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Immunotherapy in Esophagogastric Adenocarcinoma

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Abstract
Immunotherapy, particular PD-1/L1 inhibition, is a relevant treatment approach in esophagogastric adenocarcinoma. To date, single-agent activity is limited to the chemotherapy refractory setting and molecularly defined subgroups. Currently, ongoing trials, which are likely to relevantly change the landscape of treatment for this disease in the next years, evaluate different combination approaches with chemotherapy and/or molecular targeted agents in different disease settings. The German AIO study group has launched several combination trials in the perioperative, first-line, and advanced disease setting to further define the role of immunotherapy in esophagogastric adenocarcinoma.

Introduction

Immunotherapy has changed the treatment landscape in a variety of tumors, particularly in lung, head and neck, bladder, and renal cancer and melanoma. In gastrointestinal cancer, immunotherapy with PD-1/L1 inhibitors has demonstrated relevant efficacy in patients with high mutational burden detected by the underlying mechanism, the loss of mismatch repair enzymes (deficient mismatch repair [dMMR]), or its surrogate microsatellite instability (MSI-H) but only limited single-agent efficacy in biomarker unselected esophagogastric adenocarcinoma (EGA). This review summarizes the currently available data on immunotherapy in EGA based on clinical data fully published (PubMed) or presented at ASCO (Annual Meeting, Gastrointestinal Cancers Meeting) and ESMO (Annual Symposium, World Congress on Gastrointestinal Cancer) for the years 2015–2018.

Single-Agent PD-1/L1 or CTLA-4 Inhibitors

Previously Untreated Locally Advanced/Metastatic (First-Line Setting)

To date, there are only very few data on single-agent PD-1/L1 inhibitors in first-line setting for EGA. In a small cohort of the KEYNOTE (KN) 059 trial, including 31 patients, half of them Asian, all PD-L1 positive and HER-2 negative, the overall response rate (ORR) with pembrolizumab was 26% [1]. This approach was continued as one of the three study arms in KN 062 comparing single-agent pembrolizumab alone or in combination with platinum/fluoropyrimidine chemotherapy versus chemotherapy alone. The trial has completed recruitment and results are awaited in 2019 (refer to Table 1).

Maintenance after First-Line Platinum/Fluoropyrimidine

The concept of switch maintenance was initially evaluated in a randomized phase II trial comparing ipilimumab at 10 mg/kg with best supportive care after at least stable disease with first-line platinum/fluoropyrimidine chemotherapy [2]. With 114 patients randomized 1:1,

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Table 1. Ongoing phase II/III trial for esophagogastric adenocarcinoma including immunotherapy

Setting	Trial	Patients	Treatment
Perioperative	**DANTE/FLOT 8**	**295**	**FLOT ± atezolizumab**
	KN 585	860	FP + cisplatin/FLOT + pembrolizumab or placebo
Adjuvant	CM 844	700	S1 or CAPOX ± nivolumab
Postoperative after CRT	CM 577	760	Nivolumab vs. placebo
First line			
HER2 negative			
PD-L1 >1 (CPS)	KN 062	764	FP + cisplatin ± pembrolizumab vs. pembrolizumab singe agent
PD-L1 independent	**MOONLIGHT**	**118**	**FOLFOX ± nivolumab/ipilimumab**
	CM 649	2,005	FP + oxaliplatin ± nivolumab vs. nivolumab/ipilimumab
	KN 859	780	FP + platin + pembrolizumab or placebo
HER2 positive	**INTEGA**	**97**	**FOLFOX + trastuzumab + nivolumab vs. trastuzumab + nivolumab + ipilimumab**
	KN 811	732	FP + platin + trastuzumab + pembrolizumab or placebo
First line maintenance	JAVELIN 100	499	FP + oxaliplatin (12 weeks) followed by continuation of chemotherapy vs. avelumab
Second line	**RAP**	**59**	**Ramucirumab, avelumab, paclitaxel**

AIO-run trials are highlighted in bold. FLOT, 5FU/leucovorin, oxaliplatin, docetaxel; FOLFOX, 5FU/leucovorin, oxaliplatin; FP, fluoropyrimidine; KN, KEYNOTE; CM, CheckMate.

immune-related progression-free survival was numerically inferior with ipilimumab (HR 1.44, $p = 0.097$), but overall survival (OS) was similar. Data on maintenance with avelumab after first-line chemotherapy is available from an uncontrolled phase IB cohort with 89 patients showing modest ORR of 9% and a disease control rate of 57% [3]. The phase III Javelin GASTRIC 100 trial has completed recruitment and will provide comparative efficacy data on continuation of chemotherapy versus avelumab maintenance.

