Critical Reviews in Oncology / Hematology 133 (2019) 25–32

Contents lists available at ScienceDirect

Critical Reviews in Oncology / Hematology

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

Immunotherapy in advanced gastric cancer, is it the future?

C. Coutzac[a,b], S. Pernot[a,b], N. Chaput[c,d], A. Zaanan[a,b,*]

[a] Department of Gastroenterology and Digestive Oncology, European Georges Pompidou Hospital, Assistance Publique-Hôpitaux de Paris, Paris, France
[b] Paris Descartes University, Sorbonne Paris Cité, Paris, France
[c] Gustave Roussy Cancer Campus, Laboratory of Immunomonitoring in Oncology, CNRS-UMS 3655 and INSERM-US23, Villejuif, F-94805, France
[d] University Paris-Saclay, Faculté de Pharmacie, Chatenay-Malabry, F-92296, France

ARTICLE INFO

Keywords:
Advanced gastric cancer
Immunotherapy
CTLA-4
PD-1
PD-L1

ABSTRACT

The prognosis of advanced gastric cancer remains extremely poor despite the use of standard therapies such as chemotherapy and biological agents. Blocking immune checkpoint especially programmed cell death-1 (PD-1) and its ligand (PD-L1 or B7-H1), has proven efficacy in several solid cancers, and seems to become a potential option in gastric cancer treatment. This review will focus on data describing the immune microenvironment of gastric tumors on which blocking PD-1/PD-L1 axis may have an anti-tumor efficacy. Then, the encouraging results of clinical trials evaluating anti-PD-1/PD-L1-based therapeutic strategy in first or later-line settings will be discuss. Finally, clinical outcomes according to PD-L1 expression, mismatch repair phenotype and other potential predictive biomarkers of anti-tumor response will be described. Altogether, immunotherapy seems promising in advanced gastric cancer in monotherapy or in combining strategies probably for a specific subgroup of patients who need to be better identified.

1. Introduction

Despite the development of biologic agents in the last decade, the prognosis of advanced gastric cancer remains extremely poor. In worldwide, gastric cancer is the fourth leading cause of cancer-related deaths, estimated at 723 000 deaths in 2012 (GLOBOCAN Cancer Fact Sheets: stomach Cancers, n.d). The enhancement of Helicobacter *pylori's (H. pylori)* screening and its eradication permitted to decrease the incidence of gastric cancer, whereas in parallel non-*H. pylori* related cancer are increasing, such as gastroesophageal junction (GEJ) cancer, gastric cancer related to atrophic gastritis, or signet-ring cell carcinoma (Anderson et al., 2018; Karimi et al., 2014). However, the 5-year overall survival (OS) rate of metastatic gastric adenocarcinoma is still estimated around 5–20% (Wagner et al., 2017). The management of advanced/metastatic gastric cancer in first-line treatment is based on chemotherapy regimen according to the expression of human epidermal growth factor receptor 2 (HER2) (Zaanan et al., 2018). The doublet combination of platinium salts with fluoropyrimidine is considered as a standard of care (Smyth et al., 2016). For HER2-positive advanced gastric cancer, the randomized phase III ToGA trial demonstrated a significant improvement of survival with the addition of trastuzumab (Bang et al., 2010; Yazici et al., 2016). In second-line setting, taxane (docetaxel, paclitaxel), or irinotecan are the validated therapeutic options for patients with adequate condition status (Smyth et al., 2016). More recently, two phase III trials have demonstrated that ramucirumab (anti-VEGFR2 monoclonal antibody) as single agent (Fuchs et al., 2014) or in association with paclitaxel (Wilke et al., 2014), was associated with a survival benefit. However, recent phase III randomized trials targeting epidermal growth factor receptor (EGFR) (Lordick et al., 2013; Waddell et al., 2013) or Mesenchymal and Epithelial Transition Factor (HGF)-Hepatocyte Growth Factor Receptor (MET) (Cunningham et al., 2015; Shah et al., 2015) pathways have not demonstrated efficacy in patients with advanced gastric cancer.

Concomitantly to the development of biological agents, immunotherapy has revolutionized the oncology landscape by targeting the host immune system. Blocking immune checkpoints such as cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), programmed cell death-1 (PD-1) and its ligand (PD-L1 or B7-H1), has proven efficacy in several solid cancers (Ribas and Wolchok, 2018). Immunotherapy's efficacy seems to be associated to the immune microenvironment of the tumor and its immunogenicity. Recent results suggest that targeting immune checkpoint may become a future therapeutic option in gastric cancer. This review will focus on scientific background of immune checkpoint inhibitors in advanced gastric cancer and the encouraging clinical data's for these patients.

* Corresponding author at: Department of Gastroenterology and Digestive Oncology, European Georges Pompidou Hospital, AP-HP, Paris Descartes University, Paris, France.
E-mail address: aziz.zaanan@aphp.fr (A. Zaanan).

https://doi.org/10.1016/j.critrevonc.2018.10.007
Received 8 June 2018; Received in revised form 2 September 2018; Accepted 28 October 2018

2. Immunological effects of targeting immune checkpoints

In the last decade, immunotherapy has become an important and challenging issue for anti-tumor treatments. Classically, the T cell activation needs 3 signals: (i) the interaction between the T-cell receptor (TCR) and major histocompatibility complex (MHC)/peptide; (ii) a co-stimulatory signal defined as the interaction between CD28 molecule expressed on T lymphocytes and CD80/CD86 (B7 molecules) expressed on antigen-presenting cells (APC); and (iii) implies IL-2/IL-2 receptor signaling pathway. These 3 signals lead to lymphocyte cycle progression, survival and differentiation. CTLA-4 and PD-1 are implicated in self-tolerance by limiting lymphocyte proliferation. The TCR/MHC signaling induces CTLA-4 expression on activated T cells, which is a co-inhibitory molecule that binds CD80/CD86 with higher affinity than CD28. Thus, blocking CTLA-4 induces effector T cell activation against tumor cells. PD-1 is also a co-inhibitory molecule expressed on activated T lymphocytes, especially on intra-tumoral antigen-specific $CD8^+$ T cells (Ahmadzadeh et al., 2009) and binds its ligand PD-L1 or PD-L2 expressed on immune and/or tumor cells. Tumor-intrinsic oncogenic pathways (Xu-Monette et al., 2017), IFNg released by T cell responses (Isogawa et al., 2005), gamma chain cytokines (IL-2, IL-7, and IL-15), IL-21, LPS, BCR activation, IL-10, IL-4 and granulocyte macrophage colony-stimulating factor (GM-CSF) are mechanisms involved in PD-L upregulation (Dong et al., 1999; Freeman et al., 2000; Latchman et al., 2001; Selenko-Gebauer et al., 2003). The PD-1/PD-L1 interaction induces T lymphocyte exhaustion (Barber et al., 2006), apoptosis (Deng et al., 2015) or anergy (Goldberg et al., 2007; Martin-Orozco et al., 2006, p.; Probst et al., 2005), leading to immune escape mechanism and tumor progression. Monoclonal antibodies blocking immune checkpoints such as anti-CTLA-4 (ipilimumab and tremelimuab), anti-PD-1 (nivolumab and pembrolizumab) and anti-PD-L1 (avelumab, atezolizumab, durvalumab) (Fig. 1A), have proven efficacy in melanoma (Hodi et al., 2010; Robert et al., 2011, 2015), non-small cell lung cancer (Garon et al., 2015), renal cell carcinoma (Motzer et al., 2015), recurrent squamous cell carcinoma of the head and neck (Ferris et al., 2016), Merkel cell carcinoma (Nghiem et al., 2016) and deficient mismatch repair (dMMR) colorectal and non-colorectal cancers (Le et al., 2015). Blocking immune checkpoint induces T lymphocyte activation against tumor cells by avoiding their interaction with their ligands. Nowadays, these immune checkpoint inhibitors are the most studied and used in clinical practice. Several studies have observed associations between patients clinical benefits and an increase proliferation of intra-tumoral $CD8^+$ memory T cells (Iwai et al., 2005; Ribas et al., 2016; Wong et al., 2007), T cell cytotoxicity enhancement and pro-inflammatory cytokines production by antigen-specific T cells (Simon et al., 2016) in patients with various cancer treated with these molecules. While these agents seem to be promising, their long-term efficacy concerns around 20% of patients in all types of cancers. Therefore, a better understanding of immune checkpoint blockades mechanisms is necessary to improve patients' selection and clinical benefit for these therapies.

