Immune-related Toxicities in PD-1 and PD-L1 Immunotherapies: a Systematic Review and Meta-analysis

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Immune-related Toxicities in PD-1 and PD-L1 Immunotherapies: a Systematic Review and Meta-analysis

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Running Title: Immune-related toxicities with anti-PD-1 or anti-PD-L1 antibodies

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Abstract 286 (limit 300)

Objective: Use of programmed cell death 1 (PD-1) immunotherapies is rapidly expanding across cancers. Proper clinical management requires understanding associated immune-related adverse events (irAE) that can include organ toxicities, non-specific signs/symptoms, and increasingly recognized musculoskeletal problems. We set out to evaluate rates of serious organ-specific irAEs, non-specific possibly immune-related symptoms, and musculoskeletal problems with anti-PD1 agents overall and compared to control therapies.

Design: Systematic review and meta-analysis of randomized controlled trials comparing an anti-PD-1 or anti-PD-L1 monoclonal antibody to standard treatment in patients with cancer.

Data Sources: Databases including Medline, Embase, Cochrane Library, Web of Science, and Scopus, were searched up to March 16, 2017 and combined with data available on ClinicalTrials.gov.

Eligibility criteria for selecting studies: Studies including primary clinical trial data on cancer patients with recurrent or metastatic disease.

Appraisal and Data Extraction: Three independent investigators extracted data on adverse events from ClinicalTials.gov and the published reports. Risk of bias was assessed with the Cochrane risk of bias tool by two independent investigators.

Results: Thirteen relevant studies were included; adverse event data was available on ClinicalTrials.gov for 8. Studies compared nivolumab (n=6), pembrolizumab (n=5) or atezolizumab (n=2) to chemotherapy (n=11), targeted agents (n=1) or both (n=1). While serious organ-specific irAEs were rare, rates of hypothyroidism (OR 7.56; 95% CI: 4.53- to 12.61), pneumonitis (OR 5.37; 95%CI: 2.73- to 10.56), and colitis (OR 2.88; 95% CI: 1.30- to 6.37) were increased with anti-PD1 agents compared to standard treatment, as was rash (OR 2.34; 95%CI 2.73– to 10.56). Incidence of fatigue (32%) and diarrhea (19%) were high but similar to control. Reporting of musculoskeletal problems was inconsistent; rates varied but were >20% in some studies for back pain and arthraligia.

Conclusions: Organ-specific irAEs are uncommon with anti-PD-1 agents but risk is increased compared to control therapies; non-specific symptoms are largely similar. Musculoskeletal problems are inconsistently reported but toxicities may be common.

Print Abstract (word count 290, limit 300)

Study question: What are the rates of serious organ-specific immune-related adverse events (irAE), non-specific possibly immune-related symptoms, and musculoskeletal problems with anti- programmed cell death 1 (PD-1) immunotherapuetic agents overall and compared to control therapies?

Methods: Systematic review and meta-analysis of randomized controlled trials comparing an anti-PD-1 or anti-PD-L1 monoclonal antibody to standard treatment in patients with cancer. Multiple databases were searched up to March 16, 2017 to identify studies reporting primary clinical trial data. Three independent investigators extracted data on adverse events from ClinicalTrials.gov and published reports. We calculated overall event rates using the total number of patients across trials. We performed meta-analysis for each outcome, pooling odds ratios of event rates from each study using a random effects or fixed effects model depending on heterogeneity.

Study answer and limitations: Thirteen relevant studies were included; adverse event data was available on ClinicalTrials.gov for 8. Studies compared nivolumab (n=6), pembrolizumab (n=5) or atezolizumab (n=2) to chemotherapy (n=11), targeted agents (n=1) or both (n=1). While serious organ-specific irAEs were rare, rates of hypothyroidism (OR 7.56; 95% CI: 4.53 to 12.61), pneumonitis (OR 5.37; 95%CI: 2.73 to 10.56), and colitis (OR 2.88; 95% CI: 1.30 to 6.37) were increased with anti-PD1 agents compared to standard treatment, as was rash (OR 2.34; 95%CI 2.73 to 10.56). Incidence of fatigue (32%) and diarrhea (19%) were high but similar to control arms. Reporting of musculoskeletal problems was inconsistent; rates varied but were >20% in some studies for back pain and arthraligia.

What this study adds: Organ-specific irAEs are uncommon with anti-PD-1 agents but risk is increased compared to control therapies; non-specific symptoms are largely similar. Musculoskeletal problems are inconsistently reported but toxicities may be common.

Funding, competing interests, data sharing: This study was supported in part by the NIH/NCI P30 CA008748 Cancer Center Support Grant. Authos report no relevant competing interests.

Summary box

Use of anti-neoplastic immunotherapies targeting programmed cell death 1 or its ligand (anti-PD-1 agents) is rapidly expanding across cancers. Proper clinical management requires understanding associated immune-related adverse events (irAE) that can include organ toxicities, non-specific signs/symptoms, and increasingly recognized musculoskeletal problems. However, rates of these toxicities are unclear and publications from clinical trials may inconsistently report unexpected toxicities. Our systematic review and meta-analysis suggests that organ-specific irAEs are uncommon with anti-PD-1 agents but that risk is increased compared to control therapies; non-specific symptoms such as fatigue are largely similar. Musculoskeletal problems are inconsistently reported but toxicities may be common.

Introduction

The development and rapid uptake of checkpoint inhibitors, a modern form of immunotherapy, has resulted in a paradigm shift in the management of numerous cancers. In 2011, ipilumuab, an anti-CTLA-4 antibody, became the first checkpoint inhibitor approved by the Food and Drug Administration (FDA) for the treatment of advanced melanoma. While ipilimumab remains in use only for melanoma, checkpoint inhibitors directed at the programmed death-1 pathway, or "anti-PD1 agents" have received approval for the treatment of multiple cancers. Anti-PD1 agents include monoclonal antibodies directed at both PD-1 (pembrolizumab and nivolumab) and its ligand PD-L1 (avelumab, atezolizumab, durvalumab). As of May 2017, at least one of the anti-PD1 agents has been approved in advanced melanoma, non-small cell lung cancer, renal cell carcinoma, Hodgkin's lymphoma, head and neck cancer, bladder urothelial cancer, merkel cell carcinoma, and tumors of any organ with high microsatellite instability (MSI-H). In addition, anti-PD1 agents are also currently under investigation in at least 135 clinical trials for additional metastatic cancers, earlier stage cancers and in combination with other immunotherapeutic and non-immunotherapeutic drugs which will further fuel their use.(1)

Immunotherapy, as a drug class, boosts the body's natural defense against cancer. These drugs have toxicities, collectively known as immune-related adverse events (irAEs), that represent immune effects on normal tissue that can result from misdirected stimulation of the immune system. While anti-PD1 agents are overall less toxic than standard chemotherapy,(2-8) certain organ-specific irAEs including hypothyroidism, colitis, pnemonitis and hepatitis have routinely been reported in clinical trials of anti-PD1 agents, and more general toxicities that might be related to immune activation, including fatigue, rash and diarrhea, have been common.(2, 7, 8) Despite less clarity about their prevalence, other toxicities potentially attributable to systemic inflammation, particularly musculoskeletal problems, have also been described in patients treated with anti-PD1 agents and may negatively impact quality of life.(9,

10) Given the rapidly expanding population of patients exposed to anti-PD1 agents and the wide spectrum of potential immune-related effects(1), understanding toxicities associated with anti-PD1 drugs is critical for clinicians caring for these patients in various settings.

We performed a systematic review and meta-analysis of immune-related toxicities of anti-PD1 and anti-PD-L1 inhibitors. We included organ-specific and other toxicities potentially related to inflammation and gathered data from both ClinicalTrials.gov and published literature. We hypothesized that 1) rates of organ-specific irAEs including hypothyroidism, colitis, pneumonitis and hepatitis would be low overall but higher with anti-PD1 agents than with standard therapies and that 2) rates of general possibly immune-related toxicities specifically fatigue, diarrhea and rash, would be higher than organ-specific irAE's but would not be increased compared to standard therapies. We also hypothesized that musculoskeletal problems would be common with anti-PD1 agents, but inconsistently documented.

Methods

We conducted a literature search to identify randomized clinical trials comparing single agent anti-PDL or anti PD-L1 checkpoint inhibitor therapy to a standard active treatment in patients with cancer to evaluate rates of immune-related toxicities including organ-specific irAE's, general symptoms, and musculoskeletal problems and to calculate risks compared to control therapies. We performed the study in adherence with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.(11)

Data Sources and Searches

We electronically searched 5 databases (MEDLINE [via PubMed], Embase, Cochrane Central Register of Controlled Trials [Cochrane Library], Web of Science, and Scopus) from the inception of all searched databases in August 2016 and updated the search in March 2017. For PubMed, Embase, and Cochrane, we used both controlled vocabulary and text words for synonymous terminology within titles and abstracts in the development of search strategies.

Web of Science and Scopus were searched using only text word searching of titles and abstracts. The search strategy contained two concepts that were linked together with the AND operator: (1) Nivolumab, Pembrolizumab, Ipilimumab, Avelumab, Tremelimumab, Atezolizumab, Durvalumab, checkpoint inhibitors; and (2) phase 2 clinical trials, phase 3 clinical trials, randomized controlled trials (See Figure 1 for a complete list of search terms). All search results were combined in a bibliographic management tool (EndNote) with duplicates eliminated using the Bramer method.(12)

Study Selection

We included studies that addressed a cancer and reported results of a randomized study of an anti-PD-1 or anti-PD-L1 monoclonal antibody. We excluded reviews, commentaries, studies published only in abstract form, quality-of-life studies, cost-effectiveness analyses, and those in which the effect of the drug could not be ascertained, such as when the control was a different dose of the same drug or another immunotherapeutic agent. (Figure 1) Study selection was performed in two stages. Two authors (S.B., Z.W.) screened all titles and abstracts for full-text review. Three authors (S.B., D.K., Z.W.) reviewed and discussed the remaining 18 full-text articles and included 13 studies. Disagreements were resolved by concensus. All included studies represented unique trials.

Data Extraction and Quality Assessment

Data from each study was extracted by two of the following three authors (S.B., D.K., N.K.) and disagreements were resolved by concensus involving all three. From each study, we extracted patient characterisitics (sex, performance status, and age), the sizes of intervention and control groups, median treatment time, and median follow-up. Two authors (D.K., A.Y.) independently assessed the quality of all articles included in the review using the Cochrane Risk

of Bias Tool(13) and used a weighted Cohen's κ coefficient to measure agreement. Differences were resolved by consensus.

Our primary outcome was the incidence of commonly described organ-specific irAEs (hypothyroidism, colitis, hypophysitis, pnemonitis and hepatitis) and more general signs and symptoms that could be related to immune activation (diarrhea, rash and fatigue). Our secondary outcome was the incidence of adverse events consistent with musculoskeletal problems (back pain, arthritis, arthralgia, myalgia and musculoskeletal pain). We first searched for adverse event data on ClinicalTrials.gov, available as of 3/28/2017. For studies for which full toxicity information was not posted on ClinicalTrials.gov, we used information from the publication and directly contacted study authors of the study or pharmaceutical sponsors for additional information. We recorded data on adverse events reported as either "serious" or "other" on ClinicalTrials.gov. For data extracted from published reports, we used the Common Terminology of Clinical Adverse Events (CTCAE) categorization to identify grades 3-5 as "serious" and CTCAE grades 1-2 as "other". For studies with information available from both sources, we prioritized data from ClinicalTrials.gov over toxicity data from the publications. If the study did not report a specific adverse event, we assumed that the event did not occur. Data from different dosing arms within the same study were extracted and reported separately.

Data Synthesis and Analysis

We calculated overall event rates by dividing the total number of patients across trials with a given toxicity by the total number at risk. We examined the number of events for each irAE of interest to determine whether meta-analysis was feasible. For each included study, we calculated odds ratios and 95% confidence intervals for event rates in the intervention arm compared to control based on the reported number of events and sample size. We used the I-squared index (I^2) and Cochran's Q statistics to examine heterogeneity across trials for each outcome. If significant heterogeneity was not present ($p>0.1$), pooled OR and 95% CI were

estimated with a fixed effects model using the inverse-variance method. A random-effects model using the inverse-variance method was used to calculate pooled OR and 95% CI if significant heterogeneity was present. Studies were weighted based on the inverse of the variance of the effect estimate. If a study included more than one intervention arm (e.g. Herbst(14) and Ribas(15) reported 2mg/kg and 10mg/kg arms for pembrolizaumab), we separately compared each intervention arm to the control arm. We conducted subgroup analyses to examine studies by control group treatment (chemotherapy vs. targeted therapy). We assessed for publication bias using funnel plots. All statistical analyses were conducted using Review Manager 5.3 (Copenhagen, Denmark).

Role of Funding Source

No external funding was obtained specifically for this review but the effort was supported in part by the NIH/NCI P30 CA008748 Cancer Center Support Grant. The funder had no role in the design of the study; the collection, analysis, and interpretation of the data; or approval of the finished manuscript.

Results

Our search identified 2,486 records; 18 underwent full-text review and 13 were included for quantitiative synthesis and meta-analysis (Figure 2).(14-26) Included articles were published (online) between November 2014 and February 2017. Funnel plots showed no evidence of publication bias (not shown).

Study Characteristics

All studies were international multi-center studies funded by the pharmaceutical industry, with intervention group sample sizes ranging from 59 to 609 patients. Seven were completed in patients with metastatic non-small cell lung cancer (14, 16, 17, 21, 23, 24, 26), 3 in melanoma

(15, 19, 20) , and one each in renal cell carcinoma (18), bladder cell carcinoma (25), and head and neck squamous cell carcinoma (22). Patients in the intervention arm received nivolumab in 6 studies (16-20, 22), pembrolizumab in 5 studies (14, 15, 23-25) and atezolizumab in 2 studies (21, 26). One trial evaluated the combinationof pembrolizumab with chemotherapy (carboplatin, and pemetrexed) compared to chemotherapy (carboplatin and pemetrexed) alone.(23) In two studies of pembrolizumab, two different doses 2mg/kg and 10mg/kg were compared to each other, in addition to a standard control.(14, 15) The control arm was a single chemotherapy agent in six studies (14, 16, 17, 19, 21, 26), a doublet chemotherapy in one study (23), a small molecule inhibitor in one study (18) and investigators' choice in four studies.(15, 20, 22, 25) Across studies, the primary endpoint was survival, with adverse events reported as secondary outcomes. All studies continued treatment until progression of disease or severe toxicity. The median treatment time in the investigational arm ranged from 3 to 8 months and the median duration of follow-up across studies was 13.1 months (range 5.1 to -25 months). As of March 27, 2017, adverse event data was available on Clinicaltrials.gov for 8 studies.

Quality of included studies

There was high inter-rater agreement for risk-of-bias assessments (κ 0.89) and overall risk of bias was unclear (Table 1).(13) All studies but one were open-label with primary outcome of overall survival. Outcome assessors for secondary outcomes were blinded in 7 studies (54%), but because toxicity reporting is performed by clinicians directly caring for patients, reports of toxicity rates in these open-label studies were by definition unmasked. We found no evidence of selective reporting or incomplete outcome data reporting for the primary outcomes, though some studies were ongoing and included only preliminary data. Further because toxicity outcomes were not collected and reported differently we could not assess their selective reporting.

Organ-specific Immune-related Toxicities

A total of 6,676 patients were evaluated across the 13 studies with 3,803 in the investigational arm (nivolumab 1,534, pembrolizumab 1,459, and azetolizmumab 751) and 2,873 in control arms (chemotherapy including cetuximab 2,476, or a biological agent 397). All studies reported organ-specific irAEs of interest. Looking at any-grade organ-specific irAEs, among the 3,803 total patients exposed to anti-PD1 agents 214 (5.6%) had hypothyroidism, 85 (2.2%) had pneumonitis, 25 (0.7%) had colitis, 6 (0.2%) had hepatitis, and 4 (0.1%) had hypophysitis. The most common "serious" irAE was pneumonitis which occured in 54 (1.4%) patients, while serious colitis, hypothyroidism, hepatitis and hypophysitis occurred in 18 (0.5%), 6 (0.2%), 5 (0.1%) and 4 (0.1%) patients respectively. Rates of organ-specific "serious" irAEs by specific drug are shown in Table 2.

In the meta-analysis, compared to patients treated in control arms, those treated with anti-PD1 agents were at a higher risk for any grade hypothyroidism (OR 6.92; 95% CI 3.25 to 14.75, P<.001) (Figure 3), pneumonitis (OR 3.82; 95% CI 1.27 to 11.45, P=0.02) (Figure 4), and colitis (OR 2.88, 95% CI, 1.30 to 6.37, P=.009) (Figure 5). When we excluded the study in which the control treatment was everolimus, a drug known to causes pneumonitis, the risk of pneumonitis with anti-PD1 agents was even higher (OR 5.37; 95% CI 2.73 to 10.56, P<0.00001). Patients treated with the anti-PD1 agent were not at increased risk of hepatitis (Figure 6), though events were rare.

