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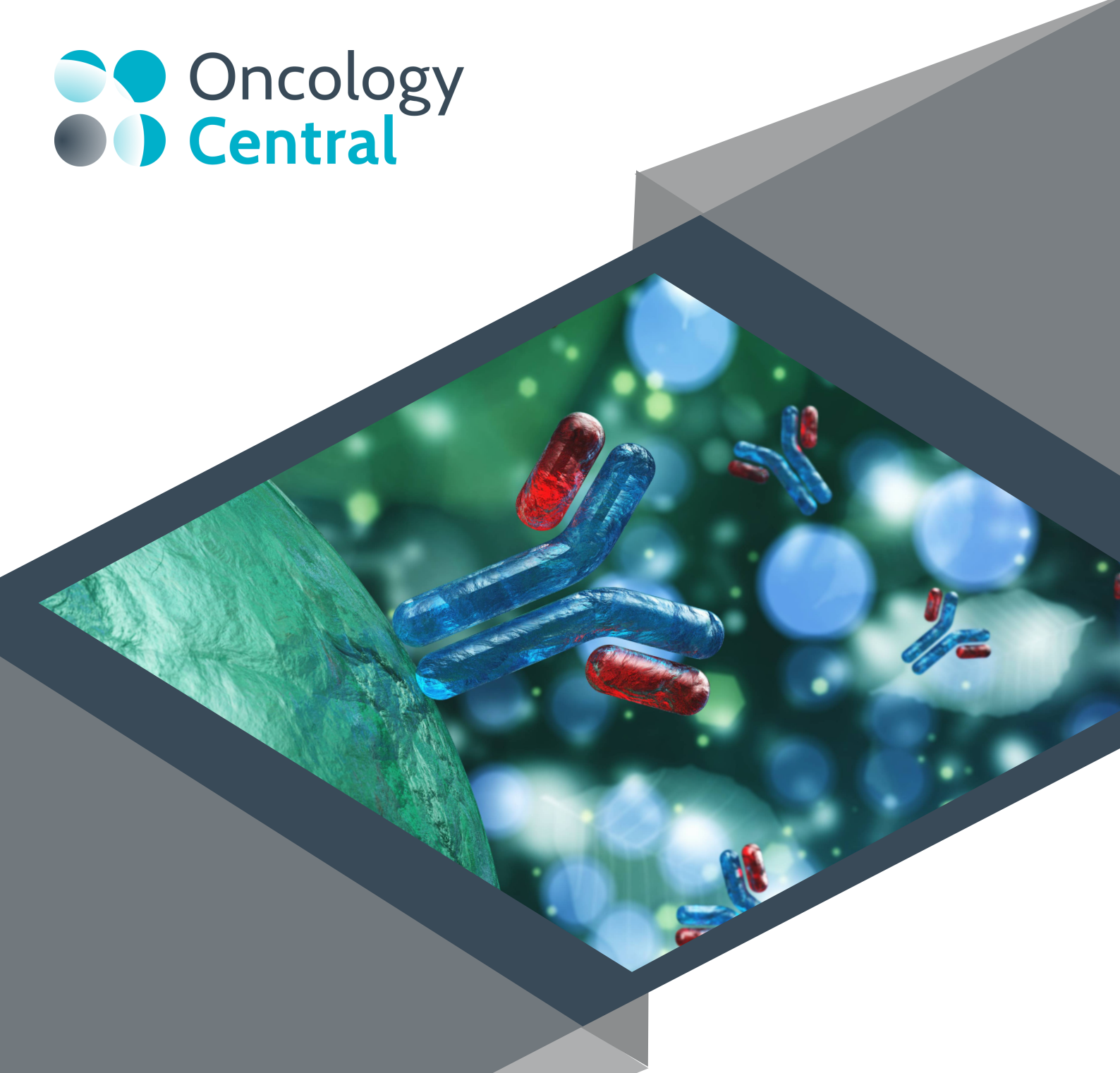

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Immuno-oncology: practical clinical advancements

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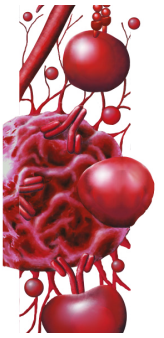

Controversies about COVID-19 and anticancer treatment with immune checkpoint inhibitors

Melissa Bersanelli*,[1,2]

[1]Medical Oncology Unit, University Hospital of Parma, Parma, Italy

[2]Medicine & Surgery Department, University of Parma, Parma, Italy

*Author for correspondence: Tel.: +39 0521 702 316; bersamel@libero.it

"Since ICI can restore the immune-competence, if on one hand it can be paradoxically needed to develop the cytokine storm characterizing the acute respiratory distress syndrome (ARDS) phase, on the other hand the epidemiological features of SARS-CoV-2 infection lay for a lower probability to affect these patients compared with their chemo-treated immune-suppressed counterpart."

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Corona virus disease-19 pandemic & cancer patients

On 11 March, the WHO formally declared the corona virus disease-19 (COVID-19) outbreak a pandemic [1]. After the first cluster of cases emerged from Wuhan, in China, at the end of 2019, up today almost 287000 cases of infections from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) have been diagnosed across all five continents in the last few months [2,3].

COVID-19 morbidity and mortality have been linked to elderly age and comorbidities, leading to a poorer outcome to the viral infection for frail patients and more often resulting in hospitalization, intensive care unit admittance and need for invasive tracheal intubation [4]. Among such individuals, cancer patients represent a large subgroup at high risk of developing coronavirus infection and its severe complications. A recent nationwide analysis in China demonstrated that, of 1590 COVID-19 cases from 575 hospitals, 18 had a history of cancer (1 vs 0.29% of cancer incidence in the overall Chinese population, respectively), with lung cancer as the most frequent diagnosis [5]. Patients with cancer were observed to have a higher risk of severe events compared with patients without cancer (39 vs 8%; p = 0.0003). Moreover, cancer patients who underwent recent chemotherapy or surgery had a higher risk of clinically severe events than did those not receiving treatment. With the limit of a small sample size, the authors concluded that patients with cancer might have a higher risk of COVID-19, and poorer outcomes, than individuals without cancer. As a consequence, they recommended to consider an intentional postponing of adjuvant chemotherapy or elective surgery for stable cancer in endemic areas [5].

Nevertheless, as subsequently highlighted by other authors, the true incidence of COVID-19 in patients with cancer would be more informative in assessing whether such patients have an increased risk (and morbidity) from this viral illness [6]. Furthermore, the limited cancer patient population described in this first report from the literature, was curiously characterized by the lack of individuals receiving anticancer immunotherapy. Indeed, only chemotherapy and surgery were cited among treatments received by patients in the month prior to developing COVID-19. Maybe, this could simply be due to the casualty of a small sample, or otherwise, it could suggest that cancer patients receiving immunotherapy are less prone to develop COVID-19 or to be admitted in hospital due to severe coronavirus symptoms. Currently, we are aware of the probably higher incidence of misdiagnosed coronavirus infections compared with that reported and updated every day; it is likely that a great portion of healthy and young population develop COVID-19 with mild symptoms, not requiring hospital admittance and thus escaping the laboratory confirmation of the disease [7]. Cancer patients undergoing treatment with anti-PD-1/PD-L1 or anti-

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CTLA-4 immune checkpoint inhibitors (ICI) currently used in everyday practice to treat solid tumors such as melanoma, lung cancer, renal carcinoma, urothelial cancers and head and neck carcinoma constitute a growing oncological population [8]. Their specific susceptibility to bacterial or viral infections has not been investigated. Considering that immunotherapy with ICI is able to restore the cellular immunocompetence, as we previously suggested in the context of influenza infection, the patient undergoing immune checkpoint blockade could be more immunocompetent than cancer patients undergoing chemotherapy [9,10].

Potential interference between COVID-19 pathogenesis & immune checkpoint blockade

In the recent weeks, in the countries heavily interested by the COVID-19 outbreak, such as Italy, the scientific associations recommended the prudential postponing of active cancer treatments, especially for stable patients not needing urgent interventions [11]. On one hand, this recommendation could be reasonable for advanced cancer patients receiving chemotherapy, with the risk of hematological toxicity and of worsening an immunosuppressed status, thus favoring COVID-19 morbidity [5]. On the other hand, some oncologists are even currently wondering about the risk of administering ICI in the middle of the COVID-19 outbreak, essentially due to two major concerns.

The first seems to be represented by the potential overlap between the coronavirus-related interstitial pneumonia and the possible pneumological toxicity from anti-PD-1/PD-L1 agents. Even if lung toxicity is not the most frequent adverse event of ICI, it can be life threatening. The overall incidence rate of ICI-related pneumonitis ranges from 2.5–5% with anti-PD-1/PD-L1 monotherapy to 7–10% with anti-CTLA-4/anti-PD-1 combination therapy [12]. The dominant radiological pattern of lung immune-related adverse events (irAEs) is organizing pneumonia, but ICI-related pneumonitis could exhibit a variety of patterns, also including nonspecific interstitial pneumonitis [13]. Despite being rarer than other irAEs, pneumonitis is the most fatal AE associated with PD-1/PD-L1 inhibitor therapy, accounting for 35% of treatment-related toxic deaths [14]. Considering that underlying lung disease, particularly including interstitial pneumopathy, is considered a risk factor for ICI-related pneumonitis, it could be reasonable taking into account the risk of treating patients while they are developing an initial form of COVID-19. The synergy between the two lung injuries, despite only hypothetical, cannot be surely ruled out. Nevertheless, such an epidemiological coincidence should not prevent the oncologist from offering a potentially effective and often well-tolerated treatment even in the middle of the COVID-19 outbreak, since the duration of the pandemic is still currently unpredictable. This is true in particular considering the potentially curative aim of ICI treatment in the context of highly responsive diseases, such as melanoma and renal cell carcinoma and in the adjuvant setting even more than in the advanced disease.

The second concern seems to be represented by a possible negative interference of ICI in the pathogenesis of COVID-19. Cytokine-release syndrome (CRS) is a phenomenon of immune hyperactivation typically described in the setting of T cell-engaging immunotherapy, including CAR-T cell therapy but also anti-PD-1 agents [15]. CRS is characterized by elevated levels of IL-6, IFN- γ and other cytokines, provoking consequences and symptoms related to immune activation, ranging from fever, malaise and myalgias to severe organ toxicity, lung failure and death. In parallel, one of the most important mechanism underlying the deterioration of disease in COVID-19 is represented by the cytokine storm, leading to acute respiratory distress syndrome or even multiple organ failure [16]. The cytometric analyses of COVID-19 patients showed reduced counts of peripheral CD4 and CD8 T cells, while their status was hyperactivated. In addition, an increased concentration of highly proinflammatory CCR6+ Th17 in CD4 T cells has been reported, and CD8 T cells were found to harbor high concentrations of cytotoxic granules, suggesting that overactivation of T cells tends to contribute to the severe immune injury of the disease [17]. Moreover, the pathological findings associated with acute respiratory distress syndrome in COVID-19 showed abundant interstitial mononuclear inflammatory infiltrate in the lungs, dominated by lymphocytes, once again implying that the immune hyperactivation mechanisms are at least partially accountable for COVID-19 severity [17]. Considering these aspects, the hypothesis of a synergy between ICI mechanisms and COVID-19 pathogenesis, both contributing to a counter-producing immune hyperactivation, cannot be excluded.

In spite of this fascinating rationale, we should remember that ICI-induced CRS is a quite rare phenomenon as well as that the cytokine storm is not an early event in the COVID-19 pathogenesis, indeed characterizing the late phase of its most severe manifestation, occurring in a minority of patients. It is not likely that cancer patients are still receiving ICI during this phase of the viral illness. Obviously, in the current pandemic scenario, careful attention should be dedicated in delaying treatment for those patients presenting flu-like symptoms at the time of the intended ICI treatment.

Therapeutic implications: tocilizumab & the risk of hasty conclusions

Since its first outbreak in China, COVID-19 was empirically treated with antiviral therapy, first employing agents already used in prior severe acute respiratory syndrome epidemics [18]. Then, several randomized clinical trials were initiated in China and more recently in Italy, investigating different treatment options, varying from classical antiviral drugs as lopinavir/ritonavir, to newer antiviral as remdesivir, to unconventional agents such as chloroquine and hydroxychloroquine [19]. The latest treatment frontier against COVID-19 seems to be represented by a recombinant humanized monoclonal antibody, named tocilizumab, which binds the human IL-6 receptor, inhibiting its signal transduction [20]. Tocilizumab is currently used for rheumatoid arthritis, but its efficacy has been demonstrated also against ICI-induced irAEs, starting from the rationale of an ICI-induced systemic inflammatory response syndrome similar to CRS [21]. Moreover, along with the improvement in symptoms related to systemic inflammatory response syndrome, some authors reported a clinical improvement in other irAEs with tocilizumab used in cancer patients with immune-related toxicity from anti-PD-1 agents [21,22].

With these premises, the risk of hasty conclusions is around the corner. In fact, one can argue that the alleged tocilizumab efficacy both for treating COVID-19 and irAEs might suggest a potentially increased danger from SARS-CoV-2 infection for ICI-treated patients, maybe hypothesizing a synergy in the promotion of the viral morbidity. Nevertheless, this is probably a thoughtless deduction.

First, it can be a matter of time. The time at which the COVID-19 patient develops the pathologic hyperactivation of the immune response, eventually contributing to the final injury, is probably in the late phase of the disease manifestation, occurring together with the respiratory distress [17]. Furthermore, the time matters also in the case of ICI therapy, since the majority of patients develop irAEs within the first 6 months from the first administration [12]. Thus, a certain caution for ICI administration during the pandemics could be applied mostly for those patients needing therapy initiation or in their first months of treatment.

Second, it is probably a matter of patient. Patients more prone to developing immune hyperactivation are probably those more likely to respond to ICI [23]. There is a possibility that such patients would be also more prone to fall in the cytokine storm in the case of SARS-CoV-2 infection. Nevertheless, these patients do not correspond to the average advanced cancer patient, who is supposed to be immunosuppressed, with a blunted immune status [6]. The epidemiology of the COVID-19 observed up today suggests that SARS-CoV-2 tends to infect more frequently the frail patient populations, such as the elderly and cancer patients [4,5]. Cancer is usually associated with overexpression of immunosuppressive cytokines, suppression of proinflammatory danger signals, impaired dendritic cell maturation, and enhanced immunosuppressive leukocyte populations [6]. Since ICI can restore the immune-competence, if on one hand it can be paradoxically needed to develop the cytokine storm characterizing the acute respiratory distress syndrome (ARDS) phase, on the other hand the epidemiological features of SARS-CoV-2 infection lay for a lower probability to affect these patients compared with their chemo-treated immune-suppressed counterpart.

Third, the efficacy of tocilizumab for COVID-19 is still under investigation, with still unexplored backstage and with uncomfortable upstream evidence coming from the setting of influenza infection. Despite clinical studies associating IL-6 with high disease severity in influenza-infected patients and its levels correlated directly with symptom occurrence in human influenza virus infection, the role of this cytokine is still ambiguous [24]. It was demonstrated in mice models that IL-6 is essential for preventing virus-induced neutrophil cell death and H1N1-associated mortality, limiting influenza-induced cytokine storm and protecting against fatal lung pathology [25]. Furthermore, IL-6 is crucial in secondary infections to recall virus-specific memory CD4 T cells, favoring virus clearance and host survival, as supported by the inability of IL-6 deficient mice to control influenza viral titers in the lung [25]. Such preclinical evidence suggests that, despite probably being harmful in the ARDS phase, IL-6 role could be crucial, in the early phase of the viral infection, to defuse the pathogenesis of severe and lethal forms of influenza. Thus, hoping for positive results from tocilizumab randomized clinical trial on COVID-19 patients, we could only argue about the evident diversity of this viral infection from previous SARS outbreaks and even more from influenza epidemics, probably both in terms of clinical features and of pathogenetic implications.

Conclusion

Clinical decisions about cancer patients deserving immunotherapy in the current context of the COVID-19 pandemic should be characterized by separated reflections, avoiding generalizations and remembering their deeply different immunological status compared with that of cancer patients undergoing chemotherapy or targeted agents. In the end, beyond any charming scientific speculations, it is unfortunately likely that in this COVID-19 pandemic,

the greatest risk for cancer patients is the unavailability of the usually high-level medical services, since all our hospital resources, in terms of structures, tools and healthcare professionals, are currently strongly dedicated to the outbreak management.

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References

1. Adhanom Ghebreyesus T. WHO – Director-General's opening remarks at the media briefing on COVID-19 – 11 March. (2020). www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020
2. Munster VJ, Koopmans M, van Doremalen N, van Riel D, de Wit E. A Novel coronavirus emerging in china – key questions for impact assessment. *N. Engl. J. Med.* 382(8), 692–694 (2020).
3. Johns Hopkins Coronavirus Resource Center. Coronavirus COVID-19 global cases by the center for systems science and engineering. (2020). https://coronavirus.jhu.edu/map.html
4. Rothan HA, Byrareddy SN. The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. *J. Autoimmun.* 26, 102433 (2020).
5. Liang W, Guan W, Chen R *et al.* Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. *Lancet Oncol.* 21(3), 335–337 (2020).
6. Xia Y, Jin R, Zhao J, Li W, Shen H. Risk of COVID-19 for cancer patients. *Lancet Oncol.* 20, S1470–S2045 (2020).
7. Bai Y, Yao L, Wei T *et al.* Presumed asymptomatic carrier transmission of COVID-19. *JAMA* doi:10.1001/jama.2020.2565 (2020) (Epub ahead of print).
8. Bersanelli M, Buti S. From targeting the tumor to targeting the immune system: transversal challenges in oncology with the inhibition of the PD-1/PD-L1 axis. *World J. Clin. Oncol.* 8(1), 37–53 (2017).
9. Bersanelli M, Giannarelli D, Castrignanò P *et al.* INfluenza vaccine indication during therapy with immune checkpoint inhibitors: a transversal challenge. The INVIDIa study. *Immunotherapy.* 10(14), 1229–1239 (2018).
10. Bersanelli M, Scala S, Affanni P *et al.* Immunological insights on influenza infection and vaccination during immune checkpoint blockade in cancer patients. *Immunotherapy* 12(2), 105–110 (2020).
11. AIOM (Associazione Italiana di Oncologia Medica). Comunicato AIOM per emergenza Corona virus. (2020). www.aiom.it/comunicato-aiom-per-emergenza-corona-virus/
12. Choi J, Lee SY. Clinical characteristics and treatment of immune-related adverse events of immune checkpoint inhibitors. *Immune Netw.* 20(1), e9 (2020).
13. Kalisz KR, Ramaiya NH, Laukamp KR, Gupta A. Immune checkpoint inhibitor therapy-related pneumonitis: patterns and management. *Radiographics* 39, 1923–1937 (2019).
14. Wang DY, Salem JE, Cohen JV *et al.* Fatal toxic effects associated with immune checkpoint inhibitors: a systematic review and meta-analysis. *JAMA Oncol* 4, 1721–1728 (2018).
15. Rotz SJ, Leino D, Szabo S, Mangino JL, Turpin BK, Pressey JG. Severe cytokine release syndrome in a patient receiving PD-1-directed therapy. *Pediatr. Blood Cancer* 64, 12 (2017).
16. Chen C, Zhang XR, Ju ZY, He WF. Advances in the research of cytokine storm mechanism induced by corona virus disease 2019 and the corresponding immunotherapies. *Zhonghua Shao Shang Za Zhi* 36(0), E005 (2020).
17. Xu Z, Shi L, Wang Y *et al.* Pathological findings of COVID-19 associated with acute respiratory distress syndrome. *Lancet Respi. Med.* doi:10.1016/S2213-2600(20)30076-X (2020) (Epub ahead of print).
18. Lim J, Jeon S, Shin HY *et al.* Case of the index patient who caused tertiary transmission of COVID-19 infection in korea: the application of lopinavir/ritonavir for the treatment of COVID-19 infected pneumonia monitored by quantitative RT-PCR. *J. Korean Med. Sci.* 17 35(6), e79 (2020).
19. Zhang Q, Wang Y, Qi C, Shen L, Li J. Clinical trial analysis of 2019-nCoV therapy registered in China. *J. Med. Virol.* doi:10.1002/jmv.25733 (2020) (Epub ahead of print).
20. Xu X, Han M, Li T *et al.* Effective treatment of severe COVID-19 patients with tocilizumab. chinaXiv:202003.00026v1 (2020). www.chinaxiv.org/abs/202003.00026
21. Stroud CR, Hegde A, Cherry C *et al.* Tocilizumab for the management of immune mediated adverse events secondary to PD-1 blockade. *J. Oncol. Pharm. Pract.* 25(3), 551–557 (2019).
22. Horisberger A, La Rosa S, Zurcher JP *et al.* A severe case of refractory esophageal stenosis induced by nivolumab and responding to tocilizumab therapy. *J. Immunother. Cancer* 6(1), 156 (2018).