Advanced Disease (Second-/Third-Line Setting)

There are several single arm trials or cohorts from phase IB trials available on the efficacy of PD-1/L1 inhibitors in the advanced EGA setting with ORR about 12% in the unselected population and about 15–22% in PD-L1-positive patients [3–6]. Rarely, higher response rates in very small cohorts are reported (40%, 2 out of 5 patients) [7].

The phase III ATTRACTION 02 trial comparing nivolumab to placebo in patients with at least two prior therapies for EGA in a 2:1 randomized, double-blind setting demonstrated improved OS (5.3 vs. 4.1 months; HR = 0.63 [95% CI 0.51–0.78], $p < 0.0001$) and ORR 11 versus 0% ORR in favor of nivolumab [8]. The 12-month survival rate was 10.9% with placebo and 26.2% with nivolumab, which is clinically relevant. In subgroup analyses, the efficacy was shown independent of PD-L1 status (in tumor cells), Lauren classification, or location.

Two very recent trials, JAVELIN Gastric 300 and KN 061, were not able to demonstrate significantly better efficacy in comparison with active treatment in third line (JAVELIN) or second line (KN 061). In JAVELIN Gastric 300, 371 patients independent of PD-L1 status were randomized between avelumab versus chemotherapy with paclitaxel or irinotecan [9]. There was no difference in OS, with a HR of 1.1 (95% CI 0.9–1.4). However, in the PD-L1 (tumor proportion score), positive subgroups OS curves seem to cross earlier, thus indicating some predictive role of PD-L1. In the phase III KN 061, 592 patients (with 66% PD-L1 positive according to the combined positivity score [CPS]; $n = 395$) were randomized between pembrolizumab or placebo (inclusion of PD-L1-negative patients was limited to one-third) [10]. Regarding the primary endpoint, improvement in OS in the CPS >1 population, the trial was negative, with a HR of 0.82 (95% CI 0.66–1.02), still numerically favoring the pembrolizumab arm. In the exploratory post hoc subgroup of patients with CPS >10 (18% of this patient population), HR was 0.64 (95% CI 0.41–1.02), favoring the treatment with pembrolizumab with clearly separating OS curves. Thus, CPS >10 might be the relevant biomarker in second line to detect patients who may have a better outcome with single-agent pembrolizumab compared to chemotherapy. This finding in KN 061 is supported by the recent presentation of the KN 181 comparing pembrolizumab with taxanes or irinotecan in second-line EGA or squamous cell esophageal carcinoma, showing a significant

OS benefit in esophageal cancer with CPS >10 (HR 0.69; 95% CI 0.52–0.93) [26]. Notably, the squamous cell carcinoma and the overall cohort was not positive regarding the hierarchical primary OS endpoint (HR 0.78 and HR 0.89, respectively).

Combination Regimen Including PD-1/L1 and/or CTLA-4 Inhibitors

Combination with Chemotherapy

First-line combination data are available for pembrolizumab and nivolumab both with fluoropyrimidine and platinum. In one cohort of the KN 059 trial including 25 PD-L1-positive patients, a 60% ORR and an estimated 1-year OS rate of 55% were reported for the addition of pembrolizumab to 5FU/cisplatin [11]. In addition, preliminary results of the phase II/III ATTRACTION-04 trial provided interim feasibility and efficacy data for nivolumab in combination with oxaliplatin and S-1 (tegafur-gimeracil-oteracil) or capecitabine, with an ORR of 67 and 71%, respectively [12].

In the further-line setting, the combination of nivolumab and ipilimumab was evaluated in the CheckMate (CM) 032 trial with different dosages of nivolumab and ipilimumab (Nivo 1 mg/kg and Ipi 3 mg/kg or Nivo 3 mg/kg and Ipi 1 mg/kg) in 49 or 52 patients that had received ≥1 prior therapy, resulting in an ORR of 24 or 8% and 1-year OS rate of 35 or 24%, respectively [6].

