

World Journal of *Gastroenterology*

World J Gastroenterol 2018 July 7; 24(25): 2647-2784



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World Journal of Gastroenterology
Volume 24 Number 25 July 7, 2018

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World Journal of Gastroenterology (*WJG*) is now indexed in Current Contents[®]/Clinical Medicine, Science Citation Index Expanded (also known as SciSearch[®]), Journal Citation Reports[®], Index Medicus, MEDLINE, PubMed, PubMed Central and Directory of Open Access Journals. The 2018 edition of Journal Citation Reports[®] cites the 2017 impact factor for *WJG* as 3.300 (5-year impact factor: 3.387), ranking *WJG* as 35th among 80 journals in gastroenterology and hepatology (quartile in category Q2).

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NAME OF JOURNAL
World Journal of Gastroenterology

ISSN
ISSN 1007-9327 (print)
ISSN 2219-2840 (online)

LAUNCH DATE
October 1, 1995

FREQUENCY
Weekly

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Pleasanton, CA 94588, USA
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PUBLICATION DATE
July 7, 2018

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Advances in immuno-oncology biomarkers for gastroesophageal cancer: Programmed death ligand 1, microsatellite instability, and beyond

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Author contributions: Lin EM, Gong J and Chao J contributed to conception and design, provision of study materials, and collection and assembly of data; all authors contributed to data analysis and interpretation, manuscript writing, and final approval of manuscript.

Conflict-of-interest statement: Chao J has received research support (institutional), consulting, and speaker fees from Merck; Klempner SJ has received research support from Leap Therapeutics and Astellas (institutional), and consulting fees from Boston Biomedical and Lilly Oncology. The remaining authors declare no conflicts of interest.

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Manuscript source: Invited manuscript

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Received: March 30, 2018

Peer-review started: March 30, 2018

First decision: May 17, 2018

Revised: May 23, 2018

Accepted: June 16, 2018

Article in press: June 16, 2018

Published online: July 7, 2018

Abstract

Blockade of the programmed death ligand 1 (PD-L1) and programmed cell death 1 (PD-1) receptor axis represents an effective form of cancer immunotherapy. Preclinical evidence initially suggested that gastric and gastroesophageal junction (GEJ) cancers are potentially immunotherapy-sensitive tumors. Early phase clinical trials have demonstrated promising antitumor activity with PD-1/PD-L1 blockade in advanced or metastatic gastric/GEJ cancer. Microsatellite instability (MSI) and PD-L1 expression have been shown to predict higher response to PD-1 inhibitors as highlighted by the recent approvals of pembrolizumab in treatment-refractory solid tumors with MSI status and the third-line or greater treatment of PD-L1 positive advanced gastric/GEJ cancers. However, predictive and prognostic biomarkers remain an ongoing need. In this review, we detail the preclinical evidence and early tissue biomarker analyses illustrating potential predictive biomarkers to PD-1/PD-L1 blockade in gastric/GEJ cancer. We also review the clinical development of PD-1/PD-L1 inhibitors in gastric/GEJ cancer and

highlight several areas in need of future investigation in order to optimize the efficacy of PD-1/PD-L1 blockade in gastric/GEJ cancer.

Key words: Immunotherapy; Programmed cell death 1; Programmed death ligand 1; Microsatellite instability; Gastric cancer

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Core tip: Programmed death ligand 1 (PD-L1) and microsatellite instability have recently entered into clinical practice as recommended biomarker testing for the use of immune checkpoint inhibitors in gastroesophageal cancer. However, PD-L1 still does not carry the highest sensitivity and specificity with variability in testing reported. Incorporation of PD-L1 expression from the tumor microenvironment with counting of immune cells appears to be the most effective strategy to date. Future efforts focusing on composite biomarkers in ongoing research from combinatorial immuno-oncology strategies are necessary to drive the field forward.

Lin EM, Gong J, Klempner SJ, Chao J. Advances in immuno-oncology biomarkers for gastroesophageal cancer: Programmed death ligand 1, microsatellite instability, and beyond. *World J Gastroenterol* 2018; 24(25): 2686-2697 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v24/i25/2686.htm> DOI: <http://dx.doi.org/10.3748/wjg.v24.i25.2686>

INTRODUCTION

T-cell activation and tolerance are partly regulated by the B7 family of proteins^[1]. B7-H1, a transmembrane protein in the B7 family also known as programmed death ligand 1 (PD-L1), has been shown to negatively regulate T-cell-mediated immune responses when bound by the programmed cell death 1 (PD-1) receptor^[1-3]. Deficiency of PD-1 leads to impaired tolerance, as demonstrated by the development of pathologies resembling lupus and graft-versus-host disease in mice with PD-1 gene disruption, and in transgenic mice with the PD-1 null mutation, respectively^[4].

Many tumors upregulate PD-L1 expression, which can be enhanced by interferon-gamma signaling^[3,5]. PD-L1 expression leads to apoptosis of tumor-reactive T cells and tumor growth^[5]. Tumorigenesis and tumor dissemination are also increased, but these effects were reversed when anti-PD-L1 antibody was administered^[6]. Therefore, activation of the PD-1/PD-L1 axis was a putative mechanism for tumors to evade host tumor antigen-specific T-cell immunity, leading to the concept of PD-1/PD-L1 blockade as a potential form of cancer immunotherapy^[3,5,6]. Initial phase I studies of

humanized monoclonal IgG4 antibodies against PD-1 and PD-L1 in patients with advanced solid tumors were soon conducted, demonstrating both tumor shrinkage and extended disease stabilization^[7]. This paved the way for the development of the first Food and Drug Administration (FDA)-approved PD-1 inhibitors, pembrolizumab and nivolumab, which achieved durable objective responses in early trials^[7-9].

Cancers of the stomach and esophagus are among the 8 major global cancers that account for > 60% of total cases and deaths worldwide^[10]. In 2012, an estimated 1.4 million cases of gastroesophageal cancer were reported, resulting in 1.1 million deaths globally. Approximately 2/3 of patients with gastroesophageal cancer develop metastatic disease during the course of their disease and despite sequencing of available active systemic agents, prognosis remains poor in advanced disease with a median overall survival (OS) of 8-10 mo^[11]. Despite the rapidly growing number of FDA approvals for PD-1/PD-L1 inhibitors in cancer therapy, the first approval of a PD-1 inhibitor specifically for advanced gastroesophageal cancer occurred on September 22, 2017 with the approval of pembrolizumab^[12]. Likewise, the PD-1 inhibitor nivolumab received concurrent regulatory approval in Japan for unresectable advanced or recurrent gastric cancer^[13]. Although clinical activity is established, biomarkers to optimize patient selection remain an area of significant need in gastroesophageal cancers.

In this review, we highlight the clinical development of PD-1 inhibitors leading up to the recent approvals of pembrolizumab and nivolumab in advanced gastroesophageal cancer. In particular, we discuss preclinical rationale, early biomarker studies, and results currently available from major phase I-III trials investigating PD-1/PD-L1 inhibitors in advanced or metastatic gastroesophageal cancer.

INITIAL STUDIES INTO THE IMMUNOGENICITY OF GASTROESOPHAGEAL CANCER

Landmark analyses by The Cancer Genome Atlas (TCGA) proposed classifications based on comprehensive genomic profiling for 4 subtypes of gastric cancer: Epstein-Barr virus (EBV)-infection, microsatellite instability (MSI), genomic stability, and chromosomal instability^[14]. Similarly, classifications were proposed for 3 molecular subtypes of esophageal squamous cell carcinoma (SCC)^[15]. Of particular interest were findings suggestive that a relevant proportion of gastric cancer cases may be inherently receptive to immune checkpoint blockade, given that EBV-positive subtypes representing 9% of cases were characterized by genomic amplification of chromosomal region 9p24.1, the locus of genes encoding PD-L1 and PD-L2, and 21.7% of cases demonstrated MSI^[14]. In-silico analyses

from RNA-sequencing data also identified gastric cancers as one of the tumor types associated with immune cytolytic activity^[16].

A meta-analysis recently demonstrated that tumor and tumor-infiltrating immune cell PD-L1 expression by immunohistochemistry (IHC) is predictive of response to PD-1/PD-L1 inhibitors [odds ratio (OR) 2.26, 95% confidence interval (CI): 1.85-2.75, $P < 0.001$] among advanced solid tumors studied across 41 trials^[17]. However, growing evidence suggests that PD-L1 expression alone as the sole predictor of response to PD-1/PD-L1 blockade may not be sufficient, given the lack of response still observed in some PD-L1-expressing tumors, and response in PD-L1 negative patients^[18]. Furthermore, there is increasing focus on immune properties of the tumor microenvironment (TME) including density of CD8+ tumor-infiltrating lymphocytes (TILs), expression of various immune checkpoints, and other immune cell phenotypes that may serve as predictive biomarkers for PD-1/PD-L1 blockade^[18-21]. Analyses of PD-L1 expression and the TME in gastroesophageal cancers, however, have been limited and only recently have investigations begun to report findings on these topics.

Many studies have focused on quantifying PD-L1 expression and its clinical significance among gastroesophageal cancers. Among histological types of esophageal cancers, SCCs were observed to have higher PD-L1 expression^[22]. In another study, presence of TILs and PD-L2 in esophageal cancers were inversely correlated, in contrast to PD-L1 expression, which had no significant correlation with TILs^[23]. PD-L1 positivity, however, was associated with significantly poorer prognosis - especially in more advanced stages - and found to be an independent prognostic factor upon multivariate analysis^[23].