3. Blocking PD-1/PD-L1 axis in gastric cancer: scientific basis

The immune microenvironment of tumors and especially tumor-infiltrating lymphocytes (TILs) is emerging as a prognostic and predictive factor in many solid tumors (Fridman et al., 2012). Several studies evaluated the correlation between intra-tumoral immune cells and gastric cancer prognosis (Chang et al., 2014; Kang et al., 2017a). High density of $CD3^+$, cytotoxic $CD8^+$ and memory T cells is associated with survival benefit in patients with gastric cancer (Lee et al., 2008; Wakatsuki et al., 2013). High number of intratumoral Natural Killer (NK) cells is also associated with better overall survival (Ishigami et al., 2000). In parallel, important advances have been recently made in the molecular classification of gastric cancer, establishing 4 genomic subtypes (Fig. 1B): (i) chromosomal instability (CIN; 50% of all gastric tumors), (ii) genomically stable (GS, 20%) subtype with mutation in motility and adhesion molecules, (iii) microsatellite instability tumors (MSI; 22%), and (iiii) Epstein-Barr virus positive cancers (EBV; 8%) (Cancer Genome Atlas Research Network, 2014). The subgroups of EBV positive and MSI phenotype gastric cancer characterized by a high TILs density are associated with a better cancer-specific survival compared to the other subtypes of tumors (Chiaravalli et al., 2006; Grogg et al., 2003; Kang et al., 2016, 2017a; Zhang et al., 2015). In parallel of tumor T-cell infiltration, several studies have monitored PD-L1 expression on tumor and immune cells in gastric cancer. The relationship between PD-L1 expression and prognosis is still controversial in gastric cancer. PD-L1 tumors expression is either considered as a prognosis factor of clinical benefit (Böger et al., 2016; Kawazoe et al., 2017), or conversely as a negative predictive marker (Chang et al., 2016). However, a meta-analysis showed from 15 eligible studies covering 3291 patients, that PD-L1 level was inversely correlated with the overall survival in all stage gastric cancer (Hazard Ratio, HR = 1.46 (95% CI 1.08–1.98); P = 0.01, random-effect) (Gu et al., 2017). High density of intra-tumoral or stromal $CD8^+$ T cells with high percentage of PD-L1 expression seems to be associated to a worse progression-free survival and overall survival (Thompson et al., 2017). This result suggests that not only TILs density is important, but also the balance between pro-inflammatory and immunosuppressive function in tumor microenvironment. In the same previous cited meta-analysis, PD-L1 was highly expressed in patients with deeper tumor infiltration, positive lymph-node metastasis, EBV positive and MSI tumors. Chronic EBV infection leads to produce Th1 antiviral responses by triggering the production of IFNg, which is required in anti-tumoral response. In MSI tumors, somatic mutations amplify the number of neoantigens recognized by immune cells. The density of tumor-infiltrating cytotoxic T cells is enhanced in MSI tumors compared to microsatellite-stable (MSS) cancers (Schwitalle et al., 2008). These results suggest that EBV positive and MSI phenotype gastric cancers may be suitable targets for immunotherapy owing to their important immunogenicity. Altogether, tumoral PD-L1 overexpression owing to its immunosuppressive function, seems to be associated to poor prognosis, however, it may be also a positive predictive marker of immunotherapy efficiency.

4. Checkpoint inhibitors and clinical outcomes in advanced gastric cancer

The first clinical studies have evaluated the checkpoint inhibitors after chemotherapy failure.

4.1. In second or later treatment line

- The Asian ATTRACTION 02 phase III randomized trial comparing nivolumab (anti-PD-1) to placebo in patients with unresecable advanced gastric cancer pretreated with two or more chemotherapy regimens has just been published (Kang et al., 2017b). Overall survival was significantly increased in the nivolumab group compared to the control group, with respectively a median of 5.3 and 4.1 months (HR, 0·63, 95% CI 0·51–0·78; p < 0·0001) (Table 1). Based on this trial, nivolumab was approved in Japan for the treatment of unresectable advanced or recurrent gastric cancer progressed after chemotherapy. It has to be noted that results from trials among Asian patients with gastric cancer should not be extrapolated to patients in Western countries as there are significant differences between these two populations in epidemiology, etiology, prognosis, and treatment efficacy (Kim et al., 2016).

- The KEYNOTE-059 phase II trial evaluated 3 cohorts of patients with advanced gastric and GEJ cancer. In the cohort 1, 259 patients were treated with pembrolizumab as monotherapy in third or later line of chemotherapy. The objective response rate (ORR) and disease control rate (DCR, defined as stable disease + partial response + complete response ≥ 2 months) were 12% and 27% respectively, and the median

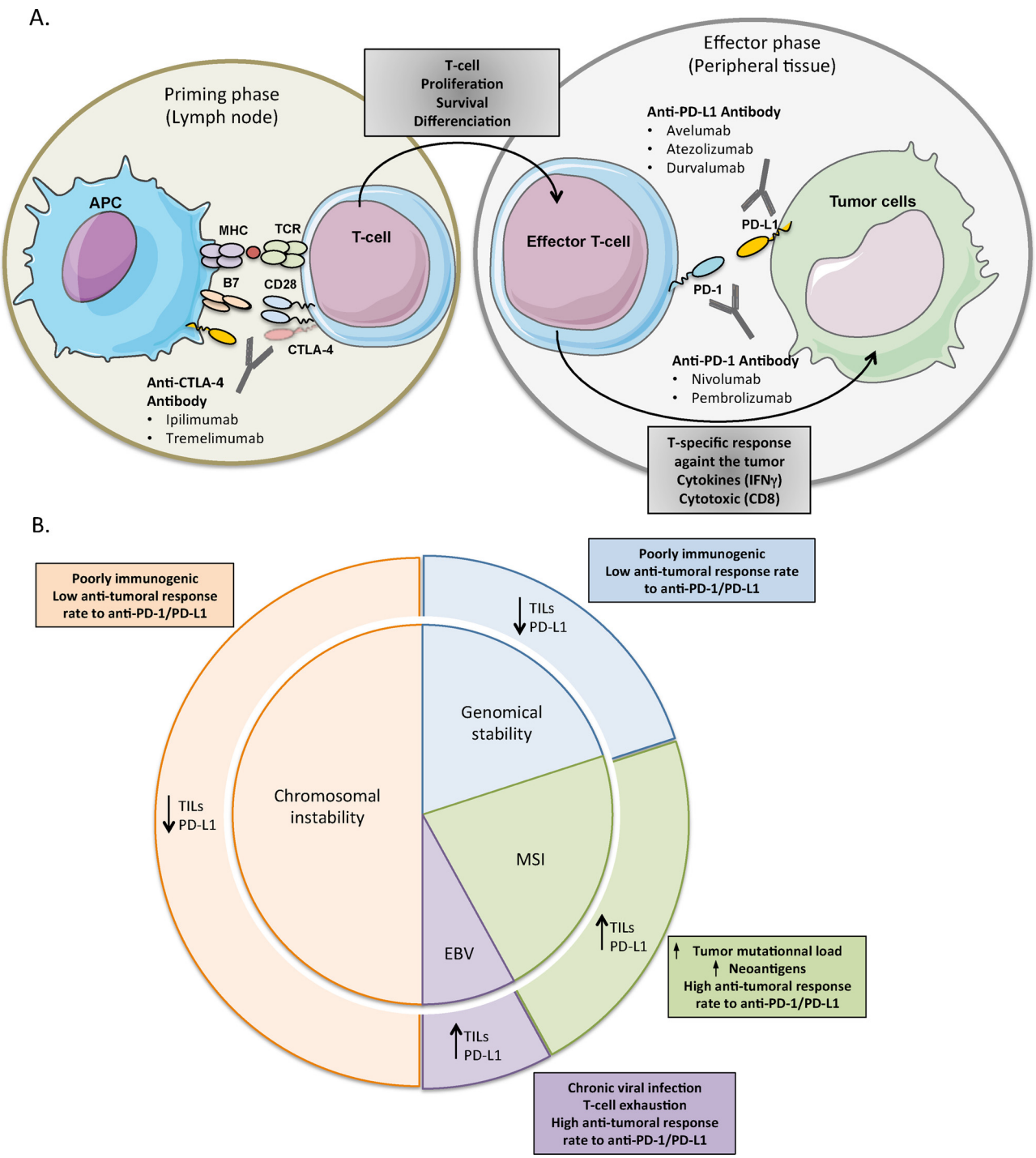

Fig. 1. A.Mechanisms of immune checkpoint blockade. Cytotoxic-T-lymphocyte-antigen 4 (CTLA-4) and programmed-death 1 are expressed on the surface of activated T cells in lymph nodes and in peripheral tissues respectively. They interact with their ligands (CD80/CD86 for CTLA-4 and PD-L1 for PD-1) on antigen-presenting cells (APC), result in tumor immune evasion. Monoclonal antibodies blocking CTLA-4, PD1 and PD-L1 restore T-cell mediated anti-tumor responses. B. Gastric cancer divided into molecular subtypes: Epstein–Barr virus (EBV)-positive (purple), microsatellite instability (MSI, green), genomically stable (GS, blue) and chromosomal instability (CIN, orange). Immunological features of molecular subtypes of tumors especially tumor-infiltrating lymphocytes (TILs) and PD-L1 expression are represented as well as their potential response to anti-PD-1/PD-L1 therapy. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

OS was 5.6 months (Fuchs et al., 2018a) (Table 1). The ORR tended to be higher in PD-L1 positive (PD-L1+ defined as "Combined Positive Score" (CPS) ≥ 1) vs PD-L1 negative (PD-L1-) (16% vs 6%). Based on results from this large early-phase trial, Food Drug Administration (FDA) approved pembrolizumab after two or more prior lines of therapy for patients whose tumor overexpressed PD-L1.

- Combination of immunotherapies is studied in the CheckMate 032 phase I/II study that included patients with advanced gastric (G)/oesophageal (E) and GEJ cancer who progressed on one or more line of chemotherapy. Three cohorts received respectively nivolumab (3 mg/kg; N3), nivolumab (1 mg/kg) plus ipilimumab (anti-CTLA-4) (3 mg/kg) (N1 + I3) and nivolumab (3 mg/kg) plus ipilimumab (1 mg/kg) (N3 + I1) (Janjigian et al., 2018) (Table 1). The objective response rate (ORR) was 12% in N3, 24% in N1 + I3, and 8% in N3 + I1. In patients

Table 1
Clinical outcomes reported in previous trials.