Different approaches – PD-1/L1 inhibitors alone or combined with anti-CTLA-4 and chemotherapy with anti-PD-L1 alone or combined with anti CTLA-4 – are currently evaluated in randomized trials in different settings. The combination of pembrolizumab with platinum/fluoropyrimidine-containing CTx compared to pembrolizumab single agent is studied in a PD-L1-positive (CPS) population (KN 062) and has completed recruitment, with results awaited in 2019. The corresponding nivolumab trial is conducted in an PD-L1 all-comer first-line population, although again OS in PD-L1-positive patients serves as primary endpoint (CM 649) [13]. The second experimental arm in CM 649 evaluates the combination of nivolumab-ipilimumab but was recently stopped, whereas the randomization into chemotherapy ± nivolumab continued. The MOONLIGHT trial by the AIO study group currently investigates a 4-drug combination with 5FU/oxaliplatin (FOLFOX) with or without nivolumab and low-dose ipilimumab (1 mg/kg every 6 weeks) (NCT03647969).

Further combination trials are ongoing in the adjuvant setting (Table 1), assessing the addition of PD-1/L1 to either perioperative treatment with fluoropyrimidine/platinum ± docetaxel (KN 585) or in the pure adjuvant setting to S1 or capecitabine/oxaliplatin (CM 844). The German AIO group currently runs the DANTE/FLOT 8 trial assessing the addition of atezolizumab to the FLOT regimen.

Combination with Targeted Agents/Antibodies

HER2-Positive Disease

The standard treatment in HER2-positive disease remains first-line trastuzumab in combination with fluoropyrimidine and platinum [14]. In contrast to metastatic breast cancer, the addition or the sequence with further HER2-targeting agents (pertuzumab and trastuzumab-emtansine) was not successful [15, 16].

Based on preclinical data, the combination of HER2-targeting agents and PD-1/L1 inhibition seems to be synergistic [17]. Early clinical data of the combination of an HER2-targeting Fc-optimized antibody (margetuximab) with pembrolizumab in EGA patients after prior trastuzumab showed an ORR of 18% [18].

The German AIO currently conducts the randomized phase II INTEGA trial comparing the combination of trastuzumab, nivolumab, and ipilimumab (chemotherapy-free arm) versus FOLFOX, trastuzumab, and nivolumab (NCT03409848). In addition, a large phase III trial investigates the addition of pembrolizumab to chemotherapy and trastuzumab (KN 811).

Antiangiogenesis

The efficacy of antiangiogenic agents in EGA is clearly established in the advanced disease setting with ramucirumab as single agent or in combination with paclitaxel [19, 20]. Preliminary data of ramucirumab and pembrolizumab in treatment-naïve and previously treated patients has shown feasibility and modest efficacy of the combination, with a disease control rate of 68 and 46% in untreated and previously treated patients, respectively [21, 22]. Based on these data, the further development of this combination is warranted, with one potential approach applied in the AIO RAP trial investigating the combination of ramucirumab, avelumab, and paclitaxel in second-line EGA patients (EudraCT: 2018-002938-20).

Biomarkers for Checkpoint Inhibition in EGA

PD-L1 status, as mentioned above, determined by the CPS seems to be a predictor for PD-1 inhibitor benefit compared to chemotherapy in second-line EGA [10]. In the refractory setting with PD-1 inhibitor compared to best supportive care (ATTRACTION 02 trial), the predictive effect of PD-L1 was limited, although the hazard ratio was numerically better in the PD-L1 (tumor cells) >1 subgroup (HR 0.51) compared to the PD-L1 ≤1 subgroup (HR 0.72) [23].

Furthermore, dMMR or MSI-H is highly relevant for prediction of efficacy in EGA, similar to other tumor types [24]. Although limited by the small patient numbers, patients with dMMR/MSI-H tumors treated with nivolumab showed an ORR of 57% (n = 7) compared to 9% in pMMR/MSS patients (n = 167) in the ATTRACTION 02 trial. In a subgroup of 27 MSI-H patients treated in KN 61 either with pembrolizumab or paclitaxel, ORR was 47% versus 17%, respectively [10].

Beside dMMR/MSI-H and PD-L1 positivity by CPS, EBV plays a highly predictive role in determining response to PD-1 inhibitors in EGA [25]. However, particularly EBV status and, to a lesser extent, dMMR/MSI-H status are largely overlapping with PD-L1 positivity according to CPS score. Further biomarkers, e.g., immune signatures, are currently under investigation.

Conclusion

Checkpoint inhibition is a relevant treatment approach in EGA, although at the moment limited to the chemotherapy-refractory setting and molecularly defined subgroups if applied as single agent. There is a huge amount of clinical trials currently investigating immunotherapy in different settings and combinations, likely resulting in the expanded application in EGA.

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