PD-L1 is not expressed by normal gastric tissue^[24], and either not expressed or weakly expressed by gastric adenomas^[24,25]. However, 30%-65% of invasive gastric cancers express PD-L1^[25-30], and expression was found to correlate to depth of invasion, lymph node metastasis, distant metastasis, and tumor size^[24,26,27,31,32]. EBV-positive gastric cancers had higher rates of PD-L1 expression in tumor and immune cells more often than EBV-negative gastric cancers^[29,33-36]. In particular, Derks *et al.*^[29] found that among EBV-positive gastric cancers from the TCGA dataset, PD-L1 was expressed in immune cells in 94% of the cases, whereas only 50% of the cases had tumor cell expression of PD-L1. Among EBV-negative gastric cancers, only those with MSI were found to express PD-L1 within tumor cells. However, EBV-negative cancers without MSI had inflammatory cell expression of PD-L1 in 35% of the cases, and these inflammatory cells were present only at the invasive margin as opposed to deeply infiltrating the tumor. Interestingly, findings of tumor-infiltrating PD-L1+ inflammatory cells occurred only in cancers with

EBV positivity or MSI^[29], and among gastric cancers in another study, these were noted to have upregulated immune escape pathway genes^[34]. Mismatch repair (MMR) deficiency has also been associated with PD-L1 expression in other series^[30,37].

The relationship between other immune checkpoint molecules and PD-1/PD-L1 among gastric cancers has also been an increasing focus of interest. Expression of FOXP3, a transcription factor involved in regulatory T cell (Treg) function and development, correlated to PD-1 expression among patients with stages II and III gastric cancers^[38]. Another study found significant correlation between FOXP3+ Tregs and PD-L1 expression, and significantly higher expression of both was found in patients with more advanced clinicopathological stage and lymph node metastasis; patients with higher levels of FOXP3+ Tregs and PD-L1 expression had poorer prognosis^[39]. Blood levels of both PD-1 and the molecule T-cell immunoglobulin-3 (Tim-3), which downregulates T helper 1 and cytotoxic cells, were elevated in gastric cancer patients^[40]. In addition, PD-1+ and Tim-3+ CD8 T cells produced less IFN-gamma compared to PD-1 negative- and Tim-3-negative cells, suggestive of T-cell dysfunction^[40-42]. In a gastric cancer surgical series, post-operative circulating CD4+ and CD8+ T-cells were found to upregulate PD-1 and lymphocyte activation gene 3 (LAG-3), another co-inhibitor of T-cell activation^[43]. Gastric cancer tumor cells have also been reported to more commonly express cytotoxic T-lymphocyte antigen 4 (CTLA-4), a major immune checkpoint molecule with known therapeutic strategies, than PD-L1 (86.7% vs 44.9%, respectively)^[44]. However, gastric cancer TILs expressed more PD-L1 and PD-1 than CTLA-4^[44].

Investigation of PD-1/PD-L1 expression among TILs and the TME has also grown. Gastric cancer expression of PD-L1 was associated with TILs that were positive for CD3, CD8, or FOXP3^[45]. PD-L1+ gastric cancers tended to have stromal immune cells expressing PD-1 and PD-L1, and those with PD-L1+ immune cells had increased depth of invasion, although PD-L1+ tumor cells had greater prognostic impact than did PD-L1+ immune cells^[36]. Although both PD-L1 expression and increased CD3+ TIL density in the TME of gastric cancers were significantly associated with improved 5-year disease-free survival (DFS) and OS, there was no significant correlation between PD-L1 expression and CD3+ TIL density, leading to the hypothesis that tumor production of immunosuppressive proteins may be a mechanism intrinsic to the tumor^[46]. Among gastric and GEJ adenocarcinomas, the majority (44%) expressed PD-L1 in the immune stroma, whereas a minority (12%) expressed PD-L1 on tumor cell membranes^[47]. Increased density of CD8+ T cells was associated with PD-L1 expression, as well as with worse progression-free and overall survival, suggestive of adaptive immune resistance^[47]. In a study of gastric signet-

Table 1 Phase I clinical trials of programmed cell death 1 inhibitors involving advanced gastroesophageal cancer

<i>n</i>	Primary tumor	Doses	Primary endpoint	Results	Ref.
277 ¹	NSCLC, melanoma, cutaneous, mucosal, ocular, RCC, clear cell, non-clear cell, other (CRC, gastric, esophageal, HNSCC, sarcoma, ovarian, breast, pancreatic, uterine, pancreaticoduodenal)	Atezolizumab at escalating doses up to 20 mg/kg every 3 wk	Safety, tolerability, DLT, and RP2D	13% grade 3-4 TRAEs: 5 fatigue; 3 each of increased ALT, increased AST, hypoxia; 2 each of asthenia, dyspnea, myalgia, anemia, hyperglycemia, hyponatremia, cardiac tamponade, hypophosphatemia, tumor lysis syndrome; 1 each of nausea, headache, influenza-like illness, pain, vomiting ORR 18% overall; 21% of NSCLC, 26% of melanoma, 13% of RCC, and 13% of other malignancies (CRC, gastric, HNSCC)	[49]
151	Gastric or GEJ	Avelumab (MSB0010718C) 10 mg/kg every 2 wk until progression, toxicity, or withdrawal	Safety, efficacy	9.9% TRAEs grade ≥ 3: fatigue, asthenia, increased GGT, thrombocytopenia, anemia; 1 treat-ment-related death 14 patients with unconfirmed response: 9.7% patients on 2 nd line therapy (all PRs), 9.0% patients on 1 st -line maintenance (2 CRs, 6 PRs); disease control rate 29% for 2 nd line, 57.3% for 1 st line maintenance	JAVELIN [50]
39	PD-L1+ Gastric (previously treated)	Pembrolizumab 10 mg/kg every 2 wk for 2 yr or PD	Safety, tolerability, ORR	13% grade 3-4 TRAEs: 2 grade 3 fatigue, 1 each of grade 3 pemphigoid, hypothyroidism, neuropathy, and 1 grade 4 pneumonitis ORR 22% (95%CI: 10-39)	KEYNOTE 012 [51]
23	PD-L1+ SCC or adenocarcinoma of esophagus or GEJ	Pembrolizumab 10 mg/kg every 2 wk up to 2 yr or until PD, intolerable toxicity, or investigator decision	Safety, ORR	17.4% grade 3-4 TRAEs: 2 with decreased lymphocytes, other 2 patients AE was not specified ORR 30.4% (95%CI: 13.2%-52.9%)	KEYNOTE 028 [53]

¹Note that 175 patients were "efficacy-evaluable". PD: Progressive disease; SD: Stable disease; ORR: Overall response rate; TRAE: Treatment-related adverse effects; DCR: Disease control rate; DLT: Dose limiting toxicities; RP2D: Recommended phase 2 dose.

ring cell carcinoma, a histologic subtype historically associated with poor prognosis, the presence of CD3+ TILs was associated with increased expression of PD-1 and PD-L1, presence of MSI, and an improved OS^[48].

PD-L1 BIOMARKER ANALYSES FROM PHASE I TRIALS

Multiple early phase clinical trials of immune checkpoint inhibitors incorporated cohorts of gastroesophageal cancers to establish early signals of anti-tumor activity and exploratory biomarker analyses (Table 1). The anti-PD-L1 antibody atezolizumab was studied in multiple malignancies including gastroesophageal cancer and found to have grade 3-4 TRAEs in 13% of patients as well as an overall response rate^[10] of 18%^[49]. PD-L1

expression by IHC was determined using an anti-human PD-L1 rabbit monoclonal antibody (clone SP142; Ventana, Tucson, AZ, United States), with the authors scoring both tumor cells and immune cells. Response was significantly associated with the presence of PD-L1 positivity in tumor-infiltrating immune cells ($P = 0.007$), but not tumor cells ($P = 0.079$), with better response among patients with greater IHC scores. Among 141 gastric cancer cases included in the trial, 18% demonstrated PD-L1 expression in immune cells, compared with 5% demonstrating PD-L1 expression in tumor cells. Likewise, the JAVELIN phase Ib trial examined the anti-PD-L1 inhibitor avelumab as first-line maintenance or second-line therapy in a gastric and GEJ cancer cohort^[50]. The study demonstrated a disease control rate (DCR) of 57.3% and 29.0% in first- and second-line therapy, respectively. Patients receiving

avelumab exhibited increased ORR if harboring PD-L1 positivity of at least 1% tumor cell staining by an IHC assay (Dako, clone 73-10). However, responses were also observed even in cases with PD-L1 expression < 1% albeit at a lower proportion. TRAEs of grade 3 or higher occurred in 9.9%, with one treatment-related death due to hepatic failure.

KEYNOTE 012 was an open-label trial across 13 centers that investigated pembrolizumab for previously treated gastric cancer^[51]. Presence of tumor PD-L1 expression was a requirement for enrollment, with 40% of the patients screened demonstrating PD-L1-positive tumors. PD-L1 expression was detected using the 22C3 antibody with a prototype assay using QualTek or Dako platforms. Tumor positivity was based on a cutoff of at least 1% of scorable tumor cells or immune cells exhibiting membrane staining, or the presence of PD-L1-positive mononuclear inflammatory cells existing in the interface between tumor and stromal cells. ORR was 22% (95%CI: 10-39) comprised exclusively of partial responses^[52] as no complete responses (CRs) were observed. Median progression-free survival (PFS) was 1.9 mo (95%CI: 1.8-3.5) and median OS was 11.4 mo (95%CI: 5.7-not reached). 44% of patients with a mononuclear inflammatory cell density of 3 had PR, whereas a 0-2 density score corresponded to a PR rate of 15%. Focusing on tumor cell staining, 24% of patients with a tumor score of 0 had a response, compared to 17% of those with a score of at least 1 (Table 1). As such, there did not appear to be an absolute lower cutoff that could reliably exclude the possibility of response. KEYNOTE 028 investigated pembrolizumab in patients with advanced solid malignancy also requiring tumor expression of PD-L1 as detected by IHC in tumor or stroma, including those with SCC or adenocarcinoma of the esophagus or GEJ^[53]. Among esophageal cancers screened, 45% met the criteria for PD-L1 expression. For the patients treated, 13.0% attained stable disease^[31], and ORR was reported at 30.4%, with a PFS of 30.4% and 21.7% at 6 and 12 mo, respectively (Table 1). Median duration of response (DOR) was 40.0 wk.