23. Cortellini A, Buti S, Agostinelli V *et al.* A systematic review on the emerging association between the occurrence of immune-related adverse events and clinical outcomes with checkpoint inhibitors in advanced cancer patients. *Semin. Oncol.* 46(4–5), 362–371 (2019).

24. Teijaro JR. The role of cytokine responses during influenza virus pathogenesis and potential therapeutic options. *Curr. Top. Microbiol. Immunol.* 386, 3–22 (2015).

25. Lauder SN, Jones E, Smart K *et al.* Interleukin-6 limits influenza-induced inflammation and protects against fatal lung pathology. *Eur. J. Immunol.* 43(10), 2613–2625 (2013).

Clinical Trial Protocol

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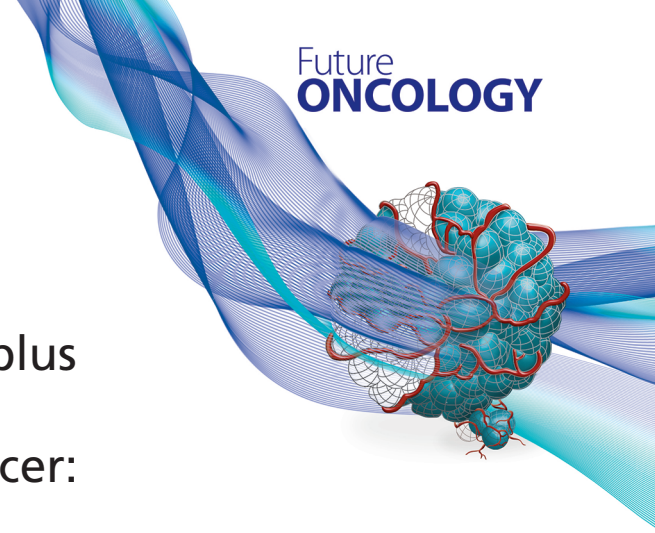

First-line pembrolizumab/placebo plus trastuzumab and chemotherapy in HER2-positive advanced gastric cancer: KEYNOTE-811

Hyun Cheol Chung*[,1], Yung-Jue Bang[2], Charles S Fuchs[3], Shu-Kui Qin[4], Taroh Satoh[5], Kohei Shitara[6], Josep Tabernero[7], Eric van Cutsem[8], Maria Alsina[7], Zhu Alexander Cao[9], Jia Lu[9], Pooja Bhagia[9], Chie-Schin Shih[9] & Yelena Y Janjigian[10]

[1]Division of Medical Oncology, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, 03722, South Korea
[2]Seoul National University College of Medicine, Seoul, 03080, South Korea
[3]Yale Cancer Center, Smilow Cancer Hospital, New Haven, CT 06510, USA
[4]Cancer Center of People's Liberation Army, Nanjing, 210002, China
[5]Osaka University, Suita, Osaka, 565-0871, Japan
[6]National Cancer Center Hospital East, Kashiwa, 277-8577, Japan
[7]Vall d'Hebron University Hospital & Institute of Oncology, Barcelona, 08035, Spain
[8]University Hospitals Gasthuisberg Leuven & KU Leuven, Leuven, 03001, Belgium
[9]Department of Medical Oncology, Merck & Co., Inc., Kenilworth, NJ 07033, USA
[10]Memorial Sloan Kettering Cancer Center, New York, NY 10065, USA
*Author for correspondence: unchung8@yuhs.ac

Treatment options for patients with HER2-positive advanced gastric cancer are limited, and the prognosis for these patients is poor. Pembrolizumab has demonstrated promising antitumor activity in patients with advanced gastric or gastroesophageal junction adenocarcinoma as monotherapy, in combination with chemotherapy and in combination with trastuzumab. Combining pembrolizumab with trastuzumab and chemotherapy may therefore provide a benefit for patients with advanced HER2-positive gastric cancer. Here we aimed to describe the design of and rationale for the randomized, double-blind, placebo-controlled Phase III KEYNOTE-811 study, which will evaluate the efficacy and safety of pembrolizumab or placebo in combination with trastuzumab and chemotherapy as first-line treatment for patients with advanced HER2-positive gastric or gastroesophageal junction adenocarcinoma.

Clinical Trial Registration: NCT03615326 (ClinicalTrials.gov)

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Keywords: chemotherapy • first-line therapy • gastric cancer • gastroesophageal junction cancer • human epidermal growth factor receptor 2 • pembrolizumab • trastuzumab

Gastric cancer is the fifth most common cancer in the world and the third-leading cause of cancer-related death [1]. More than 1 million new cases were diagnosed in 2018, and 780,000 people died of the disease. The incidence of gastric cancer is substantially higher in Eastern Asia than in any other region, and it is diagnosed twice as frequently in men. Although often considered a single entity, gastric cancers can be divided into noncardia gastric cancer, arising from the distal portion of the stomach, and cardia gastric cancer, which includes cancers of the upper stomach and the gastroesophageal junction (GEJ) [2]. The primary risk factor for the development of noncardia gastric cancer is the presence of *Helicobacter pylori*, which is believed to be causative in almost 90% of cases [3]. In contrast, cardia gastric cancers are more frequently associated with obesity and gastroesophageal reflux disease [2].

In addition to their topographic categorization, gastric cancers can be divided into one of four molecular subtypes, each associated with specific genomic and prognostic characteristics [4,5]. Of note, this molecular profiling has enabled the identification of potentially targetable alterations in gastric cancer and provides an opportunity to identify biomarkers of response. The most common of these subtypes is the chromosomally unstable tumors

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(CIN) subtype, which accounts for approximately 50% of all gastric cancers [4]. This subtype is associated with intestinal type histology, elevated frequency in GEJ/cardia gastric cancer, *TP53* mutation and amplification of receptor tyrosine kinases, including HER2 [4,6]. Consequently, HER2 overexpression is observed in 10–22% of all gastric cancers [6,7].

Surgical resection can be curative for patients with early-stage gastric cancer; however, because of the largely asymptomatic nature and aggressiveness of the disease at this stage, most diagnoses are made when the disease is advanced [7,8]. The prognosis for patients with advanced-stage gastric cancer is poor, with survival ranging from approximately 4 months with best supportive care to 12 months with chemotherapy [8]. The recommended first-line treatment for most patients with advanced gastric cancer is doublet combination therapy with platinum and fluoropyrimidine [7,9]. For patients with HER2-postive disease, the recommended first-line regimen is trastuzumab (anti-HER2) in combination with platinum and fluoropyrimidine-based chemotherapy [7,9]. The inclusion of trastuzumab in the treatment regimen for gastric cancer was based on the results of the Phase III ToGA trial (ClinicalTrials.gov: NCT01041404), which showed that the addition of trastuzumab to a regimen of capecitabine + cisplatin or fluorouracil + cisplatin improved overall survival (OS) from 11.1 to 13.8 months (hazard ratio [HR], 0.74; 95% CI: 0.60–0.91; p = 0.0048) and progression-free survival (PFS) from 5.5 to 6.7 months (HR: 0.71; 95% CI: 0.59–0.85; p = 0.0002) in patients with HER2-positive gastric or GEJ cancer [10]. First-line treatment combinations with pertuzumab (anti-HER2) plus trastuzumab plus chemotherapy as well as lapatinib (tyrosine kinase inhibitor) plus chemotherapy versus placebo plus chemotherapy have not proven successful in Phase III trials thus far because of their failure to meet the primary end point in the JACOB and TRIO-013/LOGiC trials, respectively [11,12].

The choice of second-line or later therapy for patients with advanced gastric cancer is dependent on therapy previously received and on performance status [9]. The continuation of HER2 inhibitors after disease progression with trastuzumab has not been shown to be effective in prospective trials [13]. Recommended chemotherapy-based regimens include docetaxel, paclitaxel or irinotecan monotherapy; fluorouracil + irinotecan; and trifluridine and tipiracil (third-line or later therapy) [9]. The anti-vascular endothelial growth factor receptor 2 antibody ramucirumab in combination with paclitaxel is also recommended for use as second-line therapy based on the results of the Phase III RAINBOW trial (NCT01170663), which demonstrated improved survival with this combination compared with paclitaxel alone (median OS: 9.6 vs 7.4 months; HR: 0.807; 95% CI: 0.678–0.962; p = 0.017) [9,14]. Pembrolizumab, an anti-PD-1 monoclonal antibody, is recommended by the National Comprehensive Cancer Network as the preferred second-line therapy for patients with microsatellite instability-high (MSI-H) or mismatch repair deficient tumors and as a third-line therapy for patients with PD-L1–positive (combined positive score [CPS] $\geq$1) tumors [9]. The anti-PD-1 monoclonal antibody nivolumab is recommended by the Japanese Gastric Cancer Association as third-line therapy [15]. Of note, PD-1/PD-L1 inhibitors have not yet been approved by the EMA for use in patients with gastric cancer.

Given the limited survival benefit observed with currently recommended therapies, there remains a need for novel therapeutic regimens for the treatment of patients with advanced gastric cancer.

KEYNOTE-811 trial

Here we describe the design and rationale of the randomized, double-blind, placebo-controlled, Phase III KEYNOTE-811 study (NCT03615326), which will evaluate the efficacy and safety of pembrolizumab or placebo in combination with trastuzumab and chemotherapy as first-line treatment for patients with advanced HER2-positive gastric or GEJ adenocarcinoma.

Background & rationale

The PD-1/PD-L1 pathway is an important regulatory component of the immune response and plays a critical role in tumor evasion of immune surveillance [16]. A growing body of evidence indicates that PD-1 and PD-L1 are frequently overexpressed in gastric cancer and that their upregulation may be prognostic of poor outcome [17,18]. Consequently, PD-1 and PD-L1 represent promising targets for the treatment of gastric cancer.

Pembrolizumab is a highly selective, humanized, monoclonal immunoglobulin G4-κ antibody that binds to PD-1 and blocks its interactions with PD-L1 and PD-L2, thereby releasing PD-1 pathway-mediated inhibition of the antitumor immune response [19]. Pembrolizumab has demonstrated durable antitumor activity in patients with gastric cancer in several trials. In the Phase Ib KEYNOTE-012 study (NCT01848834), eight of 36 evaluable

patients in the gastric cancer cohort achieved partial response (PR) with pembrolizumab monotherapy, for an objective response rate (ORR) of 22% (95% CI: 10–39) [20]. A clinically meaningful result was also observed in cohort 1 of the Phase II KEYNOTE-059 study (NCT02335411), which investigated the efficacy of third-line or later pembrolizumab monotherapy in patients with gastric or GEJ cancer [21]. Of 259 patients enrolled in this cohort, 30 patients (12%; 95% CI: 8–16) experienced objective response; six of those patients (2%; 95% CI: 1–5) achieved complete response (CR). The median OS in this cohort was 5.6 months. The potential benefit of pembrolizumab for the treatment of gastric cancer was also investigated in the Phase III KEYNOTE-061 trial (NCT02370498), which evaluated the efficacy of pembrolizumab monotherapy compared with paclitaxel in patients with advanced gastric or GEJ cancer that had progressed on first-line chemotherapy with platinum and fluoropyrimidine [22]. After follow-up of 7.9 months, the median OS in patients with CPS ≥1 tumors – 9.1 months for pembrolizumab and 8.3 months for paclitaxel (HR: 0.82; 95% CI: 0.66–1.03; one-sided p = 0.0421) – was not significantly different between the groups. PFS and ORR were similar between the treatment groups, but responses were more durable in patients who received pembrolizumab than those who received paclitaxel (median duration of response [DOR]: 18.0 vs 5.2 months, respectively). *Post hoc* analyses of patients with CPS ≥10 tumors revealed a greater survival benefit for the pembrolizumab group than the paclitaxel group (HR: 0.64; 95% CI: 0.41–1.02) [23]. In the Phase III KEYNOTE-062 study (NCT02494583), first-line pembrolizumab or pembrolizumab + chemotherapy versus chemotherapy was evaluated in patients with CPS ≥1, HER2-negative, advanced gastric cancer [24]. Pembrolizumab monotherapy was noninferior to chemotherapy for OS in patients with CPS ≥1 tumors but resulted in a clinically meaningfully improvement for OS in patients with CPS ≥10 tumors (HR: 0.69; 95% CI: 0.49–0.97). Pembrolizumab + chemotherapy did not show superior OS and PFS in patients with CPS ≥1 tumors and OS in patients with CPS ≥10 tumors. The KEYNOTE-059 study included two additional gastric cancer cohorts in its investigation of pembrolizumab as monotherapy or in combination with chemotherapy in previously untreated patients [25]. The ORR among patients who received first-line pembrolizumab monotherapy was 26% (95% CI: 12–45; eight of 31 patients; 2 CR), and the median OS was 20.7 months. In patients who received first-line pembrolizumab in combination with a fluoropyrimidine and a cisplatin, the ORR was 60% (95% CI: 39–79; 15 of 25 patients; 1 CR) and the median OS was 13.8 months.

These data demonstrate that pembrolizumab has durable clinical benefit in patients with advanced gastric cancer and shows promise when used in combination with chemotherapy. However, for patients with HER2-positive disease, the current standard of care also includes treatment with the HER2-targeted antibody trastuzumab [7,9]. In recent years, there has been growing interest in the use of trastuzumab in combination with immune checkpoint inhibitors because of observations that the immune system substantially contributes to the therapeutic effects of HER2-targeted antibodies and that treatment with trastuzumab may increase tumor expression of PD-L1 [26,27]. The combination of trastuzumab and pembrolizumab was initially investigated in the Phase Ib/II PANACEA trial (NCT02129556) in patients with trastuzumab-resistant advanced HER2-positive breast cancer [28]. Results indicated that the combination had manageable safety and durable clinical benefit, but only in patients with PD-L1-positive (CPS ≥1) tumors. This study established proof of concept for this dual antibody approach, but the efficacy of these agents in combination with chemotherapy has not yet been established. Two early-phase trials (NCT02954536 and NCT02901301) are underway to investigate the combination of pembrolizumab, trastuzumab and chemotherapy for the treatment of gastric or GEJ cancer; both studies enrolled patients regardless of PD-L1 status. Additionally, these studies were not powered to distinguish differences based on PD-L1 status, although this was explored in NCT02954536; the authors suggested that the effect was similar regardless of PD-L1 status [29]. Results from one of these trials (NCT02954536) showed that a combination of pembrolizumab, trastuzumab and chemotherapy (oxaliplatin or cisplatin) had a manageable safety profile and promising efficacy, with an ORR of 91% (95% CI: 78–97; 32 of 35 patients; six CRs) in patients with esophagogastric adenocarcinoma [30]. In another trial (NCT02901301), the ORR was 77% with pembrolizumab, trastuzumab, capecitabine and cisplatin as first-line therapy for HER-positive advanced gastric cancer [31]; the dosing schedule and patient population are similar to those of the KEYNOTE-811 trial.

Taken together, the available evidence indicates that pembrolizumab has durable efficacy in gastric cancer and that pembrolizumab combined with trastuzumab and chemotherapy is a promising treatment option in patients with HER2-positive disease.

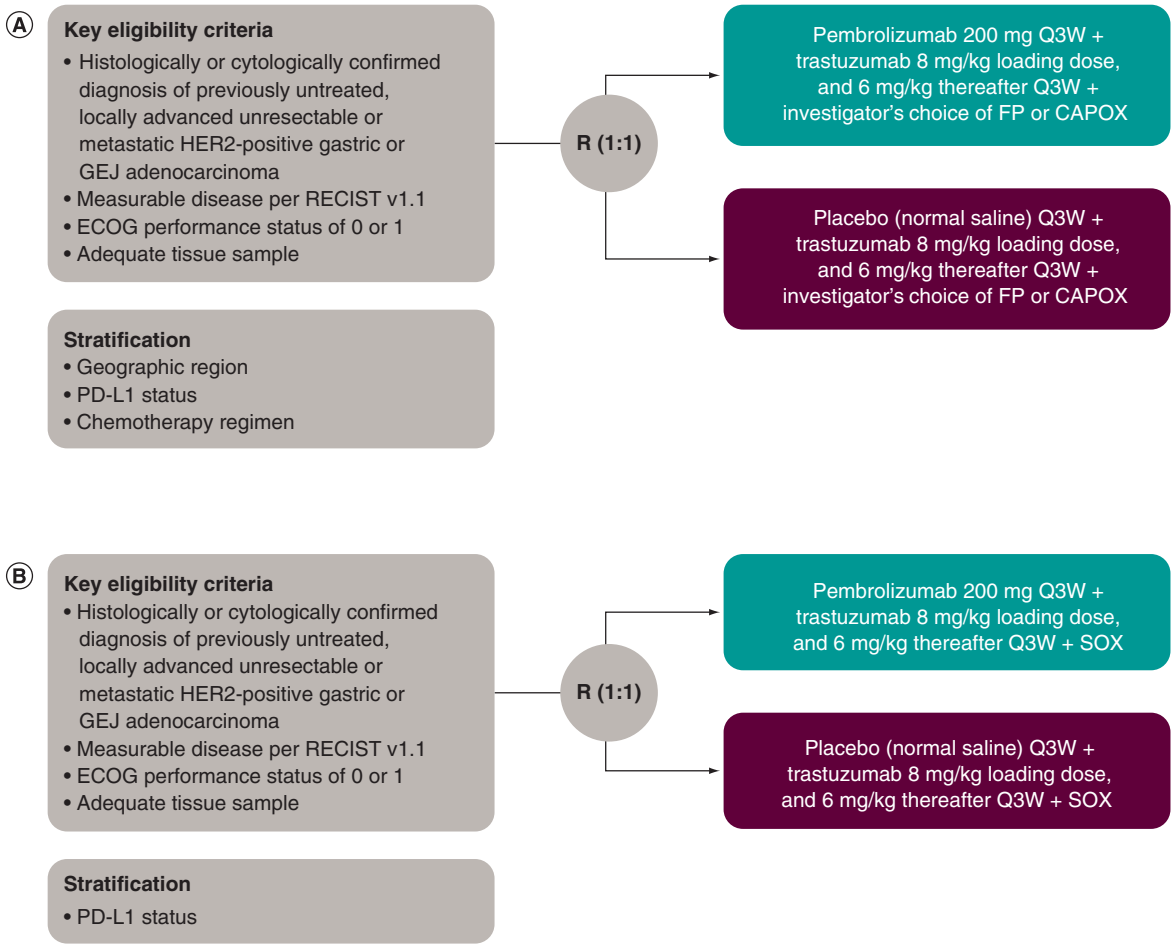

Figure 1. KEYNOTE-811 study design. (A) Global cohort. **(B)** Japan-specific S-1 + oxaliplatin cohort.
CAPOX: Capecitabine + oxaliplatin; FP: 5-Fluorouracil + cisplatin; R: Randomization; SOX: S-1 + oxaliplatin.

