maintenance therapy in patients with locally advanced or metastatic non-small-cell lung cancer (INFORM; C-TONG 0804): a multicentre, double-blind randomised phase 3 trial. Lancet Oncol. 13, 466–475.

## Biography

**Guru Sonpavde, MD** is a genitourinary medical oncologist and Associate Professor of Medicine and the director of the urologic oncology program at the University of Alabama at Birmingham (UAB) Comprehensive Cancer Center in the United States.