short review

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ASCO 2021–Gastroesophageal tumor highlights

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Summary The oncological community witnessed several practice-changing clinical reports in this years' annual congress of the American Society of Clinical Oncology (ASCO). Many immunotherapeutic agents were shown to be beneficial for upper gastrointestinal tumors. For advanced squamous cell carcinoma, immunotherapy and chemotherapy combinations revealed by the CheckMate 648 and ESCORT-1st trials have been implemented into the clinical practice. The updates on the CheckMate 649 and CheckMate 577 trials again underlined the significant clinical contribution of nivolumab in advanced and localized gastroesophageal cancer, respectively. However, this effect seems to be dependent to PD-L1 expression. Not only immunotherapy trials, but also targeted therapy studies such as the FIGHT trial investigating the anti-FGFR2b monoclonal antibody bemarituzumab attracted huge interest, not only due to extension of survival in experimental group, but also due to the innovative design of this trial. This review summarizes the highlights regarding gastroesophageal tumors at the ASCO 2021 congress.

Keywords Esophageal cancer · Gastroesophageal cancer · Gastric cancer · Immunotherapy · Targeted therapy

Introduction

The annual congress of American Society of Clinical Oncology (ASCO) took place again in a virtual format. Although trials concerning immunotherapy were in the majority, targeted therapy data including Keynote-811 and FIGHT studies were also presented. This short review aims to summarize some practice-changing abstracts of gastroesophageal tumors presented at the ASCO 2021 congress and give a future perspective of how the data might be implemented in clinical daily practice (Fig. 1).

Esophagus and gastroesophageal junction (GEJ) cancer

Esophageal cancer (EC) has been one of the diseases in oncology where hardly any treatment advances had been made until 2019. The first data of the Keynote-181 trial was presented in 2019, which changed, at least in the USA, the second-line treatment strategy of PD-L1-positive patients with esophageal squamous cell cancer (ESCC) [1]. This opened the door for various immunotherapy compounds in different settings of esophageal cancer.

The CheckMate 648 study randomly assigned 970 patients with unresectable advanced, recurrent, or metastatic ESCC to the following arms [2]: nivolumab 240 mg q2w+chemotherapy with fluorouracil (800 mg/m^2 daily, between days 1–5) and cisplatin (80 mg/m^2 at day 1) q4w; [2] nivolumab at 3 mg/kg q2w plus ipilimumab at 1 mg/kg q6w; or [3] chemotherapy alone (same schedule as first arm). The coprimary endpoints were overall survival (OS) and progression-free survival (PFS) in patients with tumor cell PD-L1 expression (tumor proportion score, TPS) ≥ 1%. This group had a highly statistically significant improvement in OS with nivolumab + chemotherapy treatment versus chemotherapy alone, 15.4 vs. 9.1 months, (hazard ratio [HR] = 0.54; 99.5% confidence interval [CI] = 0.37–0.80; $p < 0.0001$). A significant survival benefit was demonstrated for the nivolumab + ipilimumab arm versus chemotherapy alone; however the numerical OS rates were lower and there

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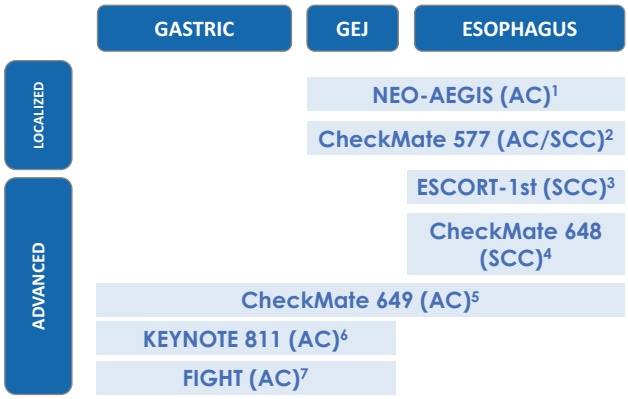