Trial	Drug treatment	Setting	ORR % (95% CI)	DCR % (95% CI)	PFS median months (95% CI)	OS median months (95% CI)
ATTRACTION-02 (phase III)	nivolumab vs placebo	≥ 2 L				
Nivolumab			11 (8–16)	40 (34–46)	1,6 (1,5–2,3)	5,3 (4,6–6,4)
Placebo			0 (0–3)	25 (18–34)	1,5 (1,5–1,5)	4,1 (3,4–4,9)
KEYNOTE-059 (cohort 1) (phase II)	pembrolizumab	≥ 2 L				
All Patients (n = 259)			12 (8 -17)	27 (22–33)	2,0 (2,0–2,1)	5,5 (4,2–6,5)
PD-L1 positive (n = 148)			16 (11 -23)	34 (26–42)	2,0 (2,0–2,1)	5,8 (4,4–7,8)
PD-L1 negative (n = 109)			6 (3 -13)	19 (12–28)	2,0 (1,9–2,0)	4,6 (3,2–6,5)
KEYNOTE-059 (cohort 2)	pembrolizumab + 5-FU (or capecitabine) and cisplatin	First-line				
All Patients (n = 25)			60 (39 -79)	80 (59–93)	6,6 (5,9–10,6)	13,8 (8,6–NR)
PD-L1 positive (n = 16)			69 (41 -89)	75 (48–93)	Not reported	Not reported
PD-L1 negative (n = 8)			38 (9 -76)	75 (35–97)	Not reported	Not reported
KEYNOTE-059 (cohort 3)	pembrolizumab	First-line				
All Patients (n = 31)			26 (12–45)	36 (19–55)	3,3 (2,0–6,0)	20,7 (9,2–20,7)
KEYNOTE-061	pembrolizumab vs paclitaxel	≥ 2 L				
Pembrolizumab			16 (11–22)	Not reported	1,5 (1,4–2,0)	0,1 (6,2–10,7)
Paclitaxel			14 (9–19)	Not reported	4,1 (3,1–4,2)	8,3 (7,6–9,0)
CheckMate032 (phase I/II)	nivolumab +/- ipilimumab	≥ 1L				
N3 (n = 59)			12	Not reported	1,4 (1,2–1,5)	6,2 (3,4–12,4)
N1 + I3 (n = 49)			24	Not reported	1,4 (1,2–3,8)	6,9 (3,7–11,5)
N3 + I1 (n = 52)			8	Not reported	1,6 (1,4–2,6)	4,8 (3,0–8,4)

Abbreviations: ORR: Objective response rate; DCR: disease control rate; PFS: progression free survival; OS: overall survival; CI: confidence interval; NR: not reached.5-FU: 5-fluorouracil.

with PD-L1 ≥ 1%, ORR reached 19% (3/16) in N3, 40% (4/10) in N1 + I3, and 23% (3/13) in N3 + I1 (Janjigian et al., 2018).

These results suggest that immunotherapy may be a potential option for heavily pretreated patients with advanced gastric cancer. However, these hopeful results must be balanced with the negative ones recently reported from KEYNOTE-061 phase III trial (n = 592), comparing pembrolizumab versus paclitaxel in second-line advanced gastric cancer (Shitara et al., 2018). They did not meet its primary endpoint of longer OS and PFS in patients whose tumors overexpress PD-L1 (CPS ≥ 1). In all pts, grade 3–5 drug-related AE incidence was 14.3% with pembrolizumab vs 34.8% with paclitaxel; 3.1% vs 5.4% discontinued due to drug-related AEs (Shitara et al., 2018). Similarly, the JAVELIN Gastric 300 phase III trial comparing avelumab (anti-PD-L1) versus physician's choice (irinotecan or paclitaxel) as a third-line treatment for advanced gastric or GEJ adenocarcinoma, regardless of PD-L1 expression, reported negative results in a recent publication (Bang et al., 2018). Interestingly, in post-hoc analysis of KEYNOTE-061 trial, OS was significantly improved in patients whose tumors overexpress PD-L1 CPS ≥ 10 (HR 0.64; 95% CI 0.41–1.02) (Fuchs et al., 2018b). In all these trials, it should be noted that immunochemistry (IHC) assay are not standardized. For example, in the Keynote-059 trial, PD-L1 positive tumors are defined as ≥ 1% stained tumor or stroma cells by IHC with a PD-L1 prototype assay (22C3 pharmDx assay; Agilent Technologies). In the Checkmate-032 trial, PD-L1 tumor expression was assessed using a validated automated IHC assay (Dako North America, Carpinteria, CA). Samples with more than 100 evaluable tumor cells and ≥ 1% PD-L1 staining of tumor cell membranes were considered PD-L1–positive. In the same line, several definitions of PD-L1 positive tumors are used without assessing their potential association with clinical response to PD-1 blockade therapies. The tumor proportion score (TPS) is the percentage of viable tumor cells with partial or complete membrane staining at any intensity and seems to have a limited utility. In parallel, the CPS defined as the number of PD-L1–staining cells (tumor cells, lymphocytes, and macrophages) divided by the total number of viable tumor cells, multiplied by 100, seems more robust, reproducible to identify responders to anti-PD-1 treatments. All these variabilities may explain differences in clinical outcomes related to the PD-L1 expression.

Altogether, clinical outcomes related to anti-PD-1/PD-L1 therapy are not improved in comparison with chemotherapy in later-line treatment for occidental population, and results of this comparison are not yet available in Asian population. Interestingly, different gene expression signatures related to T-cell function were described between Asian compared to non-Asian patients (Lin et al., 2015). The variability of immune microenvironment and their function may explain the different response to immunotherapy between these two populations. Upcoming trials may be helpful to enhance personalized therapeutic strategy especially between occidental and Asian population. The results of these different trials are detailed in Table 1.

4.2. In first-line treatment

In first-line setting, an ongoing Japanese phase II/III evaluates the efficacy of nivolumab plus chemotherapy (S-1 + oxaliplatin [SOX] versus capecitabine + oxaliplatin [CapeOX]) for patients with unresectable advanced or recurrent gastric or GEJ cancer (Chen et al., 2017). The cohort 2 of KEYNOTE-059 evaluated safety data and efficacy of pembrolizumab plus 5-fluorouracil (or capecitabine) and cisplatin in first-line treatment of HER2 negative advanced gastric or GEJ adenocarcinoma (Fuchs et al., 2016). The ORR was 60% in the overall population (n = 25). Three patients (12%) discontinued treatment because of chemotherapy-related adverse events while no patients discontinued treatment because of immune-related adverse events (Fuchs et al., 2016). In the cohort 3, patients with PD-L1 + G/GEJ adenocarcinoma were treated with pembrolizumab alone as a first-line treatment. The ORR was estimated at 25% (n = 31). One pembrolizumab-related death by pneumonitis was observed. These results suggest that pembrolizumab in earlier-line therapy and especially in chemotherapy combinations is a potential therapeutic option in this population of patients. These therapeutic strategies are under investigation for advanced gastric/GEJ cancer in ongoing randomized trials (Table 2).

4.3. Immunotherapy in combination with other anti-tumoral targeted agents

Pending results of phase III trials, combination of PD-1/PD-L1 and CTLA-4 blockade seem less convincing in view to clinical data from early studies in gastric cancer (Janjigian et al., 2017), conversely to

Table 2
Ongoing trials evaluating immune checkpoint inhibition in advanced gastric cancer.

Study identifier	Acronym	Phase	Drug treatment	First-line	Second-line	≥ 3 lines
NCT02625623	JAVELIN GASTRIC 300	III	avelumab			Yes
NCT03019588	KEYNOTE-063	III	pembrolizumab versus paclitaxel (Asian)		Yes	Yes
NCT03342417		II	ipilimumab + nivolumab		Yes	Yes
NCT02689284		I/II	margetuximab + pembrolizumab		Yes	Yes
NCT02572687		I	durvalumab + ramucirumab		Yes	Yes
NCT02935634	FRACTION-GC	II	nivolumab + ipilimumab or relatlimab		Yes	Yes
NCT02864381		II	nivolumab + Andecaliximab vs nivolumab		Yes	Yes
NCT02734004	MEDIOLA	I/II	durvalumab + olaparib	Yes	Yes	Yes
NCT02494583	KEYNOTE-062	III	pembrolizumab vs pembrolizumab + 5FU + Cisplatin vs 5FU + cisplatin	Yes		
NCT02625610	JAVELIN 100	III	avelumab after FOLFOX	Yes		
NCT02872116	CheckMate 649	III	ipilimumab + nivolumab vs chemotherapy + nivolumab	Yes		
NCT03382600	KEYNOTE-659	II	pembrolizumab +(TS-1 + cisplatin) or (TS-1 + oxaliplatin)	Yes		
NCT03409848	INTEGA	II	(nivolumab + trastuzumab) + FOLFOX vs ipilimumab	Yes		

Abbreviations: 5FU: 5-fluorouracil.

other solid tumors (Hammers et al., 2017; Hellmann et al., 2017). Several trials assessing the efficacy of immune checkpoint inhibitors are currently ongoing enrolling chemo-naïve as well as chemotherapy-refractory patients with advanced gastric cancer (Table 2). Most of all evaluate anti-PD-1 (pembrolizumab, nivolumab) or anti-PD-L1 (avelumab, durvalumab) in combination with either chemotherapy or other immunotherapy such as anti-CTLA-4 (ipilimumab), LAG-3 (anti-lymphocyte activation gene-3) inhibitor (relatlimab) and Matrix metalloproteinase-9 (MMP-9) inhibitors (Andecaliximab). In HER2 positive tumor, the INTEGA phase II trial challenges immunotherapy with first-line chemotherapy in patients receiving trastuzumab. However, the combination of these drugs increases the incidence of immune-related adverse events (IrAE), which is the main limitation for these combinations. In patients with metastatic melanoma, 65% of patients develop grade III-IV IrAE with the combination of anti-PD-1 and anti-CTLA-4, while it is estimated around 15% with PD-1/PD-L1 blockade as monotherapy, and 22 to 25% with anti-CTLA-4. In patients with gastric and GEJ cancer receiving immune checkpoint as monotherapy, the incidences of grade III-IV IrAE were similar. Immune-related adverse events most commonly involve the gastrointestinal tract, lungs, endocrine glands, skin, and liver sites. Less often, the central nervous system and cardiovascular, pulmonary, musculoskeletal, and hematologic systems are involved (Postow et al., 2018). As described in trials evaluating immunotherapy in advanced gastric cancer, all of them report manageable and consistent safety with that previous data.