General Possibly Immune-related Toxicities

All studies reported rates of fatigue and diarrhea and twelve reported rash. In the intervention arms, rates of fatigue, diarrhea and rash were seen in 1,208 (32%), 705 (19%) and 393 (10%) of patients from these studies respectively. Patients treated with anti-PD1 agents were more likely to experience rash (OR 2.34; 95% CI 1.40 to 3.91, P=0.001) (Figure 7), but

not more likely to report fatigue (OR 0.84; 95% CI 0.65~~,~~ to 1.09, P=0.19) (Figure 8) or diarrhea (OR 0.78; 95% CI 0.57~~,~~ to 1.05, P=0.10) (Figure 9) compared to patients in control arms.

Musculoskeletal toxicities

Reporting of musculoskeletal toxicities, including arthralgia, arthritis, back pain, musculoskeletal pain, and myalgia, varied across studies (Table 3). Three studies included no mention of musculoskeletal problems. On ClinicalTrials.gov, among the 8 studies for which data was posted, back pain, arthralgia, myalgia and musculoskeletal pain were reported in all studies while arthritis was reported in 2. When reported, rates of musculoskeletal problems varied across studies in intervention groups, ranging from 10-26% for arthralgia, 6-22% for back pain, 6-14% for musculoskeletal pain, and 2-12% for myalgia. Single cases of arthritis were reported in 2 studies for a rate of <1% in each. Across control groups, rates of musculoskeletal compaints ranged from 9-18% for arthralgia, 2-16% for back pain, 4-6% for musculoskeletal pain, and 4-16% for myalgia, when reported. Lack of reporting of any events for musculoskeletal toxicities precluded data pooling, so we did not perform a metaanalysis for these outcomes.

Discussion

We completed a systematic review of immune-related toxicities of anti-PD-1 or anti-PD-L1 monoclonal antibodies versus a standard treatment to further our understanding of the clinical tolerability of this emerging class of drugs. We used data from 13 randomized trials that included over 3800 patients treated with checkpoint inhibitors and extracted data from ClinicalTrials.gov, when possible, to supplement the published evidence base. We found that the risk of organ specific irAE's such as pneumonitis, hypothyroidism, and colitis are increased with anti-PD1 agents compared to standard therapies although overall event rates remain low. In contrast, compared to control arms, the risk of common adverse events that could be related

to systemic inflammation, such as diarrhea and fatigue, are not increased. Further, we found that anti-PD-1 agents seem to lead to musculoskeletal problems such as back pain, arthralgia, myalgia, and musculoskeletal pain that can negatively impact quality of life and long-term tolerability of immotherapy, though reporting of these toxicities was inconsistent.

Our study is notable for our inclusion of toxicity information from ClinicalTrials.gov and our focus on anti-PD1 agents. A recent meta-analysis evaluated the risk of immune-related adverse events in patients treated on any checkpoint inhibitor (including ipilimumab). (27) Unlike the prior study, we found an increased risk of pneumonitis with anti-PD1 agents, though colitis risk was similar. Any differences in findings are likely due to our access to more complete toxicity data through ClinicalTrials.gov and our inclusion of more studies of anti-PD1 agents. In addition, by using ClinicalTrials.gov we were able to evaluate musculoskeletal toxicities, which are likely to be important to patients.

Our findings have important implications for clinicians across multiple specialties. As use of anti-PD1 agents grows, non-oncology specialists will be increasingly called upon to manage the rare but clinically important organ-specific immune-related toxicities and the more prevalent non-specific toxicities related to systemic inflammation. (28, 29) In addition to severe toxicities such as pneumonitis and colitis, our study documents musculoskeletal problems that will require management by primary care physicians and rheumatologists.(9, 10) These problems are not surprising given that many autoimmune diseases have musculoskeletal manifestations.(30) Inflammatory arthritis from checkpoint inhibitors has already been recognized in the rheumatology community; these adverse events are likely to grow in prevalence over time.(10, 31-34) Currently, many oncology patients are treated primarily by their oncologists and may lose connections to other physicians.(35, 36) This care model may poorly serve patients treated with immunotherapy, whose cancers may remain under control but in whom a variety of complications related to immune-activation may threaten health and quality of life. Multidisciplinary clinical teams may better serve these patients long-term needs, though optimal

clinical and care delivery approaches for the early detection and proper management of immune toxicities are evolving and will require further investigation.(37, 38)

Anti-PD1 agents can achieve long-term tumor control through prolonged immune activation, so immune-related toxicies requiring management may persist, progress or even emerge over time.(29) Studies included in our analysis had a median follow-up time of 13.1 months (range 5.1-25 months), which may be inadequate for capturing the full spectrum of longer-term immune-related toxicities. With a focus on acute or short-term adverse events captured in clinical trials, our study may have underestimated the prevalence of late-developing or persistent immune-related toxicities. Better understanding of the long-term toxicities of immunotherapy will be critical to efforts to optimize care delivery. Phase 4 studies are often recommended to enhance understanding of long-term toxicities of new therapies, although they are seldom performed (39) and are time consuming. Given the rapid anticipated growth in the number of patients treated with anti-PD1 agents, institutional cohort studies could provide more immediate insights into immune-related drug toxicities with an emphasis on not just short-term, but also long-term, adverse events. In addition, investigators should publish updated toxicity information in addition to cancer outcomes as they report longer follow-up from earlier studies of checkpoint inhibitors. Little such data is currently available.

We found that despite high rates of musculoskeletal problems that may be related to immune activation, reporting of these adverse events was inconsistent and incomplete across trials. While accessing toxicity data on ClinicalTrials.gov enabled us to include information that did not appear in publications, we remained constrained by the recording methods for toxicities in clinical trials. Adverse events in clinical trials are reported using CTCAE, which prompts investigators to note the presence or absence of a symptom or an abnormal lab value and grade it based upon its clinical significance. The process is highly subjective and relies on investigator recognition and identification of syndromes of interest, thus investigators may be more likely to classify patient complaints or findings as diagnoses of which they have high

suspicion. In the case of anti-PD1 agents, investigators are aware of well-described irAE's such as colitis, pneumonitis, hypothyroidism or hepatitis and are likely to report them accurately, but they may be less aware of other potentially relevant toxicities such as musculoskeletal problems and may therefore inaccurately diagnose and record them. Emerging case reports and case series have described rheumatologic and musculoskeletal syndromes related to systemic inflammation that have been seen in clinical practice but not described in primary publications of trial results.(9, 10, 40) Similar attention has been turned to less frequent, but significant toxicities impacting the neurologic, cardiac, and ocular systems.(41-44) As these receive more attention, problems such as arthritis, arthralgia, and myalgia may become more accurately reported in future studies.

Limitations

Our study has important limitations. A major challenge of this review was the overlap in CTCAE definitions which prevents understanding the true rates of specific toxicities. For example, immune-related hepatitis could be captured as "hepatitis" or as an abnormal laboratory value (elevated AST and ALT) and immune-medidated colitis could be categorized as "colitis" or "diarrhea." This could lead to potential uncertainty regarding the quality of the data, which will need to be addressed moving forward for studies of immunologic agents. We also assumed that no events of a particular type occurred if none were reported and in our meta-analyses studies with zero events did not contribute to the pooled result. This may have led to errors in our pooled estimates, though the issue impacts the intervention and control arms equally. In addition, while a strength of our study is our use of ClinicalTrials.gov to collect more complete toxicity data than what was available in published trial reports, we were able to include adverse event data from ClinicalTrials.gov for only 8 of 13 studies. However, it is unlikely that more publicly reported data would have substantially altered our findings. In addition, we combined all non-immunotherapy agents into one category of "control", including both traditional

chemotherapy and two targeted agents, cetuximab and everolimus. We performed a subset analysis separating targeted from non-targeted control therapy. Risks of pneumonitis and rash differ for targeted therapies compared to traditional chemotherapy and odds ratios differed across control therapies, so targeted agents are presented separately. For other outcomes there was no heterogeneity based on comparator so all studies are presented together. Finally, we pooled data from studies that used different anti-PD1 drugs at variable doses so we may have missed differences in toxicity rates across drugs or based on dosage differences. Given the wide variation in drug and dose across studies we were unable to perform subgroup analyses to examine these factors. However, we found little heterogeneity across studies for toxicity outcomes, suggesting little difference based on the specific agent or the drug dose.

Recommendations for research

Our study provides insight into the adverse events from treatment with anti-PD1 agents, which have revolutionized oncologic care in the last few years. We found that anti-PD1 agents are more likely than standard treatments to cause pneumonitis, colitis, rash and hypothyroidism but not fatigue or diarrhea. We also found variable reporting of musculoskeletal problems, with high rates in some studies, suggesting that anti-PD1 agents likely do cause some bone, muscle and joint toxicities. However, due to the short interval follow up currently available from clinical trials data and a lack of clarity in the systematic capture of many adverse events, we are likely to have underestimated the true rates of toxicities. Moving forward, longer-term follow-up and specific attention to a variety of immune-related toxicities may enhance our understanding. Until then, for the practicing clinician, our findings suggest the importance of entertaining an immunologic cause of a wide spectrum of newly developed signs or symptoms in patients treated with anti-PD1 agents.

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Figure legends

Figure 1. Pubmed Search Terms

("nivolumab"[Supplementary Concept] OR "Nivolumab"[tiab] AND "Opdivo"[tiab] OR "MDX-1106"[tiab] OR "ONO-4538"[tiab] OR "BMS-936558"[tiab] OR "NIVO"[tiab] OR "pembrolizumab"[Supplementary Concept] OR "pembrolizumab" [tiab] OR "lambrolizumab"[tiab] OR "keytruda"[tiab] OR "MK-3475"[tiab] OR "SCH 900475"[tiab] OR "avelumab"[Supplementary Concept] OR "Avelumab"[tiab] OR "MSB0010718C"[tiab] OR "MPDL3280A"[Supplementary Concept] OR "MPDL3280A" [tiab] OR "atezolizumab" [tiab] OR "Tecentriq"[tiab] OR "RG7446"[tiab] OR "RO5541267"[tiab] OR "Durvalumab"[tiab] OR "MEDI4736"[tiab] OR "MEDI-4736"[tiab] OR checkpoint inhibitor*[tiab] OR "PD-1"[tiab] OR "PD-L1"[tiab]) AND (Clinical Trial, Phase III[ptyp] OR "phase 3 clinical trial"[tiab] OR "phase III clinical trial"[tiab] OR "phase 3 trial"[tiab] OR "phase III trial"[tiab] OR "phase 3 clinical study"[tiab] OR "phase III clinical study"[tiab] OR "phase 3 study"[tiab] OR "phase III study"[tiab] OR "phase 3 randomized trial"[tiab] OR "phase III randomized trial"[tiab] OR Clinical Trial, Phase II[ptyp] OR "phase 2 clinical trial"[tiab] OR "phase II clinical trial"[tiab] OR "phase 2 trial"[tiab] OR "phase II trial"[tiab] OR "phase 2 clinical study"[tiab] OR "phase II clinical study"[tiab] OR "phase 2 randomized trial"[tiab] OR "phase II randomized trial"[tiab] OR "phase 2 study"[tiab] OR "phase II study"[tiab] OR "phase 2/3 clinical trial"[tiab] OR "phase II/ III clinical trial"[tiab] OR "phase 2/3 trial"[tiab] OR "phase II/III trial"[tiab] OR "phase 2/3 clinical study"[tiab] OR "phase II/ III clinical study"[tiab] OR "phase 2/3 study"[tiab] OR "phase II/III study"[tiab] OR "phase 2/3 randomized trial"[tiab] OR "phase II/III randomized trial"[tiab] OR Randomized Controlled Trial[ptyp] OR "randomized controlled trial"[tiab] OR "RCT"[tiab])

~~Figure 2. PRISMA diagram~~

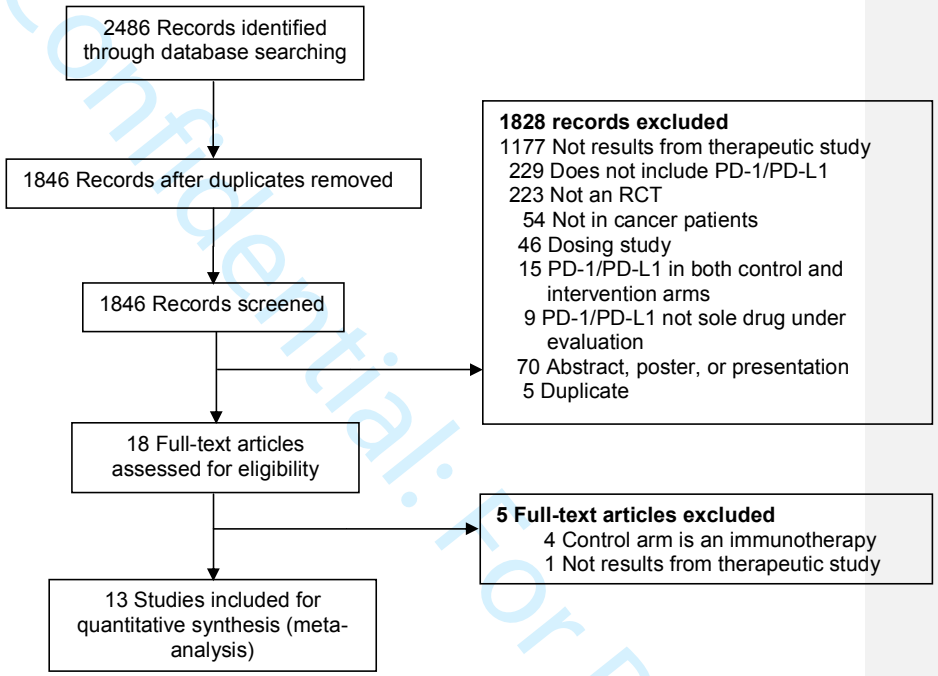


Table 1. Risk of Bias of Randomized, Controlled Trials of PD-1 and PDL-1 Inhibitors in Oncology

Study, year	Randomization	Allocation Concealment	Blinding of participants and personnel	Blinding of outcome assessors*	Incomplete outcome data	Selective outcome reporting‡	Other sources of bias
Bellmunt, 2017	Low risk	Unclear risk	High risk	Low risk	Low risk	Low risk	Low risk
Borghaei, 2015	Low risk	Low risk	High risk	High risk	Low risk	Low risk	Low risk
Brahmer, 2015	Low risk	Low risk	High risk	High risk	Low risk	Low risk	Low risk
Fehrenbacher, 2016	Low risk	Low risk	High risk	High risk	Low risk	Low risk	Low risk
Ferris, 2016	Low risk	Low risk	High risk	High risk	Low risk	Low risk	Low risk
Herbst, 2016	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	Low risk
Langer, 2016	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	Low risk
Motzer, 2015	Low risk	Low risk	High risk	High risk	Low risk	Low risk	Low risk
Reck, 2016	Low risk	Unclear risk	High risk	Low risk	Low risk	Low risk	Low risk
Ribas, 2015	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	Low risk
Rittmeyer, 2017	Low risk	Low risk	High risk	High risk	Low risk	Low risk	Low risk
Robert, 2015	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Weber, 2015	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	Low risk
Kappa	1.00	1.00	0.629	0.629	1.00	1.00	1.00

*Applies to secondary outcomes only.

