ESMO 2020 update: Pancreatic cancer

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Summary At the ESMO (European Society for Medical Oncology) 2020 several interesting albeit not practice-changing studies in the field of pancreatic cancer were presented. The Canadian phase II randomized PA.7 trial investigated the additional benefit of dual checkpoint inhibition with durvalumab and tremelimumab to a standard chemotherapy regimen as first-line treatment in patients with metastatic pancreatic ductal adenocarcinoma (mPDAC). Unfortunately, no significant improvement of responses or outcome could be achieved rendering this study a negative trial. Within the German platform-based QoliXane trial, quality of life was shown to be an essential prognosticator of survival with fatigue and nausea being independently associated with outcome of patients. Moreover, promising results could be observed with new targeted therapy approaches, which may lead to its investigation in larger randomized clinical trials.

Keywords Pancreatic cancer · ESMO 2020 · Targeted therapies · Dual immunotherapy · Quality of life

Immunotherapy in pancreatic cancer

Targeting immune checkpoints by monoclonal antibodies has led to a tremendous treatment change and improvement of prognosis of cancer patients over the last decades. Pancreatic cancer in contrast is characterized by a highly immunosuppressive microenvironment with a low tumor mutational burden and a lack of effector T-cells [1]. Only 1% of metastatic pancreatic ductal adenocarcinoma (mPDAC) patients harbor

DNA mismatch repair-deficient (MMR-D) tumors potentially representing the most immunogenic subtype. Preclinical data so far suggest a synergistic effect of combining chemotherapy with immunotherapies in pancreatic cancer models [2]. Within the currently largest non-randomized single-arm trial investigating the combination of gemcitabine, nab-paclitaxel and the anti-PD-1 antibody nivolumab as first-line therapy, objective responses could be observed in 18% of patients and a stabilization of disease in 46% of mPDAC patients [3]. However, median overall survival (OS) remained limited with 9.9 months. A dual immunotherapeutic approach was first investigated in 2019 within a phase II randomized clinical trial testing the combination of the anti-PD-L1 inhibitor durvalumab and the anti-CTLA4-inhibitor tremelimumab applied as second-line treatment [4]. Here, no additional benefit with the combination compared to durvalumab alone could be observed with a median OS of only 3.1 months. Presented at the ESMO 2020, the phase II trial PA.7 of the Canadian Cancer Trials Group first investigated the efficacy and safety of a dual checkpoint blockade combined with a standard chemotherapy regimen applied as first-line treatment of mPDAC patients [5]. Randomized in a 2:1 ratio, 180 patients received either a combination of gemcitabine (1000 mg/m², day 1, 8, 15, q28), nab-paclitaxel (125 mg/m², day 1, 8, 15, q28), durvalumab (1500 mg, day 1, q28) and tremelimumab (75 mg, q28) or gemcitabine and nab-paclitaxel alone. Despite an increased response and disease control rate within the interventional arm, median progression-free survival (PFS; 5.5 months in the interventional arm vs 5.4 months in the standard arm) as well as OS (9.8 months in the interventional arm vs 8.8 months in the standard arm) was not significantly different. Interestingly, the addition of the two immunotherapies did not result in any meaningful increase in grade

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Table 1 Summary of previous studies investigating the combination of chemotherapy with immunotherapy in pancreatic ductal adenocarcinoma (PDAC) patients

Reference	Phase	Applied chemotherapy and immunotherapy	Ptx	RR (%)	SD (%)	OS
Aglietta M et al., Ann Onc 2014 [13]	I	Gem + Tremelimumab	34	6	21	7.4 months
Weiss GJ et al., Inv New Drugs, 2018 [14]	Ib/II	Gem, nab-P + Pembrolizumab	17	25	67	15.0 months
O'Hara MH et al., AACR, 2019 [15]	Ib	Gem, nab-P + CD40 ± Nivolumab	30	58	33	N.R.
Kamath SD et al., Oncol, 2020 [16]	Ib	Gem + Ipilimumab	21	14	33	6.9 months
Wainberg ZA et al., CCR, 2020 [3]	I	Gem, nab-P + Nivolumab	50	18	46	9.9 months
Bockorny B et al., Nat Med, 2020 [17]	Ila	Nal-Iri/5-FU/LV + Pembrolizumab, Motixafortide	22	32	45	N.R.
Renouf D et al., presented at ESMO 2020 [5]	II	Gem, nab-P ± Durvalumab, Tremelimumab	180	33	38	9.8 months

ptx patients; *RR* response rate; *SD* stable disease; *OS* overall survival; *N.R* not reached; *Gem* Gemcitabine; *nab-P* nab-Paclitaxel; *nal-Iri* liposomal irinotecan