PD-L1 BIOMARKER ANALYSES FROM PHASE II TRIALS

Combination immunotherapy with nivolumab, an anti-PD-1 antibody, and ipilimumab, an anti-CTLA-4 antibody, was tested for advanced gastric, esophageal, and GEJ adenocarcinoma in the phase I/II CheckMate 032 trial (Table 2). Patients received nivolumab alone, nivolumab 1 mg/kg with ipilimumab 3 mg/kg (N1+I3), or nivolumab 3mg/kg with ipilimumab 1mg/kg (N3+I1)^[54]. Grade 3-4 TRAEs including diarrhea and elevated transaminases were reported more often in the N1+I3 group, which also achieved greater ORR regardless of PD-L1 status. PD-L1 IHC expression was

determined by examining solely tumor cell expression with staining by the 28-8 antibody. 39 of 127 assessable cases (31%) exhibited PD-L1 expression \geq 1%. While ORRs were greater in PD-L1 \geq 1% tumors (19% nivolumab alone, 40% N1+I3, 23% N3+I1), responses were still demonstrable in PD-L1 < 1% tumors (12% nivolumab alone, 22% N1+I3, 0% N3+I1). Survival outcomes reported to date have not demonstrated clear differences in median OS between the 3 arms, but as a phase II trial the study was not powered to address this difference. PD-L1 \geq 1% tumors appeared to demonstrate more favorable rates of 12-month OS in the N1+I3 (50%) vs nivolumab alone (34%) and N3+I1 (23%) groups. However, with the small numbers of PD-L1 \geq 1% tumors in each arm (16 nivolumab alone, 10 N1+I3, 13 N3+I1), it remains difficult to conclude if PD-L1 IHC assessment of tumor cells alone is robust enough to enrich for gastroesophageal cancer patients who will benefit from immune checkpoint inhibitors.

KEYNOTE 059 investigated pembrolizumab among 3 cohorts of patients with gastric and GEJ cancer: (Cohort 1) pembrolizumab after at least 2 prior regimens, (Cohort 2) pembrolizumab with cisplatin and 5-fluorouracil or capecitabine as first-line therapy, and (Cohort 3) pembrolizumab as first-line therapy among patients with at least 1% PD-L1 expression as scored by the 22C3 IHC pharmDx assay^[55]. PD-L1 positivity was defined in this study as a combined positive score (CPS) \geq 1 where the number of PD-L1 positive tumor and immune cells (lymphocytes and macrophages) were divided by the total number of tumor cells evaluated and multiplied by 100. Cohort 1 comprised the largest cohort of 259 patients, and found that those with a CPS \geq 1 (n = 148, 57%) had an ORR 15.5%, comprised of a CR rate of 2.0% and PR rate of 13.5%. Those considered to be PD-L1 negative, i.e. a CPS < 1 (n = 109), had an ORR of 6.4%, and still exhibited CRs at a rate of 2.8% and PR rate of 3.7%^[56]. As such, lack of detectable PD-L1 tumor and/or immune cell expression did not completely exclude the possibility of deriving a response, including CR in 2.8%, though likelihood of response appeared higher if PD-L1 expression was detected. PD-L1 CPS-positive patients had a median DOR of 16.3 mo, compared to 6.9 mo in PD-L1 CPS-negative patients. 51.7% had 2 prior therapies, 29.0% had 3 prior therapies, and 19.3% had 4 or more prior therapies. Patients receiving pembrolizumab as third-line therapy had greater response, with a 16.4% ORR and 3.0% CR rate, compared to those receiving fourth-line therapy^[56]. PD-L1-negative patients had an ORR of 5.5%, 1.8% CRs, and 3.7% PRs. Overall 16.6% had grade 3-5 TRAEs, leading to therapy discontinuation and death in 2 patients each.

Cohort 2, which received combined frontline chemotherapy with pembrolizumab, demonstrated a median PFS of 6.6 mo and median OS of 13.8 mo

Table 2 Phase II and III clinical trials of programmed cell death 1 inhibitors in advanced gastroesophageal cancer

<i>n</i> (phase)	Experimental arm	Control or reference arm	Primary endpoint	Results	Ref.
160 (I/II)	N1 + I3: Nivolumab 1 mg/kg every 2 wk and ipilimumab 3 mg/kg every 3 wk N3 + I1: Nivolumab 3 mg/kg and ipilimumab 1 mg/kg every 3 wk Gastric, esophageal, or GEJ cancer	N3: Nivolumab 3 mg/kg every 2 wk	ORR	N3: ORR 12%, PD-L1 \geq 1% ORR 19%, PD-L1 < 1% ORR 12% N1+I3: ORR 24%, PD-L1 \geq 1% ORR 40%, PD-L1 < 1% ORR 22% N3+I1: ORR 8%, PD-L1 \geq 1% ORR 23%, PD-L1 < 1% ORR 0%	CheckMate 032 [54]
259 (II)	Cohort 1 (after \geq 2 lines of therapy): Pembrolizumab 200 mg every 3 wk up to 2 yr, PD, decision to withdraw, or unacceptable toxicity in gastric cancer	N/A	ORR, safety, tolerability	Overall ORR 11.2% (95% CI: 7.6-15.7), CR 1.9% (95% CI: 0.6-4.4), PR 9.3% (95% CI: 6.0-13.5), SD 17% (95% CI: 12.6-22.1), PD 55.6% (95% CI 49.3-61.7) PD-L1+ ORR 15.5% (95% CI 10.1-22.4), PD-L1- ORR 5.5% (95% CI 2.0-11.6)	KEYNOTE 059 [56]
25 (II)	Cohort 2 (1 st line): pembrolizumab 200 mg every 3 wk for up to 2 yr, cisplatin (80 mg/m ² day 1), and 5-FU (800 mg/m ² D1-5 Q3W) or capecitabine (1000 mg/ m ² bid)	N/A	Safety, ORR	Cohort 2: ORR 60% (39-79) overall, 73% (45-92) PD-L1+, 38% (9-76) PD-L1-. Median PFS 7 mo	KEYNOTE 059 [55]
31 (II)	Cohort 3 (PD-L1+, 1 st line): pembrolizumab 200 mg every 3 wk for up to 2 yr Gastric or GEJ cancer	N/A	Safety, ORR	Cohort 3: ORR 26% (12-45). Median PFS 3 mo	KEYNOTE 059 [55]
41 (II)	Pembrolizumab 10 mg/kg every 2 wk Cohort A: Mismatch repair (MMR)-deficient colorectal cancers (CRC) Cohort C: MMR-deficient non-CRC	Cohort B: MMR-proficient CRC	ORR, PFS	MMR-deficient CRC: ORR 40%, PFS 78%; median PFS and OS not reached MMR-proficient CRC: ORR 0%, PFS 11%; median PFS 2.2 mo, OS 5.0 mo MMR-deficient non-CRC: ORR 71%, PFS 67%	Keynote-016 [58]
86 (II)	Pembrolizumab 10 mg/kg every 2 wk for MMR-deficient cancers (12 tumor types)	N/A	ORR, PFS	Objective radiographic response 53%, CR 21%; median PFS and OS not reached	[59]
493 (III)	Nivolumab 3 mg/kg every 2 wk until unacceptable toxicity or PD in gastric/GEJ cancers	Placebo	OS	Nivolumab: median OS 5.32 mo, 6-mo OS 46.4%, 12-mo OS 26.6%, ORR 11.2%, median PFS 1.61 mo Placebo: median OS 4.14 mo, 6-mo OS 34.7%, 12-mo OS 10.9%, ORR 0%, median PFS 1.45 mo	ATTRACTION-02 [57]

PD: Progressive disease; ORR: Overall response rate; CI: Confidence interval; OS: Overall survival.

among this smaller cohort of 25 patients. PD-L1 CPS-positive patients had an ORR of 69%, compared to 38% for PD-L1 CPS-negative patients. Thus, the latter appeared in line with historical trials of doublet platinum and fluoropyrimidine chemotherapy in advanced gastric cancer. The presence of PD-L1 CPS positivity would suggest that the addition of pembrolizumab can help achieve deeper responses with chemotherapy. However, this should be cautiously interpreted with the limited number of patients analyzed. Cohort 3, which was single-agent pembrolizumab in first-line therapy but

selecting for tumors that had PD-L1 CPS \geq 1, led to a promising ORR of 26%, median PFS of 3.3 mo, and a median OS of 20.7 mo. Grade 3-5 TRAEs occurred in 18% (cohort 1), 76% (cohort 2), and 23% (cohort 3), with cohort 2 not unexpectedly demonstrating more toxicities associated with use of cytotoxic chemotherapy. Findings from cohort 1 of KEYNOTE 059 ultimately led to the accelerated FDA approval of pembrolizumab in third-line and beyond treatment of PD-L1 positive by the CPS criteria advanced or metastatic gastric or GEJ adenocarcinoma in September of 2017^[12].

PD-L1 BIOMARKER ANALYSIS FROM PHASE III TRIALS

Nivolumab was investigated in a phase III trial of 493 patients with gastric and GEJ cancer who had advanced or recurrent disease after 2 or more lines of chemotherapy^[57]. Patients receiving nivolumab had significantly improved median OS of 5.2 mo, PFS 1.61 mo, and ORR 11.2%, compared to 4.14 mo, 1.45 mo, and 0%, respectively in patients receiving placebo (all $P < 0.0001$). 11.5% of the nivolumab group and 5.5% of the placebo group suffered TRAEs of grade 3 or higher. An exploratory analysis was conducted of PD-L1 biomarker expression using the 28-8 antibody for IHC and defining PD-L1 positivity as staining in $\geq 1\%$ of tumor cells only. Tumor testing was able to be retrospectively conducted on 192 patient samples, with 26 patients (14%) harboring tumors with PD-L1 positivity in $\geq 1\%$ of tumor cells. Median OS appeared improved with nivolumab vs. placebo regardless of PD-L1 positive (5.22 mo vs 3.83 mo) or PD-L1 negative (6.05 mo vs 4.19 mo) tumor status. As such, definitive conclusions on tumor PD-L1 status influencing the likelihood of benefit from nivolumab therapy could not be drawn with the limited numbers of PD-L1 positive tumors observed. Subsequently, nivolumab garnered regulatory approval in Japan for third-line and beyond therapy for advanced gastric cancer irrespective of PD-L1 biomarker testing.