Study design

KEYNOTE-811 is an international, multicenter, randomized, double-blind, placebo-controlled, Phase III study consisting of two cohorts (Figure 1). The global cohort will receive pembrolizumab or placebo in combination with trastuzumab and either cisplatin + 5-fluorouracil (FP) or oxaliplatin + capecitabine (CAPOX); the Japan-specific cohort will receive pembrolizumab or placebo in combination with trastuzumab and S-1 + oxaliplatin (SOX). Eligible patients will be randomly assigned 1:1 to receive pembrolizumab 200 mg or placebo (normal saline) + trastuzumab (8 mg/kg loading dose; 6 mg/kg thereafter) by intravenous infusion every 3 weeks and investigator's choice of FP or CAPOX in the global cohort or SOX in the Japan-specific cohort (Table 1). Treatment will continue until confirmed disease progression, unacceptable toxicity, investigator or patient decision to withdraw from the study, noncompliance with treatment or trial procedures, or completion of 35 cycles of study treatment (~2 years). Patients with progressive disease (PD) whose conditions are clinically stable may continue on treatment at the discretion of the investigator. Patients who have attained CR may stop study treatment after receiving ≥8 doses of pembrolizumab or placebo in total and ≥2 doses after attaining confirmed CR. Patients with stable disease (SD) or better may be eligible for an additional 17 doses of pembrolizumab if their disease progresses while they are off study treatment provided they meet prespecified criteria.

Randomization will be performed centrally using an interactive voice/web response system. Pembrolizumab or placebo assignment will be masked in a double-blind fashion. Patients in the global cohort will be stratified by geographic region (Europe, Israel, North America and Australia vs Asia vs rest of world), PD-L1 status (positive [CPS ≥1] vs negative [CPS <1]), and chemotherapy regimen (FP vs CAPOX). Patients in the Japan-specific cohort will be stratified by PD-L1 status (positive vs negative).

Table 1. Study treatments.

Treatment	Dose	Frequency	Route of administration	Dosing time of each 3-week cycle
Pembrolizumab	200 mg	Q3W	IV infusion	Day 1 of each cycle
Placebo (normal saline)	NA	Q3W	IV infusion	Day 1 of each cycle
FP[†]				
– Cisplatin[‡]	80 mg/m^2[¶]	Q3W	IV infusion	Day 1 of each cycle
– 5-Fluorouracil	800 mg/m^2/day[¶]	Continuous	IV infusion	Days 1–5 of each cycle
CAPOX[†]				
– Oxaliplatin	130 mg/m^2[¶]	Q3W	IV infusion	Day 1 of each cycle
– Capecitabine	1000 mg/m^2[¶]	BID	Oral	Days 1–14 of each cycle
SOX[§]				
– S-1	<1.25 m^2; BSA: 40 mg[¶] 1.25 to <1.5 m^2; BSA: 50 mg[¶] ≥1.5 m^2; BSA: 60 mg[¶]	BID	Oral	Days 1–14 of each cycle
– Oxaliplatin	130 mg/m^2[¶]	Q3W	IV infusion	Day 1 of each cycle
– Trastuzumab	8 mg/kg loading dose 6 mg/kg maintenance dose	Q3W	IV infusion	Day 1 of each cycle

[†]Choice of chemotherapy backbone to be decided by the investigator before randomization.
[‡]Duration of cisplatin treatment may be capped at 6 cycles per local country guidelines; however, treatment with 5-fluorouracil may continue per protocol.
[§]SOX received only by patients in the Japan-specific cohort.
[¶]Body surface area to be calculated per local guidance.
BID: Twice daily; CAPOX: Capecitabine + oxaliplatin; FP: 5-Fluorouracil + cisplatin; IV: Intravenous; Q3W: Every 3 weeks; SOX: S-1 + oxaliplatin.

Eligibility criteria, planned sample size & study period

Eligibility criteria are described in detail in Table 2. In brief, eligible patients are men or women aged ≥18 years with a histologically or cytologically confirmed diagnosis of previously untreated, locally advanced unresectable or metastatic HER2-positive gastric or GEJ adenocarcinoma. The planned sample size is approximately 692 patients in the global cohort and 40 patients in the Japan-specific cohort, for a total of 732 patients. The estimated time after the first participant is randomly assigned to the time of the final analysis is approximately 56 months. The study started in October 2018, and the estimated completion date is 20 March 2024.

Study end points

The primary end points are PFS and OS. PFS is defined as the time from randomization to the first documented disease progression per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) by blinded independent central review (BICR) or death from any cause, whichever occurs first. OS is defined as the time from randomization to death from any cause.

Secondary end points are ORR and DOR, per RECIST v1.1 by BICR and safety. DOR is defined as the time from first response (CR or PR) to subsequent disease progression or death from any cause, whichever occurs first.

Exploratory end points include health-related quality of life (HRQOL; assessed using the European Organization for the Research and Treatment of Cancer [EORTC] Quality of Life Questionnaire core 30 items [QLQ C30] and the gastric cancer module [STO22]), characterization of utilities (assessed using the EuroQol 5D 5-level [EQ-5D-5L] questionnaire), molecular biomarkers and PFS and ORR per immune-related RECIST by investigator review.

Study procedures

Disease progression and tumor response will be assessed using computed tomography (CT) or, if CT is contraindicated, magnetic resonance imaging (MRI). Initial imaging will be performed within 28 days before randomization. The first on-study imaging assessment will be performed 6 weeks after randomization, and subsequent imaging will be performed every 6 weeks (or more frequently if clinically indicated). Imaging will continue until confirmation of progressive disease by BICR, initiation of new anticancer treatment, withdrawal of consent or death. Response will be confirmed by repeat imaging ≥4 weeks after the first documentation of response. Patients who experience disease progression or start new anticancer therapy will be followed up for survival status by telephone every 12 weeks until death, withdrawal of consent, or end of study, whichever occurs first.

Table 2. Eligibility criteria.

Inclusion criteria	Exclusion criteria
• Male or female • Age ≥18 years • Previously untreated histologically or cytologically confirmed locally advanced unresectable or metastatic gastric or GEJ adenocarcinoma • HER2-positive disease, defined as either IHC 3+ or IHC 2+ in combination with ISH+ (or FISH), as assessed by BICR on primary or metastatic tumor • Measurable disease per RECIST v1.1 by site investigator • Willing to use adequate contraception methods throughout the study and for 7 months after the last dose of study treatment • ECOG PS 0 or 1 • Life expectancy ≥6 months • Willing to provide a tumor tissue sample adequate for PD-L1 and MSI biomarker analysis • Adequate cardiac function, defined as left ventricular ejection fraction ≥55% as determined by MUGA scan or ECHO and QT interval calculated according to the Fridericia method (≤470 ms for men and ≤480 ms for women) • Adequate hematologic function, defined as ANC ≥1500/μl, platelet count ≥100,000/μl and hemoglobin ≥9.0 g/dl or ≥5.6 mmol/l • Adequate renal function, defined as creatinine ≤1.5 × ULN or measured or calculated creatinine clearance ≥60 ml/min for those with creatinine levels 1.5 × ULN • Adequate hepatic function, defined as total bilirubin ≤1.5 × ULN or direct bilirubin ≤ULN for those with total bilirubin levels >1.5 × ULN, ALT/AST levels ≤2.5 × ULN or ≤5 × ULN for those with liver metastases, and albumin ≥2.5 g/dl • Adequate coagulation function, defined as INR ≤1.5 × ULN, unless the patient is receiving anticoagulant therapy with PT or aPTT/PTT is within the therapeutic range • Written informed consent	• Previously received neoadjuvant or adjuvant therapy for locally advanced or metastatic disease (as long as it was completed ≥6 months before randomization without disease progression) • Major surgery, open biopsy or significant traumatic injury ≤28 days before randomization, or anticipated need for major surgery during the study treatment period • Radiotherapy ≤14 days of randomization • Known additional malignancy that is progressing or has necessitated active treatment within the past 5 years (except BCC or SCC of the skin that has undergone potentially curative treatment or in situ cervical cancer) • Known active CNS metastases and/or carcinomatous meningitis (patients with previously treated brain metastases may be eligible if disease is radiologically and clinically stable) • Active autoimmune disease that has necessitated systemic treatment (other than replacement therapy) in the past 2 years • Diagnosis of immunodeficiency or receiving long-term systemic steroid therapy (≥10 mg/day prednisone equivalent) or any other form of immunosuppression therapy within 7 days before the first dose of study treatment • History of (noninfectious) pneumonitis treated with steroids or current pneumonitis • History of active tuberculosis • Active infection necessitating systemic therapy • Poorly controlled diarrhea • Accumulation of pleural, ascitic or pericardial fluid necessitating drainage or diuretic drugs ≤2 weeks before enrollment • History or current evidence of any condition, therapy, or laboratory abnormality that might confound the study results or interfere with study participation • Peripheral neuropathy grade >1 • Psychiatric or substance abuse disorder that could impede cooperation with study requirements • Positive urine pregnancy test ≤72 h before randomization (females of childbearing potential) • Pregnant or breastfeeding or expecting to conceive or father children within the projected study duration • Active or clinically significant cardiac disease • Known history of HIV, HBV or HCV infection • Known hypersensitivity (grade ≥3) to any of the study drugs or their excipients • Active infection necessitating systemic therapy • Allogeneic tissue or solid organ transplant • Previous treatment with anti-PD-1, anti-PD-L1 or anti-PD-L2, or with an agent directed to another stimulatory or co-inhibitory T-cell receptor (e.g., CTLA4, OX40 and CD137) • Immunized with live vaccine ≤30 days before first dose of study treatment • Participation in study of investigational agent or device ≤4 weeks before the first dose of study treatment

ANC: Absolute neutrophil count; aPTT: Activated partial thromboplastin time; BCC: Basal cell carcinoma; BICR: Blinded-independent central review; CNS: Central nervous system; ECHO: Echocardiogram; ECOG: Eastern Cooperative Oncology Group; FISH: Fluorescent *in-situ* hybridization; GEJ: Gastroesophageal junction; HBV: Hepatitis B virus; HCV: Hepatitis C virus; HIV: Human immunodeficiency virus; IHC: Immunohistochemistry; INR: International normalized ratio; ISH: *In-situ* hybridization; MSI: Microsatellite instability; MUGA: Multigated acquisition; PT: Prothrombin time; PTT: Partial thromboplastin time; RECIST v1.1: Response Evaluation Criteria in Solid Tumors version 1.1; SCC: Squamous cell carcinoma; ULN: Upper limit of normal.

Safety will be monitored throughout the study and for 30 days after the end of treatment (90 days for serious adverse events and events of clinical interest). Safety analyses will include incidence, cause and outcome of adverse events and changes in vital signs and laboratory values. Adverse events will be assessed as defined by the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.

Patient-reported outcome assessments (QLQ-C30, QLQ-STO22 and EQ-5D-5L) will be completed by patients electronically at cycles 1, 2, 3, 4 and 5, and every 2 cycles thereafter up to 1 year or end of treatment, whichever comes first, and at the 30-day posttreatment follow-up visit. PD-L1 expression will be assessed using the PD-L1 IHC 22C3 pharmDx assay (Agilent Technologies, CA, USA) and measured using CPS. Additional biomarker investigation may include genomic, metabolic and proteomic analyses.

Statistical analysis

Efficacy will be assessed in the intent-to-treat population (all randomly assigned patients) by treatment group. Safety will be assessed in all randomly assigned patients who received ≥1 dose of study treatment according to the treatment received. Primary hypotheses for PFS and OS will be evaluated by comparing pembrolizumab + trastuzumab and chemotherapy with placebo + trastuzumab and chemotherapy using a stratified log-rank test. The hazard ratio will

be estimated using a stratified Cox regression model, and event rates over time will be estimated using the Kaplan–Meier method. ORR will be compared between treatment groups using the stratified Miettinen and Nurminen method. The overall Type I error over the primary end points (PFS and OS) and the key secondary end point (ORR) is strongly controlled at 2.5% (one-sided), with initially 0.2% allocated to ORR, 0.3% to PFS and 2% to OS.

For ORR, with a sample size of approximately 260 patients at the first interim analysis, the study has approximately 90% power for detecting a 25-percentage point difference in ORR (73 vs 48%) at an initially assigned 0.002 (one-sided) significance level. For PFS, there will be approximately 606 events at the PFS final analysis; the study has approximately 95% power for detecting an HR of 0.7 at an initially assigned 0.003 (one-sided) significance level. For OS, there will be approximately 551 deaths at the OS final analysis; the study has approximately 90% power for detecting an HR of 0.75 at an initially assigned 0.020 (one-sided) significance level.

The Japan-specific cohort will be analyzed separately. Three interim analyses are planned based on projected enrollment and event accrual rates. An external data monitoring committee will review the results of the interim analyses to determine whether the study will continue per prespecified criteria.

Conclusion

There is promising evidence that pembrolizumab used in combination with trastuzumab + chemotherapy may provide significant clinical benefit with manageable toxicity in patients with advanced gastric cancer. Here we have described the methodology of the KEYNOTE-811 study, an ongoing Phase III trial designed to evaluate the efficacy and safety of pembrolizumab in combination with trastuzumab + chemotherapy as first-line treatment for patients with advanced HER2-positive gastric or GEJ adenocarcinoma. The study aims to show that the addition of pembrolizumab to a regimen of trastuzumab + chemotherapy will result in improved survival compared with treatment with trastuzumab + chemotherapy alone. It is hoped that the results of KEYNOTE-811 will further define the role of pembrolizumab and the feasibility of a dual antibody strategy in patients with advanced gastric cancer.

Executive summary

- Most patients with gastric cancer receive diagnoses at the advanced stage of the disease, when prognosis is poor.
- Given the limited survival benefit observed with currently recommended therapies, there remains a need for novel therapeutic regimens to treat patients with advanced gastric cancer.

Background & rationale

- A growing body of evidence indicates that PD-1 and PD-L1 are frequently overexpressed in gastric cancer and that their upregulation may be prognostic of poor outcome.
- Pembrolizumab has shown durable clinical benefit in patients with advanced gastric cancer and is particularly promising when used in combination with chemotherapy.
- Combining trastuzumab and chemotherapy with pembrolizumab in the first-line setting might be beneficial for patients with HER2-positive disease.

KEYNOTE-811 study design & eligibility criteria

- KEYNOTE-811 is an international, multicenter, randomized, double-blind, placebo-controlled, Phase III study evaluating the efficacy and safety of pembrolizumab in combination with trastuzumab and chemotherapy as first-line treatment of patients with advanced/metastatic HER2-positive gastric cancer.
- Eligible patients with a histologically or cytologically confirmed diagnosis of previously untreated, locally advanced unresectable or metastatic HER2-positive gastric or gastroesophageal junction adenocarcinoma will be randomly assigned to receive pembrolizumab or placebo in combination with trastuzumab and chemotherapy (cisplatin + 5-fluorouacil or oxaliplatin + capecitabine [S-1 + oxaliplatin will be given in the Japan-specific cohort]).

Outcome measures/end points

- The primary end points are progression-free survival and overall survival.

Conclusion

- It is hoped that the KEYNOTE-811 study will further define the role of pembrolizumab and the feasibility of a dual antibody strategy in patients with advanced gastric cancer.

Supplementary data

An infographic accompanies this paper and is included at the end of the references section in the PDF version. To view or download this infographic in your browser please click here: www.futuremedicine.com/doi/suppl/10.2217/fon-2020-0737

Author contributions

Conception, design or planning of the study: HC Chung, YJ Bang, CS Fuchs, T Satoh, K Shitara, J Tabernero, E van Cutsem, ZA Cao, J Lu, P Bhagia, CS Shih and YY Janjigian. Acquisition of the study: HC Chung, YJ Bang, S-K Qin, T Satoh, K Shitara, M Alsina, J Lu, CS Shih and YY Janjigian. Analysis of the data: HC Chung, S-K Qin, T Satoh, CS Shih and YY Janjigian. Interpretation of the results: HC Chung, K Shitara, E van Cutsem, ZA Cao, CS Shih and YY Janjigian. Drafting of the manuscript: HC Chung, T Satoh, K Shitara, J Tabernero, J Lu, YY Janjigian. Critically reviewing or revising the manuscript for important intellectual content: HC Chung, YJ Bang, CS Fuchs, S-K Qin, T Satoh, K Shitara, J Tabernero, E van Cutsem, M Alsina, ZA Cao, P Bhagia, CS Shih and YY Janjigian. Final approval: all authors.

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Ethical conduct of research

The authors attest that the study protocol was approved by the appropriate ethics committee or institutional review board at each participating center. The study was conducted in accordance with standards of Good Clinical Practice and the Declaration of Helsinki. All participants will provide written informed consent before enrollment.

Data sharing statement

Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., NJ, USA's data sharing policy, including restrictions, is available at http://engagezone.msd.com/ds_documentation.php. Requests for access to the clinical study data can be submitted through the EngageZone site or via email to dataaccess@merck.com.