5. Biomarkers of check point inhibitor efficacy in gastric cancer

PD-L1 expression on tumors cells is a potential marker for predicting patient response to anti-PD-1/PD-L1 agents. Several studies have assessed clinical outcomes according to PD-L1 expression status.

In the cohort 1 of KEYNOTE 059 study (pembrolizumab as monotherapy in L3 or later), as mentioned above, the ORR and DCR were respectively estimated at 16% and 33% in PD-L1 + tumors, versus 6% and 19% in PD-L1- tumors (Fuchs et al., 2018a). In the cohort 2 of KEYNOTE 059 study (pembrolizumab plus 5FU and cisplatin in L1), the ORR was 73% in PD-L1 + (n = 16), and 38% in PD-L1- (n = 8) tumors (Fuchs et al., 2016). In pretreated patients from the Checkmate-032 study, patients with PD-L1 ≥ 1%, the ORR was better in PD-L1 + (CPS ≥ 1%) (19% in N3, 40% in N1 + I3, and 23% in N3 + I1) than in PD-L1- tumors (CPS < 1%) (12%, 22%, and 0%, respectively) (Janjigian et al., 2017). Conversely, in KEYNOTE-061 and JAVELIN GASTRIC 300 studies, no clinical improvement was observed in PD-L1 positive tumors. The main limitations of PD-L1 expression are i) the absence of standard thresholds considered to be overexpressed, ii) in most cases, PD-L1 expression is evaluated at a single time-point that may underestimate its predictive value and, iii) the lack of standardisation of the assays used to evaluate PD-L1 expression (Hansen and Siu, 2016). For all these reasons, the predictive value of PD-L1 expression still needs to be validated in prospective trials.

Other fields of research are being developed such as the clinical benefit of immune checkpoint inhibitors in patients with MSI solid cancer (Le et al., 2015). Indeed, MSI cancers are characterized by a large number of mutation-associated neoantigens encoded by tumors cells (Dolcetti et al., 1999; Lengauer et al., 1998). These neoantigens are recognized by immune cells which enhance the accumulation of intraepithelial activated cytotoxic $CD8^+$ T lymphocytes (Maby et al., 2015; Schwitalle et al., 2008). In gastric cancer, dMMR tumors represent around 20% of patients. Recently, deficiency mismatch repair (dMMR) was shown to predict clinical response of solid tumors to pembrolizumab (Le et al., 2015, 2017). Among the 86 chemotherapy-refractory patients with MSI solid tumors (including 5 patients with gastric cancer), the ORR and complete response rate were 53% and 21% respectively (Le et al., 2017). The authors demonstrated *in vivo* the expansion of neoantigen-specific T cell clones that were reactive to tumor's mutant neopeptides. These observations support the hypothesis that mismatch repair deficient phenotype might be considered as a predictive marker for immune checkpoint blockade efficacy. Since 2017, pembrolizumab was approved by FDA for the treatment of patients with unresectable or metastatic MSI or dMMR solid tumors that have progressed after prior treatment and who have no satisfactory alternative treatment options, as well as for patients with MSI or dMMR colorectal cancer following progression on a fluoropyrimidine, oxaliplatin, and irinotecan. In patients with advanced gastric cancer included the cohort 1 of KEYNOTE-059, the ORR and the DCR were respectively 57% and 71% in MSI tumors (n = 7), versus 9% and 22% in non-MSI tumors (n = 167) (Fuchs et al., 2018a). The MMR status seems to be a helpful tool to better select patients who benefit from immunotherapy. Ongoing studies are evaluating immunotherapy in patients with non-colorectal MSI tumors, including advanced gastric cancer (AcSé nivolumab NCT03012581).

In parallel, EBV-positive cancers (around 10% of gastric cancer) are also enriched in cytotoxic T lymphocytes (Kuzushima et al., 1999; Shibata et al., 1991). As known, EBV is associated to several malignant diseases such as Hodgkin's lymphomas and nasopharyngeal carcinomas. Monoclonal antibodies blocking PD-1/PD-L1 axis have improved OS in these cancers localizations (Ansell et al., 2015; Ferris et al., 2016) suggesting that virus-induced cancer may be more sensitive to immunotherapy provided that an increased benefit is found in the subgroup of EBV patients, which has never been reported to date. Despite the absence of studies evaluating clinical outcomes of immunotherapy in patients with EBV-positive tumors, this criterion appears to be very interesting to select patient for this treatment. Altogether, it may be a breakthrough to systematically evaluate clinical outcomes of immunotherapy according to the cancer genome atlas subtypes, especially for MSI and EBV status.

Finally, *H. pylori* status has been poorly assessed in the different trials evaluating clinical outcomes of immunotherapy in advanced gastric cancer. *H. pylori* infection induces important innate and adaptive immune responses leading to chronic inflammation and gastric cancer occurs in only 1 to 3% of patients infected by *H.* pylori. However, despite these immune responses, the host is unable to achieve bacterial eradication. Early reports have suggested an impaired T-cell response to *H.* pylori (Paziak-Domańska et al., 2000). Previous studies demonstrated that gastric epithelial cells (GEC) function as Antigen Presenting cells (APC) by expressing constitutively MHC class II (Ye et al., 1997). Interestingly, *H. pylori* infection induces up-regulation of costimulatory molecules (CD86 and CD80) among GEC (Ye et al., 1997). *in vitro*, PD-1 is increased among GEC after *H. pylori* infection and is involved in immunosuppressive functions of T cells, which may contribute to carcinogenesis (Das et al., 2006). Evidence from small studies observed an up-regulation of PD-1 and PD-L1 in human *H. pylori*-related gastric carcinoma (Lu et al., 2011). These preliminary results need further investigations but suggest that *H. pylori*-related cancer may be a potential target for immune checkpoint blockade.

6. Conclusion

Although scientific background such as TILs density and PD-L1 expression, seem to be in favor of PD-1/PD-L1 blockade in gastric adenocarcinoma, more clinical outcomes are needed to change therapeutic strategy. Indeed, anti-PD-1 treatment seems promising compared to placebo in heavily pretreated patients with gastric cancer ($\geq$ 2 lines), and was approved in Japan. However in this setting, when compared to chemotherapy, anti-PD-1 therapy failed to show benefit in phase III trials. Ongoing randomized trials will be shortly available to confirm (or not) immunotherapy as a validated therapeutic option in advanced gastric cancer, especially in earlier-line strategy. Moreover, research concerning the tumor microenvironment and the influence of immunotherapy on its modulation are mandatory to better select patients who will benefit from these therapeutics. PD-L1 expression, MSI phenotype, EBV status appears to be interesting predictive biomarkers and must be improved and validated in prospective studies. In the same way, clinical responses to immunotherapy must now be evaluated according to molecular classification in order to improve personalized patient management. Finally, promising results on the efficacy and the safety of combination of immunotherapies with each other's and/or with chemotherapy in several solid tumors are available. Further investigations are ongoing to evaluate these settings in gastric cancer.

Conflicts of interest

C. Coutzac reports honoria from AMGEN. N. Chaput reports scientific grants from Cytune Pharma, GSK, Sanofi, and participated in advisor board for AstraZeneca; Sanofi and AstraZeneca lecture fee. S. Pernot reports honoria from AMGEN and Sanofi. Dr Zaanan has participated in consulting or/and advisory boards for Merck Serono, Amgen, Roche, Sanofi and Lilly.

References

Ahmadzadeh, M., Johnson, L.A., Heemskerk, B., Wunderlich, J.R., Dudley, M.E., White, D.E., Rosenberg, S.A., 2009. Tumor antigen-specific CD8 T cells infiltrating the tumor express high levels of PD-1 and are functionally impaired. Blood 114, 1537–1544. https://doi.org/10.1182/blood-2008-12-195792.

Anderson, W.F., Rabkin, C.S., Turner, N., Fraumeni, J., Joseph, F., Rosenberg, P.S., Camargo, M.C., 2018. The changing face of noncardia gastric cancer incidence among US non-Hispanic Whites. JNCI: J. Natl. Cancer Inst. https://doi.org/10.1093/jnci/djx262. djx262-djx262.

Ansell, S.M., Lesokhin, A.M., Borrello, I., Halwani, A., Scott, E.C., Gutierrez, M., Schuster, S.J., Millenson, M.M., Cattry, D., Freeman, G.J., Rodig, S.J., Chapuy, B., Ligon, A.H., Zhu, L., Grosso, J.F., Kim, S.Y., Timmerman, J.M., Shipp, M.A., Armand, P., 2015. PD-1 blockade with nivolumab in relapsed or refractory Hodgkin's lymphoma. N. Engl. J. Med. 372, 311–319. https://doi.org/10.1056/NEJMoa1411087.

Bang, Y.-J., Ruiz, E.Y., Van Cutsem, E., Lee, K.-W., Wyrwicz, L., Schenker, M., Alsina, M., Ryu, M.-H., Chung, H.-C., Evesque, L., Al-Batran, S.-E., Park, S.H., Lichinitser, M., Boku, N., Moehler, M.H., Hong, J., Xiong, H., Hallwachs, R., Conti, I., Taieb, J., 2018. Phase 3, randomised trial of avelumab versus physician's choice of chemotherapy as third-line treatment for patients with advanced gastric or gastro-oesophageal junction cancer: primary analysis of JAVELIN Gastric 300. Ann. Oncol. https://doi.org/10.1093/annonc/mdy264.