MSI AS A BIOMARKER IN GASTRIC CANCER

The seminal phase II trial by Le *et al.*^[58] demonstrated metastatic colorectal cancers (CRCs) which demonstrated deficient DNA mismatch repair (dMMR) and harbored MSI had a higher propensity to respond to pembrolizumab in comparison to CRCs with proficient MMR and were microsatellite stable (MSS). It is now well recognized that dMMR tumors harbor a high mutational burden translating into the production of tumor neoantigens which evade immune response through the upregulation of immune checkpoints^[59]. In addition to dMMR and pMMR CRCs, they included a third cohort of dMMR tumors regardless of histology. Both dMMR CRC and non-CRC cohorts demonstrated encouraging ORRs of 40% and 67%, respectively. Le *et al.*^[60] subsequently expanded the study further to 86 patients inclusive of 12 tumor types with dMMR, which continued to demonstrate a high ORR of 53% and CR rate of 21%, with median PFS and OS not reached at the time of reporting. Gastroesophageal cancers among 5 patients were included as one of the 12 tumor histologies. Three of the 5 patients exhibited CRs, while 2 of 5 had progressive disease to comprise an ORR of 60%. The high and durable ORRs of pembrolizumab in MSI-high (MSI-H) non-CRC tumors also led to efforts to retrospectively identify patients with MSI-H

gastroesophageal cancers from the KEYNOTE-012 and KEYNOTE-028 trials. Pooling of these datasets with the study by Le *et al.*^[60] in addition to the MSI-H cohort of the ongoing KEYNOTE-158 umbrella trial (NCT02628067), subsequently led to the identification of 9 gastric/GEJ adenocarcinoma patients with reportable responses^[61]. Among the 9 cases, 5 (56%) demonstrated an objective response, with median DOR ranging from 5.8 mo to 22.1 mo and ongoing at last analysis. These studies eventually culminated in the unprecedented FDA approval of pembrolizumab in treatment-refractory MSI-H solid tumors, regardless of tissue histology^[62].

Cohort 1 of the KEYNOTE-059 trial also conducted an analysis for microsatellite instability, and among 174 assessable cases, 7 were MSI-H (4%). Of these 7 MSI-H gastric/GEJ cancers, the ORR was 57.1% (14.3% CR, 42.9% PR), and a disease control rate (DCR) of 71.4% was also achieved^[56]. In contrast, the non-MSI-H subset had an ORR of 9.0% (2.4% CRs, 6.6% PRs) and DCR of 22.2%. Given that MSI-H status and PD-L1 positivity tend to occur together, it is likely that all MSI-H patients in this cohort were PD-L1 positive. In assuming that 4/7 of these MSI-H patients would have responded to pembrolizumab (ORR of 57.1%), subtracting these cases from the PD-L1+ cohort only marginally affects the ORR to pembrolizumab in this cohort (13.5% from the original 15.5%). MSI biomarker analysis was also conducted retrospectively in the gastroesophageal cohorts of the Checkmate 032 trial^[63]. Among 72 assessable cases, 11 (15%) were considered MSI-H tumors. Seven of the cases belonged in the nivolumab alone cohort, and 2 each in the N1+I3 and N3+I1 cohorts, thus no definitive comparison could be made of responses in MSI-H cases among the 3 treatment arms. Regardless, ORR was 2/7 (29%) with nivolumab alone, 1/2 (50%) with N1+I3, and 1/2 (50%) with N3+I1. Similar to the data from KEYNOTE-059, the DCR with nivolumab alone among MSI-H gastroesophageal tumors was 71%. Among non-MSI-H tumors, the ORR was 11% with nivolumab alone, 19% with N1+I3, and 5% with N3+I1.

In conclusion, MSI is present in a small, but clinically relevant proportion of gastroesophageal cancers. Responses to PD-1 inhibitors appear to be more favorable in this subset from the small numbers of patients reported in the literature to date. However, lack of MSI does not exclude the potential for response, and it is apparent that primary resistance in MSI-H tumors still exists by the reported cases with no evidence of response to immune checkpoint inhibitors.

MOVING BEYOND PD-L1 AND MSI BIOMARKERS

Other potential predictive biomarkers are gaining interest, and advances in determining prognosis with the assistance of immune markers are ongoing. Dai *et al.*^[64]

studied the prognostic value of multiple methods of immune marker detection in stage I-IV gastric cancers. PD-L1 expression and TIL infiltration were evaluated by IHC; PD-L1 expression was associated with higher TIL density, and TIL density correlated to lower rates of disease progression and improved survival. Increased mRNA levels of multiple immune markers including PD-L1, CTLA-4, FOXP3, and LAG-3, as detected by real-time quantitative polymerase chain reaction were found in patients with better OS. In-situ hybridization demonstrated a correlation between EBV positivity and PD-L1 expression as well as higher TIL infiltration.

Tumor mutational burden (TMB) has also been of interest as a predictive biomarker for immunotherapy strategies in multiple other tumors^[49,65,66]. MSI-H tumors with defective dMMR certainly exemplify high TMB with analyses by Llosa *et al.*^[59] reporting on average 1782 mutations per tumor by whole-exome sequencing in cases of MMR deficiency, compared to 73 in cases with MMR proficiency ($P = 0.007$). Such findings translated into clinical benefit with an association between greater mutation rates and prolonged PFS with pembrolizumab ($P = 0.02$). Clinically available targeted next-generation sequencing panels have also reliably captured TMB in gastrointestinal malignancies^[67]. Klemperer *et al.*^[67] reported from a large case series of tumors sequenced using the FoundationOne platform (Cambridge, MA, United Kingdom) that high TMB, defined as > 20 mutations/Mb, existed in 3% of 2065 esophageal cases and 5% of 1485 stomach cancers. Ongoing investigation is required to determine whether there is an ideal TMB cutoff that predicts high likelihood of response to immune checkpoint inhibition in gastroesophageal cancer. An early report from Ku *et al.*^[68] utilizing the Memorial Sloan Kettering IMPACT panel suggested that having ≥ 14 mutations/Mb corresponded to greater benefit from immune checkpoint inhibition (2-year OS rate 15% vs 60%, $P = 0.094$). However, the proportion of patients comprising this high TMB subset was small (6/55 patients), with 4 of the 6 being comprised of dMMR tumors^[68]. The frequency of other genomic alterations which lead to hypermutated phenotypes such as *POLE* mutations have also been characterized in gastroesophageal cancers, but appear to comprise an even lower proportion ($< 1\%$) than dMMR^[67]. A follow-up report of gastroesophageal cancers sequenced by the IMPACT panel appeared to suggest that a cutoff of > 9.7 mutations/Mb, representing the top quartile of 40 patients treated with immune checkpoint inhibitors, correlated to greater benefit (median OS 16.8 mo vs 6.62 mo, $P = 0.058$)^[69]. Interestingly, 2 patients with durable responses lasting > 12 mo had low TMB (1.9 and 3.3 mutations/Mb), with one of the cases being EBV+. As such, the detection of low TMB does not appear to entirely exclude response to immune checkpoint inhibitors. A recent phase I trial in on the anti-PD-1 antibody SHR-1210 in ESCC supported somatic nonsynonymous mutational load (by WES) as a biomarker of predictive benefit with higher TMB associated with benefit ($P = 0.048$)^[70].

With greater understanding of the dynamics of immune signaling necessary for antitumor responses, immune gene expression profiling has also entered into the forefront of biomarker analyses. High throughput assays such as the NanoString platform (Seattle, WA, United States) were applied to the early KEYNOTE-012 gastric dataset in attempts to enrich for tumor biomarkers beyond PD-L1 expression to be predictive of pembrolizumab response^[51]. Muro *et al.*^[71] reported that high scores from a 6-gene interferon γ signature (*STAT1*, *HLA-DRA*, *IFNG*, *IDO1*, *CXCL9*, *CXCL10*) correlated to response, but conclusive results were limited by small patient numbers. Likewise, the same 6-gene signature was examined in the KEYNOTE-028 esophageal dataset, and a correlation to pembrolizumab response was also observed with higher scores. Lastly, Fuchs *et al.*^[56] reported from the larger dataset of cohort 1 from KEYNOTE-059 that a higher score from an 18-gene T-cell inflamed signature (*CCL5*, *CD27*, *CD274 (PD-L1)*, *CD276 (B7-H3)*, *CD8A*, *CMKLR1*, *CXCL9*, *CXCR6*, *HLA-DQA1*, *HLA-DRB1*, *HLA-E*, *IDO1*, *LAG3*, *NKG7*, *PDCD1LG2 (PD-L2)*, *PSMB10*, *STAT1*, *TIGIT*) was significantly associated with improved response to pembrolizumab ($P = 0.014$). Thus, immune gene expression profiling in conjunction with PD-L1 IHC scoring may provide greater specificity to predicting response to anti-PD-1 therapy.