‡Applies to primary outcomes only and not to toxicity outcomes

Table 2. Incidence of Severe Organ-specific Immune-related Adverse Events, by Drug

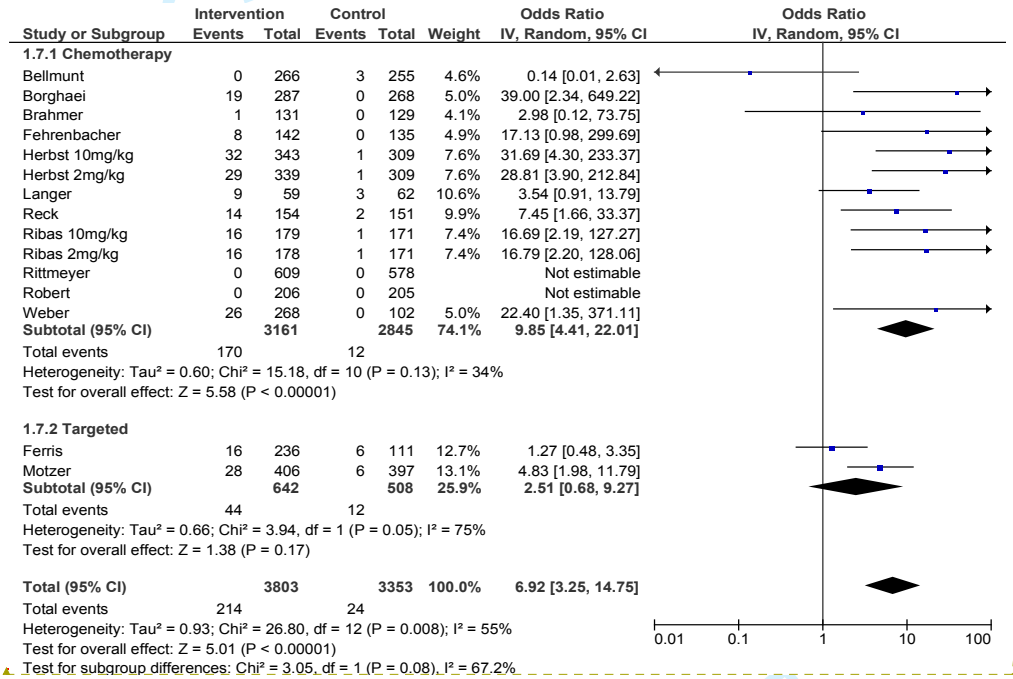
	Colitis		Hepatitis		Pneumonitis		Hypothyroidism	
	All*	Serious†	All	Serious	All	Serious	All	Serious
Atezolizumab (N=751)	4 (0.5)	1 (0.1)	3 (0.4)	2 (0.3)	6 (0.8)	4 (0.5)	8 (1)	1 (0.1)
Nivolumab (N =1534)	5 (0.3)	5 (0.3)	0	0	34 (2)	17 (1)	90 (6)	3 (0.2)
Pembrolizumab, (N =1518) §	16 (1)	12 (0.8)	3 (0.2)	3 (0.2)	45 (3)	33 (2)	116 (8)	2 (0.1)
Total (N=3803)	25 (0.7)	18 (0.5)	6 (0.4)	5 (0.1)	85 (2)	54 (1)	214 (6)	6 (0.4)

* Includes both "serious" and "other" adverse events if data was extracted from ClinicalTrials.gov; includes all Common Terminology of Clinical Adverse Events (CTCAE) grades if data was extracted from the publication only

‡ Represents "serious" adverse events if data was extracted from ClinicalTrials.gov; represents CTCAE grades 3, 4, or 5 if data was extracted from the publication only

§ Includes both the 2mg/kg and 10mg/kg dosing arms of Herbst, 2016 and Ribas, 2015

~~Figure 3. Forest Plot of Hypothyroidism in Patients Treated with Anti-PD1 Agents Versus Control~~



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~~Figure 4. Forest Plot of Pneumonitis in Patients Treated with Anti-PD1 Agents Versus Control~~

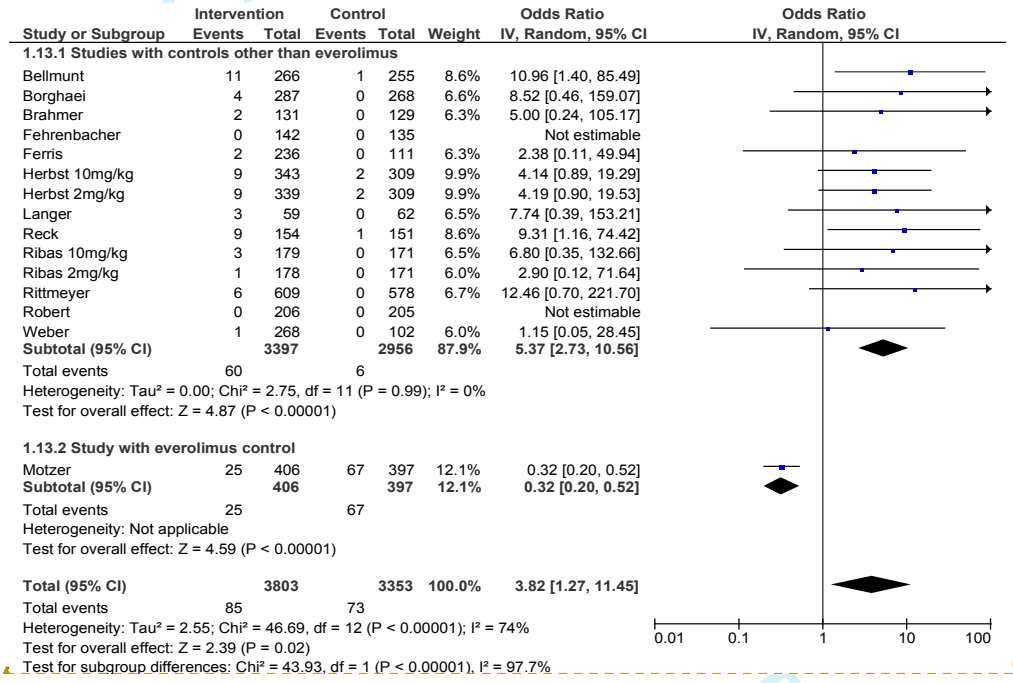

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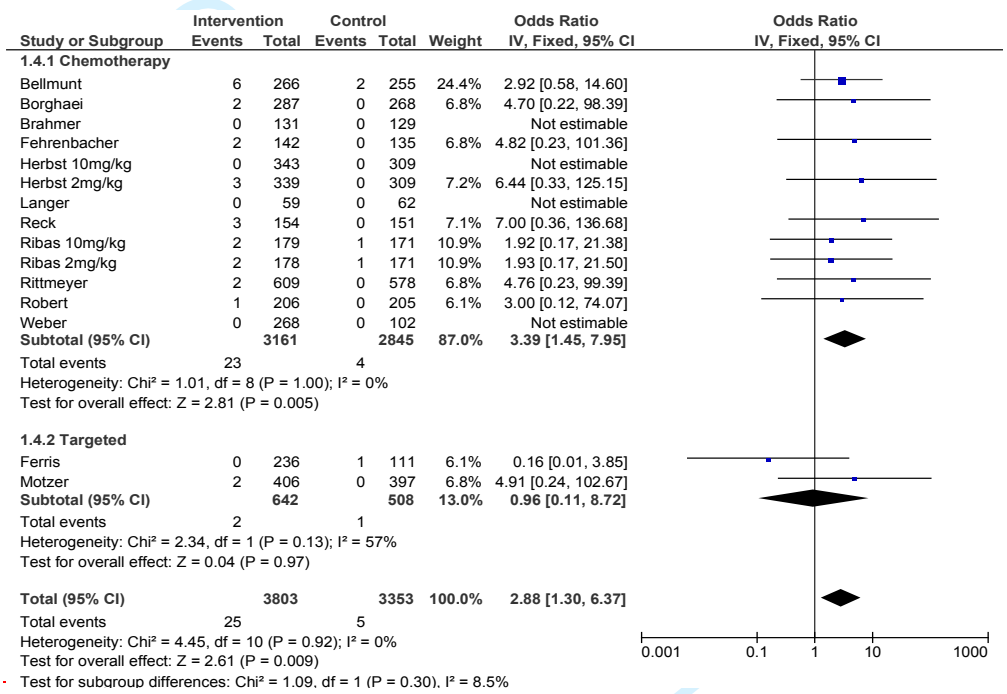
Figure 5. Forest Plot of Colitis in Patients Treated with Anti-PD1 Agents Versus Control



~~Figure 6. Forest Plot of Hepatitis in Patients Treated with Anti-PD1 Agents Versus Control~~

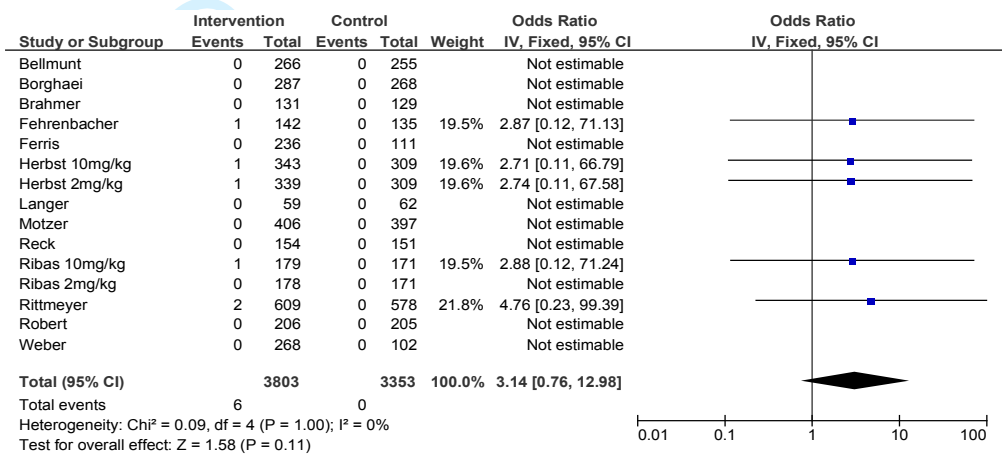


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Figure 7. Forest Plot of Rash in Patients Treated with Anti-PD1 Agents Versus Control

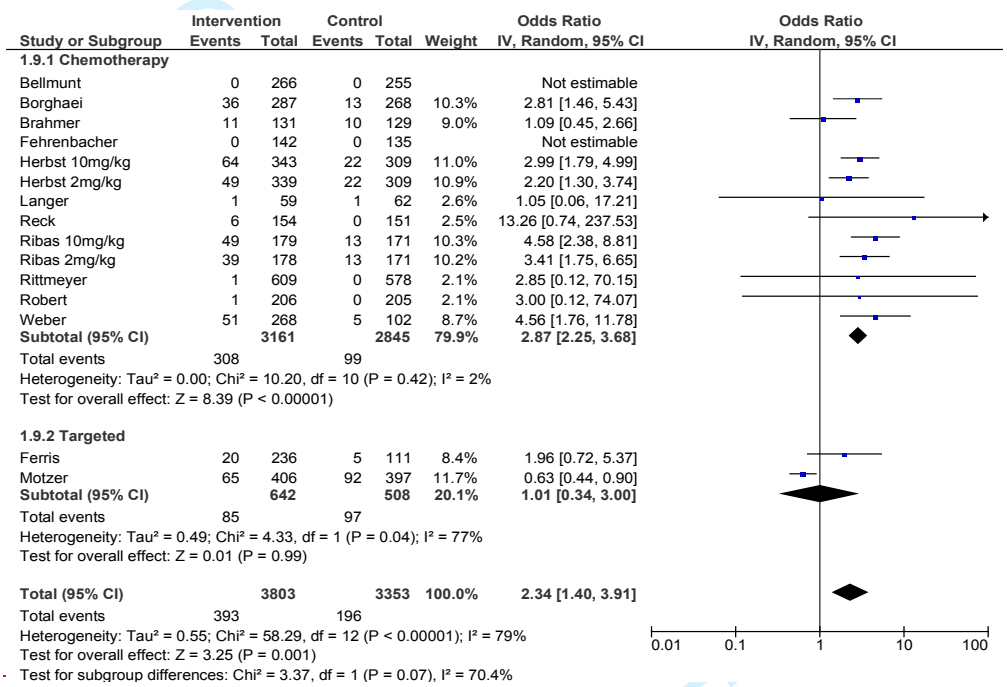


Figure 8. Forest Plot of Fatigue in Patients Treated with Anti-PD1 Agents Versus Control

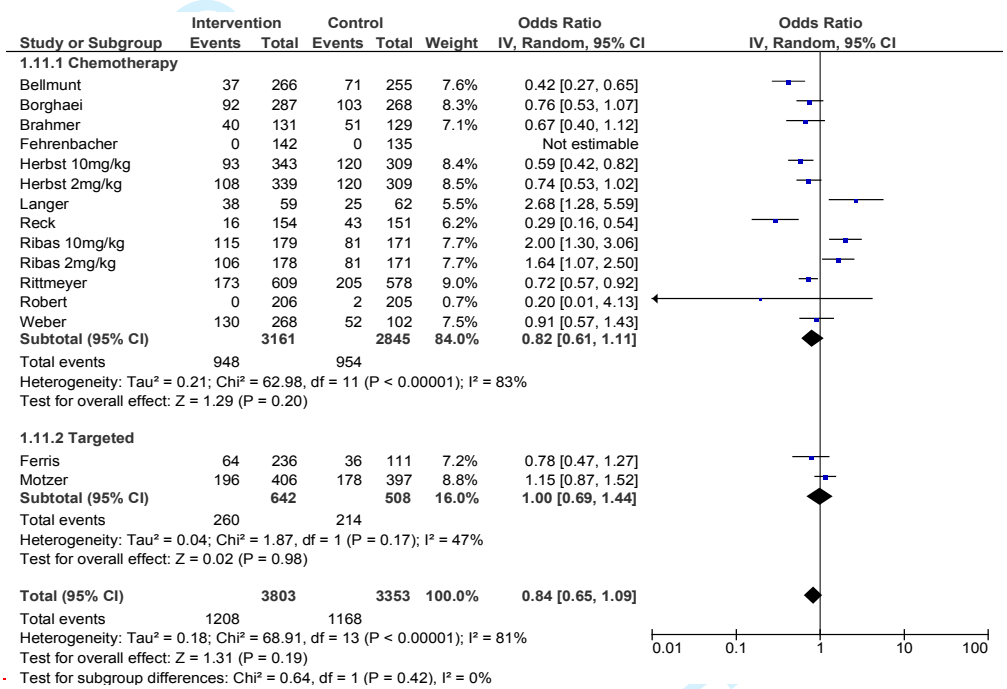


Figure 9. Forest Plot of Diarrhea in Patients Treated with Anti-PD1 Agents Versus Control

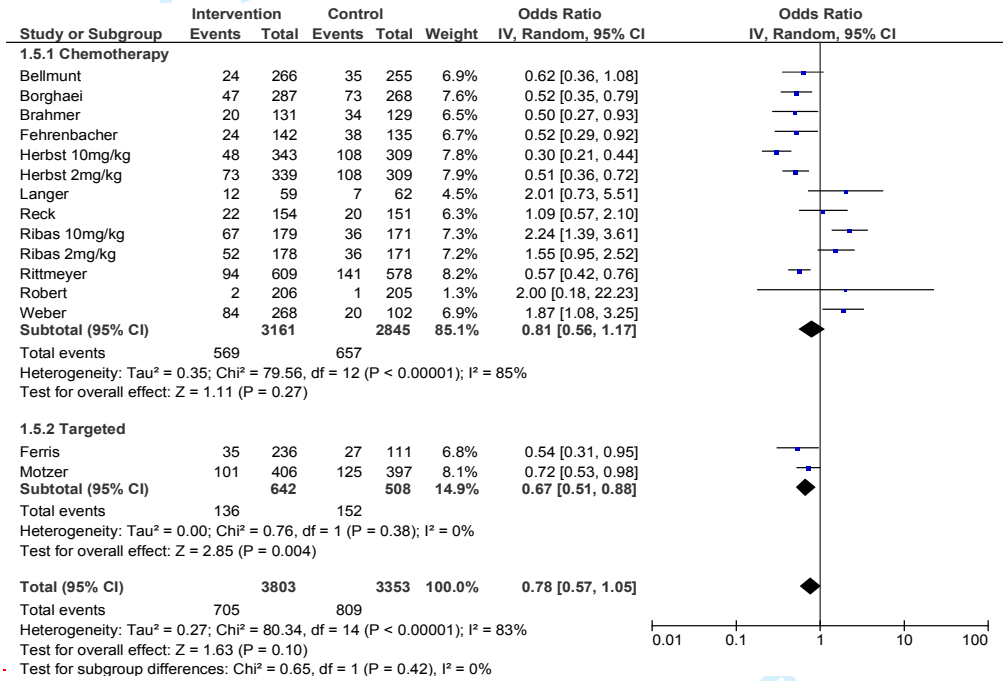


Table 3. Incidence of musculoskeletal toxicities

Author, Year	Drug	Inter-vention, *n*	Arthritis, *n* (%)		Arthralgia, *n* (%)		Back pain, *n* (%)		Musculoskeletal pain, *n* (%)		Myalgia, *n* (%)	
			All*	Grades 3-5†	All	Grades 3-5	All	Grades 3-5	All	Grades 3-5	All	Grades 3-5
Bellmunt, 2017‡	Pembro	266	0	0	0	0	0	0	0	0	0	0
Borghaei, 2015	Nivo	287	0	0	47 (16)	1 (0.3)	37 (13)	2 (1)	39 (14)	1 (0.3)	35 (12)	18 (6)
Brahmer, 2015	Nivo	131	0	0	13 (10)	0	13 (10)	1 (1)	8 (6)	0	15 (11)	8 (6)
Fehren-bacher, 2016‡	Atezo	141	0	0	22 (15)	3 (2.1)	0	0	19 (13)	2 (1.4)	0	0
Ferris, 2016	Nivo	236	0	0	0	0	14 (6)	2 (1)	0	0	0	0
Herbst, 2016	Pembro, 2mg/kg	338	1 (0.3)	1 (0.3)	50 (15)	0	38 (11)	2 (1)	38 (11)	2 (0.6)	48 (14)	25 (7)
	Pembro, 10mg/kg	343	0	0	41 (12)	1 (0.3)	41 (12)	2 (1)	34 (10)	0	48 (14)	17 (5)
Langer, 2016‡	Pembro, combined§	59	0	0	0	0	0	0	0	0	0	0
Motzer, 2015	Nivo	406	0	0	82 (20)	2 (0.5)	90 (22)	7 (2)	41 (10)	1 (0.2)	14 (3)	39 (10)
Reck, 2016‡	Pembro	154	0	0	0	0	0	0	0	0	0	0
Ribas, 2015	Pembro, 2mg/kg	178	0	0	47 (26)	0	30 (17)	0	19 (11)	1 (0.6)	11 (6)	22 (12)
	Pembro, 10mg/kg	179	0	0	35 (20)	2 (1.1)	28 (16)	2 (1)	15 (8)	1 (0.6)	11 (6)	14 (8)
Rittmeyer, 2017‡	Atezo	609	0	0	73 (12)	3 (0.5)	67 (11)	7 (1)	64 (11)	4 (0.7)	91 (15)	39 (6)
Robert, 2015	Nivo	206	0	0	0	0	0	0	0	0	0	0
Weber, 2015	Nivo	268	1 (0.4)	1 (0.4)	62 (23)	1 (0.4)	58 (22)	6 (2)	32 (12)	0	10 (4)	26 (10)
Total		3803	2 (0.05)	2 (0.05)	472 (12)	13 (0.3)	416 (11)	31 (0.8)	309 (8)	12 (0.3)	301 (8)	211 (6)