Fig. 1 Highlighted abstracts concerning gastroesophageal tumors at the ASCO 2021 meeting. Abstracts, which were not mentioned within the text were also included. *GEJ* gastroesophageal junction. [1]Reynolds JV, ASCO 2021, Abstract No: 4004, [2]Kelly RJ, ASCO 2021, Abstract No: 4003, [3]Xu RH, ASCO 2021, Abstract No: 4000, [4]Chau I, ASCO 2021, Abstract No: 4001, [5]Moehler MH, ASCO 2021, Abstract No: 4002, [6]Janjigian YY, ASCO 2021, Abstract no: 4013, [7]Catenacci DVT, ASCO 2021, Abstract No: 4010

has been a cross-over of the survival curves after 6 months of treatment indicating rapid progressing patients under nivolumab + ipilimumab treatment (OS = 13.2 vs 10.7 months; HR = 0.64; 99.5% CI = 0.46–0.90; $p = 0.001$). According to subgroup analysis, patients with negative TPS seemed to benefit from immunotherapy + chemotherapy, albeit to a lesser extent. Therefore, further investigations, including combined positive score (CPS) analysis, will provide us more information on appropriate patient selection. Furthermore, cross-over of the survival curves for nivolumab + ipilimumab arm raised critical concern, which definitely needs further explanation regarding which patients particularly progressed early under this chemotherapy-free regimen. With the available data, it is justified to suggest that nivolumab + chemotherapy is a safe and relevant option for the first-line treatment of patients with advanced or metastatic ESCC and TPS ≥ 1%.

There have also been highlights in resectable EC. In the CheckMate 577 trial [3], nivolumab demonstrated a significant and clinically meaningful improvement in disease-free survival (DFS; primary endpoint) vs placebo (22.4 vs 11.0 months; HR = 0.69; 96.4% CI = 0.56–0.86; $p = 0.0003$) and was well tolerated in patients with resected (R0) stage II/III EC/GEJC who received neoadjuvant chemoradiotherapy and had residual pathologic disease. In the ASCO congress, updated survival analyses with regard to distant metastasis-free survival (DMFS) and PFS2 were demonstrated. Median DMFS was 28.3 vs 17.6 months with nivolumab vs placebo (HR = 0.74; 95% CI = 0.60–0.92). Median PFS2 was not reached with nivolumab vs 32.1 months with placebo (HR = 0.77; 95% CI = 0.60–0.99). The US Food and Drug Administration (FDA) already approved nivolumab as adjuvant treatment for patients with resected EC/GEJC who received neoadjuvant CRT with residual pathologic disease both for adenocarcinoma and SCC patients.

Table 1 Pathological data and adverse events of chemotherapy and chemoradiotherapy arms of the NEO-AEGIS study

	Arm A (MAGIC/FLOT) [%]	Arm B (CROSS) [%]
R0 (negative margins)	82	95
ypN0	44.5	60.1
Tumor regression grade 1&2	12.1	41.7
Pathologic complete response	5	16
Neutropenia (Grade 3/4)	14.1	2.8
Neutropenic sepsis	2.7	0.6
Postoperative in-hospital deaths	3	3
Postoperative pneumonia/ARDS	20/0.6	16/4.3
Anastomotic leak	12	11.7
Clavien-Dindo > III < V	23.6	22

ARDS acute respiratory distress syndrome

It is however a matter of debate which neoadjuvant treatment option is optimal for EC and GEJC patients. Another highlight of ASCO 2021 was the Neo-AEGIS trial [4], which aimed to answer this question and randomized EC/GEJC patients (only adenocarcinoma histology) to either neoadjuvant CROSS (carboplatin/paclitaxel, 41.4 Gy radiation therapy) or to peri-operative chemotherapy based on the MAGIC protocol (epirubicin, cisplatin/oxaliplatin, 5-flurouracil [5-FU]/capecitabine) and more recently FLOT (docetaxel, 5-FU, leucovorin, oxaliplatin). Of the 362 evaluable patients (178 CROSS, 184 MAGIC/FLOT [157/27]), 90% were male, 84% were cT3, and 58% cN1 (Table 1). Survival outcomes were similar in both groups. Authors concluded that this study revealed no evidence that peri-operative chemotherapy is unacceptably inferior to multimodal therapy with CROSS. It is however important to underline the selection of the chemotherapy arm of the MAGIC protocol (83%), which no longer represents the standard after the publication of FLOT data. According to histopathological regression analysis of the FLOT trial, the pCR rate of the FLOT arm is 16%, which was only 5% in the EOX arm of the Neo-AEGIS trial, indicating that the local disease control capacity of the chemotherapy arm of this trial is far beyond the standard treatment, which is currently used. The similar OS rates in both groups despite the better pathological control rate of the CROSS regimen underlines again the fact that this regimen most probably fails to induce appropriate systemic control. Since we do not have any direct comparison of CROSS and FLOT regimen, even the availability of an adjuvant immunotherapy (based on the CheckMate 577 trial) will most probably not influence the treatment decision of the patients at baseline. However, the ESOPEC trial proposed a similar design as the NEO-AEGIS trial, having the FLOT schema as a chemotherapy arm, which will hopefully

provide more clinically relevant data within the next few years [5].