Characterization of gastric cancers has become more complex, with the availability of a variety of techniques such as multiplex IHC, in-situ hybridization, and gene expression profiling. These have expanded the field of immune therapy and facilitated the study of relationships between PD-1/PD-L1 and other factors including EBV positivity, MSI, TIL density, and the presence of other immune markers. The rapidly growing recognition of the stool microbiome influencing immunotherapy responses adds additional complexity from environmental factors influencing biomarker analyses^[52,72,73]. Further investigation into these variables in advanced gastric/GEJ cancer is duly warranted to assist further development of immunotherapeutic efforts. With currently available therapies in gastric/GEJ cancer, as in other cancers, a composite score incorporating other immune checkpoints, TILs, MSI status, tumor mutational burden, and the immune profile of the TME may represent a more robust predictive biomarker for checkpoint inhibitors rather than PD-L1 expression alone. Furthermore, to optimize the antitumor efficacy of PD-1/PD-L1 inhibitors in gastric cancer, trials have been conducted and are ongoing to examine the potential of PD-1/PD-L1 inhibitors in combination with other therapies. While combination strategies are likely necessary, it may come at a cost of additive toxicity, and as such robust predictive biomarkers will truly allow for personalization of immunotherapeutic approaches.

As observed in all of the trials discussed, the majority of patients do not derive significant benefit and demonstrate primary resistance to currently studied immune checkpoint inhibitors. Identification of patients least likely to respond is equally important to optimal

response biomarker studies. Whether or not high disease burden, low mutational burden, or the IPRES (innate anti-PD-1 resistance) transcriptional signature seen in melanoma can serve as surrogates for resistance (or have a mechanistic role) in gastric and esophageal cancers remains unknown^[74-76]. Studies in the non-metastatic setting, many of which are ongoing, may aid in identifying some resistance markers and changes between locoregional and advanced disease^[77].

CONCLUSION

Cancer immunotherapeutic approaches with PD-1/PD-L1 inhibitors continue to gain considerable momentum as more disease indications are added. Preclinical and early biomarker studies provided ample evidence that gastric/GEJ cancer is an immune-sensitive tumor. Immune parameters including MSI status, TILs, PD-L1 expression, and the immune profile of the TME are among some, but not all, of the potential predictive biomarkers for checkpoint inhibitors in advanced gastric/GEJ cancer. Early phase clinical trials provided promising signals of antitumor activity of PD-1/PD-L1 blockade to advance into larger studies. Recently, pembrolizumab received FDA approval for the third-line treatment of PD-L1 CPS expressing advanced gastric/GEJ adenocarcinoma. With the CPS criterion, this represents the first biomarker testing incorporating both assaying of tumor cells and the associated immune cells within the TME. Pembrolizumab has also been approved in a tissue-agnostic indication for treatment-refractory solid tumors that are MSI-H. In the small proportion of gastroesophageal cancers harboring this biomarker, encouraging and clinically relevant responses have been reported in the few cases reported to date. Nivolumab likewise has received Japanese approval for third-line treatment in advanced gastric/GEJ adenocarcinoma, though a predictive biomarker has not been linked to this indication. We anticipate composite biomarkers will improve patient selection and potentially individualize treatment, though broader clinical implementation may be slow. The identification of more robust predictive biomarkers and development of combination therapies incorporating immune checkpoint inhibitors represent necessary and ongoing areas of investigation to optimize this class of agents in gastric/GEJ cancer.

REFERENCES

- 1 **Dong H**, Zhu G, Tamada K, Chen L. B7-H1, a third member of the B7 family, co-stimulates T-cell proliferation and interleukin-10 secretion. *Nat Med* 1999; **5**: 1365-1369 [PMID: 10581077 DOI: 10.1038/70932]
- 2 **Freeman GJ**, Long AJ, Iwai Y, Bourque K, Chernova T, Nishimura H, Fitz LJ, Malenkovich N, Okazaki T, Byrne MC, Horton HF, Fouser L, Carter L, Ling V, Bowman MR, Carreno BM, Collins M, Wood CR, Honjo T. Engagement of the PD-1 immunoinhibitory receptor by a novel B7 family member leads to negative regulation of lymphocyte activation. *J Exp Med* 2000; **192**: 1027-1034 [PMID: 11015443]
- 3 **Greenwald RJ**, Freeman GJ, Sharpe AH. The B7 family revisited. *Annu Rev Immunol* 2005; **23**: 515-548 [PMID: 15771580 DOI: 10.1146/annurev.immunol.23.021704.115611]
- 4 **Nishimura H**, Nose M, Hiai H, Minato N, Honjo T. Development of lupus-like autoimmune diseases by disruption of the PD-1 gene encoding an ITIM motif-carrying immunoreceptor. *Immunity* 1999; **11**: 141-151 [PMID: 10485649]
- 5 **Dong H**, Strome SE, Salomao DR, Tamura H, Hirano F, Flies DB, Roche PC, Lu J, Zhu G, Tamada K, Lennon VA, Celis E, Chen L. Tumor-associated B7-H1 promotes T-cell apoptosis: a potential mechanism of immune evasion. *Nat Med* 2002; **8**: 793-800 [PMID: 12091876 DOI: 10.1038/nm730]
- 6 **Iwai Y**, Ishida M, Tanaka Y, Okazaki T, Honjo T, Minato N. Involvement of PD-L1 on tumor cells in the escape from host immune system and tumor immunotherapy by PD-L1 blockade. *Proc Natl Acad Sci USA* 2002; **99**: 12293-12297 [PMID: 12218188 DOI: 10.1073/pnas.192461099]
- 7 **Brahmer JR**, Tykodi SS, Chow LQ, Hwu WJ, Topalian SL, Hwu P, Drake CG, Camacho LH, Kauh J, Odunsi K, Pitot HC, Hamid O, Bhatia S, Martins R, Eaton K, Chen S, Salay TM, Alaparthi S, Grosso JF, Korman AJ, Parker SM, Agrawal S, Goldberg SM, Pardoll DM, Gupta A, Wigginton JM. Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. *N Engl J Med* 2012; **366**: 2455-2465 [PMID: 22658128 DOI: 10.1056/NEJMoa1200694]
- 8 **Patnaik A**, Kang SP, Rasco D, Papadopoulos KP, Ellassa-Schaap J, Beeram M, Drengler R, Chen C, Smith L, Espino G, Gergich K, Delgado L, Daud A, Lindia JA, Li XN, Pierce RH, Yearley JH, Wu D, Laterza O, Lehnert M, Iannone R, Tolcher AW. Phase I Study of Pembrolizumab (MK-3475; Anti-PD-1 Monoclonal Antibody) in Patients with Advanced Solid Tumors. *Clin Cancer Res* 2015; **21**: 4286-4293 [PMID: 25977344 DOI: 10.1158/1078-0432.ccr-14-2607]
- 9 **Topalian SL**, Hodi FS, Brahmer JR, Gettinger SN, Smith DC, McDermott DF, Powderly JD, Carvajal RD, Sosman JA, Atkins MB, Leming PD, Spigel DR, Antonia SJ, Horn L, Drake CG, Pardoll DM, Chen L, Sharfman WH, Anders RA, Taube JM, McMiller TL, Xu H, Korman AJ, Jure-Kunkel M, Agrawal S, McDonald D, Kollia GD, Gupta A, Wigginton JM, Sznol M. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. *N Engl J Med* 2012; **366**: 2443-2454 [PMID: 22658127 DOI: 10.1056/NEJMoa1200690]
- 10 **Torre LA**, Siegel RL, Ward EM, Jemal A. Global Cancer Incidence and Mortality Rates and Trends--An Update. *Cancer Epidemiol Biomarkers Prev* 2016; **25**: 16-27 [PMID: 26667886 DOI: 10.1158/1055-9965.epi-15-0578]
- 11 **Shah MA**. Update on metastatic gastric and esophageal cancers. *J Clin Oncol* 2015; **33**: 1760-1769 [PMID: 25918288 DOI: 10.1200/jco.2014.60.1799]
- 12 **U.S. Food Drug Administration**. FDA grants accelerated approval to pembrolizumab for advanced gastric cancer. September 22, 2017 ed, 2017
- 13 **Squibb BM**. Japan Ministry of Health, Labor and Welfare Approves Opdivo (nivolumab) for the Treatment of Patients with Unresectable Advanced or Recurrent Gastric Cancer Which Has Progressed After Chemotherapy. 2017
- 14 **Cancer Genome Atlas Research Network**. Comprehensive molecular characterization of gastric adenocarcinoma. *Nature* 2014; **513**: 202-209 [PMID: 25079317 DOI: 10.1038/nature13480]
- 15 **Cancer Genome Atlas Research Network**; Analysis Working Group: Asan University; BC Cancer Agency; Brigham and Women's Hospital; Broad Institute; Brown University; Case Western Reserve University; Dana-Farber Cancer Institute; Duke University; Greater Poland Cancer Centre; Harvard Medical School; Institute for Systems Biology; KU Leuven; Mayo Clinic; Memorial Sloan Kettering Cancer Center; National Cancer Institute; Nationwide Children's Hospital; Stanford University; University of Alabama; University of Michigan; University of North Carolina; University of Pittsburgh; University of Rochester; University of Southern California; University of Texas MD Anderson Cancer Center; University of Washington; Van Andel Research Institute; Vanderbilt University; Washington University; Genome Sequencing Center;