Pembro=Pembrolizumab; Nivo= Nivolumab; Atezo=Atezolizumab
*Includes any adverse event if data was extracted from ClinicalTrials.gov; includes all Common Terminology of Clinical Adverse Events (CTCAE) grades if data was extracted from the publication only
† Includes “serious” adverse events if data was extracted from ClinicalTrials.gov
‡ Study results were only taken from publication. No trial results were posted on ClinicalTrials.gov as of 3/28/2017
§ Combined treatment included pembrolizumab, carboplatin, and pemetrexed

Figure 1. Pubmed Search Terms

("nivolumab"[Supplementary Concept] OR "Nivolumab"[tiab] AND "Opdivo"[tiab] OR "MDX-1106"[tiab] OR "ONO-4538"[tiab] OR "BMS-936558"[tiab] OR “NIVO”[tiab] OR "pembrolizumab"[Supplementary Concept] OR “pembrolizumab” [tiab] OR "lambrolizumab"[tiab] OR "keytruda"[tiab] OR "MK-3475"[tiab] OR “SCH 900475”[tiab] OR "avelumab"[Supplementary Concept] OR "Avelumab"[tiab] OR "MSB0010718C"[tiab] OR "MPDL3280A"[Supplementary Concept] OR “MPDL3280A” [tiab] OR "atezolizumab” [tiab] OR “Tecentriq”[tiab] OR “RG7446”[tiab] OR “RO5541267”[tiab] OR "Durvalumab"[tiab] OR "MEDI4736"[tiab] OR "MEDI-4736"[tiab] OR checkpoint inhibitor*[tiab] OR "PD-1"[tiab] OR “PD-L1”[tiab]) AND (Clinical Trial, Phase III[ptyp] OR "phase 3 clinical trial"[tiab] OR "phase III clinical trial"[tiab] OR "phase 3 trial"[tiab] OR "phase III trial"[tiab] OR "phase 3 clinical study"[tiab] OR "phase III clinical study"[tiab] OR "phase 3 study"[tiab] OR "phase III study"[tiab] OR "phase 3 randomized trial"[tiab] OR "phase III randomized trial"[tiab] OR Clinical Trial, Phase II[ptyp] OR "phase 2 clinical trial"[tiab] OR "phase II clinical trial"[tiab] OR "phase 2 trial"[tiab] OR "phase II trial"[tiab] OR "phase 2 clinical study"[tiab] OR "phase II clinical study"[tiab] OR "phase 2 randomized trial"[tiab] OR "phase II randomized trial"[tiab] OR "phase 2 study"[tiab] OR "phase II study"[tiab] OR "phase 2/3 clinical trial"[tiab] OR "phase II/ III clinical trial"[tiab] OR "phase 2/3 trial"[tiab] OR "phase II/III trial"[tiab] OR "phase 2/3 clinical study"[tiab] OR "phase II/ III clinical study"[tiab] OR "phase 2/3 study"[tiab] OR "phase II/III study"[tiab] OR "phase 2/3 randomized trial"[tiab] OR "phase II/III randomized trial"[tiab] OR Randomized Controlled Trial[ptyp] OR "randomized controlled trial"[tiab] OR "RCT"[tiab])

Figure 2. PRISMA diagram

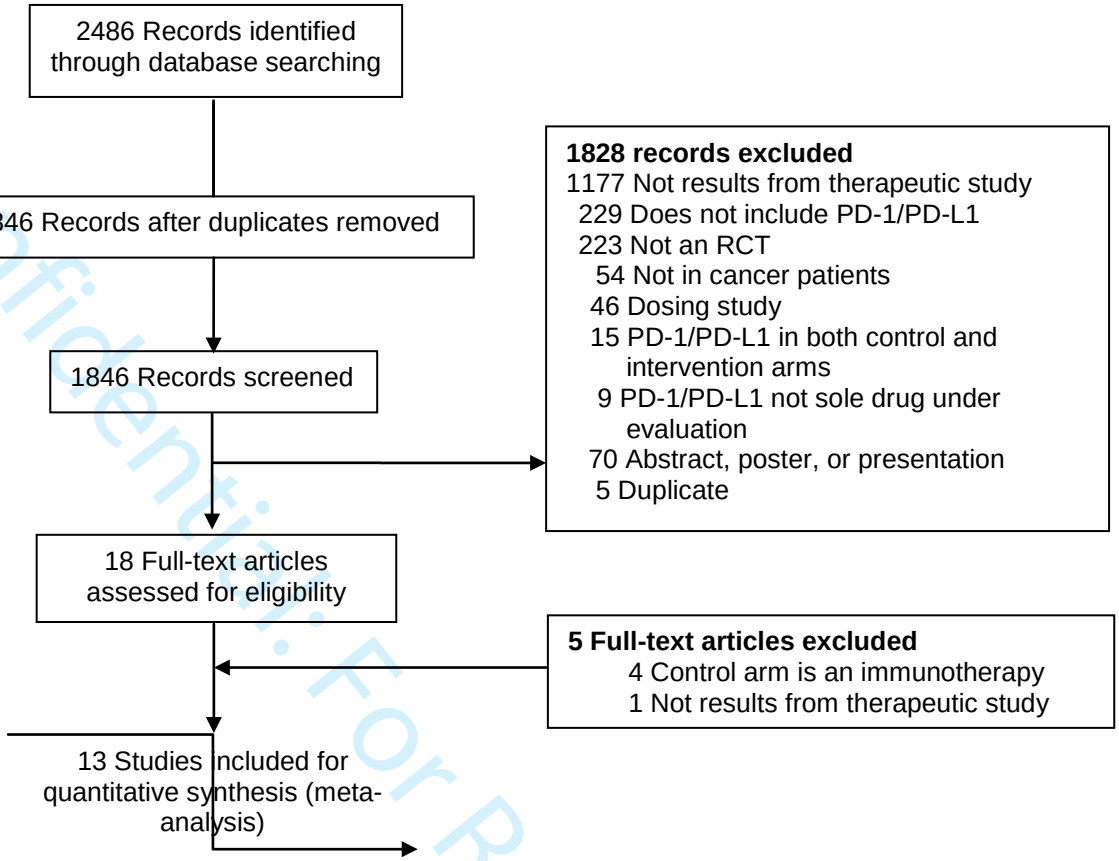


Figure 3. Forest Plot of Hypothyroidism in Patients Treated with Anti-PD1 Agents Versus Control

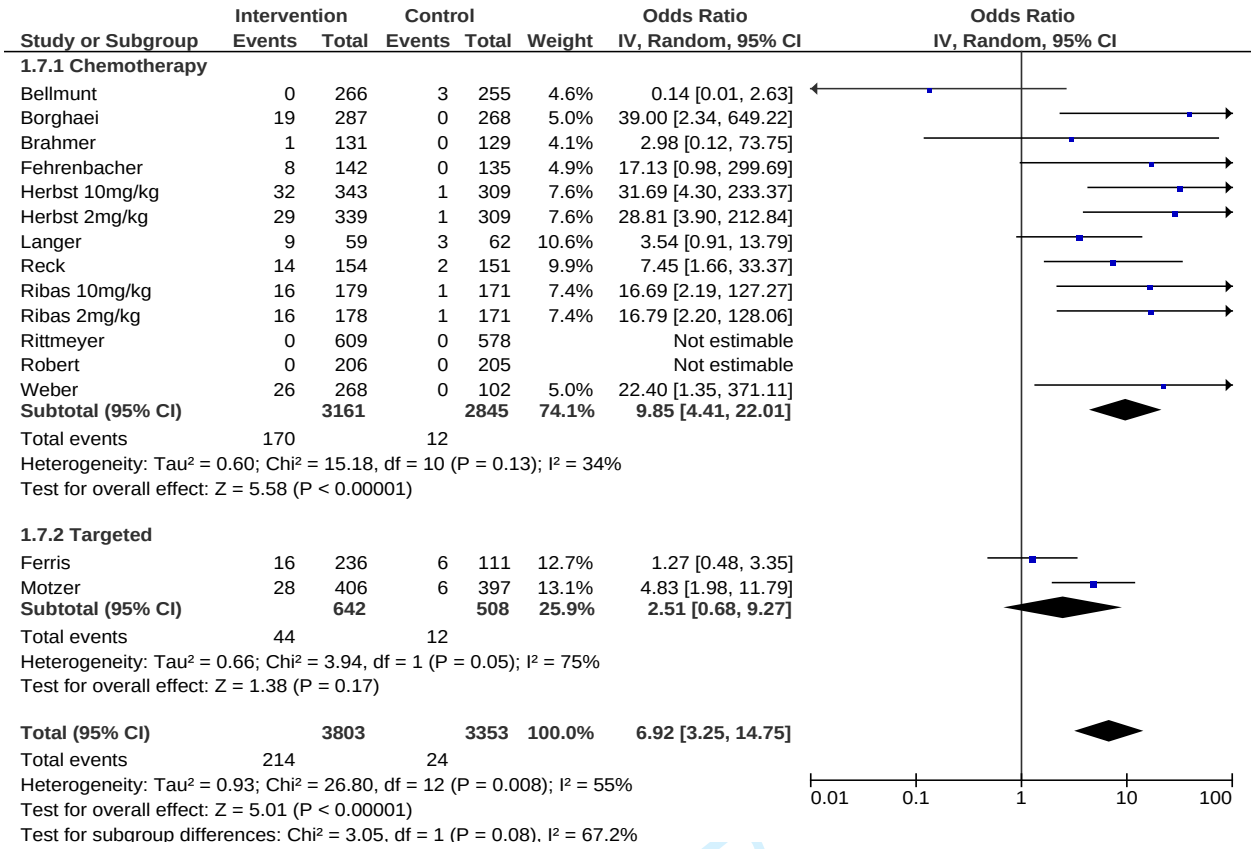


Figure 4. Forest Plot of Pneumonitis in Patients Treated with Anti-PD1 Agents Versus Control

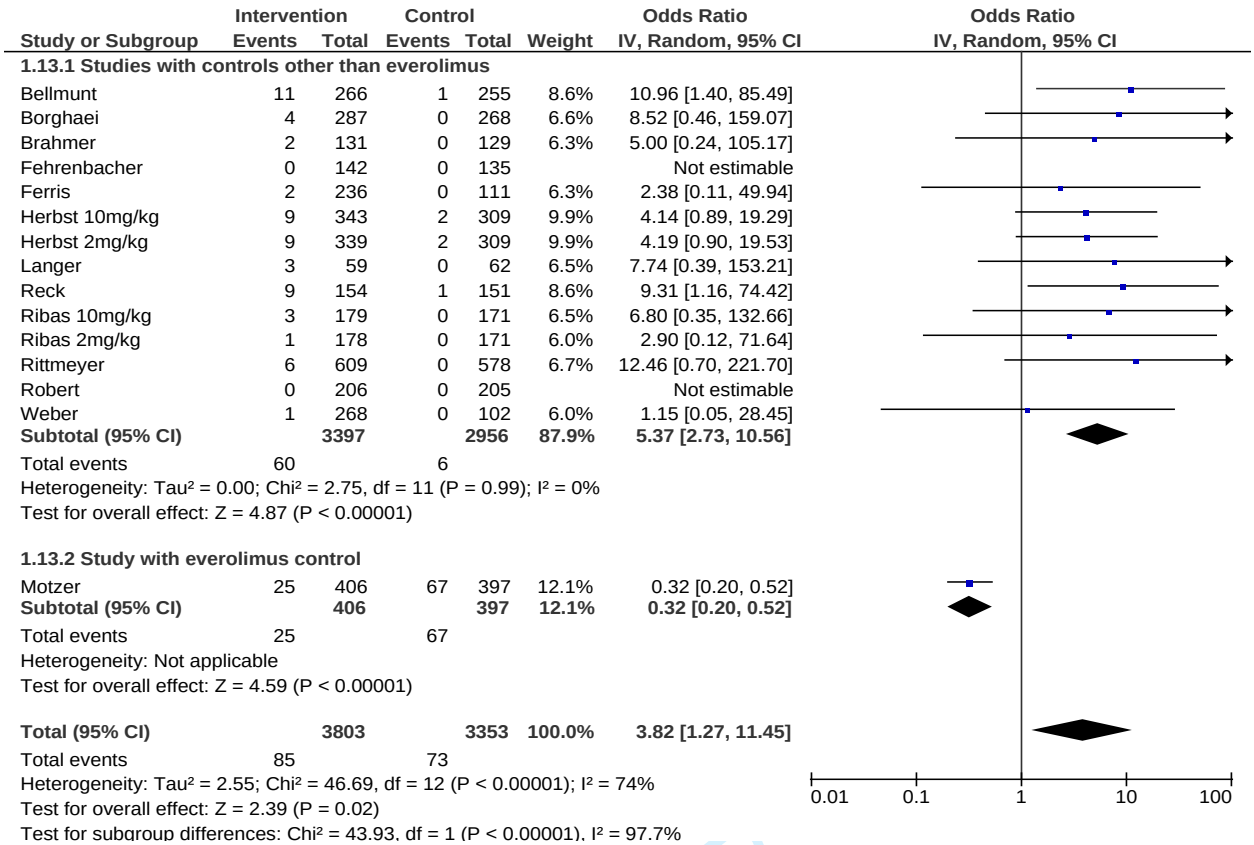


Figure 5. Forest Plot of Colitis in Patients Treated with Anti-PD1 Agents Versus Control

Study or Subgroup	Intervention Events	Intervention Total	Control Events	Control Total	Weight	Odds Ratio IV, Fixed, 95% CI
1.4.1 Chemotherapy						
Bellmunt	6	266	2	255	24.4%	2.92 [0.58, 14.60]
Borghaei	2	287	0	268	6.8%	4.70 [0.22, 98.39]
Brahmer	0	131	0	129		Not estimable
Fehrenbacher	2	142	0	135	6.8%	4.82 [0.23, 101.36]
Herbst 10mg/kg	0	343	0	309		Not estimable
Herbst 2mg/kg	3	339	0	309	7.2%	6.44 [0.33, 125.15]
Langer	0	59	0	62		Not estimable
Reck	3	154	0	151	7.1%	7.00 [0.36, 136.68]
Ribas 10mg/kg	2	179	1	171	10.9%	1.92 [0.17, 21.38]
Ribas 2mg/kg	2	178	1	171	10.9%	1.93 [0.17, 21.50]
Rittmeyer	2	609	0	578	6.8%	4.76 [0.23, 99.39]
Robert	1	206	0	205	6.1%	3.00 [0.12, 74.07]
Weber	0	268	0	102		Not estimable
Subtotal (95% CI)		**3161**		**2845**	**87.0%**	**3.39 [1.45, 7.95]**
Total events	23		4			
Heterogeneity: Chi² = 1.01, df = 8 (P = 1.00); I² = 0%						
Test for overall effect: Z = 2.81 (P = 0.005)						
1.4.2 Targeted						
Ferris	0	236	1	111	6.1%	0.16 [0.01, 3.85]
Motzer	2	406	0	397	6.8%	4.91 [0.24, 102.67]
Subtotal (95% CI)		**642**		**508**	**13.0%**	**0.96 [0.11, 8.72]**
Total events	2		1			
Heterogeneity: Chi² = 2.34, df = 1 (P = 0.13); I² = 57%						
Test for overall effect: Z = 0.04 (P = 0.97)						
Total (95% CI)		**3803**		**3353**	**100.0%**	**2.88 [1.30, 6.37]**
Total events	25		5			
Heterogeneity: Chi² = 4.45, df = 10 (P = 0.92); I² = 0%						
Test for overall effect: Z = 2.61 (P = 0.009)						
Test for subgroup differences: Chi² = 1.09, df = 1 (P = 0.30), I² = 8.5%						

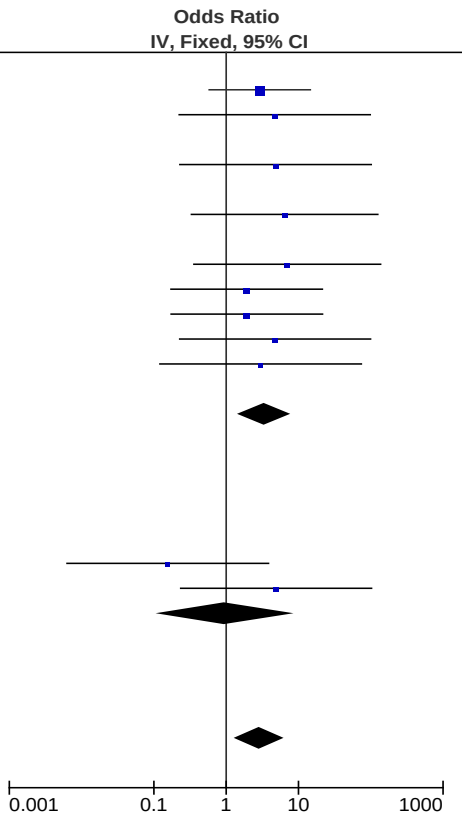


Figure 6. Forest Plot of Hepatitis in Patients Treated with Anti-PD1 Agents Versus Control