Open access

References

Papers of special note have been highlighted as: •• of considerable interest

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: Cancer J. Clin.* 68(6), 394–424 (2018).
2. Colquhoun A, Arnold M, Ferlay J, Goodman KJ, Forman D, Soerjomataram I. Global patterns of cardia and non-cardia gastric cancer incidence in 2012. *Gut* 64(12), 1881–1888 (2015).
3. Plummer M, Franceschi S, Vignat J, Forman D, De Martel C. Global burden of gastric cancer attributable to *Helicobacter pylori*. *Int. J. Cancer* 136(2), 487–490 (2015).
4. The Cancer Genome Atlas Research Network. Comprehensive molecular characterization of gastric adenocarcinoma. *Nature* 513(7517), 202–209 (2014).
5. Sohn BH, Hwang JE, Jang HJ *et al.* Clinical significance of four molecular subtypes of gastric cancer identified by The Cancer Genome Atlas Project. *Clin. Cancer Res.* 23(15), doi:10.1158/1078-0432.Ccr-16-2211 (2017).
6. van Cutsem E, Bang YJ, Feng-Yi F *et al.* HER2 screening data from ToGA: targeting HER2 in gastric and gastroesophageal junction cancer. *Gastric Cancer* 18(3), 476–484 (2015).
7. Smyth EC, Verheij M, Allum W *et al.* Gastric cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann. Oncol.* 27(Suppl. 5), v38–v49 (2016).
8. van Cutsem E, Sagaert X, Topal B, Haustermans K, Prenen H. Gastric cancer. *Lancet* 388(10060), 2654–2664 (2016).
9. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology (NCCN guidelines): gastric cancer (version 3.2020). (2020). https://www.nccn.org/professionals/physician_gls/pdf/gastric.pdf
10. Bang YJ, van Cutsem E, Feyereislova A *et al.* Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a Phase 3, open-label, randomised controlled trial. *Lancet* 376(9742), 687–697 (2010).
11. Tabernero J, Hoff PM, Shen L *et al.* Pertuzumab plus trastuzumab and chemotherapy for HER2-positive metastatic gastric or gastro-oesophageal junction cancer (JACOB): final analysis of a double-blind, randomised, placebo-controlled Phase 3 study. *Lancet Oncol.* 19(10), 1372–1384 (2018).
12. Hecht JR, Bang YJ, Qin SK *et al.* Lapatinib in combination with capecitabine plus oxaliplatin in human epidermal growth factor receptor 2-positive advanced or metastatic gastric, esophageal, or gastroesophageal adenocarcinoma: TRIO-013/lOGiC – a randomized Phase III trial. *J. Clin. Oncol.* 34(5), 443–451 (2016).
13. Zhao D, Klempner SJ, Chao J. Progress and challenges in HER2-positive gastroesophageal adenocarcinoma. *J. Hematol. Oncol.* 12(1), 50 (2019).
14. Wilke H, Muro K, van Cutsem E *et al.* Ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (RAINBOW): a double-blind, randomised Phase 3 trial. *Lancet Oncol.* 15(11), 1224–1235 (2014).
15. Japanese Gastric Cancer Association. Japanese gastric cancer treatment guidelines 2018 (5th Ed). *Gastric Cancer* 24 1–21 (2021).
16. Alsaab HO, Sau S, Alzhrani R *et al.* PD-1 and PD-L1 checkpoint signaling inhibition for cancer immunotherapy: mechanism, combinations, and clinical outcome. *Front. Pharmacol.* 8, 561 (2017).

17. Cui C, Yu B, Jiang Q, Li X, Shi K, Yang Z. The roles of PD-1/PD-L1 and its signalling pathway in gastrointestinal tract cancers. *Clin. Exp. Pharmacol. Physiol.* 46(1), 3–10 (2019).
18. Li J, Song-Hua B, Feng L *et al.* PD-1/PD-L1 antagonists in gastric cancer: current studies and perspectives. *World J. Meta-Anal.* 7(3), 101–109 (2019).
19. KEYTRUDA® (pembrolizumab) injection, for intravenous use, 06/2020. Merck Sharp & Dohme, Corp., NJ, USA (2020).
20. Muro K, Chung HC, Shankaran V *et al.* Pembrolizumab for patients with PD-L1-positive advanced gastric cancer (KEYNOTE-012): a multicentre, open-label, Phase 1b trial. *Lancet Oncol.* 17(6), 717–726 (2016).

•• **Open-label Phase Ib study (KEYNOTE-012) reporting the safety and activity of pembrolizumab in patients with PD-L1–positive recurrent or metastatic adenocaricnoma of the stomach or gastroesophageal junction.**

21. Fuchs CS, Doi T, Jang RW *et al.* Safety and efficacy of pembrolizumab monotherapy in patients with previously treated advanced gastric and gastroesophageal junction cancer: Phase 2 clinical KEYNOTE-059 trial. *JAMA Oncol.* 4(5), e180013 (2018).

•• **Single-arm, Phase II study (KEYNOTE-059) evaluating the safety and efficacy of pembrolizumab in a cohort of patients with previously treated gastric or gastroesophageal junction cancer.**

22. Shitara K, Ozguroglu M, Bang YJ *et al.* Pembrolizumab versus paclitaxel for previously treated, advanced gastric or gastro-oesophageal junction cancer (KEYNOTE-061): a randomised, open-label, controlled, Phase 3 trial. *Lancet* 392(10142), 123–133 (2018).

•• **Randomized, open-label, controlled Phase III trial (KEYNOTE-061) comparing pembrolizumab with paclitaxel in patients with advanced gastric or gastroesophageal junction cancer that progressed on first-line chemotherapy.**

23. Wainberg ZA, Fuchs CS, Tabernero J *et al.* Efficacy of pembrolizumab (pembro) monotherapy versus chemotherapy for PD-L1–positive (CPS ≥10) advanced G/GEJ cancer in the Phase II KEYNOTE-059 (cohort 1) and Phase III KEYNOTE-061 and KEYNOTE-062 studies. *J .Clin. Oncol.* 38(Suppl. 4), 427 (2020).
24. Shitara K, van Cutsem E, Bang Y-S *et al.* Pembrolizumab or pembrolizumab plus chemotherapy versus chemotherapy for first-line, advanced gastric cancer (KEYNOTE-062): a randomised, controlled Phase 3 study. *JAMA Oncol.* 6(10), 1571–1580 (2020).
25. Bang YJ, Kang YK, Catenacci DV *et al.* Pembrolizumab alone or in combination with chemotherapy as first-line therapy for patients with advanced gastric or gastroesophageal junction adenocarcinoma: results from the Phase II nonrandomized KEYNOTE-059 study. *Gastric Cancer* 22(4), 828–837 (2019).

•• **Multicohort, nonrandomized, Phase II study (KEYNOTE-059) evaluating first-line pembroliuzmab with or without chemotherapy in advanced gastric/gastroesophageal junction cancer in cohorts 2 and 3.**

26. Krasniqi E, Barchiesi G, Pizzuti L *et al.* Immunotherapy in HER2-positive breast cancer: state of the art and future perspectives. *J. Hematol. Oncol.* 12(1), 111 (2019).
27. Chaganty BKR, Qiu S, Gest A *et al.* Trastuzumab upregulates PD-L1 as a potential mechanism of trastuzumab resistance through engagement of immune effector cells and stimulation of IFNgamma secretion. *Cancer Lett.* 430, 47–56 (2018).
28. Loi S, Giobbie-Hurder A, Gombos A *et al.* Pembrolizumab plus trastuzumab in trastuzumab-resistant, advanced, HER2-positive breast cancer (PANACEA): a single-arm, multicentre, Phase 1b/2 trial. *Lancet Oncol* 20(3), 371–382 (2019).

•• **Single-arm Phase Ib/II trial (PANACEA) assessing the safety and antitumor activity of pembrolizumab added to trastuzumab in trastuzumab-resistant, advanced HER2–positive breast cancer.**

29. Janjigian YY, Chou JF, Simmons M *et al.* First-line pembrolizumab (P), trastuzumab (T), capecitabine (C) and oxaliplatin (O) in HER2-positive metastatic esophagogastric adenocarcinoma (mEGA). *J. Clin. Oncol.* 37(Suppl. 4), 62–62 (2019).
30. Janjigian YY, Maron SB, Chatila WK *et al.* First-line pembrolizumab and trastuzumab in HER2-positive oesophageal, gastric, or gastro-oesophageal junction cancer: an open-label, single-arm, Phase 2 trial. *Lancet Oncol.* 21(6), 821–831 (2020).

•• **Phase II trial of assessing the safety and efficacy of first-line pembrolizumab, trastuzumab, capecitabine and oxaliplatin in HER2–positive metastatic esophagogastric adenocarcinoma.**

31. Rha SY, Lee CK, Kim H. Targeting HER2 in combination with anti-PD-1 and chemotherapy confers a significant tumor shrinkage of gastric cancer: a multi-institutional Phase Ib/II trial of first-line triplet regimen (pembrolizumab, trastuzumab, chemotherapy) for HER2 positive advanced gastric cancer (AGC). *J. Clin. Oncol.* 38(Suppl. 4), 3081 (2020).

•• **Multi-institutional Phase Ib/II trial (PANTHERA) of first-line triple combination (pembrolizumab, trastuzumab and chemotherapy) therapy for HER2–advanced gastric cancer.**

Pembrolizumab in combination with trastuzumab and chemotherapy for HER2-positive advanced gastric cancer: KEYNOTE-811

Authors
Hyun Cheol Chung, Yung-Jue Bang, Charles S. Fuchs, Shu-Kui Qin, Taroh Satoh, Kohei Shitara, Josep Tabernero, Eric Van Cutsem, Maria Alsina, Z. Alexander Cao, Jia Lu, Pooja Bhagia, Chie-Schin Shih & Yelena Janjigian

Article URL
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Trial registration number
NCT03615326

Objectives

Primary
- Compare PFS between treatment groups
- Compare OS between treatment groups

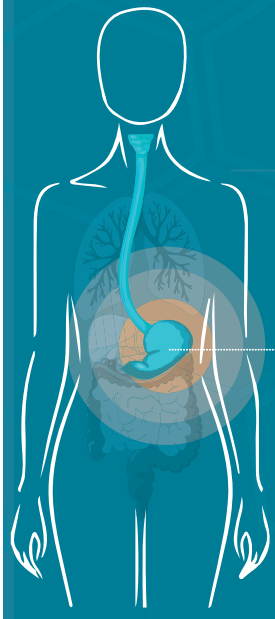
Secondary
- Compare ORR per RECIST v1.1 by BICR between treatment groups
- Compare DOR per RECIST v1.1 by BICR between treatment groups
- Assess the safety and tolerability of pembrolizumab in combination with trastuzumab + chemotherapy

Key eligibility criteria

Histologically or cytologically confirmed diagnosis of previously untreated, locally advanced unresectable or metastatic HER2-positive gastric or GEJ adenocarcinoma

- Men or women
- Age ≥18 years
- Measurable disease per RECIST v1.1
- ECOG performance status of 0 or 1
- Adequate tissue sample
- Adequate cardiac function defined as LVEF ≥55% and QT interval
- No immunodeficiency
- No active autoimmune disease

Study design and treatment including planned sample size, planned study period and study procedures



Randomly assigned (1:1) | Double-blind | Placebo-controlled | Phase III

The planned sample size is ~ 692 patients in the global cohort and 40 patients in the Japan-specific cohort, for a total of 732 patients

GLOBAL COHORT

Stratification
- Geographic region (Europe, Israel, North America and Australia vs Asia vs rest of the world
- PD-L1 status (positive [CPS ≥1] vs negative [CPS <1])
- Chemotherapy regimen (FP vs CAPOX)

R (1:1)
- Pembrolizumab 200 mg + trastuzumab 8 mg/kg loading dose, and 6 mg/kg thereafter + investigator's choice of FP or CAPOX Q3W
- Placebo (normal saline) + trastuzumab 8 mg/kg loading dose, and 6 mg/kg thereafter + investigator's choice of FP or CAPOX Q3W

JAPAN COHORT

Stratification
- PD-L1 status (positive vs negative)

R (1:1)
- Pembrolizumab 200 mg + trastuzumab 8 mg/kg loading dose, and 6 mg/kg thereafter + SOX Q3W
- Placebo (normal saline) 200 mg + trastuzumab 8 mg/kg loading dose, and 6 mg/kg thereafter + SOX Q3W

Treatment will continue until:
- Confirmed disease progression
- Unacceptable toxicity
- Investigator or patient decision to withdraw from the study
- Noncompliance with treatment or trial procedures
- Completion of 35 cycles of study treatment (~ 2 years)

Glossary

BICR: Blinded independent central review; CAPOX: Oxaliplatin + capecitabine; CPS: Combined positive score; CR: Complete response; DOR: Duration of response; EORTC: European Organization for the Research and Treatment of Cancer; QLQ-C30: European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire core 30 items; QLQ-STO22: European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire gastric cancer module; EQ-5D-5L: EuroQoL 5D 5-level; FP: Cisplatin + 5-fluouracil; GEJ: Gastric esophageal junction; HER2: Human epidermal growth factor receptor 2; HRQOL: Health-related quality of life; LVEF: Left ventricular ejection fraction; ORR: Objective response rate; OS: Overall survival; PD-L1: Programmed death ligand 1; PFS: Progression-free survival; PR: Partial response; RECIST v1.1: Response Evaluation Criteria in Solid Tumors version 1.1; SOX: S-1 + oxaliplatin

Outcome measures/endpoints

Primary endpoints:
- PFS (defined as the time from randomization to the first documented disease progression per RECIST v1.1 by BICR or death from any cause, whichever occurs first) between treatment groups
- OS (defined as the time from randomization to death from any cause) between treatment groups

Secondary endpoints:
- ORR and DOR (defined as the time from first response [CR or PR] to subsequent disease progression or death from any cause, whichever occurs first), per RECIST v1.1 by BICR
- Safety

Exploratory endpoints:
- HRQOL (assessed using the EORTC QLQ-C30 and EORTC QLQ-STO22)
- Characterization of utilities (assessed using the EQ-5D-5L questionnaire)
- Molecular biomarkers
- PFS and ORR per immune-related RECIST by investigator review

Meta-Analysis

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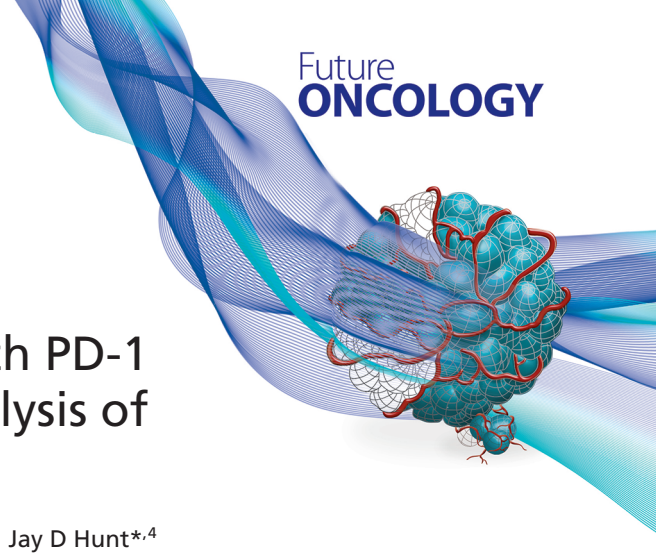

Immune-related adverse events with PD-1 versus PD-L1 inhibitors: a meta-analysis of 8730 patients from clinical trials

Guru P Sonpavde[1], Petros Grivas[2], Yushun Lin[3], Daniel Hennessy[4,5] & Jay D Hunt*[,4]

[1]Dana-Farber Cancer Institute, 450 Brookline Ave, Boston, MA 02215, USA

[2]Department of Medicine, Division of Medical Oncology, University of Washington School of Medicine, Fred Hutchinson Cancer Research Center, Seattle Cancer Care Alliance, 1144 Eastlake Ave, E. LG-465, Seattle, WA 98109, USA

[3]PharmStats, Missouri City, TX 77459, USA

[4]EMD Serono, Inc, Rockland, MA 01821, USA; an affiliate of Merck KGaA, Darmstadt, Germany

[5]Current affiliation: Constellation Pharmaceuticals, Inc, 215 First St, Suite 200, Cambridge, MA 02142, USA

*Author for correspondence: Tel.: +1 985 781 4174; jay.hunt@emdserono.com

Background: Trial-level meta-analysis to investigate differences in immune-related adverse event (irAE) profiles between anti-PD-1/PD-L1 antibodies. **Materials & methods:** Data analyzed from 8730 patients treated with anti-PD-1/PD-L1 monotherapy. Incidence and odds ratios (ORs) were calculated for irAEs overall, selected individual irAEs for individual agents and pooled estimates for anti-PD-1 or anti-PD-L1 antibodies. **Results:** For anti-PD-L1 versus anti-PD-1 antibodies, we observed a lower risk of any-grade rash, elevated alanine aminotransferase, colitis, grade ≥3 colitis, hypothyroidism and rash. For individual agents, we observed reduced risks of overall any-grade irAEs for atezolizumab versus pembrolizumab and grade ≥3 irAEs for avelumab versus pembrolizumab. **Conclusion:** irAE risk may vary between anti-PD-1 and anti-PD-L1 antibodies; however, findings are hypothesis-generating.

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Keywords: anti-PD-1 • anti-PD-L1 • immune-related adverse events • immune checkpoint inhibitor • meta-analysis

Programmed cell death 1 (PD-1) protein is expressed on the surface of activated T cells and binds to two ligands: PD-L1 and PD-L2 [1]. In normal tissues, PD-L1 inhibits T-cell activity, helping to control immune responses and prevent autoimmunity; however, PD-L1 is often aberrantly expressed by tumor cells and contributes to the inhibition of antitumor immune responses in the tumor microenvironment [1]. Immune checkpoint inhibitors (ICIs) are a class of antineoplastic agents, which include antibodies that bind to PD-1 or PD-L1. Anti-PD-1 antibodies block the binding of both PD-L1 and PD-L2 to PD-1, whereas anti-PD-L1 antibodies block the binding of PD-L1 to PD-1 and B7-1/CD80 [2,3]. For both types of antibody, target binding releases the inhibitory effects of PD-1–PD-L1 interaction on the immune response, thereby restoring immune activity, including antitumor immune responses [2,3]. To date, six anti-PD-1 or anti-PD-L1 antibodies have been approved by the US FDA for various cancers, namely the anti-PD-1 antibodies cemiplimab, nivolumab and pembrolizumab and the anti-PD-L1 antibodies atezolizumab, avelumab and durvalumab [4]. Approved anti-PD-1 and anti-PD-L1 antibodies differ in their molecular targets, epitope binding, affinity, structure and pharmacokinetic characteristics [5]. Of note, compared with other approved anti-PD-1 and PD-L1 antibodies, avelumab has a shorter halflife and unlike other agents, has shown antibody-dependent cellular cytotoxicity activity *in vitro* [6,7]. Based on these differences, it is possible that the efficacy and safety profiles – in particular, the occurrence of immune-related adverse events (irAEs) – may vary among different anti-PD-1 and anti-PD-L1 agents. To date, no head-to-head trials of different anti–PD-1 or PD-L1 antibodies have been reported.

Several meta-analyses have assessed the safety profiles of anti-PD-1 and PD-L1 antibodies; however, these assessments have had specific focuses that result in potential limitations for irAE evaluation, such as including only a subset of approved agents, estimating overall effects compared with standard chemotherapy or focusing on a subset of tumor types [6,8–19]. In addition, most meta-analyses did not evaluate potential differences among anti-PD-1 and

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anti-PD-L1 antibodies as separate classes. One recent, large meta-analysis did analyze treatment-related AEs with anti-PD-1 and anti-PD-L1 antibodies but did not focus on irAEs [19].