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- 16 **Rooney MS**, Shukla SA, Wu CJ, Getz G, Hacohen N. Molecular and genetic properties of tumors associated with local immune cytolytic activity. *Cell* 2015; **160**: 48-61 [PMID: 25594174 DOI: 10.1016/j.cell.2014.12.033]
 - 17 **Khunger M**, Hernandez AV, Pasupuleti V, Rakshit S, Pennell NA, Stevenson J, Mukhopadhyay S, Schalper K, Velcheti V. Programmed cell death 1 (PD-1) ligand (PD-L1) expression in solid tumors as a predictive biomarker of benefit from PD-1/PD-L1 axis inhibitors: A systematic review and meta-analysis. *JCO Precision Oncol* 2017; 1-15 [DOI: 10.1200/PO.1216.00030]
 - 18 **Gibney GT**, Weiner LM, Atkins MB. Predictive biomarkers for checkpoint inhibitor-based immunotherapy. *Lancet Oncol* 2016; **17**: e542-e551 [PMID: 27924752 DOI: 10.1016/s1470-2046(16)30406-5]
 - 19 **Chen YP**, Zhang Y, Lv JW, Li YQ, Wang YQ, He QM, Yang XJ, Sun Y, Mao YP, Yun JP, Liu N, Ma J. Genomic Analysis of Tumor Microenvironment Immune Types across 14 Solid Cancer Types: Immunotherapeutic Implications. *Theranostics* 2017; **7**: 3585-3594 [PMID: 28912897 DOI: 10.7150/thno.21471]
 - 20 **Iglesia MD**, Parker JS, Hoadley KA, Serody JS, Perou CM, Vincent BG. Genomic Analysis of Immune Cell Infiltrates Across 11 Tumor Types. *J Natl Cancer Inst* 2016; **108** [PMID: 27335052 DOI: 10.1093/jnci/djw144]
 - 21 **Taube JM**, Klein A, Brahmer JR, Xu H, Pan X, Kim JH, Chen L, Pardoll DM, Topalian SL, Anders RA. Association of PD-1, PD-L1 ligands, and other features of the tumor immune microenvironment with response to anti-PD-1 therapy. *Clin Cancer Res* 2014; **20**: 5064-5074 [PMID: 24714771 DOI: 10.1158/1078-0432.ccr-13-3271]
 - 22 **Grosso J**, Inzunza D, Wu Q, Simon J, Singh P, Zhang X, Phillips T, Simmons P, Cogswell J. Programmed death-ligand 1 (PD-L1) expression in various tumor types [abstract]. *J Immunother Cancer* 2013; **1**: P53 [DOI: 10.1186/2051-1426-1-S1-P53]
 - 23 **Ohigashi Y**, Sho M, Yamada Y, Tsurui Y, Hamada K, Ikeda N, Mizuno T, Yoriki R, Kashizuka H, Yane K, Tsushima F, Otsuki N, Yagita H, Azuma M, Nakajima Y. Clinical significance of programmed death-1 ligand-1 and programmed death-1 ligand-2 expression in human esophageal cancer. *Clin Cancer Res* 2005; **11**: 2947-2953 [PMID: 15837746 DOI: 10.1158/1078-0432.ccr-04-1469]
 - 24 **Sun J**, Xu K, Wu C, Wang Y, Hu Y, Zhu Y, Chen Y, Shi Q, Yu G, Zhang X. PD-L1 expression analysis in gastric carcinoma tissue and blocking of tumor-associated PD-L1 signaling by two functional monoclonal antibodies. *Tissue Antigens* 2007; **69**: 19-27 [PMID: 17212704 DOI: 10.1111/j.1399-0039.2006.00701.x]
 - 25 **Wu C**, Zhu Y, Jiang J, Zhao J, Zhang XG, Xu N. Immunohistochemical localization of programmed death-1 ligand-1 (PD-L1) in gastric carcinoma and its clinical significance. *Acta Histochem* 2006; **108**: 19-24 [PMID: 16530813 DOI: 10.1016/j.acthis.2006.01.003]
 - 26 **Geng Y**, Wang H, Lu C, Li Q, Xu B, Jiang J, Wu C. Expression of costimulatory molecules B7-H1, B7-H4 and Foxp3+ Tregs in gastric cancer and its clinical significance. *Int J Clin Oncol* 2015; **20**: 273-281 [PMID: 24804867 DOI: 10.1007/s10147-014-0701-7]
 - 27 **Zhang L**, Qiu M, Jin Y, Ji J, Li B, Wang X, Yan S, Xu R, Yang D. Programmed cell death ligand 1 (PD-L1) expression on gastric cancer and its relationship with clinicopathologic factors. *Int J Clin Exp Pathol* 2015; **8**: 11084-11091 [PMID: 26617827]
 - 28 **Böger C**, Behrens HM, Mathiak M, Krüger S, Kalthoff H, Röcken C. PD-L1 is an independent prognostic predictor in gastric cancer of Western patients. *Oncotarget* 2016; **7**: 24269-24283 [PMID: 27009855 DOI: 10.18632/oncotarget.8169]
 - 29 **Derks S**, Liao X, Chiaravalli AM, Xu X, Camargo MC, Solcia E, Sessa F, Fleitas T, Freeman GJ, Rodig SJ, Rabkin CS, Bass AJ. Abundant PD-L1 expression in Epstein-Barr Virus-infected gastric cancers. *Oncotarget* 2016; **7**: 32925-32932 [PMID: 27147580 DOI: 10.18632/oncotarget.9076]
 - 30 **Kimura K**, Nagasaka T, Mori Y, Kawai T, Fuji T, Taniguchi F, Yasui K, Toshima T, Umeda Y, Tazawa H, Goel A, Fujiwara T. Abstract 2317: PD-1 and PD-L1 expression patterns and DNA mismatch repair status for precision management of patients with gastric cancer. *Cancer Res* 2016; **76**: Abstr 2317 [DOI: 10.1158/1538-7445.AM2016-2317]
 - 31 **Liu SM**, Meng Q, Zhang QX, Wang SD, Liu ZJ, Zhang XF. [Expression and significance of B7-H1 and its receptor PD-1 in human gastric carcinoma]. *Zhonghua Zhong Liu Za Zhi* 2008; **30**: 192-195 [PMID: 18756934]
 - 32 **Qing Y**, Li Q, Ren T, Xia W, Peng Y, Liu GL, Luo H, Yang YX, Dai XY, Zhou SF, Wang D. Upregulation of PD-L1 and APE1 is associated with tumorigenesis and poor prognosis of gastric cancer. *Drug Des Devel Ther* 2015; **9**: 901-909 [PMID: 25733810 DOI: 10.2147/dddt.s75152]
 - 33 **Ma C**, Patel K, Singhi AD, Ren B, Zhu B, Shaikh F, Sun W. Programmed Death-Ligand 1 Expression Is Common in Gastric Cancer Associated With Epstein-Barr Virus or Microsatellite Instability. *Am J Surg Pathol* 2016; **40**: 1496-1506 [PMID: 27465786 DOI: 10.1097/pas.0000000000000698]
 - 34 **Wang K**, Leung SY. Abstract PR06: Genomic characterization of immune escape pathways in gastric cancer. *Cancer Immunol Res* 2015; **3**: Abstr PR06 [DOI: 10.1158/2326-6074.TUMIMM14-PR06]
 - 35 **Dong M**, Wang HY, Zhao XX, Chen JN, Zhang YW, Huang Y, Xue L, Li HG, Du H, Wu XY, Shao CK. Expression and prognostic roles of PIK3CA, JAK2, PD-L1, and PD-L2 in Epstein-Barr virus-associated gastric carcinoma. *Hum Pathol* 2016; **53**: 25-34 [PMID: 26980034 DOI: 10.1016/j.humpath.2016.02.007]
 - 36 **Saito R**, Abe H, Kunita A, Yamashita H, Seto Y, Fukayama M. Overexpression and gene amplification of PD-L1 in cancer cells and PD-L1+ immune cells in Epstein-Barr virus-associated gastric cancer: the prognostic implications. *Mod Pathol* 2017; **30**: 427-439 [PMID: 27934877 DOI: 10.1038/modpathol.2016.202]
 - 37 **Kim ST**, Klempner SJ, Park SH, Park JO, Park YS, Lim HY, Kang WK, Kim KM, Lee J. Correlating programmed death ligand 1 (PD-L1) expression, mismatch repair deficiency, and outcomes across tumor types: implications for immunotherapy. *Oncotarget* 2017; **8**: 77415-77423 [PMID: 29100397 DOI: 10.18632/oncotarget.20492]