Study or Subgroup	Intervention Events	Intervention Total	Control Events	Control Total	Weight	Odds Ratio IV, Fixed, 95% CI
Bellmunt	0	266	0	255		Not estimable
Borghaei	0	287	0	268		Not estimable
Brahmer	0	131	0	129		Not estimable
Fehrenbacher	1	142	0	135	19.5%	2.87 [0.12, 71.13]
Ferris	0	236	0	111		Not estimable
Herbst 10mg/kg	1	343	0	309	19.6%	2.71 [0.11, 66.79]
Herbst 2mg/kg	1	339	0	309	19.6%	2.74 [0.11, 67.58]
Langer	0	59	0	62		Not estimable
Motzer	0	406	0	397		Not estimable
Reck	0	154	0	151		Not estimable
Ribas 10mg/kg	1	179	0	171	19.5%	2.88 [0.12, 71.24]
Ribas 2mg/kg	0	178	0	171		Not estimable
Rittmeyer	2	609	0	578	21.8%	4.76 [0.23, 99.39]
Robert	0	206	0	205		Not estimable
Weber	0	268	0	102		Not estimable
Total (95% CI)		**3803**		**3353**	**100.0%**	**3.14 [0.76, 12.98]**
Total events	6		0			

Heterogeneity: Chi² = 0.09, df = 4 (P = 1.00); I² = 0%

Test for overall effect: Z = 1.58 (P = 0.11)

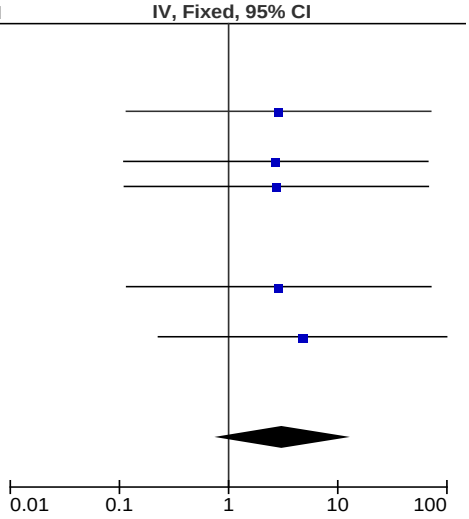


Figure 7. Forest Plot of Rash in Patients Treated with Anti-PD1 Agents Versus Control

Study or Subgroup	Intervention Events	Intervention Total	Control Events	Control Total	Weight	Odds Ratio IV, Random, 95% CI
1.9.1 Chemotherapy						
Bellmunt	0	266	0	255		Not estimable
Borghaei	36	287	13	268	10.3%	2.81 [1.46, 5.43]
Brahmer	11	131	10	129	9.0%	1.09 [0.45, 2.66]
Fehrenbacher	0	142	0	135		Not estimable
Herbst 10mg/kg	64	343	22	309	11.0%	2.99 [1.79, 4.99]
Herbst 2mg/kg	49	339	22	309	10.9%	2.20 [1.30, 3.74]
Langer	1	59	1	62	2.6%	1.05 [0.06, 17.21]
Reck	6	154	0	151	2.5%	13.26 [0.74, 237.53]
Ribas 10mg/kg	49	179	13	171	10.3%	4.58 [2.38, 8.81]
Ribas 2mg/kg	39	178	13	171	10.2%	3.41 [1.75, 6.65]
Rittmeyer	1	609	0	578	2.1%	2.85 [0.12, 70.15]
Robert	1	206	0	205	2.1%	3.00 [0.12, 74.07]
Weber	51	268	5	102	8.7%	4.56 [1.76, 11.78]
Subtotal (95% CI)		**3161**		**2845**	**79.9%**	**2.87 [2.25, 3.68]**
Total events	308		99			
Heterogeneity: Tau² = 0.00; Chi² = 10.20, df = 10 (P = 0.42); I² = 2%						
Test for overall effect: Z = 8.39 (P < 0.00001)						
1.9.2 Targeted						
Ferris	20	236	5	111	8.4%	1.96 [0.72, 5.37]
Motzer	65	406	92	397	11.7%	0.63 [0.44, 0.90]
Subtotal (95% CI)		**642**		**508**	**20.1%**	**1.01 [0.34, 3.00]**
Total events	85		97			
Heterogeneity: Tau² = 0.49; Chi² = 4.33, df = 1 (P = 0.04); I² = 77%						
Test for overall effect: Z = 0.01 (P = 0.99)						
Total (95% CI)		**3803**		**3353**	**100.0%**	**2.34 [1.40, 3.91]**
Total events	393		196			
Heterogeneity: Tau² = 0.55; Chi² = 58.29, df = 12 (P < 0.00001); I² = 79%						
Test for overall effect: Z = 3.25 (P = 0.001)						
Test for subgroup differences: Chi² = 3.37, df = 1 (P = 0.07), I² = 70.4%						

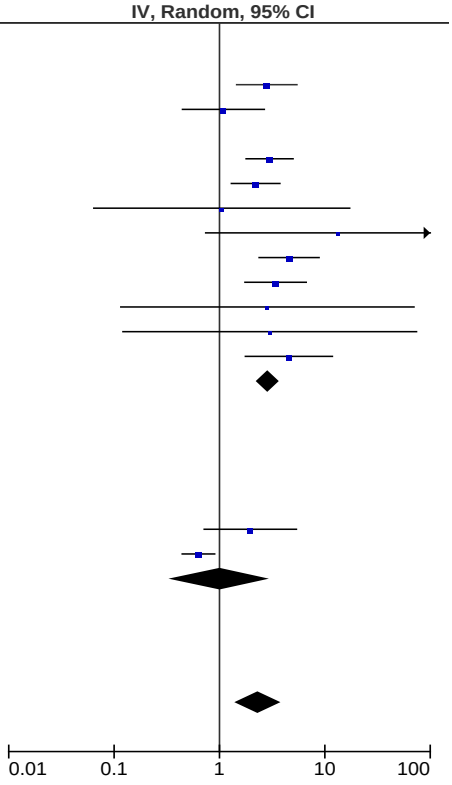
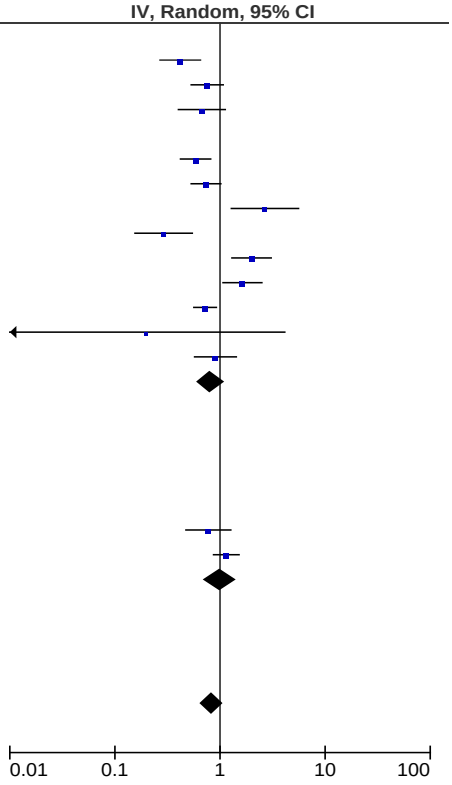


Figure 8. Forest Plot of Fatigue in Patients Treated with Anti-PD1 Agents Versus Control

Study or Subgroup	Intervention Events	Intervention Total	Control Events	Control Total	Weight	Odds Ratio IV, Random, 95% CI
1.11.1 Chemotherapy						
Bellmunt	37	266	71	255	7.6%	0.42 [0.27, 0.65]
Borghaei	92	287	103	268	8.3%	0.76 [0.53, 1.07]
Brahmer	40	131	51	129	7.1%	0.67 [0.40, 1.12]
Fehrenbacher	0	142	0	135		Not estimable
Herbst 10mg/kg	93	343	120	309	8.4%	0.59 [0.42, 0.82]
Herbst 2mg/kg	108	339	120	309	8.5%	0.74 [0.53, 1.02]
Langer	38	59	25	62	5.5%	2.68 [1.28, 5.59]
Reck	16	154	43	151	6.2%	0.29 [0.16, 0.54]
Ribas 10mg/kg	115	179	81	171	7.7%	2.00 [1.30, 3.06]
Ribas 2mg/kg	106	178	81	171	7.7%	1.64 [1.07, 2.50]
Rittmeyer	173	609	205	578	9.0%	0.72 [0.57, 0.92]
Robert	0	206	2	205	0.7%	0.20 [0.01, 4.13]
Weber	130	268	52	102	7.5%	0.91 [0.57, 1.43]
Subtotal (95% CI)		**3161**		**2845**	**84.0%**	**0.82 [0.61, 1.11]**
Total events	948		954			
Heterogeneity: Tau² = 0.21; Chi² = 62.98, df = 11 (P < 0.00001); I² = 83%						
Test for overall effect: Z = 1.29 (P = 0.20)						
1.11.2 Targeted						
Ferris	64	236	36	111	7.2%	0.78 [0.47, 1.27]
Motzer	196	406	178	397	8.8%	1.15 [0.87, 1.52]
Subtotal (95% CI)		**642**		**508**	**16.0%**	**1.00 [0.69, 1.44]**
Total events	260		214			
Heterogeneity: Tau² = 0.04; Chi² = 1.87, df = 1 (P = 0.17); I² = 47%						
Test for overall effect: Z = 0.02 (P = 0.98)						
Total (95% CI)		**3803**		**3353**	**100.0%**	**0.84 [0.65, 1.09]**
Total events	1208		1168			
Heterogeneity: Tau² = 0.18; Chi² = 68.91, df = 13 (P < 0.00001); I² = 81%						
Test for overall effect: Z = 1.31 (P = 0.19)						
Test for subgroup differences: Chi² = 0.64, df = 1 (P = 0.42), I² = 0%						



Immune-related Toxicities in PD-1 and PD-L1 Immunotherapies: a Systematic Review and Meta-analysis

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Running Title: Immune-related toxicities with anti-PD-1 or anti-PD-L1 antibodies

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Abstract 286 (limit 300)

Objective: Use of programmed cell death 1 (PD-1) immunotherapies is rapidly expanding across cancers. Proper clinical management requires understanding associated immune-related adverse events (irAE) that can include organ toxicities, non-specific signs/symptoms, and increasingly recognized musculoskeletal problems. We set out to evaluate rates of serious organ-specific irAEs, non-specific possibly immune-related symptoms, and musculoskeletal problems with anti-PD1 agents overall and compared to control therapies.

Design: Systematic review and meta-analysis of randomized controlled trials comparing an anti-PD-1 or anti-PD-L1 monoclonal antibody to standard treatment in patients with cancer.

Data Sources: Databases including Medline, Embase, Cochrane Library, Web of Science, and Scopus, were searched up to March 16, 2017 and combined with data available on ClinicalTrials.gov.

Eligibility criteria for selecting studies: Studies including primary clinical trial data on cancer patients with recurrent or metastatic disease.

Appraisal and Data Extraction: Three independent investigators extracted data on adverse events from ClinicalTials.gov and the published reports. Risk of bias was assessed with the Cochrane risk of bias tool by two independent investigators.

Results: Thirteen relevant studies were included; adverse event data was available on ClinicalTrials.gov for 8. Studies compared nivolumab (n=6), pembrolizumab (n=5) or atezolizumab (n=2) to chemotherapy (n=11), targeted agents (n=1) or both (n=1). While serious organ-specific irAEs were rare, rates of hypothyroidism (OR 7.56; 95% CI: 4.53-12.61), pneumonitis (OR 5.37; 95%CI: 2.73-10.56), and colitis (OR 2.88; 95% CI: 1.30-6.37) were increased with anti-PD1 agents compared to standard treatment, as was rash (OR 2.34; 95%CI 2.73- 10.56). Incidence of fatigue (32%) and diarrhea (19%) were high but similar to control. Reporting of musculoskeletal problems was inconsistent; rates varied but were >20% in some studies for back pain and arthraligia.

Conclusions: Organ-specific irAEs are uncommon with anti-PD-1 agents but risk is increased compared to control therapies; non-specific symptoms are largely similar. Musculoskeletal problems are inconsistently reported but toxicities may be common.

Introduction

The development and rapid uptake of checkpoint inhibitors, a modern form of immunotherapy, has resulted in a paradigm shift in the management of numerous cancers. In 2011, ipilumuab, an anti-CTLA-4 antibody, became the first checkpoint inhibitor approved by the Food and Drug Administration (FDA) for the treatment of advanced melanoma. While ipilimumab remains in use only for melanoma, checkpoint inhibitors directed at the programmed death-1 pathway, or "anti-PD1 agents" have received approval for the treatment of multiple cancers. Anti-PD1 agents include monoclonal antibodies directed at both PD-1 (pembrolizumab and nivolumab) and its ligand PD-L1 (avelumab, atezolizumab, durvalumab). As of May 2017, at least one of the anti-PD1 agents has been approved in advanced melanoma, non-small cell lung cancer, renal cell carcinoma, Hodgkin's lymphoma, head and neck cancer, bladder urothelial cancer, merkel cell carcinoma, and tumors of any organ with high microsatellite instability (MSI-H). In addition, anti-PD1 agents are also currently under investigation in at least 135 clinical trials for additional metastatic cancers, earlier stage cancers and in combination with other immunotherapeutic and non-immunotherapeutic drugs which will further fuel their use.(1)

Immunotherapy, as a drug class, boosts the body's natural defense against cancer. These drugs have toxicities, collectively known as immune-related adverse events (irAEs), that represent immune effects on normal tissue that can result from misdirected stimulation of the immune system. While anti-PD1 agents are overall less toxic than standard chemotherapy,(2-8) certain organ-specific irAEs including hypothyroidism, colitis, pnemonitis and hepatitis have routinely been reported in clinical trials of anti-PD1 agents, and more general toxicities that might be related to immune activation, including fatigue, rash and diarrhea, have been common.(2, 7, 8) Despite less clarity about their prevalence, other toxicities potentially attributable to systemic inflammation, particularly musculoskeletal problems, have also been described in patients treated with anti-PD1 agents and may negatively impact quality of life.(9,

10) Given the rapidly expanding population of patients exposed to anti-PD1 agents and the wide spectrum of potential immune-related effects(1), understanding toxicities associated with anti-PD1 drugs is critical for clinicians caring for these patients in various settings.

We performed a systematic review and meta-analysis of immune-related toxicities of anti-PD1 and anti-PD-L1 inhibitors. We included organ-specific and other toxicities potentially related to inflammation and gathered data from both ClinicalTrials.gov and published literature. We hypothesized that 1) rates of organ-specific irAEs including hypothyroidism, colitis, pneumonitis and hepatitis would be low overall but higher with anti-PD1 agents than with standard therapies and that 2) rates of general possibly immune-related toxicities specifically fatigue, diarrhea and rash, would be higher than organ-specific irAE's but would not be increased compared to standard therapies. We also hypothesized that musculoskeletal problems would be common with anti-PD1 agents, but inconsistently documented.

Methods

We conducted a literature search to identify randomized clinical trials comparing single agent anti-PDL or anti PD-L1 checkpoint inhibitor therapy to a standard active treatment in patients with cancer to evaluate rates of immune-related toxicities including organ-specific irAE's, general symptoms, and musculoskeletal problems and to calculate risks compared to control therapies. We performed the study in adherence with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.(11)

Data Sources and Searches

We electronically searched 5 databases (MEDLINE [via PubMed], Embase, Cochrane Central Register of Controlled Trials [Cochrane Library], Web of Science, and Scopus) from the inception of all searched databases in August 2016 and updated the search in March 2017. For PubMed, Embase, and Cochrane, we used both controlled vocabulary and text words for synonymous terminology within titles and abstracts in the development of search strategies.

Web of Science and Scopus were searched using only text word searching of titles and abstracts. The search strategy contained two concepts that were linked together with the AND operator: (1) Nivolumab, Pembrolizumab, Ipilimumab, Avelumab, Tremelimumab, Atezolizumab, Durvalumab, checkpoint inhibitors; and (2) phase 2 clinical trials, phase 3 clinical trials, randomized controlled trials (See Figure 1 for a complete list of search terms). All search results were combined in a bibliographic management tool (EndNote) with duplicates eliminated using the Bramer method.(12)

Study Selection

We included studies that addressed a cancer and reported results of a randomized study of an anti-PD-1 or anti-PD-L1 monoclonal antibody. We excluded reviews, commentaries, studies published only in abstract form, quality-of-life studies, cost-effectiveness analyses, and those in which the effect of the drug could not be ascertained, such as when the control was a different dose of the same drug or another immunotherapeutic agent. (Figure 1) Study selection was performed in two stages. Two authors (S.B., Z.W.) screened all titles and abstracts for full-text review. Three authors (S.B., D.K., Z.W.) reviewed and discussed the remaining 18 full-text articles and included 13 studies. Disagreements were resolved by concensus. All included studies represented unique trials.

Data Extraction and Quality Assessment

Data from each study was extracted by two of the following three authors (S.B., D.K., N.K.) and disagreements were resolved by concensus involving all three. From each study, we extracted patient characterisitics (sex, performance status, and age), the sizes of intervention and control groups, median treatment time, and median follow-up. Two authors (D.K., A.Y.) independently assessed the quality of all articles included in the review using the Cochrane Risk

of Bias Tool(13) and used a weighted Cohen's κ coefficient to measure agreement. Differences were resolved by consensus.