To investigate whether irAE profiles may vary among anti-PD-1 and anti-PD-L1 antibodies and among individual agents, we conducted a trial-level meta-analysis of irAEs reported in Phase I–IV trials of anti-PD-1 and PD-L1 agents across tumor types.

Materials & methods

Literature searches

An initial PubMed search was performed on 31 May 2018, including literature published from 1 December 2010, onwards, using the following keywords: atezolizumab, IMvigor, avelumab, JAVELIN, durvalumab, Imfinzi, nivolumab, CheckMate, pembrolizumab and KEYNOTE. Following the FDA approval of cemiplimab for the treatment of cutaneous squamous cell carcinoma, an additional search was performed for REGN2810, Libtayo or cemiplimab on 28 February 2019. To be eligible for analysis, articles were required to have reported proportions of patients who experienced irAEs (per author definitions) following anti-PD-1 or anti-PD-L1 monotherapy in a clinical trial (with the assumption that definitions of irAEs were aligned according to guidance provided by regulatory authorities to pharmaceutical companies). Articles were excluded if AEs were not determined to be specifically 'immune related' or 'of special interest'. We included articles that reported Phase Ib, II, III and IV studies; however, only patients treated with a recommended Phase II dose or approved dose of each agent were analyzed. For randomized Phase II or III studies, only patients in study arms treated with anti-PD-1 or PD-L1 monotherapy were included. Patients from a single trial reported in >1 article were included in the analysis only once. Data from individual articles were abstracted independently by two authors and consensus was required for the data to be included in the analysis.

Statistical methods

The primary outcomes for this meta-analysis were the incidence (defined as the number of patients with an irAE (either specific or overall irAEs) divided by the total number of patients analyzed for the irAE and odds ratios (ORs) of irAEs overall (any grade and grade ≥3) and the following individual irAEs: colitis, elevated AST level, hypothyroidism, pneumonitis and rash. irAEs were selected for consistency with those reported in a previous meta-analysis by De Velasco *et al.* [20], which were chosen as representative irAEs for specific organs or systems (i.e., gastrointestinal, hepatic, endocrine, pulmonary and cutaneous irAEs). Elevated ALT level was added as another irAE of interest because it is considered to be a more specific marker of liver damage than AST [21]. Due to variations in irAE reporting between the clinical studies included in the analysis, data for some irAEs were not consistently available. Incidences were therefore calculated using the total number of patients with a specific irAE divided by the total population of patients from studies in which data for the specific irAE were reported. Incidences and ORs were estimated for individual anti-PD-1 and PD-L1 antibodies, as pooled estimates for anti-PD-1 and anti-PD-L1 antibodies and for individual anti-PD-1 and PD-L1 antibodies compared with summary estimates for all other anti-PD-1 and PD-L1 antibodies; no adjustment for multiple testing was performed. Incidences were calculated using R software (version 3.5.0) with package meta and metaprop functions using both the fixed and random-effects models; between-study variance (τ^2) and heterogeneity (I^2; assessed using Cochran Q test) were calculated. Logit transformations of proportions were performed and ORs with corresponding 95% CIs were computed assuming normal distribution. Because between-study heterogeneity as assessed by the I^2 statistic was ≥50%, data from the random-effects models are presented. To explore the possibility that irAE risk was affected by patient age (for all irAEs), lung cancer or pneumonitis, ORs and corresponding 95% CIs that included these covariates were calculated using R software (R version 3.5.0) with the metafor package using generalized linear (mixed-effects) models (rma.glmm function; data not shown). Selection of lung cancer and pneumonitis as covariates was based on knowledge that a number of agents included in the analysis had been studied in multiple lung cancer trials, while others had not been studied extensively in this tumor type, and that patients with lung cancer can have an increased risk of pneumonitis irrespective of treatment modality [22]. Therefore, including a disproportionate number of lung cancer trials could have confounded the analysis and this bias would not have been captured in the standard random-effects model. However, neither age nor lung cancer was associated with pneumonitis irAEs.

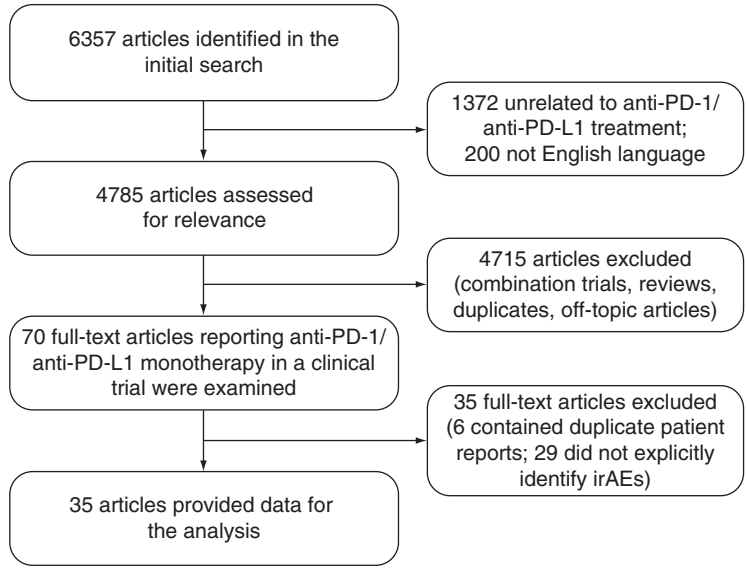


Figure 1. Flow diagram of the article selection process.
irAE: Immune-related adverse event.

Results

Eligible studies

Of 6357 articles identified in literature searches and screened for relevance, 35 articles reporting data from 8730 patients treated with anti-PD-1/PD-L1 monotherapy were analyzed (Supplementary Table 1 & Figure 1). These articles reported data from Phase I (n = 18), Phase II (n = 15), Phase III (n = 8) and Phase IV (n = 1) trials. Data were analyzed for avelumab, atezolizumab, durvalumab, nivolumab and pembrolizumab. We identified a single potentially relevant article reporting a study of cemiplimab; however, this report did not explicitly report data for irAEs; thus, cemiplimab data could not be included in this analysis.

Incidence of irAEs

Across all eligible studies of anti-PD-1 or anti-PD-L1 monotherapy, irAEs of any grade occurred in 1111 of 6507 patients (17.1%), including grade ≥3 irAEs in 196 of 4921 patients (4.0%). Incidences of selected individual irAEs across anti-PD-1 and anti-PD-L1 agents and for individual agents are shown in Table 1 & Supplementary Table 2, respectively.

Occurrence of irAEs with anti-PD-L1 versus anti-PD-1 antibodies

Pooled estimates of irAEs overall and selected irAEs were calculated for anti-PD-1 antibodies (nivolumab and pembrolizumab) and anti-PD-L1 antibodies (atezolizumab, avelumab and durvalumab). Empirical ORs suggested a potentially higher risk with anti-PD-1 versus anti-PD-L1 antibodies for a number of any-grade irAEs, including rash (OR: 4.34; 95% CI: 2.25–8.39), elevated ALT level (OR: 4.64; 95% CI: 1.36–15.83) and colitis (OR: 2.53; 95% CI: 1.29–4.95), as shown in Figure 2. Empirical ORs also suggested a potentially higher risk for some grade ≥3 irAEs with anti-PD-1 versus anti-PD-L1 antibodies, including colitis (OR: 3.79; 95% CI: 1.92–7.51), hypothyroidism (OR: 2.85; 95% CI: 1.15–7.04) and rash (OR: 4.38; 95% CI: 1.62–11.82).

Comparison of irAEs with individual agents versus pooled data for other agents

Summary estimates of irAEs (overall and selected individual irAEs) were calculated for each anti-PD-1/PD-L1 antibody individually and compared with pooled estimates for all other anti-PD-1/PD-L1 antibodies combined (Figure 3). Comparisons of overall irAEs could not include nivolumab because overall irAE data were not reported in nivolumab trials. Compared with other agents, the risk of irAEs observed for atezolizumab was lower with atezolizumab for overall any-grade irAEs (OR: 0.31; 95% CI: 0.21–0.46) whereas the CI was wide for grade ≥3 irAEs (OR: 0.40; 95% CI: 0.03–5.85). For avelumab compared with other agents, a lower risk of any-grade irAEs (OR: 0.44; 95% CI: 0.18–1.06) and grade ≥3 irAEs (OR: 0.38; 95% CI: 0.25–0.58) was observed, although the CI for any-grade irAEs crossed 1. For pembrolizumab compared with other agents, the risk of grade ≥3 irAEs appeared to be higher (OR: 1.89; 95% CI: 1.05–3.41), whereas the CI for any-grade irAEs crossed 1 (OR: 1.44; 95% CI: 0.87–2.40). For durvalumab compared with other agents, the risk of irAEs overall with durvalumab appeared to

Table 1. Incidence of immune-related adverse events overall and selected individual immune-related adverse events (any grade and grade ≥3) with anti-PD-1/PD-L1 monotherapy.

	Anti-PD-1		Anti-PD-L1	
	Number of events/total number of patients, n/N† (%)	95% CI	Number of events/total number of patients, n/N† (%)	95% CI
Any-grade irAEs	493/2307 (21.8)	0.017–0.029	618/4200 (16.2)	0.108–0.238
– Colitis	56/2933 (2.2)	0.011–0.084	31/3094 (0.9)	0.005–0.016
– Elevated ALT	32/1116 (3.1)	0.01–0.088	9/1543 (0.7)	0.004–0.013
– Elevated AST	43/1351 (3.1)	0.064–0.101	54/3725 (1.2)	0.006–0.024
– Hypothyroidism	280/3536 (8.1)	0.027–0.039	179/3270 (5.7)	0.037–0.087
– Pneumonitis	103/3497 (3.2)	0.077–0.136	110/4786 (1.9)	0.008–0.044
– Rash	171/1797 (10.3)	0.049–0.086	141/4510 (2.6)	0.015–0.045
Grade ≥3 irAEs	106/1747‡ (6.5)	0.011–0.021	90/3174 (3.6)	0.022–0.058
– Colitis	31/2562 (1.5)	0.007–0.043	9/3094 (0.4)	0.002–0.007
– Elevated ALT	13/1116 (1.8)	0.004–0.055	2/517 (0.8)	0.002–0.029
– Elevated AST	18/1351 (1.5)	0.004–0.013	13/2699 (0.6)	0.004–0.011
– Hypothyroidism	7/2776 (0.8)	0.01–0.02	5/2960 (0.3)	0.001–0.006
– Pneumonitis	25/2820 (1.4)	0.008–0.03	31/3450 (1.3)	0.006–0.026
– Rash	12/1510 (1.6)	0.017–0.029	5/3174 (0.4)	0.002–0.008

†Patients who experienced more than one event were only counted once.
‡Data not reported in studies of nivolumab; thus, data for irAEs overall (any grade and grade ≥3) in the anti-PD-1 category are for pembrolizumab only.
irAE: Immune-related adverse event.

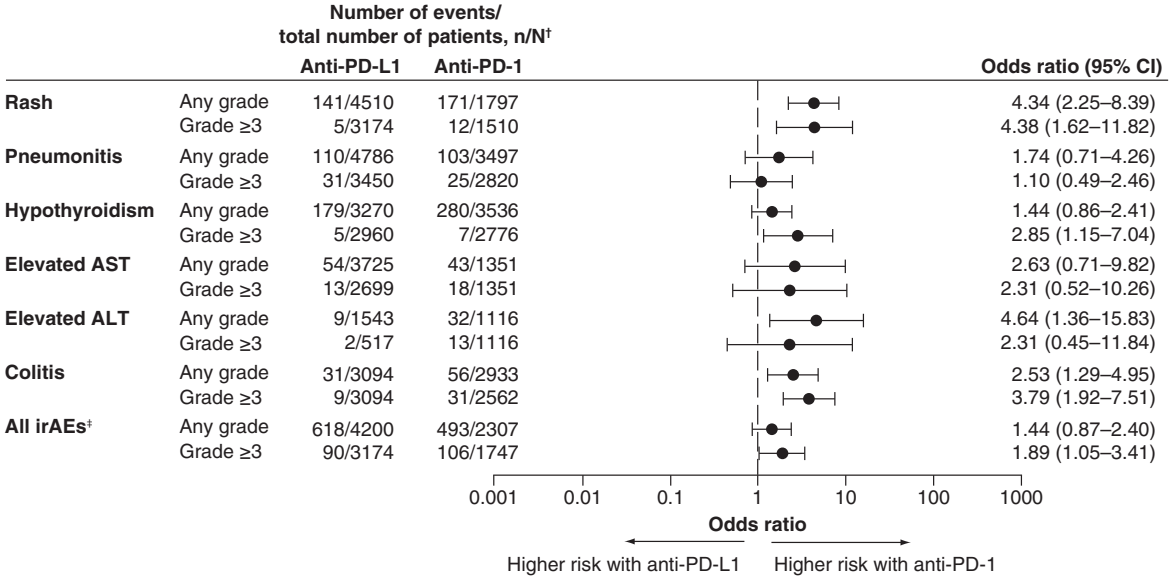


Figure 2. Odds ratios and 95% CIs for selected immune-related adverse events from pooled size-effect estimates of anti-programmed cell death 1 protein versus anti-programmed cell death 1 ligand 1 treatment.
†Patients who experienced more than one event were only counted once.
‡The incidence of irAEs overall was not reported in studies of nivolumab; thus, the pooled estimate for 'all irAEs' with anti-PD-1 antibodies (any grade and grade ≥3) is based on the summary estimate for pembrolizumab only.
irAE: Immune-related adverse event.

be higher for any-grade irAEs (OR: 2.06; 95% CI: 1.32–3.21), whereas the CI was wide for grade ≥3 irAEs (OR: 0.94; 95% CI: 0.43–2.04).

For individual irAEs, several potential differences between individual agents and pooled data for other agents were observed (Figure 3), including a lower risk of all individual any-grade irAEs with atezolizumab; a lower risk of any-grade pneumonitis and grade ≥3 colitis, pneumonitis and rash with avelumab; a higher risk of grade

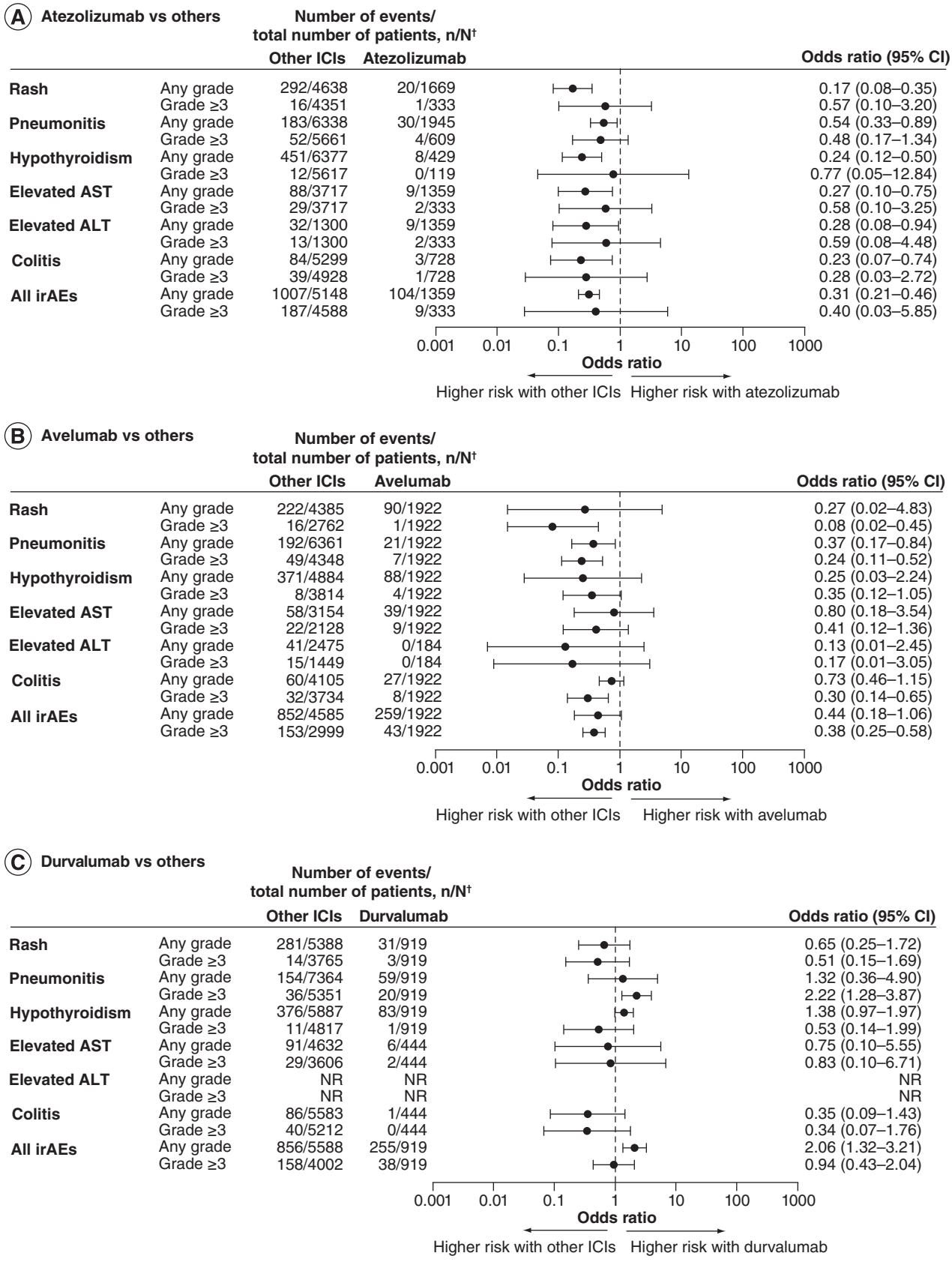


Figure 3. Summary estimates for comparisons of immune-related adverse event incidence with individual anti-programmed cell death 1 protein/programmed cell death 1 ligand 1 antibodies versus pooled estimates for other agents.

†Patients who experienced more than one event were only counted once.

ICI: Immune checkpoint inhibitor; irAE: Immune-related adverse event; NR: Not reported.