- 38 **Eto S**, Yoshikawa K, Nishi M, Higashijima J, Tokunaga T, Nakao T, Kashihara H, Takasu C, Iwata T, Shimada M. Programmed cell death protein 1 expression is an independent prognostic factor in gastric cancer after curative resection. *Gastric Cancer* 2016; **19**: 466-471 [PMID: 26210691 DOI: 10.1007/s10120-015-0519-7]
- 39 **Hou J**, Yu Z, Xiang R, Li C, Wang L, Chen S, Li Q, Chen M, Wang L. Correlation between infiltration of FOXP3+ regulatory T cells and expression of B7-H1 in the tumor tissues of gastric cancer. *Exp Mol Pathol* 2014; **96**: 284-291 [PMID: 24657498 DOI: 10.1016/j.yexmp.2014.03.005]
- 40 **Takano S**, Saito H, Ikeguchi M. An increased number of PD-1+ and Tim-3+ CD8+ T cells is involved in immune evasion in gastric cancer. *Surg Today* 2016; **46**: 1341-1347 [PMID: 26801344 DOI: 10.1007/s00595-016-1305-9]
- 41 **Saito H**, Kuroda H, Matsunaga T, Osaki T, Ikeguchi M. Increased PD-1 expression on CD4+ and CD8+ T cells is involved in immune evasion in gastric cancer. *J Surg Oncol* 2013; **107**: 517-522 [PMID: 23129549 DOI: 10.1002/jso.23281]
- 42 **Lu X**, Yang L, Yao D, Wu X, Li J, Liu X, Deng L, Huang C, Wang Y, Li D, Liu J. Tumor antigen-specific CD8+ T cells are negatively regulated by PD-1 and Tim-3 in human gastric cancer. *Cell Immunol* 2017; **313**: 43-51 [PMID: 28110884 DOI: 10.1016/j.cellimm.2017.01.001]
- 43 **Takaya S**, Saito H, Ikeguchi M. Upregulation of Immune Checkpoint Molecules, PD-1 and LAG-3, on CD4+ and CD8+ T Cells after Gastric Cancer Surgery. *Yonago Acta Med* 2015; **58**: 39-44 [PMID: 26190896]
- 44 **Schlößer HA**, Drebber U, Kloth M, Thelen M, Rothschild SI, Haase S, Garcia-Marquez M, Wennhold K, Berth F, Urbanski A, Alakus H, Schauss A, Shimabukuro-Vornhagen A, Theurich S, Warnecke-Ebertz U, Stippel DL, Zippelius A, Büttner R, Hallek M, Hölscher AH, Zander T, Mönig SP, von Bergwelt-Baildon M. Immune checkpoints programmed death 1 ligand 1 and cytotoxic T lymphocyte associated molecule 4 in gastric adenocarcinoma. *Oncotarget* 2015; **5**: e1100789 [PMID: 27467911 DOI: 10.1080/2162402x.2015.1100789]
- 45 **Kawazoe A**, Kuwata T, Kuboki Y, Shitara K, Nagatsuma AK, Aizawa M, Yoshino T, Doi T, Ohtsu A, Ochiai A. Clinicopathological features of programmed death ligand 1 expression with tumor-infiltrating lymphocyte, mismatch repair, and Epstein-Barr virus status in a large cohort of gastric cancer patients. *Gastric Cancer* 2017; **20**: 407-415 [PMID: 27629881 DOI: 10.1007/s10120-016-0631-3]
- 46 **Kim JW**, Nam KH, Ahn SH, Park DJ, Kim HH, Kim SH, Chang H, Lee JO, Kim YJ, Lee HS, Kim JH, Bang SM, Lee JS, Lee KW. Prognostic implications of immunosuppressive protein expression in tumors as well as immune cell infiltration within the tumor microenvironment in gastric cancer. *Gastric Cancer* 2016; **19**: 42-52 [PMID: 25424150 DOI: 10.1007/s10120-014-0440-5]
- 47 **Thompson ED**, Zahurak M, Murphy A, Cornish T, Cuka N, Abdelfatah E, Yang S, Duncan M, Ahuja N, Taube JM, Anders RA, Kelly RJ. Patterns of PD-L1 expression and CD8 T cell infiltration in gastric adenocarcinomas and associated immune stroma. *Gut* 2017; **66**: 794-801 [PMID: 26801886 DOI: 10.1136/gutjnl-2015-310839]
- 48 **Jin S**, Xu B, Yu L, Fu Y, Wu H, Fan X, Wei J, Liu B. The PD-1, PD-L1 expression and CD3+ T cell infiltration in relation to outcome in advanced gastric signet-ring cell carcinoma, representing a potential biomarker for immunotherapy. *Oncotarget* 2017; **8**: 38850-38862 [PMID: 28418918 DOI: 10.18632/oncotarget.16407]
- 49 **Herbst RS**, Soria JC, Kowanetz M, Fine GD, Hamid O, Gordon MS, Sosman JA, McDermott DF, Powderly JD, Gettinger SN, Kohrt HE, Horn L, Lawrence DP, Rost S, Leabman M, Xiao Y, Mokatrik A, Koeppen H, Hegde PS, Mellman I, Chen DS, Hodi FS. Predictive correlates of response to the anti-PD-L1 antibody MPDL3280A in cancer patients. *Nature* 2014; **515**: 563-567 [PMID: 25428504 DOI: 10.1038/nature14011]
- 50 **Chung HC**, Arkenau HT, Wyrwicz L, Oh DY, Lee KW, Infante JR, Lee SS, Lee J, Keilholz U, Mita AC, Plummer ER, Kemeny M, Melichar B, Smith DM, Chin KM, von Heydebreck A, Cuillerot JM, Kang YK, Safran H. Avelumab (MSB0010718C; anti-PD-L1) in patients with advanced gastric or gastroesophageal junction cancer from JAVELIN solid tumor phase Ib trial: Analysis of safety and clinical activity. *J Clin Oncol* 2016; **34**: 4009 [DOI: 10.1200/JCO.2016.34.15_suppl.4009]
- 51 **Muro K**, Chung HC, Shankaran V, Geva R, Catenacci D, Gupta S, Eder JP, Golan T, Le DT, Burtneess B, McRee AJ, Lin CC, Pathiraja K, Luncford J, Emancipator K, Juco J, Koshiji M, Bang YJ. Pembrolizumab for patients with PD-L1-positive advanced gastric cancer (KEYNOTE-012): a multicentre, open-label, phase Ib trial. *Lancet Oncol* 2016; **17**: 717-726 [PMID: 27157491 DOI: 10.1016/s1470-2045(16)00175-3]
- 52 **Gopalakrishnan V**, Spencer CN, Nezi L, Reuben A, Andrews MC, Karpins TV, Prieto PA, Vicente D, Hoffman K, Wei SC, Cogdill AP, Zhao L, Hudgens CW, Hutchinson DS, Manzo T, Petaccia de Macedo M, Cotechini T, Kumar T, Chen WS, Reddy SM, Szczepaniak Sloane R, Galloway-Pena J, Jiang H, Chen PL, Shpall EJ, Rezvani K, Alousi AM, Chemaly RF, Shelburne S, Vence LM, Okhuysen PC, Jensen VB, Swennes AG, McAllister F, Marcelo Riquelme Sanchez E, Zhang Y, Le Chatelier E, Zitvogel L, Pons N, Austin-Breneman JL, Haydu LE, Burton EM, Gardner JM, Sirmans E, Hu J, Lazar AJ, Tsujikawa T, Diab A, Tawbi H, Glitza IC, Hwu WJ, Patel SP, Woodman SE, Amaria RN, Davies MA, Gershenwald JE, Hwu P, Lee JE, Zhang J, Coussens LM, Cooper ZA, Futreal PA, Daniel CR, Ajami NJ, Petrosino JF, Tetzlaff MT, Sharma P, Allison JP, Jenq RR, Wargo JA. Gut microbiome modulates response to anti-PD-1 immunotherapy in melanoma patients. *Science* 2018; **359**: 97-103 [PMID: 29097493 DOI: 10.1126/science.aan4236]
- 53 **Doi T**, Piha-Paul SA, Jalal SI, Mai-Dang H, Saraf S, Koshiji M, Csiki I, Bennouna J. Updated results for the advanced esophageal carcinoma cohort of the phase Ib KEYNOTE-028 study of pembrolizumab. *J Clin Oncol* 2016; **34**: Abstr 4046 [DOI: 10.1200/jco.2016.34.4_suppl.7]
- 54 **Janjigian YY**, Ott PA, Calvo E, Kim JW, Ascierto PA, Sharma P, Peltola KJ, Jaeger D, Evans TRJ, De Braud FG, Chau I, Tschika M, Harbison CT, Cai W, Bendell JC, Le DT. Nivolumab ± ipilimumab in pts with advanced (adv)/metastatic chemotherapy-refractory (CTx-R) gastric (G), esophageal (E), or gastroesophageal junction (GEJ) cancer: CheckMate 032 study. *J Clin Oncol* 2017; **35**: Abstr 4014 [DOI: 10.1200/JCO.2017.35.15_suppl.4014]
- 55 **Wainberg ZA**, Jalal S, Muro K, Yoon HH, Garrido M, Golan T, Doi T, Catenacci DV, Geva R, Ku G, Bleeker J, Bang YJ, Hara H, Chung HC, Savage M, Wang J, Koshiji M, Dalal R, Fuchs CS. KEYNOTE-059 Update: Efficacy and safety of pembrolizumab alone or in combination with chemotherapy in patients with advanced gastric or gastroesophageal (G/GEJ) cancer. *Ann Oncol* 2017; **28**: LBA28_PR [DOI: 10.1093/annonc/mdx440.020]
- 56 **Fuchs CS**, Doi T, Jang RW, Muro K, Satoh T, Machado M, Sun W, Jalal SI, Shah MA, Metges JP, Garrido M, Golan T, Mandala M, Wainberg ZA, Catenacci DVT, Ohtsu A, Shitara K, Geva R, Bleeker J, Ko AH, Ku G, Philip P, Enzinger PC, Bang YJ, Levitan D, Wang J, Rosales M, Dalal RP, Yoon HH. 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* 2018; **4**: e180013 [PMID: 29543932 DOI: 10.1001/jamaoncol.2018.0013]
- 57 **Kang YK**, Satoh T, Ryu MH, Chao Y, Kato K, Chung HC, Chen JS, Muro K, Kang WK, Yoshikawa T, Oh SC, Tamura T, Lee KW, Boku N, Chen LT. Nivolumab (ONO-4538/BMS-936558) as salvage treatment after second or later-line chemotherapy for advanced gastric or gastro-esophageal junction cancer (AGC): A double-blinded, randomized, phase III trial. *J Clin Oncol* 2017; **35**: Abstract 02 [DOI: 10.1200/JCO.2017.35.4_suppl.2]
- 58 **Le DT**, Uram JN, Wang H, Bartlett BR, Kemberling H, Eyring AD, Skora AD, Luber BS, Azad NS, Laheru D, Biedrzycki B, Donehower RC, Zaheer A, Fisher GA, Crocenzi TS, Lee JJ, Duffy SM, Goldberg RM, de la Chapelle A, Koshiji M, Bhajee F, Huebner T, Hruban RH, Wood LD, Cuka N, Pardoll DM, Papadopoulos N, Kinzler KW, Zhou S, Cornish TC, Taube JM, Anders RA, Eshleman JR, Vogelstein B, Diaz LA Jr. PD-1 Blockade in Tumors with Mismatch-Repair Deficiency. *N Engl J Med* 2015; **372**: 2509-2520 [PMID: 26028255 DOI: 10.1056/NEJMoa1500596]