Gastric/GEJ cancer

After presentation of the CheckMate 649 trial, nivolumab + chemotherapy became standard in CPS ≥ 5 patients with advanced or metastatic EC/GEJ and gastric adenocarcinoma [6]. However, it has been a debate since then whether patients with CPS < 5 derive a benefit. Nevertheless, the FDA approved this treatment combination in all advanced gastroesophageal adenocarcinoma patients irrespective of CPS. In ASCO 2021, Moehler et al. gave a short hint on the efficacy of nivolumab in CPS < 1 and < 5 patients [7]. According to the subgroup analyses, survival times between the nivolumab + chemotherapy arm versus chemotherapy mono seems to be very similar, indicating that the benefit of nivolumab which was seen within the whole patient population is mainly derived by the patients who are CPS ≥ 5. Authors stressed the better overall response rate (ORR) in the nivolumab + chemotherapy arm, which might translate into enhanced OS in longer follow-up. The decision of the European Medicines Agency (EMA) is awaited.

Since publication of the pivotal TOGA trial [8], there has been a huge attempt to target human epidermal growth factor receptor 2 (Her2) using different agents or combinations, which unfortunately failed to show efficacy. Keynote-811 is a phase III trial [9] where patients with Her2-positive metastatic gastric or GEJC were randomized either to pembrolizumab + standard of care (SOC, anti-Her2 and chemotherapy) or placebo + SOC. Primary endpoints of the study were OS and PFS; secondary endpoints were ORR, duration of response and safety. Study group predefined a protocol-prespecified interim analysis of ORR, which was 74.4% (95% CI = 66.2–81.6) for pembrolizumab + SOC vs 51.9% (43.0–60.7) for placebo + SOC (difference, 22.7 percentage points, $p = 0.00006$). The authors concluded that adding pembrolizumab to SOC resulted in a substantial, statistically significant increase in ORR as first-line therapy for HER2+ metastatic G/GEJ cancer; responses were durable and safety was manageable. It is, however, important to mention that the OS data is immature and it is not clear how far this improvement of ORR will be seen in the OS. Nevertheless, the FDA approved pembrolizumab in this subpopulation of patients based on this protocol-prespecified first interim analysis.

Already at ASCO-GI 2021, targeted therapy celebrated its comeback with the FIGHT trial [10]. FIGHT is an international phase II trial which included patients with advanced or metastatic gastroesophagel cancer, whose tumor express fibroblast growth factor receptor 2b (FGFR2b). FGFR2b was investigated either with immunohistochemistry (IHC) or with ctDNA. Patients were treated with mFOLFOX6 and randomized to bemarituzumab, a monoclonal antibody against FGFR2b. Of the 155 patients, 149 (96%) were FGFR2b+ by IHC, 26 (17%) by ctDNA, and 20 (13%) by both. Bemarituzumab arm had a median OS of 19.2 months (95% CI = 13.6–not reached) vs 13.5 months (95% CI = 9.3–15.9) for placebo (HR = 0.60; 95% CI = 0.38–0.94) for the intent-to-treat population; for the subset of patients with FGFR2b+ ≥ 10% by IHC, the median OS for bemarituzumab was 25.4 months (95% CI = 13.8–not reached) vs 11.1 months (95% CI = 8.4–13.8) for placebo (HR = 0.41; 95% CI = 0.23–0.74). A phase III study testing the same hypothesis has already been initiated. The FIGHT trial design included some very interesting features which will hopefully inspire the scientists in designing the future clinical trials: (i) Patients were allowed to receive 1× mFOLFOX treatment during the screening phase, which helped to increase patients enrollment and offer the standard treatment to the patients without any time delay; (ii) Biomarker analysis included both IHC and ctDNA in order to precisely select the appropriate subgroup of patients which might benefit from the treatment; (iii) Survival analyses were reported not only on the positivity of FGFR2b but also on the different cut-offs of cell positivity of FGFR2b.

Discussion

No change of survival outcome in patients with gastroesophageal tumors had been observed for decades. This trend now seems to have changed, since various immunotherapy compounds have been shown to be beneficial in patients with gastroesophageal tumors, both in advanced and metastatic setting [11]. However, novel data raised many critical questions: Which biomarker is appropriate for daily clinical use: PD-L1 TPS or CPS? Which chemotherapy backbone is more beneficial? Is a chemotherapy-free combination realistic/possible? Do novel biomarker concepts have a role in clinical practice, such as microbiome or ctDNA? Does immunotherapy have a role in neoadjuvant setting for all patients? Can immunotherapy and targeted therapy be combined? Do some specific subgroups of patients derive similar benefit from the treatment, e.g., female patients, Caucasian patients? Does the improved outcome of patients translate into enhanced quality of life (QoL)? Is the financial toxicity of novel drugs affordable? Answers to these questions will shape the treatment algorithm of gastroesophageal patients in upcoming years.