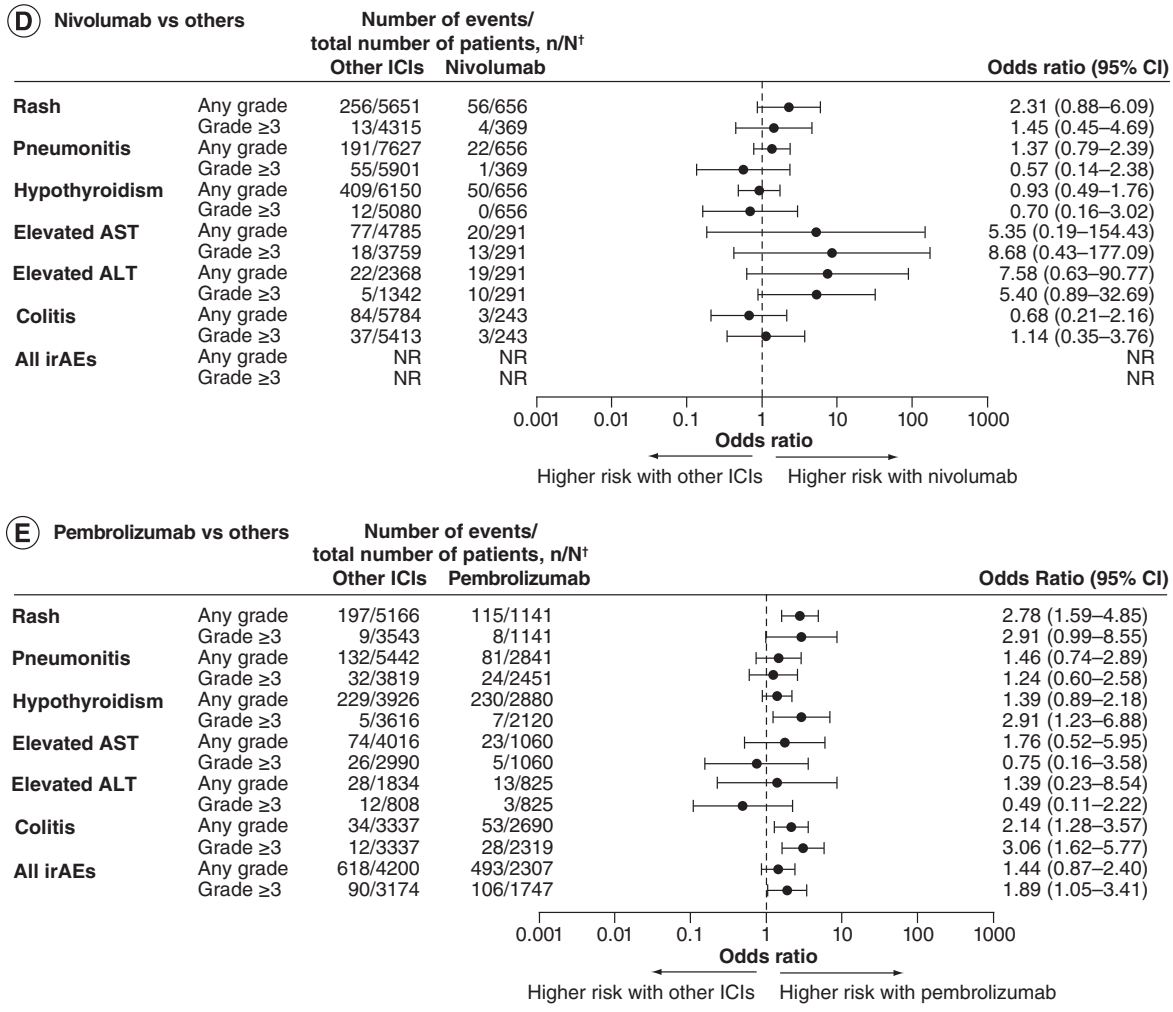


Figure 3. Summary estimates for comparisons of immune-related adverse event incidence with individual anti-programmed cell death 1 protein/programmed cell death 1 ligand 1 antibodies versus pooled estimates for other agents (cont.).

†Patients who experienced more than one event were only counted once.

ICI: Immune checkpoint inhibitor; irAE: Immune-related adverse event; NR: Not reported.

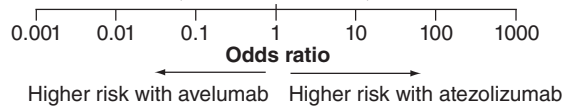
≥3 pneumonitis with durvalumab; and a higher risk of any-grade colitis and rash, as well as grade ≥3 colitis and hypothyroidism with pembrolizumab. For nivolumab, the occurrence of individual irAEs was comparable with that seen in pooled data for other agents. No differences were seen in the risk of other irAEs between agents.

Pairwise comparisons of irAEs for individual agents

Results for pairwise comparisons were mostly consistent with comparisons of individual agents with pooled data for other agents. In pairwise comparisons of anti-PD-L1 antibodies, no substantial differences were found in irAEs (overall and selected irAEs) with atezolizumab versus avelumab or nivolumab; similarly, no substantial differences were noted with nivolumab versus pembrolizumab (Figure 4). However, compared with durvalumab, a lower risk of irAEs was observed for overall any-grade irAEs with both atezolizumab and avelumab, overall grade ≥3 irAEs with avelumab, any-grade hypothyroidism and rash with atezolizumab and grade ≥3 pneumonitis with both atezolizumab and avelumab. The risk of several irAEs appeared lower with anti-PD-L1 antibodies atezolizumab and avelumab than with anti-PD-1 antibodies nivolumab and pembrolizumab. However, the risk of overall any-grade irAEs appeared to be increased with durvalumab versus pembrolizumab.

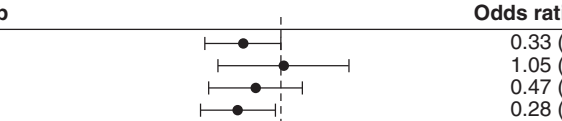
A Atezolizumab vs avelumab

		Number of events/ total number of patients, n/N†		Odds ratio (95% CI)
		Avelumab	Atezolizumab	
Rash	Any grade	90/1922	20/1669	0.83 (0.04–15.74)
	Grade ≥3	1/1922	1/333	5.71 (0.59–55.10)
Pneumonitis	Any grade	21/1922	30/1945	1.47 (0.64–3.37)
	Grade ≥3	7/1922	4/609	1.68 (0.50–5.67)
Hypothyroidism	Any grade	88/1922	8/429	0.96 (0.10–9.50)
	Grade ≥3	4/1922	0/119	1.82 (0.10–34.56)
Elevated AST	Any grade	39/1922	9/1359	0.43 (0.11–1.69)
	Grade ≥3	9/1922	2/333	1.34 (0.29–6.22)
Elevated ALT	Any grade	0/184	9/1359	2.68 (0.16–46.38)
	Grade ≥3	0/184	2/333	3.39 (0.12–93.12)
Colitis	Any grade	27/1922	3/728	0.31 (0.09–1.02)
	Grade ≥3	8/1922	1/728	0.78 (0.07–8.18)
All irAEs	Any grade	259/1922	104/1359	0.77 (0.31–1.89)
	Grade ≥3	43/1922	9/333	0.94 (0.07–13.69)



B Atezolizumab vs durvalumab

		Number of events/ total number of patients, n/N†		Odds ratio (95% CI)
		Durvalumab	Atezolizumab	
Rash	Any grade	31/919	20/1669	0.33 (0.11–0.97)
	Grade ≥3	3/919	1/333	1.05 (0.16–6.87)
Pneumonitis	Any grade	59/919	30/1945	0.47 (0.12–1.80)
	Grade ≥3	20/919	4/609	0.28 (0.10–0.83)
Hypothyroidism	Any grade	83/919	8/429	0.20 (0.10–0.42)
	Grade ≥3	1/919	0/119	1.36 (0.07–28.56)
Elevated AST	Any grade	6/444	9/1359	0.45 (0.06–3.13)
	Grade ≥3	2/444	2/333	0.70 (0.07–6.77)
Elevated ALT	Any grade	NR	NR	NR
	Grade ≥3	NR	NR	NR
Colitis	Any grade	1/444	3/728	0.69 (0.11–4.15)
	Grade ≥3	0/444	1/728	0.83 (0.05–13.10)
All irAEs	Any grade	255/919	104/1359	0.20 (0.12–0.33)
	Grade ≥3	38/919	9/333	0.44 (0.03–6.83)



C Atezolizumab vs nivolumab

		Number of events/ total number of patients, n/N†		Odds ratio (95% CI)
		Nivolumab	Atezolizumab	
Rash	Any grade	56/656	20/1669	0.12 (0.04–0.35)
	Grade ≥3	4/369	1/333	0.45 (0.07–2.85)
Pneumonitis	Any grade	22/656	30/1945	0.44 (0.25–0.77)
	Grade ≥3	1/369	4/609	0.86 (0.16–4.72)
Hypothyroidism	Any grade	50/656	8/429	0.28 (0.11–0.70)
	Grade ≥3	0/656	0/119	1.07 (0.05–23.93)
Elevated AST	Any grade	20/291	9/1359	0.07 (0.002–2.14)
	Grade ≥3	13/291	2/333	0.11 (0.004–2.86)
Elevated ALT	Any grade	19/291	9/1359	0.07 (0.006–0.85)
	Grade ≥3	10/291	2/333	0.19 (0.02–2.20)
Colitis	Any grade	3/243	3/728	0.36 (0.07–1.80)
	Grade ≥3	3/243	1/728	0.26 (0.02–3.25)
All irAEs	Any grade	NR	NR	NR
	Grade ≥3	NR	NR	NR

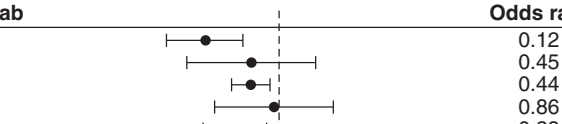


Figure 4. Summary estimates for comparisons of immune-related adverse event incidence between individual anti-programmed cell death 1 protein/programmed cell death 1 ligand 1 antibodies.

†Patients who experienced more than one event were only counted once.

irAE: Immune-related adverse event; NR: Not reported.

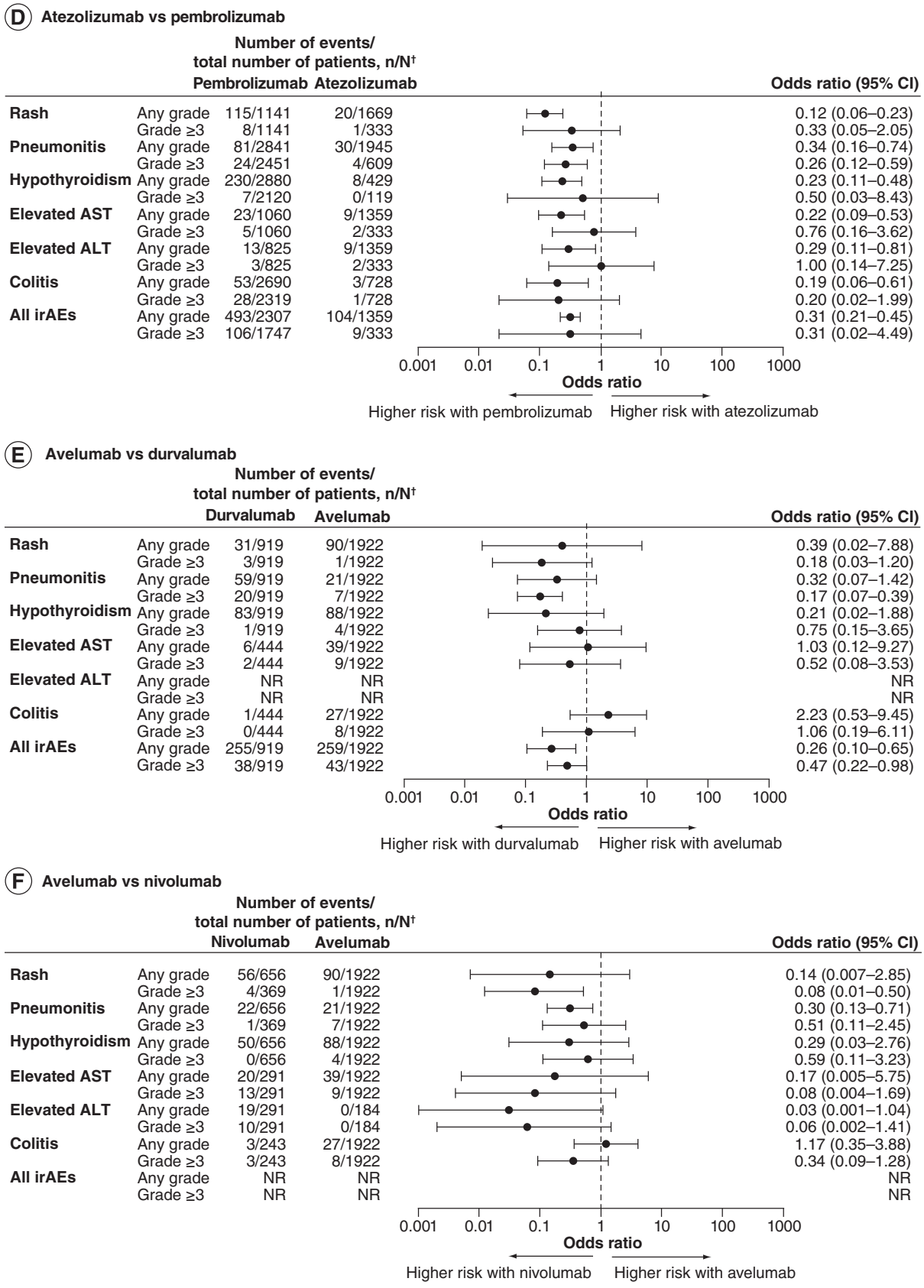


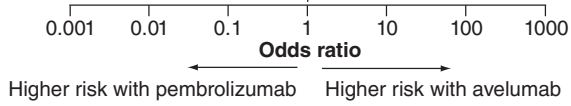
Figure 4. Summary estimates for comparisons of immune-related adverse event incidence between individual anti-programmed cell death 1 protein/programmed cell death 1 ligand 1 antibodies (cont.).

†Patients who experienced more than one event were only counted once.

irAE: Immune-related adverse event; NR: Not reported.

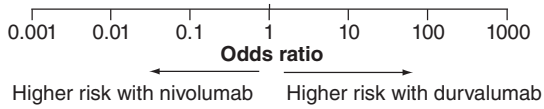
G Avelumab vs pembrolizumab

		Number of events/ total number of patients, n/N† Pembrolizumab	Avelumab	Odds ratio (95% CI)
Rash	Any grade	115/1141	90/1922	0.14 (0.008–2.54)
	Grade ≥3	8/1141	1/1922	0.06 (0.009–0.36)
Pneumonitis	Any grade	81/2841	21/1922	0.34 (0.16–0.74)
	Grade ≥3	24/2451	7/1922	0.26 (0.12–0.59)
Hypothyroidism	Any grade	230/2880	88/1922	0.23 (0.03–2.10)
	Grade ≥3	7/2120	4/1922	0.27 (0.09–0.84)
Elevated AST	Any grade	23/1060	39/1922	0.52 (0.14–1.96)
	Grade ≥3	5/1060	9/1922	0.57 (0.21–1.50)
Elevated ALT	Any grade	13/825	0/184	0.11 (0.006–1.96)
	Grade ≥3	3/825	0/184	0.30 (0.02–5.32)
Colitis	Any grade	53/2690	27/1922	0.11 (0.39–0.99)
	Grade ≥3	28/2319	8/1922	0.26 (0.12–0.57)
All irAEs	Any grade	493/2307	259/1922	0.40 (0.17–0.96)
	Grade ≥3	106/1747	43/1922	0.33 (0.22–0.50)



H Durvalumab vs nivolumab

		Number of events/ total number of patients, n/N† Nivolumab	Durvalumab	Odds ratio (95% CI)
Rash	Any grade	56/656	31/919	0.36 (0.10–1.26)
	Grade ≥3	4/369	3/919	0.43 (0.11–1.65)
Pneumonitis	Any grade	22/656	59/919	0.94 (0.24–3.65)
	Grade ≥3	1/369	20/919	3.04 (0.71–13.12)
Hypothyroidism	Any grade	50/656	83/919	1.37 (0.73–2.58)
	Grade ≥3	0/656	1/919	0.79 (0.12–5.07)
Elevated AST	Any grade	20/291	6/444	0.16 (0.004–7.24)
	Grade ≥3	13/291	2/444	0.15 (0.005–4.92)
Elevated ALT	Any grade	NR	NR	NR
	Grade ≥3	NR	NR	NR
Colitis	Any grade	3/243	1/444	0.52 (0.09–3.17)
	Grade ≥3	3/243	0/444	0.32 (0.04–2.26)
All irAEs	Any grade	NR	NR	NR
	Grade ≥3	NR	NR	NR



I Durvalumab vs pembrolizumab

		Number of events/ total number of patients, n/N† Pembrolizumab	Durvalumab	Odds ratio (95% CI)
Rash	Any grade	115/1141	31/919	0.37 (0.15–0.91)
	Grade ≥3	8/1141	3/919	0.31 (0.08–1.18)
Pneumonitis	Any grade	81/2841	59/919	1.06 (0.29–3.94)
	Grade ≥3	24/2451	20/919	1.57 (0.88–2.80)
Hypothyroidism	Any grade	230/2880	83/919	1.11 (0.77–1.60)
	Grade ≥3	7/2120	1/919	0.36 (0.09–1.42)
Elevated AST	Any grade	23/1060	6/444	0.50 (0.07–3.43)
	Grade ≥3	5/1060	2/444	1.08 (0.16–7.44)
Elevated ALT	Any grade	NR	NR	NR
	Grade ≥3	NR	NR	NR
Colitis	Any grade	53/2690	1/444	0.28 (0.07–1.15)
	Grade ≥3	28/2319	0/444	0.25 (0.05–1.28)
All irAEs	Any grade	493/2307	255/919	1.56 (1.03–2.35)
	Grade ≥3	106/1747	38/919	0.71 (0.34–1.47)

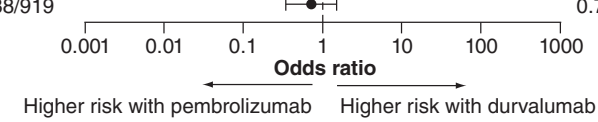


Figure 4. Summary estimates for comparisons of immune-related adverse event incidence between individual anti-programmed cell death 1 protein/programmed cell death 1 ligand 1 antibodies (cont.).

†Patients who experienced more than one event were only counted once.

irAE: Immune-related adverse event; NR: Not reported.

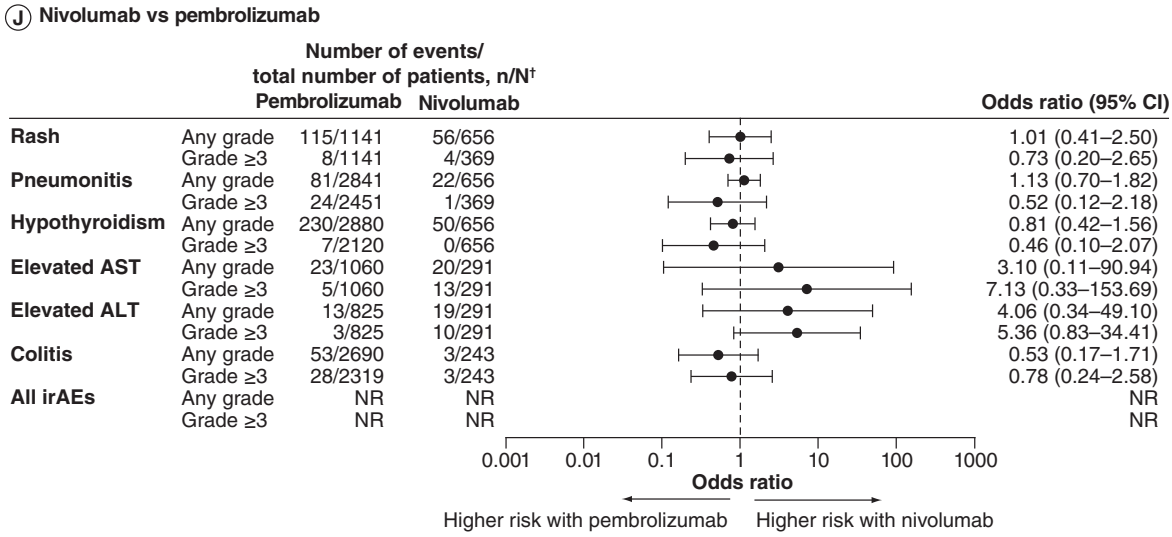


Figure 4. Summary estimates for comparisons of immune-related adverse event incidence between individual anti-programmed cell death 1 protein/programmed cell death 1 ligand 1 antibodies (cont.).
†Patients who experienced more than one event were only counted once.
irAE: Immune-related adverse event; NR: Not reported.