Our primary outcome was the incidence of commonly described organ-specific irAEs (hypothyroidism, colitis, hypophysitis, pnemonitis and hepatitis) and more general signs and symptoms that could be related to immune activation (diarrhea, rash and fatigue). Our secondary outcome was the incidence of adverse events consistent with musculoskeletal problems (back pain, arthritis, arthralgia, myalgia and musculoskeletal pain). We first searched for adverse event data on ClinicalTrials.gov, available as of 3/28/2017. For studies for which full toxicity information was not posted on ClinicalTrials.gov, we used information from the publication and directly contacted study authors of the study or pharmaceutical sponsors for additional information. We recorded data on adverse events reported as either "serious" or "other" on ClinicalTrials.gov. For data extracted from published reports, we used the Common Terminology of Clinical Adverse Events (CTCAE) categorization to identify grades 3-5 as "serious" and CTCAE grades 1-2 as "other". For studies with information available from both sources, we prioritized data from ClinicalTrials.gov over toxicity data from the publications. If the study did not report a specific adverse event, we assumed that the event did not occur. Data from different dosing arms within the same study were extracted and reported separately.

Data Synthesis and Analysis

We calculated overall event rates by dividing the total number of patients across trials with a given toxicity by the total number at risk. We examined the number of events for each irAE of interest to determine whether meta-analysis was feasible. For each included study, we calculated odds ratios and 95% confidence intervals for event rates in the intervention arm compared to control based on the reported number of events and sample size. We used the I-squared index (I^2) and Cochran's Q statistics to examine heterogeneity across trials for each outcome. If significant heterogeneity was not present ($p>0.1$), pooled OR and 95% CI were

estimated with a fixed effects model using the inverse-variance method. A random-effects model using the inverse-variance method was used to calculate pooled OR and 95% CI if significant heterogeneity was present. Studies were weighted based on the inverse of the variance of the effect estimate. If a study included more than one intervention arm (e.g. Herbst(14) and Ribas(15) reported 2mg/kg and 10mg/kg arms for pembrolizaumab), we separately compared each intervention arm to the control arm. We conducted subgroup analyses to examine studies by control group treatment (chemotherapy vs. targeted therapy). We assessed for publication bias using funnel plots. All statistical analyses were conducted using Review Manager 5.3 (Copenhagen, Denmark).

Role of Funding Source

No external funding was obtained specifically for this review but the effort was supported in part by the NIH/NCI P30 CA008748 Cancer Center Support Grant. The funder had no role in the design of the study; the collection, analysis, and interpretation of the data; or approval of the finished manuscript.

Results

Our search identified 2,486 records; 18 underwent full-text review and 13 were included for quantitiative synthesis and meta-analysis (Figure 2).(14-26) Included articles were published (online) between November 2014 and February 2017. Funnel plots showed no evidence of publication bias (not shown).

Study Characteristics

All studies were international multi-center studies funded by the pharmaceutical industry, with intervention group sample sizes ranging from 59 to 609 patients. Seven were completed in patients with metastatic non-small cell lung cancer (14, 16, 17, 21, 23, 24, 26), 3 in melanoma

(15, 19, 20) , and one each in renal cell carcinoma (18), bladder cell carcinoma (25), and head and neck squamous cell carcinoma (22). Patients in the intervention arm received nivolumab in 6 studies (16-20, 22), pembrolizumab in 5 studies (14, 15, 23-25) and atezolizumab in 2 studies (21, 26). One trial evaluated the combinationof pembrolizumab with chemotherapy (carboplatin, and pemetrexed) compared to chemotherapy (carboplatin and pemetrexed) alone.(23) In two studies of pembrolizumab, two different doses 2mg/kg and 10mg/kg were compared to each other, in addition to a standard control.(14, 15) The control arm was a single chemotherapy agent in six studies (14, 16, 17, 19, 21, 26), a doublet chemotherapy in one study (23), a small molecule inhibitor in one study (18) and investigators' choice in four studies.(15, 20, 22, 25) Across studies, the primary endpoint was survival, with adverse events reported as secondary outcomes. All studies continued treatment until progression of disease or severe toxicity. The median treatment time in the investigational arm ranged from 3 to 8 months and the median duration of follow-up across studies was 13.1 months (range 5.1-25 months). As of March 27, 2017, adverse event data was available on Clinicaltrials.gov for 8 studies.

Quality of included studies

There was high inter-rater agreement for risk-of-bias assessments (κ 0.89) and overall risk of bias was unclear (Table 1).(13) All studies but one were open-label with primary outcome of overall survival. Outcome assessors for secondary outcomes were blinded in 7 studies (54%), but because toxicity reporting is performed by clinicians directly caring for patients, reports of toxicity rates in these open-label studies were by definition unmasked. We found no evidence of selective reporting or incomplete outcome data reporting for the primary outcomes, though some studies were ongoing and included only preliminary data. Further because toxicity outcomes were not collected and reported differently we could not assess their selective reporting.

Organ-specific Immune-related Toxicities

A total of 6,676 patients were evaluated across the 13 studies with 3,803 in the investigational arm (nivolumab 1,534, pembrolizumab 1,459, and azetolizmumab 751) and 2,873 in control arms (chemotherapy including cetuximab 2,476, or a biological agent 397). All studies reported organ-specific irAEs of interest. Looking at any-grade organ-specific irAEs, among the 3,803 total patients exposed to anti-PD1 agents 214 (5.6%) had hypothyroidism, 85 (2.2%) had pneumonitis, 25 (0.7%) had colitis, 6 (0.2%) had hepatitis, and 4 (0.1%) had hypophysitis. The most common "serious" irAE was pneumonitis which occured in 54 (1.4%) patients, while serious colitis, hypothyroidism, hepatitis and hypophysitis occurred in 18 (0.5%), 6 (0.2%), 5 (0.1%) and 4 (0.1%) patients respectively. Rates of organ-specific "serious" irAEs by specific drug are shown in Table 2.

In the meta-analysis, compared to patients treated in control arms, those treated with anti-PD1 agents were at a higher risk for any grade hypothyroidism (OR 6.92; 95% CI 3.25, 14.75, P<.001) (Figure 3), pneumonitis (OR 3.82; 95% CI 1.27, 11.45, P=0.02) (Figure 4), and colitis (OR 2.88, 95% CI, 1.30, 6.37, P=.009) (Figure 5). When we excluded the study in which the control treatment was everolimus, a drug known to causes pneumonitis, the risk of pneumonitis with anti-PD1 agents was even higher (OR 5.37; 95% CI 2.73, 10.56, P<0.00001). Patients treated with the anti-PD1 agent were not at increased risk of hepatitis (Figure 6), though events were rare.

General Possibly Immune-related Toxicities

All studies reported rates of fatigue and diarrhea and twelve reported rash. In the intervention arms, rates of fatigue, diarrhea and rash were seen in 1,208 (32%), 705 (19%) and 393 (10%) of patients from these studies respectively. Patients treated with anti-PD1 agents were more likely to experience rash (OR 2.34; 95% CI 1.40, 3.91, P=0.001) (Figure 7), but not

more likely to report fatigue (OR 0.84; 95% CI 0.65, 1.09, P=0.19) (Figure 8) or diarrhea (OR 0.78; 95% CI 0.57, 1.05, P=0.10) (Figure 9) compared to patients in control arms.

Musculoskeletal toxicities

Reporting of musculoskeletal toxicities, including arthralgia, arthritis, back pain, musculoskeletal pain, and myalgia, varied across studies (Table 3). Three studies included no mention of musculoskeletal problems. On ClinicalTrials.gov, among the 8 studies for which data was posted, back pain, arthralgia, myalgia and musculoskeletal pain were reported in all studies while arthritis was reported in 2. When reported, rates of musculoskeletal problems varied across studies in intervention groups, ranging from 10-26% for arthralgia, 6-22% for back pain, 6-14% for musculoskeletal pain, and 2-12% for myalgia. Single cases of arthritis were reported in 2 studies for a rate of <1% in each. Across control groups, rates of musculoskeletal compaints ranged from 9-18% for arthralgia, 2-16% for back pain, 4-6% for musculoskeletal pain, and 4-16% for myalgia, when reported. Lack of reporting of any events for musculoskeletal toxicities precluded data pooling, so we did not perform a metaanalysis for these outcomes.

Discussion

We completed a systematic review of immune-related toxicities of anti-PD-1 or anti-PD-L1 monoclonal antibodies versus a standard treatment to further our understanding of the clinical tolerability of this emerging class of drugs. We used data from 13 randomized trials that included over 3800 patients treated with checkpoint inhibitors and extracted data from ClinicalTrials.gov, when possible, to supplement the published evidence base. We found that the risk of organ specific irAE's such as pneumonitis, hypothyroidism, and colitis are increased with anti-PD1 agents compared to standard therapies although overall event rates remain low. In contrast, compared to control arms, the risk of common adverse events that could be related

to systemic inflammation, such as diarrhea and fatigue, are not increased. Further, we found that anti-PD-1 agents seem to lead to musculoskeletal problems such as back pain, arthralgia, myalgia, and musculoskeletal pain that can negatively impact quality of life and long-term tolerability of immotherapy, though reporting of these toxicities was inconsistent.

Our study is notable for our inclusion of toxicity information from ClinicalTrials.gov and our focus on anti-PD1 agents. A recent meta-analysis evaluated the risk of immune-related adverse events in patients treated on any checkpoint inhibitor (including ipilimumab). (27) Unlike the prior study, we found an increased risk of pneumonitis with anti-PD1 agents, though colitis risk was similar. Any differences in findings are likely due to our access to more complete toxicity data through ClinicalTrials.gov and our inclusion of more studies of anti-PD1 agents. In addition, by using ClinicalTrials.gov we were able to evaluate musculoskeletal toxicities, which are likely to be important to patients.

Our findings have important implications for clinicians across multiple specialties. As use of anti-PD1 agents grows, non-oncology specialists will be increasingly called upon to manage the rare but clinically important organ-specific immune-related toxicities and the more prevalent non-specific toxicities related to systemic inflammation. (28, 29) In addition to severe toxicities such as pneumonitis and colitis, our study documents musculoskeletal problems that will require management by primary care physicians and rheumatologists.(9, 10) These problems are not surprising given that many autoimmune diseases have musculoskeletal manifestations.(30) Inflammatory arthritis from checkpoint inhibitors has already been recognized in the rheumatology community; these adverse events are likely to grow in prevalence over time.(10, 31-34) Currently, many oncology patients are treated primarily by their oncologists and may lose connections to other physicians.(35, 36) This care model may poorly serve patients treated with immunotherapy, whose cancers may remain under control but in whom a variety of complications related to immune-activation may threaten health and quality of life. Multidisciplinary clinical teams may better serve these patients long-term needs, though optimal

clinical and care delivery approaches for the early detection and proper management of immune toxicities are evolving and will require further investigation.(37, 38)

Anti-PD1 agents can achieve long-term tumor control through prolonged immune activation, so immune-related toxicies requiring management may persist, progress or even emerge over time.(29) Studies included in our analysis had a median follow-up time of 13.1 months (range 5.1-25 months), which may be inadequate for capturing the full spectrum of longer-term immune-related toxicities. With a focus on acute or short-term adverse events captured in clinical trials, our study may have underestimated the prevalence of late-developing or persistent immune-related toxicities. Better understanding of the long-term toxicities of immunotherapy will be critical to efforts to optimize care delivery. Phase 4 studies are often recommended to enhance understanding of long-term toxicities of new therapies, although they are seldom performed (39) and are time consuming. Given the rapid anticipated growth in the number of patients treated with anti-PD1 agents, institutional cohort studies could provide more immediate insights into immune-related drug toxicities with an emphasis on not just short-term, but also long-term, adverse events. In addition, investigators should publish updated toxicity information in addition to cancer outcomes as they report longer follow-up from earlier studies of checkpoint inhibitors. Little such data is currently available.

We found that despite high rates of musculoskeletal problems that may be related to immune activation, reporting of these adverse events was inconsistent and incomplete across trials. While accessing toxicity data on ClinicalTrials.gov enabled us to include information that did not appear in publications, we remained constrained by the recording methods for toxicities in clinical trials. Adverse events in clinical trials are reported using CTCAE, which prompts investigators to note the presence or absence of a symptom or an abnormal lab value and grade it based upon its clinical significance. The process is highly subjective and relies on investigator recognition and identification of syndromes of interest, thus investigators may be more likely to classify patient complaints or findings as diagnoses of which they have high

suspicion. In the case of anti-PD1 agents, investigators are aware of well-described irAE's such as colitis, pneumonitis, hypothyroidism or hepatitis and are likely to report them accurately, but they may be less aware of other potentially relevant toxicities such as musculoskeletal problems and may therefore inaccurately diagnose and record them. Emerging case reports and case series have described rheumatologic and musculoskeletal syndromes related to systemic inflammation that have been seen in clinical practice but not described in primary publications of trial results.(9, 10, 40) Similar attention has been turned to less frequent, but significant toxicities impacting the neurologic, cardiac, and ocular systems.(41-44) As these receive more attention, problems such as arthritis, arthralgia, and myalgia may become more accurately reported in future studies.

Limitations

Our study has important limitations. A major challenge of this review was the overlap in CTCAE definitions which prevents understanding the true rates of specific toxicities. For example, immune-related hepatitis could be captured as "hepatitis" or as an abnormal laboratory value (elevated AST and ALT) and immune-medidated colitis could be categorized as "colitis" or "diarrhea." This could lead to potential uncertainty regarding the quality of the data, which will need to be addressed moving forward for studies of immunologic agents. We also assumed that no events of a particular type occurred if none were reported and in our meta-analyses studies with zero events did not contribute to the pooled result. This may have led to errors in our pooled estimates, though the issue impacts the intervention and control arms equally. In addition, while a strength of our study is our use of ClinicalTrials.gov to collect more complete toxicity data than what was available in published trial reports, we were able to include adverse event data from ClinicalTrials.gov for only 8 of 13 studies. However, it is unlikely that more publicly reported data would have substantially altered our findings. In addition, we combined all non-immunotherapy agents into one category of "control", including both traditional

chemotherapy and two targeted agents, cetuximab and everolimus. We performed a subset analysis separating targeted from non-targeted control therapy. Risks of pneumonitis and rash differ for targeted therapies compared to traditional chemotherapy and odds ratios differed across control therapies, so targeted agents are presented separately. For other outcomes there was no heterogeneity based on comparator so all studies are presented together. Finally, we pooled data from studies that used different anti-PD1 drugs at variable doses so we may have missed differences in toxicity rates across drugs or based on dosage differences. Given the wide variation in drug and dose across studies we were unable to perform subgroup analyses to examine these factors. However, we found little heterogeneity across studies for toxicity outcomes, suggesting little difference based on the specific agent or the drug dose.

Recommendations for research

Our study provides insight into the adverse events from treatment with anti-PD1 agents, which have revolutionized oncologic care in the last few years. We found that anti-PD1 agents are more likely than standard treatments to cause pneumonitis, colitis, rash and hypothyroidism but not fatigue or diarrhea. We also found variable reporting of musculoskeletal problems, with high rates in some studies, suggesting that anti-PD1 agents likely do cause some bone, muscle and joint toxicities. However, due to the short interval follow up currently available from clinical trials data and a lack of clarity in the systematic capture of many adverse events, we are likely to have underestimated the true rates of toxicities. Moving forward, longer-term follow-up and specific attention to a variety of immune-related toxicities may enhance our understanding. Until then, for the practicing clinician, our findings suggest the importance of entertaining an immunologic cause of a wide spectrum of newly developed signs or symptoms in patients treated with anti-PD1 agents.