Bang, Y.-J., Van Cutsem, E., Feyereislova, A., Chung, H.C., Shen, L., Sawaki, A., Lordick, F., Ohtsu, A., Omuro, Y., Satoh, T., Aprile, G., Kulikov, E., Hill, J., Lehle, M., Rüschoff, J., Kang, Y.-K., ToGA Trial Investigators, 2010. 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, 687–697. https://doi.org/10.1016/S0140-6736(10)61121-X.

Barber, D.L., Wherry, E.J., Masopust, D., Zhu, B., Allison, J.P., Sharpe, A.H., Freeman, G.J., Ahmed, R., 2006. Restoring function in exhausted CD8 T cells during chronic viral infection. Nature 439, 682–687. https://doi.org/10.1038/nature04444.

Böger, C., Behrens, H.-M., Mathiak, M., Krüger, S., Kalthoff, H., Röcken, C., 2016. PD-L1 is an independent prognostic predictor in gastric cancer of Western patients. Oncotarget 7, 24269–24283. https://doi.org/10.18632/oncotarget.8169.

Cancer Genome Atlas Research Network, 2014. Comprehensive molecular characterization of gastric adenocarcinoma. Nature 513, 202–209. https://doi.org/10.1038/nature13480.

Chang, H., Jung, W.Y., Kang, Y., Lee, H., Kim, A., Kim, H.K., Shin, B.K., Kim, B.-H., 2016. Programmed death-ligand 1 expression in gastric adenocarcinoma is a poor prognostic factor in a high CD8+ tumor infiltrating lymphocytes group. Oncotarget 7, 80426–80434. https://doi.org/10.18632/oncotarget.12603.

Chang, W.-J., Du, Y., Zhao, X., Ma, L.-Y., Cao, G.-W., 2014. Inflammation-related factors predicting prognosis of gastric cancer. World J. Gastroenterol. 20, 4586–4596. https://doi.org/10.3748/wjg.v20.i16.4586.

Chen, L., Kang, Y., Tanimoto, M., Boku, N., n.d, 2017. ATTRACTION-04 (ONO-4538-37): a randomized, multicenter, phase 2/3 study of Nivolumab (Nivo) Plus chemotherapy in Patients (Pts) with previously untreated unresectable advanced or recurrent gastric/gastroesophageal junction cancer. Ann. Oncol. 28 (suppl_5), v209–v268. https://doi.org/10.1093/annonc/mdx369.

Chiaravalli, A.M., Feltri, M., Bertolini, V., Bagnoli, E., Furlan, D., Cerutti, R., Novario, R., Capella, C., 2006. Intratumour T cells, their activation status and survival in gastric carcinomas characterised for microsatellite instability and Epstein-Barr virus infection. Virchows Arch. 448, 344–353. https://doi.org/10.1007/s00428-005-0066-4.

Cunningham, D., Tebbutt, N.C., Davidenko, I., Murad, A.M., Al-Batran, S.-E., Ilson, D.H., Tjulandin, S., Gotovkin, E., Karaszewska, B., Bondarenko, I., Tejani, M.A., Udrea, A.A., Tehfe, M.A., Baker, N., Oliner, K.S., Zhang, Y., Hoang, T., Sidhu, R., Catenacci, D.V.T., 2015. Phase III, randomized, double-blind, multicenter, placebo (P)-controlled trial of rilotumumab (R) plus epirubicin, cisplatin and capecitabine (ECX) as first-line therapy in patients (pts) with advanced MET-positive (pos) gastric or gastroesophageal junction (G/GEJ) cancer: RILOMET-1 study. JCO 33, 4000. https://doi.org/10.1200/jco.2015.33.15_suppl.4000.

Das, S., Suarez, G., Beswick, E.J., Sierra, J.C., Graham, D.Y., Reyes, V.E., 2006. Expression of B7-H1 on gastric epithelial cells: its potential role in regulating t cells during Helicobacter pylori infection. J. Immunol. 176, 3000–3009. https://doi.org/10.4049/jimmunol.176.5.3000.

Deng, R., Cassady, K., Li, X., Yao, S., Zhang, M., Racine, J., Lin, J., Chen, L., Zeng, D., 2015. B7H1/CD80 interaction augments PD-1-dependent T cell apoptosis and ameliorates graft-versus-host disease. J. Immunol. 194, 560–574. https://doi.org/10.4049/jimmunol.1402157.

Dolcetti, R., Viel, A., Doglioni, C., Russo, A., Guidoboni, M., Capozzi, E., Vecchiato, N., Macrì, E., Fornasarig, M., Boiocchi, M., 1999. High prevalence of activated intraepithelial cytotoxic t lymphocytes and increased neoplastic cell apoptosis in colorectal carcinomas with microsatellite instability. Am. J. Pathol. 154, 1805–1813. https://doi.org/10.1016/S0002-9440(10)65436-3.

Dong, H., Zhu, G., Tamada, K., Chen, L., 1999. B7-H1, a third member of the B7 family, co-stimulates T-cell proliferation and interleukin-10 secretion. Nat. Med. 5, 1365–1369. https://doi.org/10.1038/70932.

Ferris, R.L., Blumenschein, G.J., Fayette, J., Guigay, J., Colevas, A.D., Licitra, L., Harrington, K., Kasper, S., Vokes, E.E., Even, C., Worden, F., Saba, N.F., Iglesias Docampo, L.C., Haddad, R., Rordorf, T., Kiyota, N., Tahara, M., Monga, M., Lynch, M., Geese, W.J., Kopit, J., Shaw, J.W., Gillison, M.L., 2016. Nivolumab for recurrent squamous-cell carcinoma of the head and neck. N. Engl. J. Med. https://doi.org/10.1056/NEJMoa1602252. 0, null.

Freeman, G.J., Long, A.J., Iwai, Y., Bourque, K., Chernova, T., Nishimura, H., Fitz, L.J., Malenkovich, N., Okazaki, T., Byrne, M.C., Horton, H.F., Fouser, L., Carter, L., Ling, V., Bowman, M.R., Carreno, B.M., Collins, M., Wood, C.R., Honjo, T., 2000. Engagement of the PD-1 immunoinhibitory receptor by a novel B7 family member leads to negative regulation of lymphocyte activation. J. Exp. Med. 192, 1027–1034.

Fridman, W.H., Pagès, F., Sautès-Fridman, C., Galon, J., 2012. The immune contexture in human tumours: impact on clinical outcome. Nat. Rev. Cancer 12, 298–306. https://doi.org/10.1038/nrc3245.

Fuchs, C.S., Doi, T., Jang, R.W., Muro, K., Satoh, T., Machado, M., Sun, W., Jalal, S.I., Shah, M.A., Metges, J.-P., Garrido, M., Golan, T., Mandala, M., Wainberg, Z.A., Catenacci, D.V., Ohtsu, A., Shitara, K., Geva, R., Bleeker, J., Ko, A.H., Ku, G., Philip, P., Enzinger, P.C., Bang, Y.-J., Levitan, D., Wang, J., Rosales, M., Dalal, R.P., Yoon, H.H., 2018a. 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. https://doi.org/10.1001/jamaoncol.2018.0013.

Fuchs, C.S., Ohtsu, A., Tabernero, J., Van Cutsem, E., Wang, J.D., Lam, B., Dalal, R., Koshiji, M., Bang, Y.-J., 2016. Preliminary safety data from KEYNOTE-059:

pembrolizumab plus 5-fluorouracil (5-FU) and cisplatin for first-line treatment of advanced gastric cancer. JCO 34, 4037. https://doi.org/10.1200/JCO.2016.34.15_suppl.4037.

Fuchs, C.S., Ozguroglu, M., Bang, Y.-J., Di Bartolomeo, M., Mandala, M., Ryu, M.-H., Fornaro, L., Olesiński, T., Caglevic, C., Chung, H.C., Muro, K., Goekkurt, E., Mansoor, W., McDermott, R.S., Shacham-Shmueli, E., Chen, X., Kang, S.P., Mayo, C.A., Ohtsu, A., Shitara, K., 2018b. Pembrolizumab (pembro) vs paclitaxel (PTX) for previously treated advanced gastric or gastroesophageal junction (G/GEJ) cancer: phase 3 KEYNOTE-061 trial. JCO 36, 4062. https://doi.org/10.1200/JCO.2018.36.15_suppl.4062.

Fuchs, C.S., Tomasek, J., Yong, C.J., Dumitru, F., Passalacqua, R., Goswami, C., Safran, H., Dos Santos, L.V., Aprile, G., Ferry, D.R., Melichar, B., Tehfe, M., Topuzov, E., Zalcberg, J.R., Chau, I., Campbell, W., Sivanandan, C., Pikiel, J., Koshiji, M., Hsu, Y., Liepa, A.M., Gao, L., Schwartz, J.D., Tabernero, J., REGARD Trial Investigators, 2014. Ramucirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (REGARD): an international, randomised, multicentre, placebo-controlled, phase 3 trial. Lancet 383, 31–39. https://doi.org/10.1016/S0140-6736(13)61719-5.

Garon, E.B., Rizvi, N.A., Hui, R., Leighl, N., Balmanoukian, A.S., Eder, J.P., Patnaik, A., Aggarwal, C., Gubens, M., Horn, L., Carcereny, E., Ahn, M.-J., Felip, E., Lee, J.-S., Hellmann, M.D., Hamid, O., Goldman, J.W., Soria, J.-C., Dolled-Filhart, M., Rutledge, R.Z., Zhang, J., Lunceford, J.K., Rangwala, R., Lubiniecki, G.M., Roach, C., Emancipator, K., Gandhi, L., 2015. Pembrolizumab for the treatment of non-small-cell lung cancer. KEYNOTE-001 Investigators. N. Engl. J. Med. 372, 2018–2028. https://doi.org/10.1056/NEJMoa1501824.