Discussion

Despite the increasing clinical use of ICIs in the treatment of a multitude of cancers, there is currently limited evidence to differentiate individual anti-PD-1 and PD-L1 antibodies based on safety. It has been speculated previously that anti-PD-L1 antibodies may cause fewer irAEs than anti-PD-1 antibodies because of their different binding activity; specifically, antibodies that target PD-1, but not PD-L1, also block the binding of PD-L2, which may have a regulatory role in immune regulation [23,24]. In the absence of head-to-head studies, meta-analyses provide a method for examining potential differences in the risk of irAEs with ICI treatment.

This meta-analysis explored the five anti-PD-1 and PD-L1 antibodies that have been administered to the highest numbers of patients in clinical trials: atezolizumab, avelumab, durvalumab, nivolumab and pembrolizumab. Data for cemiplimab could not be analyzed because irAE data were not specifically reported within the evaluation period. Our findings suggest that potential differences might exist regarding the risk of irAEs with individual anti-PD-1 or anti-PD-L1 antibodies. Consistent with previous meta-analyses, we observed a lower risk in pooled analyses for overall any-grade and grade ≥3 irAEs with anti-PD-L1 antibodies compared with available data for anti-PD-1 antibodies (from pembrolizumab studies only) [9,19]. Reduced risks were also observed for overall any-grade irAEs with atezolizumab and grade ≥3 irAEs avelumab versus pembrolizumab; however, an increased risk of any-grade irAEs was observed with durvalumab versus other agents combined and versus other individual anti-PD-L1 antibodies. No differences were observed between atezolizumab and avelumab, suggesting that the *in vitro* antibody-dependent cellular cytotoxicity activity and shorter halflife of avelumab may not affect the incidence of irAEs, which is consistent with the notion that irAEs result from longer-term immunological effects of ICIs. We also found no notable differences between nivolumab and pembrolizumab.

Because of the various limitations of our meta-analysis, no firm conclusions can be drawn regarding the relative risk of irAEs with individual anti-PD-1 or anti-PD-L1 antibodies and data should be interpreted with caution. These limitations include: the retrospective nature of the analysis; small incidences and large confidence intervals for a number of irAEs; lack of patient-level data; inclusion of patients with various tumor types and disease/treatment settings; different trial designs; differences in prior treatment before trial enrollment; variability in monitoring intervals and follow-up periods, exclusion of patients with autoimmune or inflammatory conditions from trials; and a focus on a few selected individual irAEs. In particular, methods of irAE definition, evaluation and data collection have evolved over time and may vary between agents and studies; thus, any differences among agents may be due in part to the different methodologies and definitions employed by investigators and sponsors. Furthermore, the incidence of overall irAEs was not reported in studies of nivolumab, meaning that the pooled estimate for overall irAEs with anti-PD-1 antibodies could be based on only pembrolizumab data. Our analysis also did not account for

differences in treatment duration, which would be expected to affect the incidence of irAEs, while other selection and confounding factors may exist. At last, this was an exploratory analysis that performed a large number of comparisons without adjustments for multiplicity; thus, differences might have been observed by chance. Despite these inherent limitations, this is one of the largest meta-analyses ever conducted to answer these very important questions and can certainly inform further studies as well as discussions in the emerging literature.

Conclusion

Overall, these hypothesis-generating findings from this large meta-analysis suggest that safety profiles for irAEs may differ among individual anti-PD-1 and anti-PD-L1 antibodies; future studies are needed to validate our conclusions.

Summary points

- In the absence of head-to-head studies, meta-analyses provide a method for examining potential differences in the risk of immune-related adverse events (irAEs) with selected agents.
- To investigate potential differences in irAE profiles, we conducted a trial-level meta-analysis.
- We analyzed data from 35 manuscripts reporting Phase I–IV trials and comprising 8730 patients treated with anti-PD-1/PD-L1 monotherapy.
- Consistent with a previous meta-analysis, we observed a lower risk of overall grade ≥3 irAEs with anti-PD-L1 antibodies versus anti-PD-1 antibodies in pooled analyses.
- Compared with pembrolizumab, lower risks of overall any-grade irAEs and grade ≥3 irAEs were observed for atezolizumab and avelumab versus pembrolizumab, respectively.
- However, no firm conclusions can be drawn regarding the risk of irAEs with individual anti-PD-1 or anti-PD-L1 antibodies.
- Overall, these findings suggest that the safety profiles for irAEs may differ between individual anti-PD-1 and anti-PD-L1 antibodies.
- This is a hypothesis-generating analysis and the conclusions require further investigation.

Supplementary data

An infographic accompanies this paper and is included at the end of the references section in the PDF version. To view or download this infographic in your browser as well as the supplementary data, please click here: www.futuremedicine.com/doi/suppl/10.2217/fon-2020-1222

Author contributions

Study concept and design: D Hennessy, JD Hunt and Y Lin. Data acquisition: JD Hunt and Y Lin. Data analysis and interpretation: P Grivas, JD Hunt and GP Sonpavde. Drafting of manuscript: P Grivas, JD Hunt, Y Lin and GP Sonpavde. Critical revisions: all authors. Final approval: all authors.

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Medical writing and editorial assistance was provided by M Holland (ClinicalThinking).

Ethical conduct of research

All trials included in this meta-analysis were conducted in accordance with the International Ethical Guidelines for Biomedical Research Involving Human Subjects, the International Conference on Harmonization Guidelines for Good Clinical Practice and the Declaration of Helsinki. The trial protocols and all amendments were approved by institutional review boards or ethics committees at each participating center.

Data sharing statement

All analyses reported in this manuscript were performed using data from published literature. A full list of data sources is provided in the Supporting Information document.

References

Papers of special note have been highlighted as: • of interest

1. Sun C, Mezzadra R, Schumacher TN. Regulation and function of the PD-L1 checkpoint. *Immunity* 48(3), 434–452 (2018).
2. LaFleur MW, Muroyama Y, Drake CG, Sharpe AH. Inhibitors of the PD-1 pathway in tumor therapy. *J. Immunol.* 200(2), 375–383 (2018).
3. Buchbinder EI, Desai A. CTLA-4 and PD-1 pathways: similarities, differences, and implications of their inhibition. *Am. J. Clin. Oncol.* 39(1), 98–106 (2016).
4. Zimmermann S, Peters S. Appraising the tail of the survival curve in the era of PD-1/PD-L1 checkpoint blockade. *JAMA Oncol.* 5(10), 1403–1405 (2019).
5. Zhang N, Tu J, Wang X, Chu Q. Programmed cell death-1/programmed cell death ligand-1 checkpoint inhibitors: differences in mechanism of action. *Immunotherapy* 11(5), 429–441 (2019).

• **Summarizes the characteristics of the different immune checkpoint inhibitors.**

6. Jia M, Feng W, Kang S *et al.* Evaluation of the efficacy and safety of anti-PD-1 and anti-PD-L1 antibody in the treatment of non-small cell lung cancer (NSCLC): a meta-analysis. *J. Thorac. Dis.* 7(3), 455–461 (2015).
7. Heery CR, O'Sullivan-Coyne G, Madan RA *et al.* Avelumab for metastatic or locally advanced previously treated solid tumours (JAVELIN Solid Tumor): a phase 1a, multicohort, dose-escalation trial. *Lancet Oncol.* 18(5), 587–598 (2017).
8. Wang PF, Chen Y, Song SY *et al.* Immune-related adverse events associated with anti-PD-1/PD-L1 treatment for malignancies: a meta-analysis. *Front. Pharmacol.* 8, 730 (2017).

• **Previously reported meta-analysis of immune-related adverse event with immune checkpoint inhibitors in earlier studies.**

9. Pillai RN, Behera M, Owonikoko TK *et al.* Comparison of the toxicity profile of PD-1 versus PD-L1 inhibitors in non-small cell lung cancer: a systematic analysis of the literature. *Cancer* 124(2), 271–277 (2018).
10. Zhang T, Xie J, Arai S *et al.* The efficacy and safety of anti-PD-1/PD-L1 antibodies for treatment of advanced or refractory cancers: a meta-analysis. *Oncotarget* 7(45), 73068–73079 (2016).
11. Huang G, Sun X, Liu D *et al.* The efficacy and safety of anti-PD-1/PD-L1 antibody therapy versus docetaxel for pretreated advanced NSCLC: a meta-analysis. *Oncotarget* 9(3), 4239–4248 (2017).
12. Man J, Ritchie G, Links M, Lord S, Lee CK. Treatment-related toxicities of immune checkpoint inhibitors in advanced cancers: a meta-analysis. *Asia Pac. J. Clin. Oncol.* 14(3), 141–152 (2018).
13. Wang X, Bao Z, Zhang X *et al.* Effectiveness and safety of PD-1/PD-L1 inhibitors in the treatment of solid tumors: a systematic review and meta-analysis. *Oncotarget* 8(35), 59901–59914 (2017).
14. Khunger M, Jain P, Rakshit S *et al.* Safety and efficacy of PD-1/PD-L1 inhibitors in treatment-naive and chemotherapy-refractory patients with non-small-cell lung cancer: a systematic review and meta-analysis. *Clin. Lung Cancer* 19(3), e335–e348 (2018).
15. Wang C, Yu X, Wang W. A meta-analysis of efficacy and safety of antibodies targeting PD-1/PD-L1 in treatment of advanced nonsmall cell lung cancer. *Medicine (Baltimore)* 95(52), e5539 (2016).
16. Ciccarese C, Iacovelli R, Bria E *et al.* The incidence and relative risk of pulmonary toxicity in patients treated with anti-PD1/PD-L1 therapy for solid tumors: a meta-analysis of current studies. *Immunotherapy* 9(7), 579–587 (2017).
17. Wang DY, Ye F, Zhao S, Johnson DB. Incidence of immune checkpoint inhibitor-related colitis in solid tumor patients: a systematic review and meta-analysis. *Oncoimmunology* 6(10), e1344805 (2017).
18. Ma K, Lu Y, Jiang S, Tang J, Li X, Zhang Y. The relative risk and incidence of immune checkpoint inhibitors related pneumonitis in patients with advanced cancer: a meta-analysis. *Front. Pharmacol.* 9, 1430 (2018).

19. Wang Y, Zhou S, Yang F *et al.* Treatment-related adverse events of PD-1 and PD-L1 inhibitors in clinical trials: a systematic review and meta-analysis. *JAMA Oncol.* 5(7), 1008–1019 (2019).

- **Large meta-analysis with a slightly different focus (all adverse events), which reports complementary findings to those reported.**

20. De Velasco G, Je Y, Bosse D *et al.* Comprehensive meta-analysis of key immune-related adverse events from CTLA-4 and PD-1/PD-L1 inhibitors in cancer patients. *Cancer Immunol. Res.* 5(4), 312–318 (2017).
21. Giannini EG, Testa R, Savarino V. Liver enzyme alteration: a guide for clinicians. *CMAJ* 172(3), 367–379 (2005).
22. Suresh K, Voong KR, Shankar B *et al.* Pneumonitis in non-small cell lung cancer patients receiving immune checkpoint immunotherapy: incidence and risk factors. *J. Thorac. Oncol.* 13(12), 1930–1939 (2018).
23. Spagnuolo A, Gridelli C. Comparison of the toxicity profile of PD-1 versus PD-L1 inhibitors in non-small cell lung cancer: is there a substantial difference or not? *J. Thorac. Dis.* 10(Suppl. 33), S4065–S4068 (2018).
24. Chen DS, Irving BA, Hodi FS. Molecular pathways: next-generation immunotherapy – inhibiting programmed death-ligand 1 and programmed death-1. *Clin. Cancer Res.* 18(24), 6580–6587 (2012).

Immune-related adverse events with PD-1 vs PD-L1 inhibitors: a meta-analysis of 8730 patients from clinical trials

Authors
Guru P. Sonpavde, Petros Grivas, Yushun Lin, Daniel Hennessy, Jay D. Hunt

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A trial-level meta-analysis investigating potential differences in immune-related adverse events reported in phase I-IV trials of anti–PD-1 (nivolumab and pembrolizumab) and anti–PD-L1 antibodies (atezolizumab, avelumab, durvalumab)

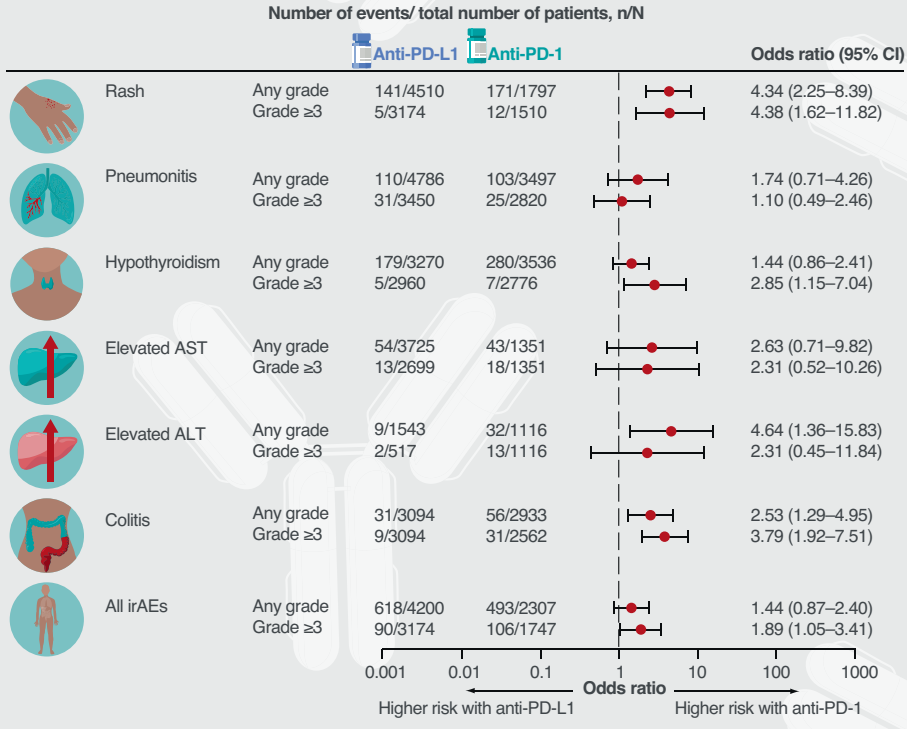
Data analyzed from 8730 patients treated with anti–PD-1/PD-L1 monotherapy

Meta-analysis explored 5 anti-PD-1 and PD-L1 antibodies that have been administered to the highest numbers of patients in clinical trials: atezolizumab, avelumab, durvalumab, nivolumab and pembrolizumab

Anti-PD-1 antibodies: nivolumab and pembrolizumab

Anti-PD-L1 antibodies: atezolizumab, avelumab and durvalumab

For anti–PD-L1 vs anti–PD-1 antibodies, we identified trends for a lower risk of rash: any-grade and grade ≥3, colitis: any-grade and grade ≥3, elevated ALT: any-grade, hypothyroidism: grade ≥3.

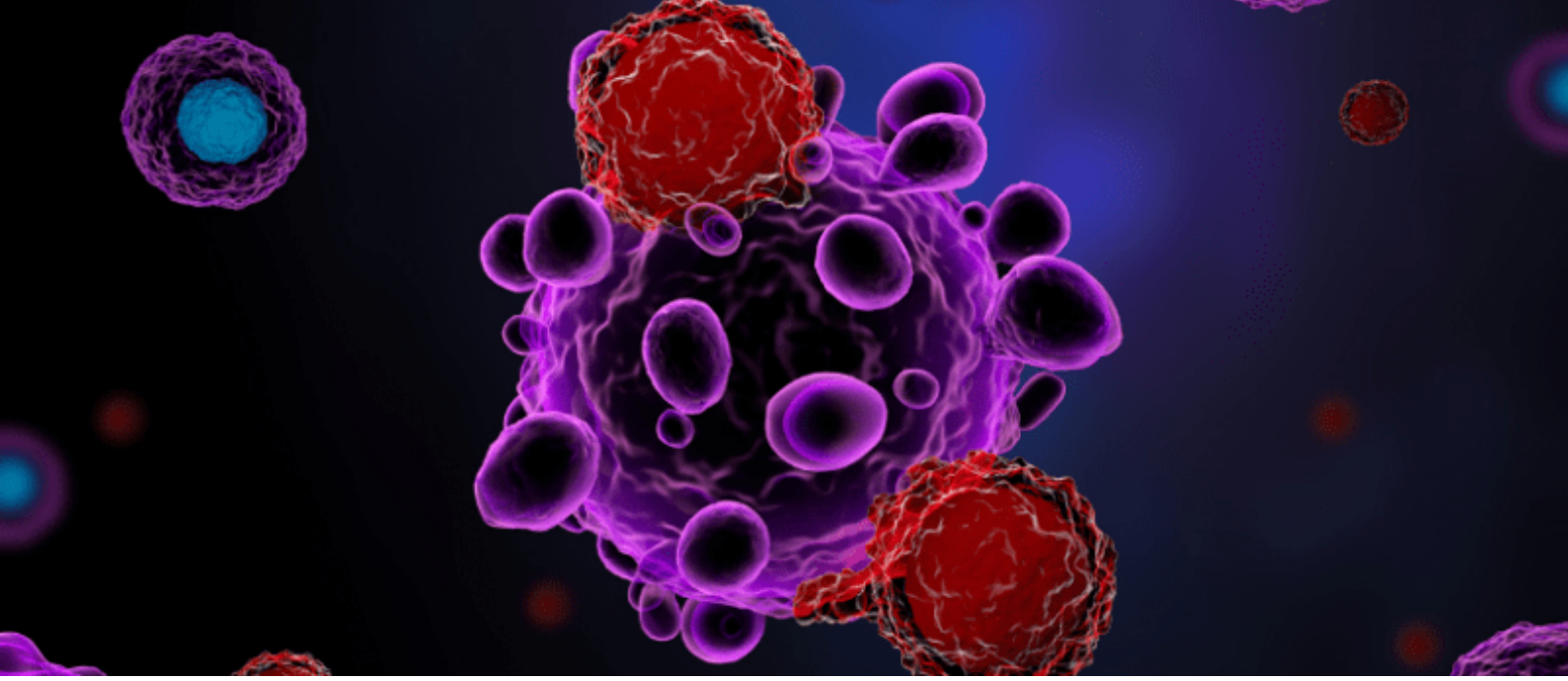


Incidence and odds ratios were calculated for irAEs overall, selected individual irAEs for individual agents, and pooled estimates for anti-PD-1 PD-L1 antibodies.