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Figure 1. Pubmed Search Terms

("nivolumab"[Supplementary Concept] OR "Nivolumab"[tiab] AND "Opdivo"[tiab] OR "MDX-1106"[tiab] OR "ONO-4538"[tiab] OR "BMS-936558"[tiab] OR "NIVO"[tiab] OR "pembrolizumab"[Supplementary Concept] OR "pembrolizumab" [tiab] OR "lambrolizumab"[tiab] OR "keytruda"[tiab] OR "MK-3475"[tiab] OR "SCH 900475"[tiab] OR "avelumab"[Supplementary Concept] OR "Avelumab"[tiab] OR "MSB0010718C"[tiab] OR "MPDL3280A"[Supplementary Concept] OR "MPDL3280A" [tiab] OR "atezolizumab" [tiab] OR "Tecentriq"[tiab] OR "RG7446"[tiab] OR "RO5541267"[tiab] OR "Durvalumab"[tiab] OR "MEDI4736"[tiab] OR "MEDI-4736"[tiab] OR checkpoint inhibitor*[tiab] OR "PD-1"[tiab] OR "PD-L1"[tiab]) AND (Clinical Trial, Phase III[ptyp] OR "phase 3 clinical trial"[tiab] OR "phase III clinical trial"[tiab] OR "phase 3 trial"[tiab] OR "phase III trial"[tiab] OR "phase 3 clinical study"[tiab] OR "phase III clinical study"[tiab] OR "phase 3 study"[tiab] OR "phase III study"[tiab] OR "phase 3 randomized trial"[tiab] OR "phase III randomized trial"[tiab] OR Clinical Trial, Phase II[ptyp] OR "phase 2 clinical trial"[tiab] OR "phase II clinical trial"[tiab] OR "phase 2 trial"[tiab] OR "phase II trial"[tiab] OR "phase 2 clinical study"[tiab] OR "phase II clinical study"[tiab] OR "phase 2 randomized trial"[tiab] OR "phase II randomized trial"[tiab] OR "phase 2 study"[tiab] OR "phase II study"[tiab] OR "phase 2/3 clinical trial"[tiab] OR "phase II/ III clinical trial"[tiab] OR "phase 2/3 trial"[tiab] OR "phase II/III trial"[tiab] OR "phase 2/3 clinical study"[tiab] OR "phase II/ III clinical study"[tiab] OR "phase 2/3 study"[tiab] OR "phase II/III study"[tiab] OR "phase 2/3 randomized trial"[tiab] OR "phase II/III randomized trial"[tiab] OR Randomized Controlled Trial[ptyp] OR "randomized controlled trial"[tiab] OR "RCT"[tiab])

Figure 2. PRISMA diagram

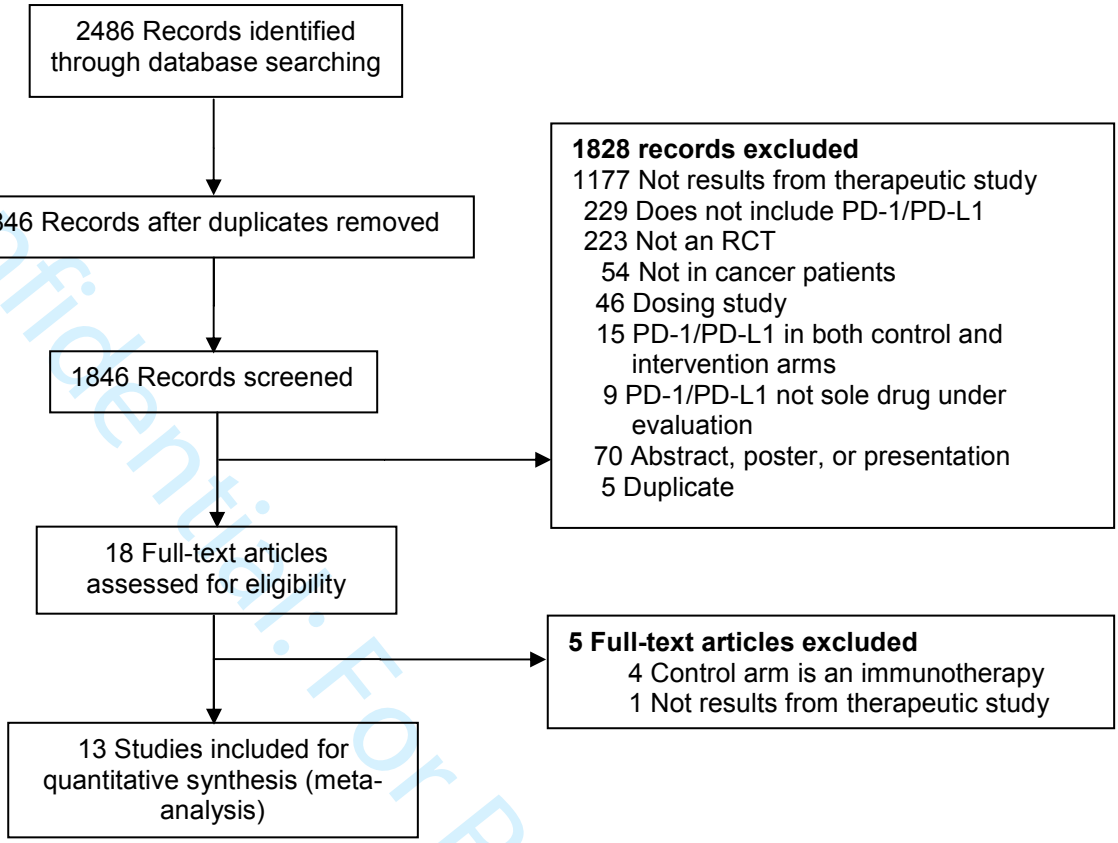

Table 1. Risk of Bias of Randomized, Controlled Trials of PD-1 and PDL-1 Inhibitors in Oncology

Study, year	Randomization	Allocation Concealment	Blinding of participants and personnel	Blinding of outcome assessors*	Incomplete outcome data	Selective outcome reporting‡	Other sources of bias
Bellmunt, 2017	Low risk	Unclear risk	High risk	Low risk	Low risk	Low risk	Low risk
Borghaei, 2015	Low risk	Low risk	High risk	High risk	Low risk	Low risk	Low risk
Brahmer, 2015	Low risk	Low risk	High risk	High risk	Low risk	Low risk	Low risk
Fehrenbacher, 2016	Low risk	Low risk	High risk	High risk	Low risk	Low risk	Low risk
Ferris, 2016	Low risk	Low risk	High risk	High risk	Low risk	Low risk	Low risk
Herbst, 2016	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	Low risk
Langer, 2016	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	Low risk
Motzer, 2015	Low risk	Low risk	High risk	High risk	Low risk	Low risk	Low risk
Reck, 2016	Low risk	Unclear risk	High risk	Low risk	Low risk	Low risk	Low risk
Ribas, 2015	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	Low risk
Rittmeyer, 2017	Low risk	Low risk	High risk	High risk	Low risk	Low risk	Low risk
Robert, 2015	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Weber, 2015	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	Low risk
Kappa	1.00	1.00	0.629	0.629	1.00	1.00	1.00

*Applies to secondary outcomes only.

‡Applies to primary outcomes only and not to toxicity outcomes

Table 2. Incidence of Severe Organ-specific Immune-related Adverse Events, by Drug

	Colitis		Hepatitis		Pneumonitis		Hypothyroidism	
	All*	Serious†	All	Serious	All	Serious	All	Serious
Atezolizumab (N=751)	4 (0.5)	1 (0.1)	3 (0.4)	2 (0.3)	6 (0.8)	4 (0.5)	8 (1)	1 (0.1)
Nivolumab (N =1534)	5 (0.3)	5 (0.3)	0	0	34 (2)	17 (1)	90 (6)	3 (0.2)
Pembrolizumab, (N =1518) §	16 (1)	12 (0.8)	3 (0.2)	3 (0.2)	45 (3)	33 (2)	116 (8)	2 (0.1)
Total (N=3803)	25 (0.7)	18 (0.5)	6 (0.4)	5 (0.1)	85 (2)	54 (1)	214 (6)	6 (0.4)

* Includes both "serious" and "other" adverse events if data was extracted from ClinicalTrials.gov; includes all Common Terminology of Clinical Adverse Events (CTCAE) grades if data was extracted from the publication only

‡ Represents "serious" adverse events if data was extracted from ClinicalTrials.gov; represents CTCAE grades 3, 4, or 5 if data was extracted from the publication only

§ Includes both the 2mg/kg and 10mg/kg dosing arms of Herbst, 2016 and Ribas, 2015

Figure 3. Forest Plot of Hypothyroidism in Patients Treated with Anti-PD1 Agents Versus Control

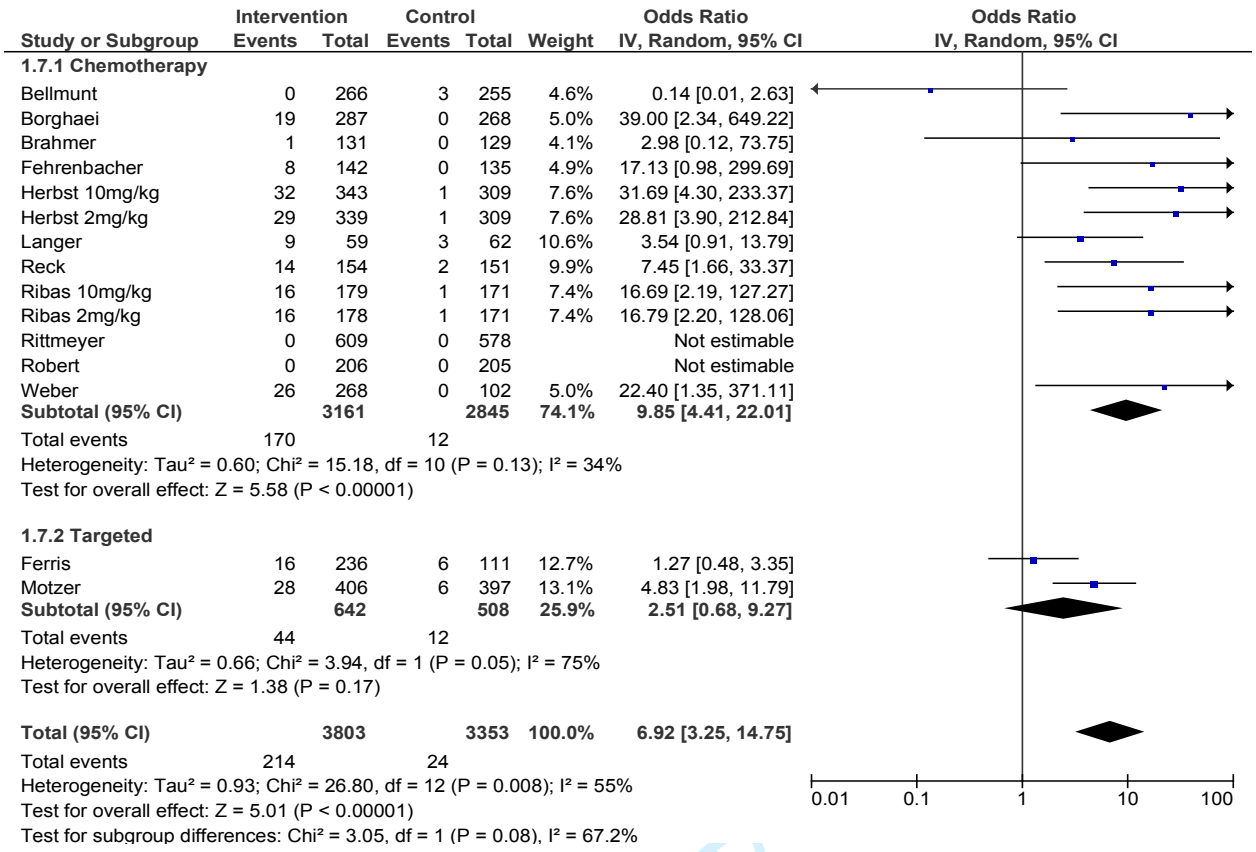

Figure 4. Forest Plot of Pneumonitis in Patients Treated with Anti-PD1 Agents Versus Control

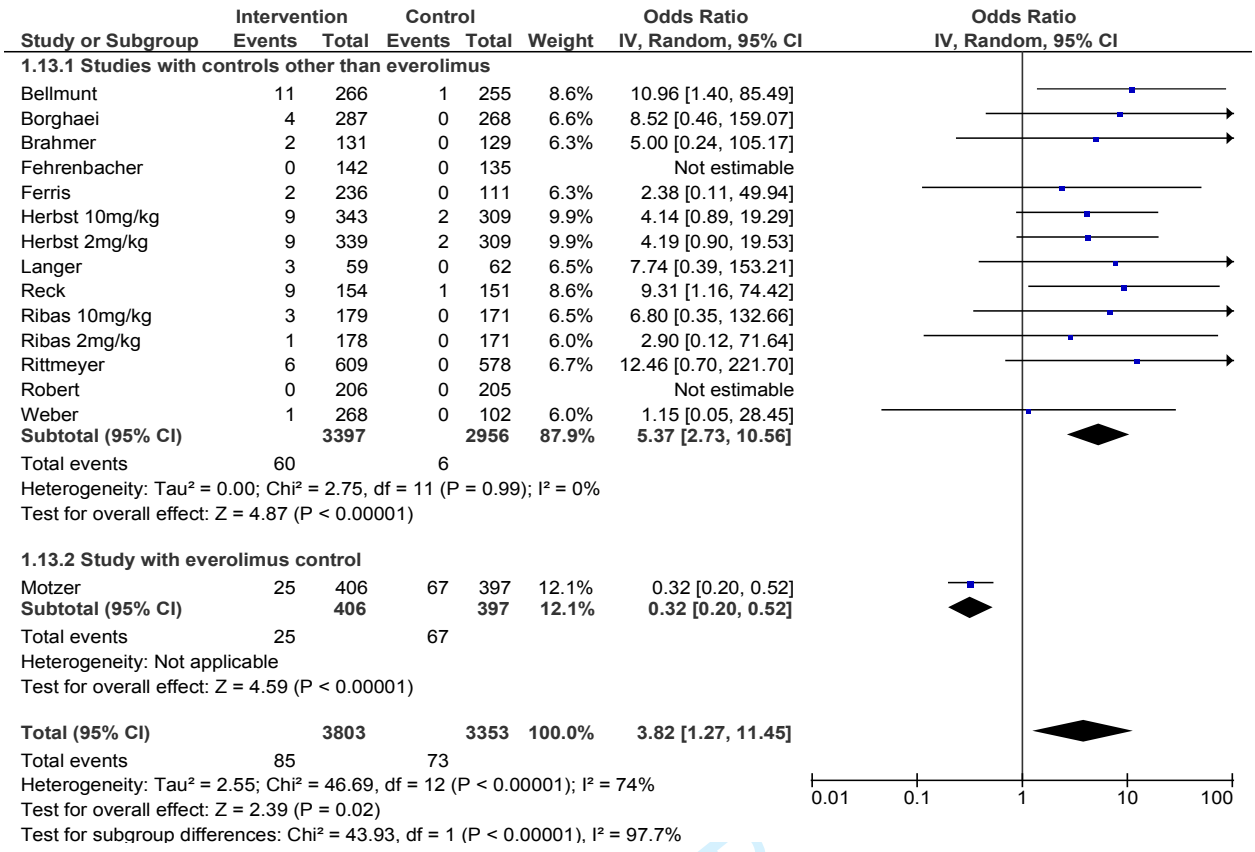

Figure 5. Forest Plot of Colitis in Patients Treated with Anti-PD1 Agents Versus Control

Study or Subgroup	Intervention Events	Intervention Total	Control Events	Control Total	Weight	Odds Ratio IV, Fixed, 95% CI
1.4.1 Chemotherapy						
Bellmunt	6	266	2	255	24.4%	2.92 [0.58, 14.60]
Borghaei	2	287	0	268	6.8%	4.70 [0.22, 98.39]
Brahmer	0	131	0	129		Not estimable
Fehrenbacher	2	142	0	135	6.8%	4.82 [0.23, 101.36]
Herbst 10mg/kg	0	343	0	309		Not estimable
Herbst 2mg/kg	3	339	0	309	7.2%	6.44 [0.33, 125.15]
Langer	0	59	0	62		Not estimable
Reck	3	154	0	151	7.1%	7.00 [0.36, 136.68]
Ribas 10mg/kg	2	179	1	171	10.9%	1.92 [0.17, 21.38]
Ribas 2mg/kg	2	178	1	171	10.9%	1.93 [0.17, 21.50]
Rittmeyer	2	609	0	578	6.8%	4.76 [0.23, 99.39]
Robert	1	206	0	205	6.1%	3.00 [0.12, 74.07]
Weber	0	268	0	102		Not estimable
Subtotal (95% CI)		**3161**		**2845**	**87.0%**	**3.39 [1.45, 7.95]**
Total events	23		4			
Heterogeneity: Chi² = 1.01, df = 8 (P = 1.00); I² = 0%						
Test for overall effect: Z = 2.81 (P = 0.005)						
1.4.2 Targeted						
Ferris	0	236	1	111	6.1%	0.16 [0.01, 3.85]
Motzer	2	406	0	397	6.8%	4.91 [0.24, 102.67]
Subtotal (95% CI)		**642**		**508**	**13.0%**	**0.96 [0.11, 8.72]**
Total events	2		1			
Heterogeneity: Chi² = 2.34, df = 1 (P = 0.13); I² = 57%						
Test for overall effect: Z = 0.04 (P = 0.97)						
Total (95% CI)		**3803**		**3353**	**100.0%**	**2.88 [1.30, 6.37]**
Total events	25		5			
Heterogeneity: Chi² = 4.45, df = 10 (P = 0.92); I² = 0%						
Test for overall effect: Z = 2.61 (P = 0.009)						
Test for subgroup differences: Chi² = 1.09, df = 1 (P = 0.30), I² = 8.5%						

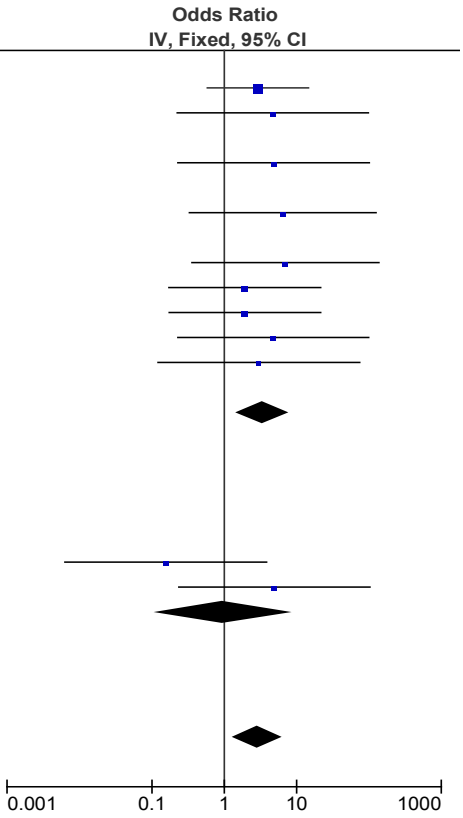

Figure 6. Forest Plot of Hepatitis in Patients Treated with Anti-PD1 Agents Versus Control