GLOBOCAN Cancer Fact Sheets: stomach Cancers [WWW Document], n.d. URL http://globocan.iarc.fr/old/FactSheets/cancers/stomach-new.asp (Accessed 12.29.17).

Goldberg, M.V., Maris, C.H., Hipkiss, E.L., Flies, A.S., Zhen, L., Tuder, R.M., Grosso, J.F., Harris, T.J., Getnet, D., Whartenby, K.A., Brockstedt, D.G., Dubensky, T.W., Chen, L., Pardoll, D.M., Drake, C.G., 2007. Role of PD-1 and its ligand, B7-H1, in early fate decisions of CD8 T cells. Blood 110, 186–192. https://doi.org/10.1182/blood-2006-12-062422.

Grogg, K.L., Lohse, C.M., Pankratz, V.S., Halling, K.C., Smyrk, T.C., 2003. Lymphocyte-rich gastric cancer: associations with Epstein-Barr virus, microsatellite instability, histology, and survival. Mod. Pathol. 16, 641–651. https://doi.org/10.1097/01.MP.0000076980.73826.C0.

Gu, L., Chen, M., Guo, D., Zhu, H., Zhang, W., Pan, J., Zhong, X., Li, X., Qian, H., Wang, X., 2017. PD-L1 and gastric cancer prognosis: a systematic review and meta-analysis. PLoS One 12https://doi.org/10.1371/journal.pone.0182692. e0182692.

Hammers, H.J., Plimack, E.R., Infante, J.R., Rini, B.I., McDermott, D.F., Lewis, L.D., Voss, M.H., Sharma, P., Pal, S.K., Razak, A.R.A., Kollmannsberger, C., Heng, D.Y.C., Spratlin, J., McHenry, M.B., Amin, A., 2017. Safety and efficacy of nivolumab in combination with ipilimumab in metastatic renal cell carcinoma: the CheckMate 016 study. JCO 35, 3851–3858. https://doi.org/10.1200/JCO.2016.72.1985.

Hansen, A.R., Siu, L.L., 2016. PD-L1 testing in cancer: challenges in companion diagnostic development. JAMA Oncol. 2, 15–16. https://doi.org/10.1001/jamaoncol.2015.4685.

Hellmann, M.D., Rizvi, N.A., Goldman, J.W., Gettinger, S.N., Borghaei, H., Brahmer, J.R., Ready, N.E., Gerber, D.E., Chow, L.Q., Juergens, R.A., Shepherd, F.A., Laurie, S.A., Geese, W.J., Agrawal, S., Young, T.C., Li, X., Antonia, S.J., 2017. Nivolumab plus ipilimumab as first-line treatment for advanced non-small-cell lung cancer (CheckMate 012): results of an open-label, phase 1, multicohort study. Lancet Oncol. 18, 31–41. https://doi.org/10.1016/S1470-2045(16)30624-6.

Hodi, F.S., O'Day, S.J., McDermott, D.F., Weber, R.W., Sosman, J.A., Haanen, J.B., Gonzalez, R., Robert, C., Schadendorf, D., Hassel, J.C., Akerley, W., van den Eertwegh, A.J.M., Lutzky, J., Lorigan, P., Vaubel, J.M., Linette, G.P., Hogg, D., Ottensmeier, C.H., Lebbé, C., Peschel, C., Quirt, I., Clark, J.I., Wolchok, J.D., Weber, J.S., Tian, J., Yellin, M.J., Nichol, G.M., Hoos, A., Urba, W.J., 2010. Improved survival with ipilimumab in patients with metastatic melanoma. N. Engl. J. Med. 363, 711–723. https://doi.org/10.1056/NEJMoa1003466.

Ishigami, S., Natsugoe, S., Tokuda, K., Nakajo, A., Che, X., Iwashige, H., Aridome, K., Hokita, S., Aikou, T., 2000. Prognostic value of intratumoral natural killer cells in gastric carcinoma. Cancer 88, 577–583.

Isogawa, M., Furuichi, Y., Chisari, F.V., 2005. Oscillating CD8(+) T cell effector functions after antigen recognition in the liver. Immunity 23, 53–63. https://doi.org/10.1016/j.immuni.2005.05.005.

Iwai, Y., Terawaki, S., Honjo, T., 2005. PD-1 blockade inhibits hematogenous spread of poorly immunogenic tumor cells by enhanced recruitment of effector T cells. Int. Immunol. 17, 133–144. https://doi.org/10.1093/intimm/dxh194.

Janjigian, Y.Y., Bendell, J., Calvo, E., Kim, J.W., Ascierto, P.A., Sharma, P., Ott, P.A., Peltola, K., Jaeger, D., Evans, J., de Braud, F., Chau, I., Harbison, C.T., Dorange, C., Tschaika, M., Le, D.T., 2018. CheckMate-032 study: efficacy and safety of nivolumab and nivolumab plus ipilimumab in patients with metastatic esophagogastric Cancer. J. Clin. Oncol. https://doi.org/10.1200/JCO.2017.76.6212. JCO2017766212.

Janjigian, Y.Y., Ott, P.A., Calvo, E., Kim, J.W., Ascierto, P.A., Sharma, P., Peltola, K.J., Jaeger, D., Evans, T.R.J., De Braud, F.G., Chau, I., Tschaika, M., Harbison, C.T., Cai, W., Bendell, J.C., Le, D.T., 2017. Nivolumab ± ipilimumab in pts with advanced (adv)/metastatic chemotherapy-refractory (CTx-R) gastric (G), esophageal (E), or gastroesophageal junction (GEJ) cancer: CheckMate 032 study. JCO 35, 4014. https://doi.org/10.1200/JCO.2017.35.15_suppl.4014.

Kang, B.W., Kim, J.G., Lee, I.H., Bae, H.I., Seo, A.N., 2017a. Clinical significance of tumor-infiltrating lymphocytes for gastric cancer in the era of immunology. World J. Gastrointest. Oncol. 9, 293–299. https://doi.org/10.4251/wjgo.v9.i7.293.

Kang, B.W., Seo, A.N., Yoon, S., Bae, H.I., Jeon, S.W., Kwon, O.K., Chung, H.Y., Yu, W., Kang, H., Kim, J.G., 2016. Prognostic value of tumor-infiltrating lymphocytes in Epstein-Barr virus-associated gastric cancer. Ann. Oncol. 27, 494–501. https://doi.org/10.1093/annonc/mdv610.

Kang, Y.-K., Boku, N., Satoh, T., Ryu, M.-H., Chao, Y., Kato, K., Chung, H.C., Chen, J.-S., Muro, K., Kang, W.K., Yeh, K.-H., Yoshikawa, T., Oh, S.C., Bai, L.-Y., Tamura, T., Lee, K.-W., Hamamoto, Y., Kim, J.G., Chin, K., Oh, D.-Y., Minashi, K., Cho, J.Y., Tsuda, M., Chen, L.-T., 2017b. Nivolumab in patients with advanced gastric or gastro-oesophageal junction cancer refractory to, or intolerant of, at least two previous chemotherapy regimens (ONO-4538-12, ATTRACTION-2): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 390, 2461–2471. https://doi.org/10.1016/S0140-6736(17)31827-5.

Karimi, P., Islami, F., Anandasabapathy, S., Freedman, N.D., Kamangar, F., 2014. Gastric Cancer: descriptive epidemiology, risk factors, screening, and prevention. Cancer Epidemiol. Biomark. Prev. 23, 700–713. https://doi.org/10.1158/1055-9965.EPI-13-1057.

Kawazoe, A., Kuwata, T., Kuboki, Y., Shitara, K., Nagatsuma, A.K., Aizawa, M., Yoshino, T., Doi, T., Ohtsu, A., Ochiai, A., 2017. 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 20, 407–415. https://doi.org/10.1007/s10120-016-0631-3.

Kim, Y.-W., Joo, J., Yoon, H.M., Eom, B.W., Ryu, K.W., Choi, I.J., Kook, M.C., Schuhmacher, C., Siewert, J.R., Reim, D., 2016. Different survival outcomes after curative R0-resection for Eastern Asian and European gastric cancer: results from a propensity score matched analysis comparing a Korean and a German specialized center. Medicine (Baltimore) 95, e4261. https://doi.org/10.1097/MD.0000000000004261.

Kuzushima, K., Nakamura, S., Nakamura, T., Yamamura, Y., Yokoyama, N., Fujita, M., Kiyono, T., Tsurumi, T., 1999. Increased frequency of antigen-specific CD8+ cytotoxic T lymphocytes infiltrating an Epstein-Barr virus–associated gastric carcinoma. J. Clin. Invest. 104, 163–171.

Latchman, Y., Wood, C.R., Chernova, T., Chaudhary, D., Borde, M., Chernova, I., Iwai, Y., Long, A.J., Brown, J.A., Nunes, R., Greenfield, E.A., Bourque, K., Boussiotis, V.A., Carter, L.L., Carreno, B.M., Malenkovich, N., Nishimura, H., Okazaki, T., Honjo, T., Sharpe, A.H., Freeman, G.J., 2001. PD-L2 is a second ligand for PD-1 and inhibits T cell activation. Nat. Immunol. 2, 261–268. https://doi.org/10.1038/85330.