- 59 **Llosa NJ**, Cruise M, Tam A, Wicks EC, Hechenbleikner EM, Taube JM, Blosser RL, Fan H, Wang H, Lubner BS, Zhang M, Papadopoulos N, Kinzler KW, Vogelstein B, Sears CL, Anders RA, Pardoll DM, Housseau F. The vigorous immune microenvironment of microsatellite instable colon cancer is balanced by multiple counter-inhibitory checkpoints. *Cancer Discov* 2015; **5**: 43-51 [PMID: 25358689 DOI: 10.1158/2159-8290.CD-14-0863]
- 60 **Le DT**, Durham JN, Smith KN, Wang H, Bartlett BR, Aulakh LK, Lu S, Kemberling H, Wilt C, Lubner BS, Wong F, Azad NS, Rucki AA, Laheru D, Donehower R, Zaheer A, Fisher GA, Crocenzi TS, Lee JJ, Greten TF, Duffy AG, Ciombor KK, Eyring AD, Lam BH, Joe A, Kang SP, Holdhoff M, Danilova L, Cope L, Meyer C, Zhou S, Goldberg RM, Armstrong DK, Bever KM, Fader AN, Taube J, Housseau F, Spetzler D, Xiao N, Pardoll DM, Papadopoulos N, Kinzler KW, Eshleman JR, Vogelstein B, Anders RA, Diaz LA Jr. Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. *Science* 2017; **357**: 409-413 [PMID: 28596308 DOI: 10.1126/science.aan6733]
- 61 **Zhang W**, Pang Q, Yan C, Wang Q, Yang J, Yu S, Liu X, Yuan Z, Wang P, Xiao Z. Induction of PD-L1 expression by epidermal growth factor receptor-mediated signaling in esophageal squamous cell carcinoma. *Onco Targets Ther* 2017; **10**: 763-771 [PMID: 28243112 DOI: 10.2147/ott.s118982]
- 62 **U.S. Food Drug Administration**. FDA approves first cancer treatment for any solid tumor with a specific genetic feature. May 24, 2017 ed, 2017
- 63 **Ott PA**, Le DT, Kim JW, Ascierto PA, Sharma P, Bono P, Peltola K, Jäger D, Evans TRJ, de Braud F, Chau I, Bendell JC, Tschaike M, Harbison CT, Zhao H, Calvo E, Janjigian Y. Nivolumab (NIVO) in patients (pts) with advanced (adv) chemotherapy-refractory (CT-Rx) esophagogastric (EG) cancer according to microsatellite instability (MSI) status: checkmate 032. *Ann Oncol* 2017; **28**: 674P [DOI: 10.1093/annonc/mdx369.058]
- 64 **Dai C**, Geng R, Wang C, Wong A, Qing M, Hu J, Sun Y, Lo AW, Li J. Concordance of immune checkpoints within tumor immune contexture and their prognostic significance in gastric cancer. *Mol Oncol* 2016; **10**: 1551-1558 [PMID: 27720576 DOI: 10.1016/j.molonc.2016.09.004]
- 65 **Rizvi NA**, Hellmann MD, Snyder A, Kvistborg P, Makarov V, Havel JJ, Lee W, Yuan J, Wong P, Ho TS, Miller ML, Rekhtman N, Moreira AL, Ibrahim F, Bruggeman C, Gasmi B, Zappasodi R, Maeda Y, Sander C, Garon EB, Merghoub T, Wolchok JD, Schumacher TN, Chan TA. Cancer immunology. Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer. *Science* 2015; **348**: 124-128 [PMID: 25765070 DOI: 10.1126/science.aal1348]
- 66 **Gong J**, Chehrizi-Raffle A, Reddi S, Salgia R. Development of PD-1 and PD-L1 inhibitors as a form of cancer immunotherapy: a comprehensive review of registration trials and future considerations. *J Immunother Cancer* 2018; **6**: 8 [PMID: 29357948 DOI: 10.1186/s40425-018-0316-z]
- 67 **Klempner SJ**, Frampton GM, Chao J, Bailey M, Stephens P, Ross JS, Miller VA, Ali SM, Schrock AB. Topography of Tumor Mutational Burden (TMB) and Immune-related Genomic Alterations (GA) Across Gastrointestinal Malignancies (GIm): A Study of 22,570 Cases. *Ann Oncol* 2017; **28**: 1169P [DOI: 10.1093/annonc/mdx376.034]
- 68 **Ku GY**, Sanchez-Vega F, Chatila W, Margolis M, Fein C, Ilson DH, Hechtman JF, Tuvy Y, Bouvier N, Kundra R, Shia J, Heins ZJ, Middha S, Zehir A, Ladanyi M, Berger MF, Tang LH, Solit DB, Schultz N, Janjigian YY. Correlation of benefit from immune checkpoint inhibitors with next gen sequencing (NGS) profiles in esophagogastric cancer (EGC) patients. *J Clin Oncol* 2017; **35**: 4025-4025 [DOI: 10.1200/JCO.2017.35.15_suppl.4025]
- 69 **Janjigian YY**, Sanchez-Vega F, Jonsson P, Chatila WK, Hechtman JF, Ku GY, Riches JC, Tuvy Y, Kundra R, Bouvier N, Vakiani E, Gao J, Heins ZJ, Gross BE, Kelsen DP, Zhang L, Strong VE, Schattner M, Gerdes H, Coit DG, Bains M, Stadler ZK, Rusch VW, Jones DR, Molena D, Shia J, Robson ME, Capanu M, Middha S, Zehir A, Hyman DM, Scaltriti M, Ladanyi M, Rosen N, Ilson DH, Berger MF, Tang L, Taylor BS, Solit DB, Schultz N. Genetic Predictors of Response to Systemic Therapy in Esophagogastric Cancer. *Cancer Discov* 2018; **8**: 49-58 [PMID: 29122777 DOI: 10.1158/2159-8290.CD-17-0787]
- 70 **Huang J**, Xu B, Mo H, Zhang W, Chen X, Wu D, Qu D, Wang X, Lan B, Yang B, Wang P, Zhang H, Yang Q, Jiao Y. Safety, Activity, and Biomarkers of SHR-1210, an Anti-PD-1 Antibody, for Patients with Advanced Esophageal Carcinoma. *Clin Cancer Res* 2018; **24**: 1296-1304 [PMID: 29358502 DOI: 10.1158/1078-0432.CCR-17-2439]
- 71 **Doi T**, Piha-Paul SA, Jalal SI, Saraf S, Lunceford J, Koshiji M, Bannouna J. Safety and Antitumor Activity of the Anti-Programmed Death-1 Antibody Pembrolizumab in Patients With Advanced Esophageal Carcinoma. *J Clin Oncol* 2018; **36**: 61-67 [PMID: 29116900 DOI: 10.1200/JCO.2017.74.9846]
- 72 **Matson V**, Fessler J, Bao R, Chongsuwat T, Zha Y, Alegre ML, Luke JJ, Gajewski TF. The commensal microbiome is associated with anti-PD-1 efficacy in metastatic melanoma patients. *Science* 2018; **359**: 104-108 [PMID: 29302014 DOI: 10.1126/science.aao3290]
- 73 **Routy B**, Le Chatelier E, Derosa L, Duong CPM, Alou MT, Daillière R, Fluckiger A, Messaoudene M, Rauber C, Roberti MP, Fidelle M, Flament C, Poirier-Colame V, Opolon P, Klein C, Iribarren K, Mondragón L, Jacquelinot N, Qu B, Ferrere G, Clémenson C, Mezquita L, Masip JR, Naltet C, Brosseau S, Kaderbhai C, Richard C, Rizvi H, Levenez F, Galleron N, Quinquis B, Pons N, Ryffel B, Minard-Colin V, Gonin P, Soria JC, Deutsch E, Lloriot Y, Ghiringhelli F, Zalcman G, Goldwasser F, Escudier B, Hellmann MD, Eggermont A, Raoult D, Albiges L, Kroemer G, Zitvogel L. Gut microbiome influences efficacy of PD-1-based immunotherapy against epithelial tumors. *Science* 2018; **359**: 91-97 [PMID: 29097494 DOI: 10.1126/science.aan3706]
- 74 **Nishino M**, Giobbie-Hurder A, Manos MP, Bailey N, Buchbinder EI, Ott PA, Ramaiya NH, Hodi FS. Immune-Related Tumor Response Dynamics in Melanoma Patients Treated with Pembrolizumab: Identifying Markers for Clinical Outcome and Treatment Decisions. *Clin Cancer Res* 2017; **23**: 4671-4679 [PMID: 28592629 DOI: 10.1158/1078-0432.CCR-17-0114]
- 75 **Snyder A**, Makarov V, Merghoub T, Yuan J, Zaretsky JM, Desrichard A, Walsh LA, Postow MA, Wong P, Ho TS, Hollmann TJ, Bruggeman C, Kannan K, Li Y, Elipenahli C, Liu C, Harbison CT, Wang L, Ribas A, Wolchok JD, Chan TA. Genetic basis for clinical response to CTLA-4 blockade in melanoma. *N Engl J Med* 2014; **371**: 2189-2199 [PMID: 25409260 DOI: 10.1056/NEJMoa1406498]
- 76 **Hugo W**, Zaretsky JM, Sun L, Song C, Moreno BH, Hu-Lieskovan S, Berent-Maoz B, Pang J, Chmielowski B, Cherry G, Seja E, Lomeli S, Kong X, Kelley MC, Sosman JA, Johnson DB, Ribas A, Lo RS. Genomic and Transcriptomic Features of Response to Anti-PD-1 Therapy in Metastatic Melanoma. *Cell* 2016; **165**: 35-44 [PMID: 26997480 DOI: 10.1016/j.cell.2016.02.065]
- 77 **Murugesu N**, Wilson GA, Birkbak NJ, Watkins T, McGranahan N, Kumar S, Abbassi-Ghadi N, Salm M, Mitter R, Horswell S, Rowan A, Phillimore B, Biggs J, Begum S, Matthews N, Hochhauser D, Hanna GB, Swanton C. Tracking the genomic evolution of esophageal adenocarcinoma through neoadjuvant chemotherapy. *Cancer Discov* 2015; **5**: 821-831 [PMID: 26003801 DOI: 10.1158/2159-8290.CD-15-0412]

P- Reviewer: Lee JI, Lin JY, Salati M **S- Editor:** Gong ZM
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ISSN 1007-9327