Study or Subgroup	Intervention Events	Intervention Total	Control Events	Control Total	Weight	Odds Ratio IV, Fixed, 95% CI
Bellmunt	0	266	0	255		Not estimable
Borghaei	0	287	0	268		Not estimable
Brahmer	0	131	0	129		Not estimable
Fehrenbacher	1	142	0	135	19.5%	2.87 [0.12, 71.13]
Ferris	0	236	0	111		Not estimable
Herbst 10mg/kg	1	343	0	309	19.6%	2.71 [0.11, 66.79]
Herbst 2mg/kg	1	339	0	309	19.6%	2.74 [0.11, 67.58]
Langer	0	59	0	62		Not estimable
Motzer	0	406	0	397		Not estimable
Reck	0	154	0	151		Not estimable
Ribas 10mg/kg	1	179	0	171	19.5%	2.88 [0.12, 71.24]
Ribas 2mg/kg	0	178	0	171		Not estimable
Rittmeyer	2	609	0	578	21.8%	4.76 [0.23, 99.39]
Robert	0	206	0	205		Not estimable
Weber	0	268	0	102		Not estimable
Total (95% CI)		**3803**		**3353**	**100.0%**	**3.14 [0.76, 12.98]**
Total events	6		0			

Heterogeneity: Chi² = 0.09, df = 4 (P = 1.00); I² = 0%

Test for overall effect: Z = 1.58 (P = 0.11)

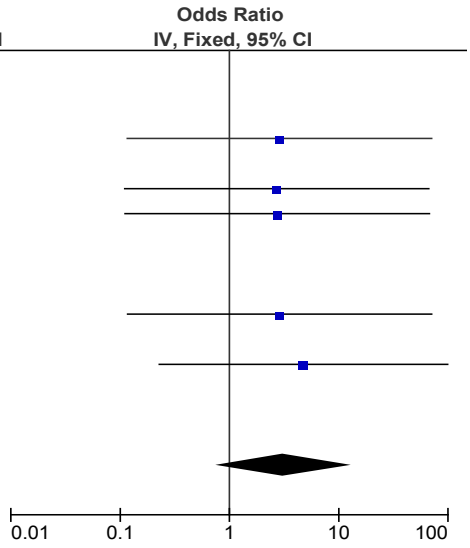

Figure 7. Forest Plot of Rash in Patients Treated with Anti-PD1 Agents Versus Control

Study or Subgroup	Intervention Events	Intervention Total	Control Events	Control Total	Weight	Odds Ratio IV, Random, 95% CI
1.9.1 Chemotherapy						
Bellmunt	0	266	0	255		Not estimable
Borghaei	36	287	13	268	10.3%	2.81 [1.46, 5.43]
Brahmer	11	131	10	129	9.0%	1.09 [0.45, 2.66]
Fehrenbacher	0	142	0	135		Not estimable
Herbst 10mg/kg	64	343	22	309	11.0%	2.99 [1.79, 4.99]
Herbst 2mg/kg	49	339	22	309	10.9%	2.20 [1.30, 3.74]
Langer	1	59	1	62	2.6%	1.05 [0.06, 17.21]
Reck	6	154	0	151	2.5%	13.26 [0.74, 237.53]
Ribas 10mg/kg	49	179	13	171	10.3%	4.58 [2.38, 8.81]
Ribas 2mg/kg	39	178	13	171	10.2%	3.41 [1.75, 6.65]
Rittmeyer	1	609	0	578	2.1%	2.85 [0.12, 70.15]
Robert	1	206	0	205	2.1%	3.00 [0.12, 74.07]
Weber	51	268	5	102	8.7%	4.56 [1.76, 11.78]
Subtotal (95% CI)		**3161**		**2845**	**79.9%**	**2.87 [2.25, 3.68]**
Total events	308		99			
Heterogeneity: Tau² = 0.00; Chi² = 10.20, df = 10 (P = 0.42); I² = 2%						
Test for overall effect: Z = 8.39 (P < 0.00001)						
1.9.2 Targeted						
Ferris	20	236	5	111	8.4%	1.96 [0.72, 5.37]
Motzer	65	406	92	397	11.7%	0.63 [0.44, 0.90]
Subtotal (95% CI)		**642**		**508**	**20.1%**	**1.01 [0.34, 3.00]**
Total events	85		97			
Heterogeneity: Tau² = 0.49; Chi² = 4.33, df = 1 (P = 0.04); I² = 77%						
Test for overall effect: Z = 0.01 (P = 0.99)						
Total (95% CI)		**3803**		**3353**	**100.0%**	**2.34 [1.40, 3.91]**
Total events	393		196			
Heterogeneity: Tau² = 0.55; Chi² = 58.29, df = 12 (P < 0.00001); I² = 79%						
Test for overall effect: Z = 3.25 (P = 0.001)						
Test for subgroup differences: Chi² = 3.37, df = 1 (P = 0.07), I² = 70.4%						

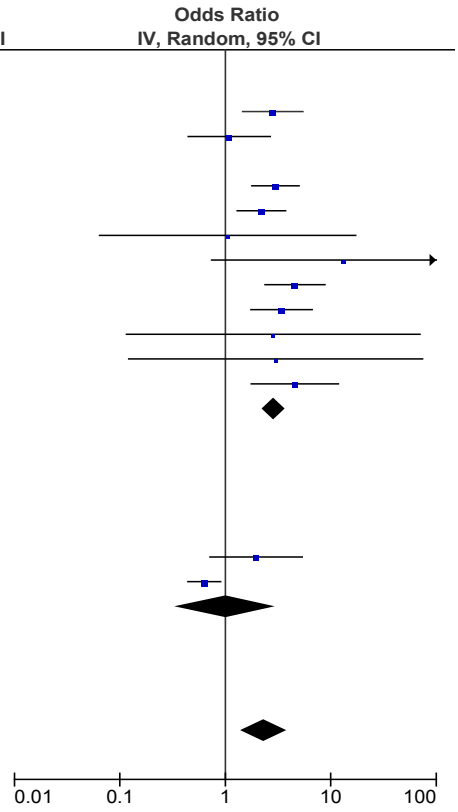

Figure 8. Forest Plot of Fatigue in Patients Treated with Anti-PD1 Agents Versus Control

Study or Subgroup	Intervention Events	Intervention Total	Control Events	Control Total	Weight	Odds Ratio IV, Random, 95% CI
1.11.1 Chemotherapy						
Bellmunt	37	266	71	255	7.6%	0.42 [0.27, 0.65]
Borghaei	92	287	103	268	8.3%	0.76 [0.53, 1.07]
Brahmer	40	131	51	129	7.1%	0.67 [0.40, 1.12]
Fehrenbacher	0	142	0	135		Not estimable
Herbst 10mg/kg	93	343	120	309	8.4%	0.59 [0.42, 0.82]
Herbst 2mg/kg	108	339	120	309	8.5%	0.74 [0.53, 1.02]
Langer	38	59	25	62	5.5%	2.68 [1.28, 5.59]
Reck	16	154	43	151	6.2%	0.29 [0.16, 0.54]
Ribas 10mg/kg	115	179	81	171	7.7%	2.00 [1.30, 3.06]
Ribas 2mg/kg	106	178	81	171	7.7%	1.64 [1.07, 2.50]
Rittmeyer	173	609	205	578	9.0%	0.72 [0.57, 0.92]
Robert	0	206	2	205	0.7%	0.20 [0.01, 4.13]
Weber	130	268	52	102	7.5%	0.91 [0.57, 1.43]
Subtotal (95% CI)		**3161**		**2845**	**84.0%**	**0.82 [0.61, 1.11]**
Total events	948		954			
Heterogeneity: Tau² = 0.21; Chi² = 62.98, df = 11 (P < 0.00001); I² = 83%						
Test for overall effect: Z = 1.29 (P = 0.20)						
1.11.2 Targeted						
Ferris	64	236	36	111	7.2%	0.78 [0.47, 1.27]
Motzer	196	406	178	397	8.8%	1.15 [0.87, 1.52]
Subtotal (95% CI)		**642**		**508**	**16.0%**	**1.00 [0.69, 1.44]**
Total events	260		214			
Heterogeneity: Tau² = 0.04; Chi² = 1.87, df = 1 (P = 0.17); I² = 47%						
Test for overall effect: Z = 0.02 (P = 0.98)						
Total (95% CI)		**3803**		**3353**	**100.0%**	**0.84 [0.65, 1.09]**
Total events	1208		1168			
Heterogeneity: Tau² = 0.18; Chi² = 68.91, df = 13 (P < 0.00001); I² = 81%						
Test for overall effect: Z = 1.31 (P = 0.19)						
Test for subgroup differences: Chi² = 0.64, df = 1 (P = 0.42), I² = 0%						

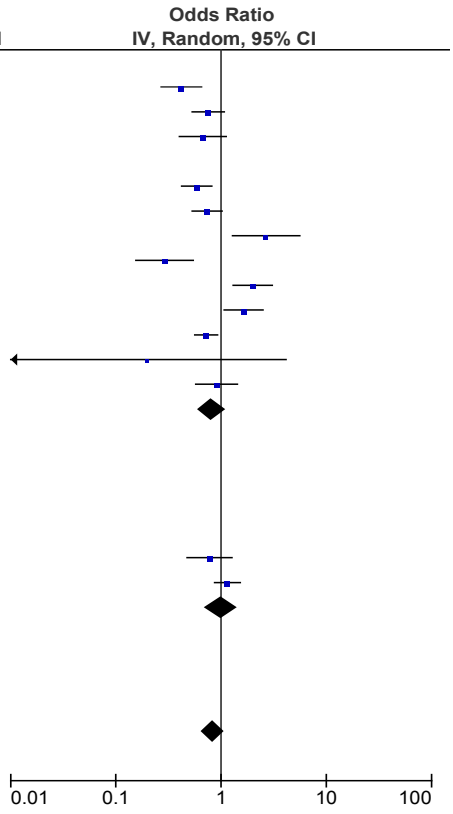

Figure 9. Forest Plot of Diarrhea in Patients Treated with Anti-PD1 Agents Versus Control

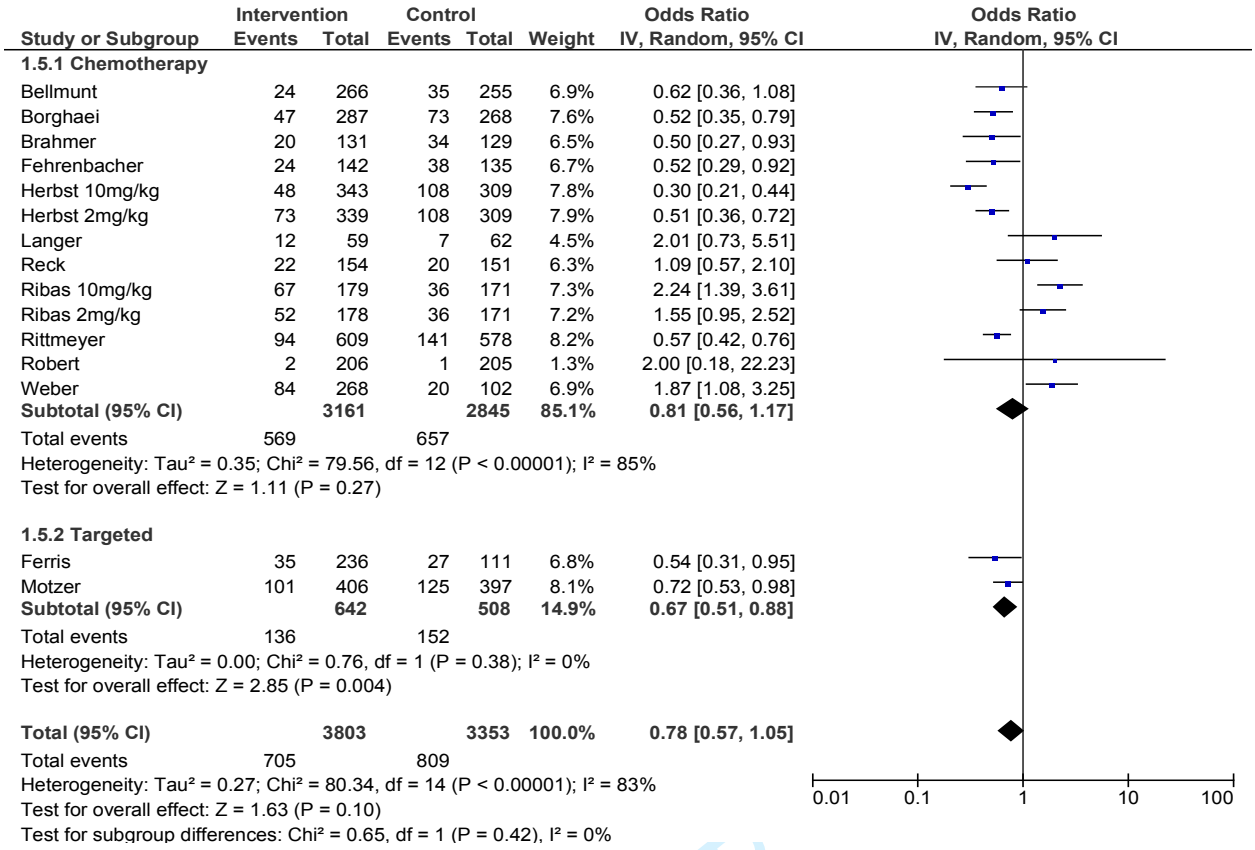

Table 3. Incidence of musculoskeletal toxicities

Author, Year	Drug	Inter-vention, *n*	Arthritis, *n* (%)		Arthralgia, *n* (%)		Back pain, *n* (%)		Musculoskeletal pain, *n* (%)		Myalgia, *n* (%)	
			All*	Grades 3-5†	All	Grades 3-5	All	Grades 3-5	All	Grades 3-5	All	Grades 3-5
Bellmunt, 2017‡	Pembro	266	0	0	0	0	0	0	0	0	0	0
Borghaei, 2015	Nivo	287	0	0	47 (16)	1 (0.3)	37 (13)	2 (1)	39 (14)	1 (0.3)	35 (12)	18 (6)
Brahmer, 2015	Nivo	131	0	0	13 (10)	0	13 (10)	1 (1)	8 (6)	0	15 (11)	8 (6)
Fehren-bacher, 2016‡	Atezo	141	0	0	22 (15)	3 (2.1)	0	0	19 (13)	2 (1.4)	0	0
Ferris, 2016	Nivo	236	0	0	0	0	14 (6)	2 (1)	0	0	0	0
Herbst, 2016	Pembro, 2mg/kg	338	1 (0.3)	1 (0.3)	50 (15)	0	38 (11)	2 (1)	38 (11)	2 (0.6)	48 (14)	25 (7)
	Pembro, 10mg/kg	343	0	0	41 (12)	1 (0.3)	41 (12)	2 (1)	34 (10)	0	48 (14)	17 (5)
Langer, 2016‡	Pembro, combined§	59	0	0	0	0	0	0	0	0	0	0
Motzer, 2015	Nivo	406	0	0	82 (20)	2 (0.5)	90 (22)	7 (2)	41 (10)	1 (0.2)	14 (3)	39 (10)
Reck, 2016‡	Pembro	154	0	0	0	0	0	0	0	0	0	0
Ribas, 2015	Pembro, 2mg/kg	178	0	0	47 (26)	0	30 (17)	0	19 (11)	1 (0.6)	11 (6)	22 (12)
	Pembro, 10mg/kg	179	0	0	35 (20)	2 (1.1)	28 (16)	2 (1)	15 (8)	1 (0.6)	11 (6)	14 (8)
Rittmeyer, 2017‡	Atezo	609	0	0	73 (12)	3 (0.5)	67 (11)	7 (1)	64 (11)	4 (0.7)	91 (15)	39 (6)
Robert, 2015	Nivo	206	0	0	0	0	0	0	0	0	0	0
Weber, 2015	Nivo	268	1 (0.4)	1 (0.4)	62 (23)	1 (0.4)	58 (22)	6 (2)	32 (12)	0	10 (4)	26 (10)
Total		3803	2 (0.05)	2 (0.05)	472 (12)	13 (0.3)	416 (11)	31 (0.8)	309 (8)	12 (0.3)	301 (8)	211 (6)

Pembro=Pembrolizumab; Nivo= Nivolumab; Atezo=Atezolizumab
*Includes any adverse event if data was extracted from ClinicalTrials.gov; includes all Common Terminology of Clinical Adverse Events (CTCAE) grades if data was extracted from the publication only
† Includes “serious” adverse events if data was extracted from ClinicalTrials.gov
‡ Study results were only taken from publication. No trial results were posted on ClinicalTrials.gov as of 3/28/2017
§ Combined treatment included pembrolizumab, carboplatin, and pemetrexed