Le, D.T., Durham, J.N., Smith, K.N., Wang, H., Bartlett, B.R., Aulakh, L.K., Lu, S., Kemberling, H., Wilt, C., Luber, B.S., Wong, F., Azad, N.S., Rucki, A.A., Laheru, D., Donehower, R., Zaheer, A., Fisher, G.A., Crocenzi, T.S., Lee, J.J., Greten, T.F., Duffy, A.G., Ciombor, K.K., Eyring, A.D., Lam, B.H., Joe, A., Kang, S.P., Holdhoff, M., Danilova, L., Cope, L., Meyer, C., Zhou, S., Goldberg, R.M., Armstrong, D.K., Bever, K.M., Fader, A.N., Taube, J., Housseau, F., Spetzler, D., Xiao, N., Pardoll, D.M., Papadopoulos, N., Kinzler, K.W., Eshleman, J.R., Vogelstein, B., Anders, R.A., Diaz, L.A., 2017. Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. Science 357, 409–413. https://doi.org/10.1126/science.aan6733.

Le, D.T., Uram, J.N., Wang, H., Bartlett, B.R., Kemberling, H., Eyring, A.D., Skora, A.D., Luber, B.S., Azad, N.S., Laheru, D., Biedrzycki, B., Donehower, R.C., Zaheer, A., Fisher, G.A., Crocenzi, T.S., Lee, J.J., Duffy, S.M., Goldberg, R.M., de la Chapelle, A., Koshiji, M., Bhaijee, F., Huebner, T., Hruban, R.H., Wood, L.D., Cuka, N., Pardoll, D.M., Papadopoulos, N., Kinzler, K.W., Zhou, S., Cornish, T.C., Taube, J.M., Anders, R.A., Eshleman, J.R., Vogelstein, B., Diaz, L.A., 2015. PD-1 blockade in tumors with mismatch-repair deficiency. New Engl. J. Med. 372, 2509–2520. https://doi.org/10.1056/NEJMoa1500596.

Lee, H.E., Chae, S.W., Lee, Y.J., Kim, M.A., Lee, H.S., Lee, B.L., Kim, W.H., 2008. Prognostic implications of type and density of tumour-infiltrating lymphocytes in gastric cancer. Br. J. Cancer 99, 1704–1711. https://doi.org/10.1038/sj.bjc.6604738.

Lengauer, C., Kinzler, K.W., Vogelstein, B., 1998. Genetic instabilities in human cancers. Nature 396, 643–649. https://doi.org/10.1038/25292.

Lin, S.J., Gagnon-Bartsch, J.A., Tan, I.B., Earle, S., Ruff, L., Pettinger, K., Ylstra, B., van Grieken, N., Rha, S.Y., Chung, H.C., Lee, J.-S., Cheong, J.H., Noh, S.H., Aoyama, T., Miyagi, Y., Tsuburaya, A., Yoshikawa, T., Ajani, J.A., Boussioutas, A., Yeoh, K.G., Yong, W.P., So, J., Lee, J., Kang, W.K., Kim, S., Kameda, Y., Arai, T., Zur Hausen, A., Speed, T.P., Grabsch, H.I., Tan, P., 2015. Signatures of tumour immunity distinguish Asian and non-Asian gastric adenocarcinomas. Gut 64, 1721–1731. https://doi.org/10.1136/gutjnl-2014-308252.

Lordick, F., Kang, Y.-K., Chung, H.-C., Salman, P., Oh, S.C., Bodoky, G., Kurteva, G., Volovat, C., Moiseyenko, V.M., Gorbunova, V., Park, J.O., Sawaki, A., Celik, I., Götte, H., Melezínková, H., Moehler, M., Arbeitsgemeinschaft Internistische Onkologie and EXPAND Investigators, 2013. Capecitabine and cisplatin with or without cetuximab for patients with previously untreated advanced gastric cancer (EXPAND): a randomised, open-label phase 3 trial. Lancet Oncol. 14, 490–499. https://doi.org/10.1016/S1470-2045(13)70102-5.

Lu, B., Chen, L., Liu, L., Zhu, Y., Wu, C., Jiang, J., Zhang, X., 2011. T-cell-mediated tumor immune surveillance and expression of B7 co-inhibitory molecules in cancers of the upper gastrointestinal tract. Immunol. Res. 50, 269–275. https://doi.org/10.1007/s12026-011-8227-9.

Maby, P., Tougeron, D., Hamieh, M., Mlecnik, B., Kora, H., Bindea, G., Angell, H.K., Fredriksen, T., Elie, N., Fauquembergue, E., Drouet, A., Leprince, J., Benichou, J., Mauillon, J., Pessot, F.L., Sesboüé, R., Tuech, J.-J., Sabourin, J.-C., Michel, P., Frébourg, T., Galon, J., Latouche, J.-B., 2015. Correlation between density of CD8+ T-cell infiltrate in microsatellite unstable colorectal cancers and frameshift mutations: a rationale for personalized immunotherapy. Cancer Res. 75, 3446–3455. https://doi.org/10.1158/0008-5472.CAN-14-3051.

Martin-Orozco, N., Wang, Y.-H., Yagita, H., Dong, C., 2006. Cutting Edge: programmed death (PD) ligand-1/PD-1 interaction is required for CD8+ T cell tolerance to tissue antigens. J. Immunol. 177, 8291–8295.

Motzer, R.J., Escudier, B., McDermott, D.F., George, S., Hammers, H.J., Srinivas, S., Tykodi, S.S., Sosman, J.A., Procopio, G., Plimack, E.R., Castellano, D., Choueiri, T.K.,

Gurney, H., Donskov, F., Bono, P., Wagstaff, J., Gauler, T.C., Ueda, T., Tomita, Y., Schutz, F.A., Kollmannsberger, C., Larkin, J., Ravaud, A., Simon, J.S., Xu, L.-A., Waxman, I.M., Sharma, P., 2015. Nivolumab versus everolimus in advanced renal-cell carcinoma. CheckMate 025 Investigators. New Engl. J. Med. 373, 1803–1813. https://doi.org/10.1056/NEJMoa1510665.

Nghiem, P.T., Bhatia, S., Lipson, E.J., Kudchadkar, R.R., Miller, N.J., Annamalai, L., Berry, S., Chartash, E.K., Daud, A., Fling, S.P., Friedlander, P.A., Kluger, H.M., Kohrt, H.E., Lundgren, L., Margolin, K., Mitchell, A., Olencki, T., Pardoll, D.M., Reddy, S.A., Shantha, E.M., Sharfman, W.H., Sharon, E., Shemanski, L.R., Shinohara, M.M., Sunshine, J.C., Taube, J.M., Thompson, J.A., Townson, S.M., Yearley, J.H., Topalian, S.L., Cheever, M.A., 2016. PD-1 blockade with pembrolizumab in advanced merkel-cell carcinoma. New Engl. J. Med. 374, 2542–2552. https://doi.org/10.1056/NEJMoa1603702.

Paziak-Domańska, B., Chmiela, M., Jarosińska, A., Rudnicka, W., 2000. Potential role of CagA in the inhibition of t cell reactivity in Helicobacter pylori infections. Cell. Immunol. 202, 136–139. https://doi.org/10.1006/cimm.2000.1654.

Postow, M.A., Sidlow, R., Hellmann, M.D., 2018. Immune-related adverse events associated with immune checkpoint blockade. New Engl. J. Med. 378, 158–168. https://doi.org/10.1056/NEJMra1703481.

Probst, H.C., McCoy, K., Okazaki, T., Honjo, T., van den Broek, M., 2005. Resting dendritic cells induce peripheral CD8+ T cell tolerance through PD-1 and CTLA-4. Nat. Immunol. 6, 280–286. https://doi.org/10.1038/ni1165.

Ribas, A., Shin, D.S., Zaretsky, J., Frederiksen, J., Cornish, A., Avramis, E., Seja, E., Kivork, C., Siebert, J., Kaplan-Lefko, P., Wang, X., Chmielowski, B., Glaspy, J.A., Tumeh, P.C., Chodon, T., Pe'er, D., Comin-Anduix, B., 2016. PD-1 blockade expands intratumoral memory t cells. Cancer Immunol. Res. 4, 194–203. https://doi.org/10.1158/2326-6066.CIR-15-0210.

Ribas, A., Wolchok, J.D., 2018. Cancer immunotherapy using checkpoint blockade. Science 359, 1350–1355. https://doi.org/10.1126/science.aar4060.

Robert, C., Schachter, J., Long, G.V., Arance, A., Grob, J.J., Mortier, L., Daud, A., Carlino, M.S., McNeil, C., Lotem, M., Larkin, J., Lorigan, P., Neyns, B., Blank, C.U., Hamid, O., Mateus, C., Shapira-Frommer, R., Kosh, M., Zhou, H., Ibrahim, N., Ebbinghaus, S., Ribas, A., 2015. Pembrolizumab versus ipilimumab in advanced melanoma. KEYNOTE-006 investigators. New Engl. J. Med. 372, 2521–2532. https://doi.org/10.1056/NEJMoa1503093.

Robert, C., Thomas, L., Bondarenko, I., O'Day, S., M D, J.W., Garbe, C., Lebbe, C., Baurain, J.-F., Testori, A., Grob, J.-J., Davidson, N., Richards, J., Maio, M., Hauschild, A., Miller Jr, W.H., Gascon, P., Lotem, M., Harmankaya, K., Ibrahim, R., Francis, S., Chen, T.-T., Humphrey, R., Hoos, A., Wolchok, J.D., 2011. Ipilimumab plus dacarbazine for previously untreated metastatic melanoma. New Engl. J. Med. 364, 2517–2526. https://doi.org/10.1056/NEJMoa1104621.

Schwitalle, Y., Kloor, M., Eiermann, S., Linnebacher, M., Kienle, P., Knaebel, H.P., Tariverdian, M., Benner, A., von Knebel Doeberitz, M., 2008. Immune response against frameshift-induced neopeptides in HNPCC patients and healthy HNPCC mutation carriers. Gastroenterology 134, 988–997. https://doi.org/10.1053/j.gastro.2008.01.015.