3/4 events compared to the standard chemotherapy regimen. In conclusion, no benefit could be observed in the overall patient population with the addition of immunotherapy. However, circulating tumor DNA (ctDNA) analyses conducted within this study may help to assess immune sensitivity in this setting. A summary of previously conducted trials investigating the combination of chemotherapy with immunotherapy in mPDAC patients is listed in Table 1. Several trials addressing this topic are currently ongoing (e.g., NCT03829501, NCT01928394).

Quality of life in metastatic disease

Pancreatic cancer is known to cause a considerable high symptom burden compared to other tumor entities. Therefore, the assessment of quality of life (QoL) within prospective randomized trials seems of major interest to support daily treatment decisions. Supposedly, efficient disease control achieved by a chemotherapy regimen prevents deterioration of QoL and therefore outweighs its potential toxicities [6, 7]. In line with this, disease progression is usually associated with a deterioration of QoL [8]. The Qoli-Xane trial presented at the ESMO 2020 is a prospective, multicenter study assessing QoL based on a platform for outcome, QoL and translational research on pancreatic cancer (Paragon) under the frontline chemotherapy combination of gemcitabine and nab-paclitaxel [9]. A total of 600 patients were included and EORTC-C30 questionnaires for the assessment of QoL were collected at baseline, 3 and 6 months respectively after initiation of treatment. They reported a median PFS of 5.9 months and a median OS of 8.9 months in line with the phase III MPACT trial investigating the combination of nab-paclitaxel and gemcitabine as first-line treatment of mPDAC patients [10]. QoL measured by the Global Health score (GHS) at baseline in general significantly predicted survival. Median time to deterioration was fairly short with only 4.7 months. Nevertheless, 61% of mPDAC patients presented with a maintained QoL after 3 months and 41% of patients after 6 months. Almost all side effects

were significantly associated with OS, but only fatigue as well as nausea and vomiting remained independent prognosticators. An increase in physical function was significantly associated with a decreased risk of death. This study therefore highlights the importance of disease control and optimization of symptom burden in mPDAC patients.

New targeted therapy approaches

Beside many ongoing studies, the poly (ADP-ribose) polymerase (PARP) inhibitor olaparib remains the only approved targeted therapy for mPDAC patients with a germline breast cancer (BRCA) mutation to date. Prospective and predictive biomarkers are urgently needed to identify new targeted therapy approaches. Dean et al. investigated the combination of gemcitabine and nab-paclitaxel with the tumor-penetrating peptide CEND1 as first-line treatment of metastatic disease [11]. By interaction with neuropilin-1, this targeted agent transforms the tumor microenvironment into a conduit potentially leading to increased local efficacy of the combined chemotherapy agents. Within their study, they observed an indeed promising overall response rate of 59% and stable diseases in 34% of patients. Albeit single-arm, observed responses were much more pronounced compared to previously reported studies of the chemotherapy regimen alone [10].

Halama et al. investigated the safety and efficacy of NOX-A12, which targets the chemokine protein CXCL12 and thereby modulates the tumor microenvironment, in combination with the PD-1-inhibitor pembrolizumab in heavily pretreated microsatellite stable metastatic colorectal cancer and mPDAC patients [12]. A tumor biopsy before and after monotherapy with this targeted agent revealed an enhanced effector immune cell infiltration of the tumor and may thereafter lead to a more effective immune response caused by immunotherapy. Albeit not separately analyzed, stable disease could be achieved in 25% of all treated patients after a median of three previously applied therapy lines. Future investigation of prog-

nostic and predictive biomarkers is urgently needed to identify potential therapeutic targets.

Take home message

- The addition of a dual checkpoint blockade with durvalumab and tremelimumab to standard chemotherapy failed to improve response rates and outcome of metastatic pancreatic ductal adenocarcinoma (mPDAC) patients.
- Quality of life is predictive for the prognosis of mPDAC patients under first-line treatment and therefore toxicity management needs to be optimized.
- New targeted therapy approaches like tumor-penetrating peptide CEND1 or NOX-A12 need to be investigated in larger clinical trials.

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Conflict of interest E.S. Bergen declares that she has no competing interests.

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