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Take home message ASCO 2021 included several phase III clinical trials with positive results which will change the treatment algorithm of gastroesophageal cancer patients, both for localized and advanced settings.

References

1. Kojima T, Shah MA, Muro K, Francois E, Adenis A, Hsu CH, et al. Randomized phase III KEYNOTE-181 study of pembrolizumab versus chemotherapy in advanced esophageal cancer. J Clin Oncol. 2020;38(35):4138–48.
2. Chau I, Doki Y, Ajani JA, Xu J, Wyrwicz L, Motoyama S, et al. Nivolumab (NIVO) plus ipilimumab (IPI) or NIVO plus chemotherapy (chemo) versus chemo as first-line (1L) treatment for advanced esophageal squamous cell carcinoma (ESCC): first results of the CheckMate 648 study. J Clin Oncol. 2021;39(suppl 15):LBA4001.
3. Kelly RJ, Ajani JA, Kuzdzal J, Zander T, Van Cutsem E, Piessen G, et al. Adjuvant nivolumab (NIVO) in resected esophageal or gastroesophageal junction cancer (EC/GEJC) following neoadjuvant chemoradiotherapy (CRT): expanded efficacy and safety analyses from CheckMate 577. J Clin Oncol. 2021;39(suppl 15):4003.
4. Reynolds JV, Preston SR, O'Neill B, Lowery AM, Baeksgaard L, Crosby T, et al. Neo-AEGIS (neoadjuvant trial in adenocarcinoma of the esophagus and esophago-gastric junction international study): preliminary results of phase III RCT of CROSS versus perioperative chemotherapy (modified MAGIC or FLOT protocol). (NCT01726452). J Clin Oncol. 2021;39(suppl 15):4004.
5. Hoeppner J, Lordick F, Brunner T, Glatz T, Bronsert P, Rothling N, et al. ESOPEC: prospective randomized controlled multicenter phase III trial comparing perioperative chemotherapy (FLOT protocol) to neoadjuvant chemoradiation (CROSS protocol) in patients with adenocarcinoma of the esophagus (NCT02509286). BMC Cancer. 2016;16:503.
6. Janjigian YY, Shitara K, Moehler M, Garrido M, Salman P, Shen L, et al. First-line nivolumab plus chemotherapy versus chemotherapy alone for advanced gastric, gastro-oesophageal junction, and oesophageal adenocarcinoma (CheckMate 649): a randomised, open-label, phase 3 trial. Lancet. 2021;398(10294):27–40.
7. Moehler MH, Shitara K, Garrido M, Salman P, Shen L, Wyrwicz L, et al. First-line (1L) nivolumab (NIVO) plus chemotherapy (chemo) versus chemo in advanced gastric cancer/gastroesophageal junction cancer/esophageal adenocarcinoma (GC/GEJC/EAC): expanded efficacy and safety data from CheckMate 649. J Clin Oncol. 2021;39(suppl 15):4002.
8. Bang YJ, Van Cutsem E, Feyereislova A, Chung HC, Shen L, Sawaki A, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. Lancet. 2010;376(9742):687–97.
9. Janjigian YY, Kawazoe A, Yanez PE, Luo S, Lonardi S, Kolesnik O, et al. Pembrolizumab plus trastuzumab and chemotherapy for HER2+ metastatic gastric or gastroesophageal junction (G/GEJ) cancer: initial findings of the global phase 3 KEYNOTE-811 study. J Clin Oncol. 2021;39(suppl 15):4013.
10. Catenacci DVT, Kang YK, Saeed A, Yamaguchi K, Qin S, Lee KW, et al. FIGHT: a randomized, double-blind, placebo-controlled, phase II study of bemarituzumab (bema) combined with modified FOLFOX6 in 1L FGFR2b+ advanced gastric/gastroesophageal junction adenocarcinoma (GC). J Clin Oncol. 2021;39(suppl 15):4010.
11. Puhr HC, Preusser M, Prager G, Ilhan-Mutlu A. New treatment options for advanced gastroesophageal tumours: mature for the current practice? Cancers (Basel). 2020;12(2):301.