Selenko-Gebauer, N., Majdic, O., Szekeres, A., Höfler, G., Guthann, E., Korthäuer, U., Zlabinger, G., Steinberger, P., Pickl, W.F., Stockinger, H., Knapp, W., Stöckl, J., 2003. B7-H1 (programmed death-1 ligand) on dendritic cells is involved in the induction and maintenance of T cell anergy. J. Immunol. 170, 3637–3644.

Shah, M.A., Bang, Y.-J., Lordick, F., Tabernero, J., Chen, M., Hack, S.P., Phan, S.-C., Shames, D.S., Cunningham, D., 2015. METGastric: a phase III study of onartuzumab plus mFOLFOX6 in patients with metastatic HER2-negative (HER2-) and MET-positive (MET+) adenocarcinoma of the stomach or gastroesophageal junction (GEC). JCO 33, 4012. https://doi.org/10.1200/jco.2015.33.15_suppl.4012.

Shibata, D., Tokunaga, M., Uemura, Y., Sato, E., Tanaka, S., Weiss, L.M., 1991. Association of Epstein-Barr virus with undifferentiated gastric carcinomas with intense lymphoid infiltration. Lymphoepithelioma-like carcinoma. Am. J. Pathol. 139, 469–474.

Shitara, K., Özgüroğlu, M., Bang, Y.-J., Bartolomeo, M.D., Mandalà, M., Ryu, M.-H., Fornaro, L., Olesiński, T., Caglevic, C., Chung, H.C., Muro, K., Goekkurt, E., Mansoor, W., McDermott, R.S., Shacham-Shmueli, E., Chen, X., Mayo, C., Kang, S.P., Ohtsu, A., Fuchs, C.S., Lerzo, G., O'Connor, J.M., Mendez, G.A., Lynam, J., Tebbutt, N., Wong, M., Strickland, A., Karapetis, C., Goldstein, D., Vasey, P., Laethem, J.-L.V., Cutsem, E.V., Berry, S., Vincent, M., Muller, B., Rey, F., Zambrano, A., Guerra, J., Krogh, M., Baeksgaard, L., Yilmaz, M., Elme, A., Magi, A., Auvinen, P., Alanko, T., Moehler, M., Kunzmann, V., Seufferlein, T., Thuss-Patience, P., Goekkurt, E., Hoehler, T., Haag, G., Al-Batran, S.-E., Castro, H., Lopez, K., Vasquez, M.A., Sandoval, M., Lam, K.O., Cuffe, S., Kelly, C., Geva, R., Shacham-Shmueli, E., Hubert, A., Beny, A., Brenner, B., Giuseppe, A., Falcone, A., Maiello, E., Passalacqua, R., Montesarchio, V., Hara, H., Chin, K., Nishina, T., Komatsu, Y., Machida, N., Hironaka, S., Satoh, T., Tamura, T., Sugimoto, N., Cho, H., Omuro, Y., Kato, K., Goto, M., Hyodo, I., Yoshida, K., Baba, H., Esaki, T., Furuse, J., Mohammed, W.Z.W., Hernandez, C.H., Garcia, J.C., Andrade, A.D., Clarke, K., Hjortland, G., Glenjen, N., Kubiatowski, T., Jacek, J., Wojtukiewicz, M., Lazarev, S., Lancukhay, Y., Afanasayev, S., Moiseyenko, V., Kostorov, V., Protsenko, S., Shirinkin, V., Sakaeva, D., Fadeeva, N., Yong, W.P., Ng, C.H.M., Robertson, B., Rapaport, B., Cohen, G., Dreosti, L., Ruff, P., Jacobs, C., Landers, G., Szpak, W., Roh, S.-Y., Lee, J., Kim, Y.H., Bang, Y.-J., Chung, H.C., Ryu, M.-H., Maqueda, M.A., Munoz, F.L., Aguilar, A.C., Aguilar, E.A., Alfonso, P.G., Rivera, F., Batle, J.F., Cid, R.P., Yeh, K.-H., Chen, J.-S., Chao, Y., Yen, C.-J., Özgüroğlu, M., Kara, O., Yalcin, S., Hochhauser, D., Chau, I., Benson, A., Shankaran, V., Shaib, W., Philip, P., Sharma, V., Siegel, R., Sun, W., Wainberg, Z., George, B., Bullock, A., Myrick, S., Faruol, J., Siegel, R., Larson, T., Becerra, C., Ratnam, S., Richards, D.A., Riche, S.L., 2018. 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, 123–133. https://doi.org/10.1016/S0140-6736(18)31257-1.

Simon, S., Vignard, V., Florenceau, L., Dreno, B., Khammari, A., Lang, F., Labarriere, N., 2016. PD-1 expression conditions T cell avidity within an antigen-specific repertoire. Oncoimmunology 5, e1104448. https://doi.org/10.1080/2162402X.2015.1104448.

Smyth, E.C., Verheij, M., Allum, W., Cunningham, D., Cervantes, A., Arnold, D., ESMO Guidelines Committee, 2016. Gastric cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann. Oncol. 27, v38–v49. https://doi.org/10.1093/annonc/mdw350.

Thompson, E.D., Zahurak, M., Murphy, A., Cornish, T., Cuka, N., Abdelfatah, E., Yang, S., Duncan, M., Ahuja, N., Taube, J.M., Anders, R.A., Kelly, R.J., 2017. Patterns of PD-L1 expression and CD8 T cell infiltration in gastric adenocarcinomas and associated immune stroma. Gut 66, 794–801. https://doi.org/10.1136/gutjnl-2015-310839.

Waddell, T., Chau, I., Cunningham, D., Gonzalez, D., Okines, A.F.C., Frances, A., Okines, C., Wotherspoon, A., Saffery, C., Middleton, G., Wadsley, J., Ferry, D., Mansoor, W., Crosby, T., Coxon, F., Smith, D., Waters, J., Iveson, T., Falk, S., Slater, S., Peckitt, C., Barbachano, Y., 2013. Epirubicin, oxaliplatin, and capecitabine with or without panitumumab for patients with previously untreated advanced oesophagogastric cancer (REAL3): a randomised, open-label phase 3 trial. Lancet Oncol. 14, 481–489. https://doi.org/10.1016/S1470-2045(13)70096-2.

Wagner, A.D., Syn, N.L., Moehler, M., Grothe, W., Yong, W.P., Tai, B.-C., Ho, J., Unverzagt, S., 2017. Chemotherapy for advanced gastric cancer. Cochrane Database Syst. Rev. 8https://doi.org/10.1002/14651858.CD004064.pub4. CD004064.

Wakatsuki, K., Sho, M., Yamato, I., Takayama, T., Matsumoto, S., Tanaka, T., Migita, K., Ito, M., Hotta, K., Nakajima, Y., 2013. Clinical impact of tumor-infiltrating CD45RO^{+} memory T cells on human gastric cancer. Oncol. Rep. 29, 1756–1762. https://doi.org/10.3892/or.2013.2302.

Wilke, H., Muro, K., Van Cutsem, E., Oh, S.-C., Bodoky, G., Shimada, Y., Hironaka, S., Sugimoto, N., Lipatov, O., Kim, T.-Y., Cunningham, D., Rougier, P., Komatsu, Y., Ajani, J., Emig, M., Carlesi, R., Ferry, D., Chandrawansa, K., Schwartz, J.D., Ohtsu, A., RAINBOW Study Group, 2014. 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, 1224–1235. https://doi.org/10.1016/S1470-2045(14)70420-6.

Wong, R.M., Scotland, R.R., Lau, R.L., Wang, C., Korman, A.J., Kast, W.M., Weber, J.S., 2007. Programmed death-1 blockade enhances expansion and functional capacity of human melanoma antigen-specific CTLs. Int. Immunol. 19, 1223–1234. https://doi.org/10.1093/intimm/dxm091.

Xu-Monette, Z.Y., Zhang, M., Li, J., Young, K.H., 2017. PD-1/PD-L1 blockade: have we found the key to unleash the antitumor immune response? Front. Immunol. 8. https://doi.org/10.3389/fimmu.2017.01597.

Yazici, O., Sendur, M.A.N., Ozdemir, N., Aksoy, S., 2016. Targeted therapies in gastric cancer and future perspectives. World J. Gastroenterol. 22, 471–489. https://doi.org/10.3748/wjg.v22.i2.471.

Ye, G., Barrera, C., Fan, X., Gourley, W.K., Crowe, S.E., Ernst, P.B., Reyes, V.E., 1997. Expression of B7-1 and B7-2 costimulatory molecules by human gastric epithelial cells: potential role in CD4+ T cell activation during Helicobacter pylori infection. J. Clin. Invest. 99, 1628–1636. https://doi.org/10.1172/JCI119325.

Zaanan, A., Bouché, O., Benhaim, L., Buecher, B., Chapelle, N., Dubreuil, O., Fares, N., Granger, V., Lefort, C., Gagniere, J., Meilleroux, J., Baumann, A.-S., Vendrely, V., Ducreux, M., Michel, P., National de Cancérologie, Thésaurus, Digestive (TNCD), 2018. Gastric cancer: french intergroup clinical practice guidelines for diagnosis, treatments and follow-up (SNFGE, FFCD, GERCOR, UNICANCER, SFCD, SFED, SFRO). Dig. Liver Dis. 50, 768–779. https://doi.org/10.1016/j.dld.2018.04.025.

Zhang, L., Qiu, M., Jin, Y., Ji, J., Li, B., Wang, X., Yan, S., Xu, R., Yang, D., 2015. Programmed cell death ligand 1 (PD-L1) expression on gastric cancer and its relationship with clinicopathologic factors. Int. J. Clin. Exp. Pathol. 8, 11084–11091.