For individual agents, we found potential trends for a reduced risk of overall any-grade irAEs for atezolizumab vs pembrolizumab and grade ≥3 irAEs for avelumab vs pembrolizumab

Overall, these hypothesis-generating findings from this large meta-analysis suggest that safety profiles for irAEs may differ among individual anti–PD-1 and anti– PD-L1 antibodies

Glossary:
ALT: Alanine aminotransferase; irAE: Immune-related adverse event; PD-1: Programmed cell death 1 protein; PD-L1: Programmed cell death 1 ligand 1.



Panel discussion: past, present and future of immuno-oncology

This panel discussion, featuring experts from institutions across the world, will focus on the key challenges outstanding in the field of immuno-oncology. It aims to assess promising new immunotherapy targets and strategies, and will discuss experts' predictions on how COVID-19 will impact cancer research long-term.

What will you learn?

- Regulatory perspectives on immuno-oncology trials and approvals
- How to manage toxicities and incorporate biomarkers into therapeutic decision making
- Promising new immunotherapy combinations
- The impact COVID-19 could have on response to immunotherapies

Who may this interest?

- Researchers and clinicians working in the multidisciplinary field of immuno-oncology
- Regulatory bodies
- Oncology investors

Speakers:

Dario Vignali

Frank Dixon Chair in Cancer Immunology (University of Pittsburgh, PA, USA)

Vignali moved to the University of Pittsburgh to become Vice Chair and Professor of Immunology, and the UPMC Hillman Cancer Center to become Co-Leader of the Cancer Immunology Program and Co-Director of the Tumor Microenvironment Center. His research focuses on gaining a better understanding of the inhibitory mechanisms that limit anti-tumor immunity in cancer.

Aaron Sato

Chief Scientific Officer (Twist Biopharma; Twist Bioscience, CA, USA)

Aaron is a proven biologics leader adept at managing teams to discover and develop novel first-in-class antibody therapeutics. Prior to Twist Bioscience, he served as Chief Scientific Officer of LakePharma (CA, USA), leading the California Antibody Center. Prior to LakePharma, he oversaw all discovery research functions both as Vice President of Protein Sciences at Surrozen, and previously, as Vice President of Research at Sutro Biopharma (both CA, USA).

Teri Heiland

Chief Scientific Officer (Immunomic Therapeutics, MD, USA)

Heiland is the Chief Scientific Officer at Immunomic Therapeutics and cofounder of the Company. She has over 20 years of senior industry leadership experience. Her primary focus and expertise is in DNA vaccine design, optimization and development. Heiland is also one of the founders of Capital Genomix (MD, USA), a biomarker and drug discovery Company and served as its VP of Research and Development until 2006.

Jarret Glasscock

Founder and CEO (Cofactor Genomics, MO, USA)

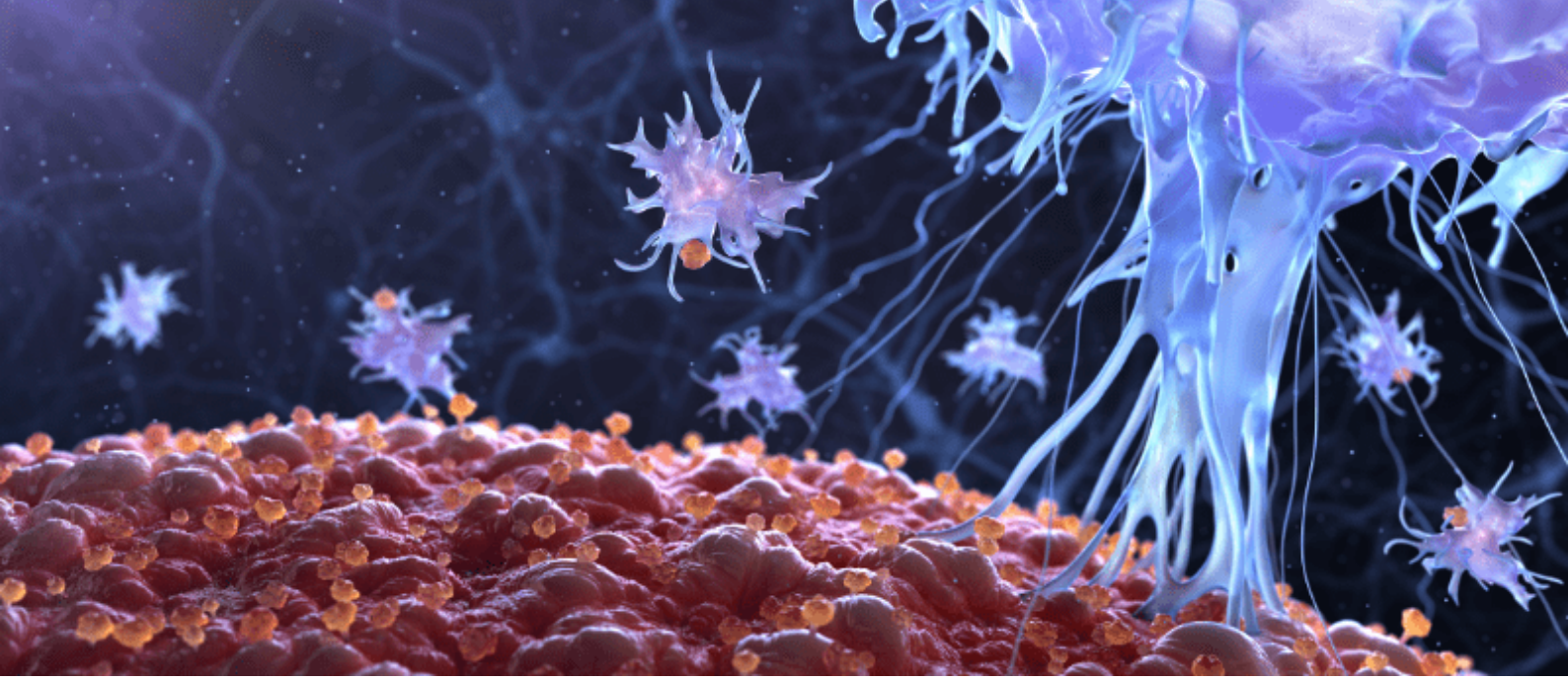
Jarret is a geneticist and computational biologist driven to translate ‘big data’ into meaningful biological signals using Predictive Immune Modeling. Prior to founding Cofactor Genomics in 2008, Jarret was faculty in the Department of Genetics at Washington University (MO, USA) and part of The Genome Institute. He was involved in the Human Genome Project and published the first Cancer Genome.

Marina Garassino

Chief of the Thoracic Oncology Unit (Instituto Nazionale dei Tumori, Milan, Italy)

Garassino leads the strategy for clinical and translational research in advanced and locally advanced NSCLC, mesothelioma and thymic malignancies at Fondazione IRCCS Istituto Nazionale dei Tumori in Milan, which is one the most important cancer centers in Italy, and in Europe. As a medical oncologist, she has done research in precision medicine and in immuno-oncology.

WATCH THE PANEL DISCUSSION:
Immuno-oncology panel discussion: the past, present and future
(oncology-central.com)



Immuno-oncology: what have been the top advancements in 2021?

Immuno-oncology can be broadly defined as those treatments that utilize the body's immune system to fight cancer from within. Combination therapies continue to yield encouraging results and other novel checkpoint inhibitors have led to an increasing number of possible treatments. However, there are still numerous hurdles that need to be overcome to make immuno-oncology a long-term option for more cancer types.

In this article, we explore the biggest advancements that have been made in the field over the past year and what remains to be tackled.

The promise of combination immunotherapies

Combination therapies continue to show promise in the immuno-oncology space as highlighted by the practice-changing Checkmate-648 results published this year.

The Phase III Checkmate-648 randomized trial demonstrated that compared to standard of care chemotherapy, both a dual immunotherapy regimen (nivolumab plus ipilimumab) and a single immunotherapy agent (nivolumab + chemotherapy) extended overall survival for patients with advanced esophageal squamous cell carcinoma. Particularly for those positive for the immune checkpoint protein PD-L1. The findings were described as a milestone for advanced esophageal cancer, which is one of the most hard-to-treat cancers. Find out more here>>>

Interestingly, the combined immunotherapy regime of nivolumab plus ipilimumab (36% reduction in mortality rate) was less effective at reducing mortality risk in the primary PD-L1–positive population than nivolumab plus chemotherapy (46% reduction in mortality rate compared to patients receiving only chemotherapy).

“Nivolumab is the first PD-1 inhibitor to demonstrate superior overall survival and durable responses in combination with either chemotherapy or ipilimumab, vs chemotherapy alone, in previously untreated patients with advanced esophageal squamous cell carcinoma,” commented Ian Chau (Royal Marsden Hospital, London, UK).

Since the discovery of immune checkpoints such as PD-1 and its ligand PD-L1, as well as CTLA-4, there have been advancements in improved survival in a subset of patients across multiple cancer types. For example, the development of immune checkpoint inhibitors plus oncogene-targeted therapy has been a key area of interest in the field of immuno-oncology combination treatments for cancer. Read more about combination therapies in this article from Future Oncology >>>.

However, despite their positives, there are caveats that need to be investigated and tracked. A recent journal article from Future Oncology explored immune-related adverse events reported in Phase I–IV trials of anti-PD-1 and PD-L1 agents across tumor types; read more here>>>.

This past year has also seen success for combination therapies for EGFR-mutant NSCLC, prostate cancer as well as MSI-H/dMMR advanced bowel cancer, the latter of which was explored in the GARNET trial. The GARNET trial tested the effectiveness of an immune checkpoint inhibitor dostarlimab (Jemperli®) in dMMR advanced or recurrent endometrial cancer and demonstrated that the immune checkpoint inhibitor shrunk tumors in 42% of patients studied, which gives a significant improvement over the previous approach. Find out more here>>>.

Pembrolizumab continues its reign of success

To write about immuno-oncology without including Keytruda® (pembrolizumab) would be improper. The so-called “wonder drug” has once again gained lots of news coverage throughout the past year.

At this year’s ASCO Annual Meeting (4–8 June 2021), the presentation of pembrolizumab data from the Phase III KEYNOTE-564 trial supported a new standard of care for some renal cell carcinoma patients.

The trial comprised 994 patients with histologically confirmed clear-cell renal cell carcinoma (RCC). Pembrolizumab demonstrated a statistically significant and clinically meaningful improvement in DFS vs placebo in the trial population. This made KEYNOTE-564 the first positive Phase III study with a checkpoint inhibitor in adjuvant RCC and therefore the results support pembrolizumab as a potential new standard of care for patients with RCC in the adjuvant setting. Read the full news story here>>>.

At the ESMO Congress 2021 (16–21 September 2021; Virtual) pembrolizumab also dominated the headlines; with survival benefit reported for cervical cancer in the KEYNOTE-826 trial and a reduction in the risk of recurrence for Stage II B/C melanoma patients in the KEYNOTE-716 trial.

Finally, the combination of lenvatinib plus pembrolizumab has been shown to provide robust antitumor activity, durable responses and manageable safety in a range of solid tumors. Find out more about the LEAP clinical trial, which is evaluating their safety and efficacy, here. Despite this success, it should be mentioned that the US indication for pembrolizumab for the treatment of patients with metastatic SCLC with disease progression on or after platinum-based chemotherapy and at least one other prior line of therapy, due to it not meeting its US FDA accelerated approval targets yet.

Expanding the accessibility of immuno-oncology agents

Although we have seen great advancements in the development of novel immuno-oncology agents and promising results from clinical trials; a key question remains. How can we expand access to these medicines? Crucial medicines such as pembrolizumab have been pulled from the Cancer Drugs Fund for certain indications.

Biosimilars can play a role in making cancer drugs more affordable and allow them to be accessed earlier in the patient care pathway.

Clinical trials also need to increase diversity, inclusion and meaningful patient participation to provide a better real-world representation of the drugs. We recently explored this topic in our panel discussion on optimizing clinical trials – watch it on-demand here.

Future Oncology's special focus issue on Patient Engagement in Cancer Research also explores this in detail, highlighting the value of patients throughout the cancer research process – access the journal content here.

Conclusion

In conclusion, the implementation of combination treatments has improved the outcomes for a variety of cancer indications over the past year. However, in order to roll out the treatment modality more successfully, there needs to be a focus on better characterizing tumors, through next-generation sequencing, as well as evaluating their associated side effects and improving patient access to the drugs themselves. Researchers should also seek to explore investigative approaches to overcome inherent shortcomings, such as those associated with reactivating T-cells and immunogenicity.

If you would like to find out more about immuno-oncology, CAR-T and oncolytic viruses make sure to check out our Spotlight on the topic and view Future Oncology's Special Focus Issue.

Oncology Central Spotlight

Immuno-oncology

For which cancer does immuno-oncology hold the most potential for improving disease management?

- Lung 37%
- Hematologic 15%
- Breast 9%
- Skin 12%
- Gastrointestinal and colorectal 9%
- Gynecologic 6%
- Rare tumors 4%
- Brain and neurologic 3%
- Endocrine and pancreatic 1%
- Genitourinary 3%
- Head and neck 1%

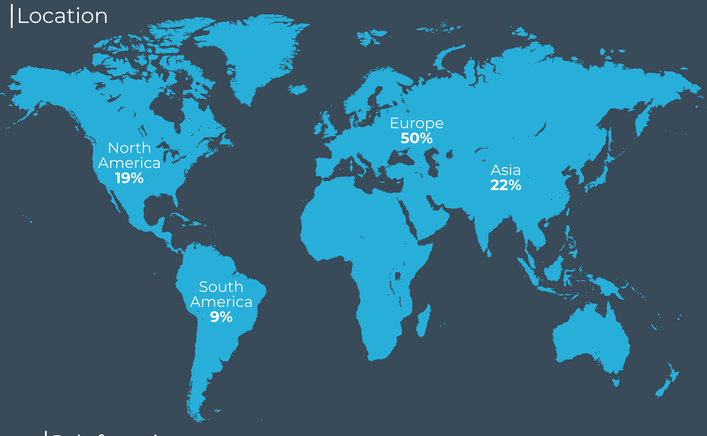
Which immunotherapy combination has the most clinical potential?

- Immune checkpoint inhibitors
- Targeted therapy
- Chemotherapy
- Nivolumab + ipilimumab

What advancements could help to further the field of immuno-oncology?

Who are our survey respondents?

Location

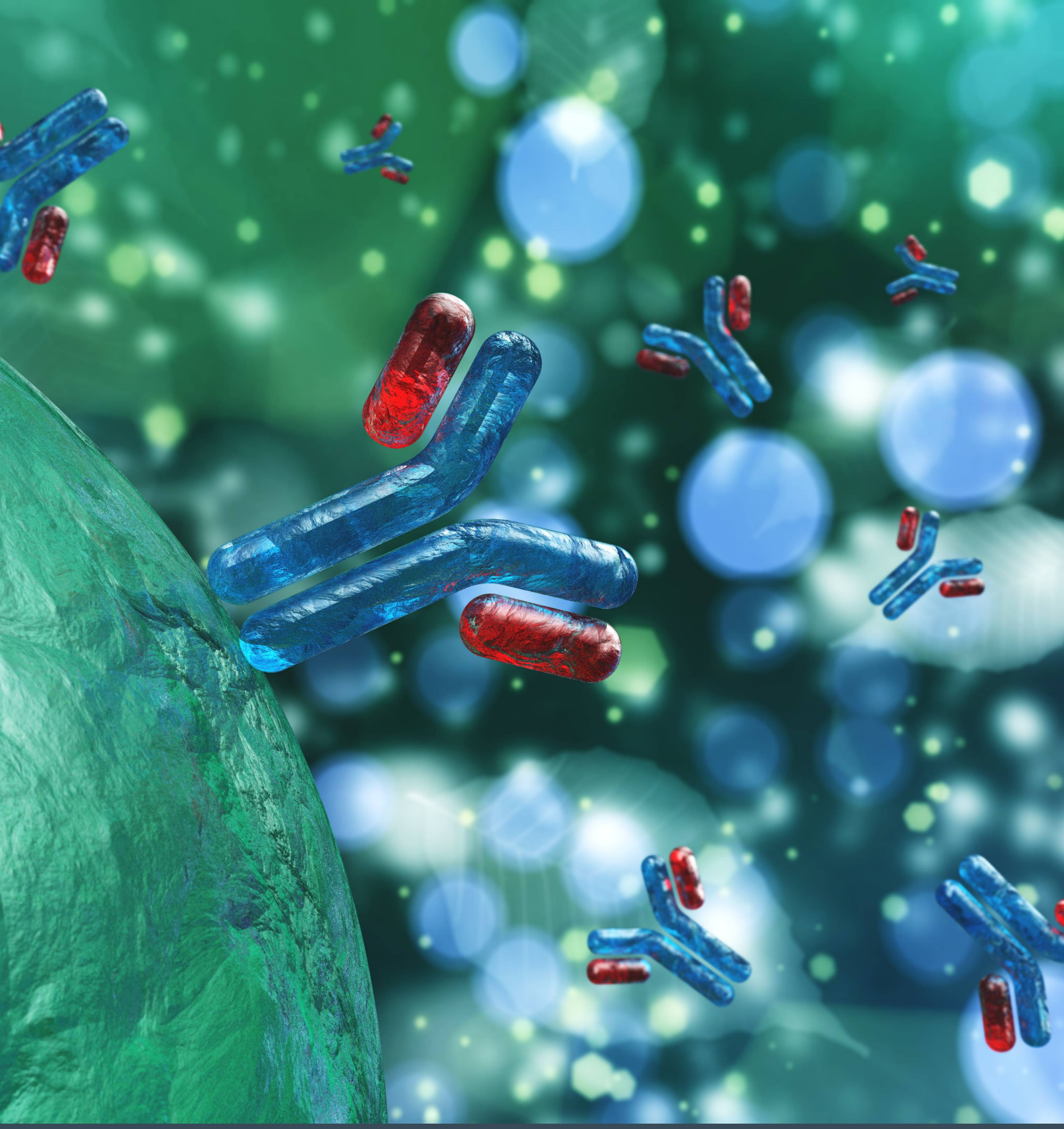


Job function

- Medical/Hospital professional **58%**
- Scientist/Researcher **31%**
- Senior Management **5%**
- Librarian/Information specialist **2%**
- Student **4%**

fsg

Oncology Central Spotlight



Contact us

Editorial Department

Senior Editor
Jade Parker
j.parker@oncology-central.com

Business Development and Support

Commercial Director
Sarah Mayes
s.mayes@future-science-group.com