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Advances in pancreatic cancer treatment

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Summary Pancreatic cancer, one of the most challenging malignancies to treat, is characterized by poor survival rates. The identification of novel effective therapies, optimization of treatments for the elderly population, and elucidation of the role of chemoradiotherapy are critical issues. Recent studies presented at the American Society of Clinical Oncology (ASCO) 2024 annual meeting have demonstrated advancements in the treatment of this aggressive disease. This review summarizes three notable studies: the phase I trial of IBI389, the phase II GIANT trial, and the phase II/III GABARNANCE trial, each contributing new insights into therapeutic strategies for pancreatic ductal adenocarcinoma (PDAC).

Keywords Pancreatic cancer · PDAC · Targeted therapy · Claudin 18.2 · Borderline resectable

Phase I trial of IBI389: a novel bispecific antibody for advanced PDAC

Anti-claudin 18.2 therapies have shown promising activity in gastric and gastroesophageal junction (GEJ) cancers. Clinical data from pivotal trials, such as the phase II/III SPOTLIGHT and GLOW studies evaluating zolbetuximab, an anti-claudin 18.2 monoclonal antibody, have demonstrated improved outcomes in patients with advanced claudin 18.2-positive gastric/GEJ adenocarcinoma when combined with standard chemotherapy backbones [1, 2].

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Claudin 18.2 (CLDN18.2) seems to be emerging as an interesting target for the treatment of pancreatic cancer. CLDN18.2 is expressed in a significant portion (60%) of PDAC cases, making it a viable target for novel therapies. This year at ASCO, three abstracts were presented for this target [3–5].

One of these studies was presented by Hao et al. which explored the safety and preliminary efficacy of IBI389, a bispecific antibody targeting CLDN18.2 and CD3, in patients with advanced PDAC. IBI389 aims to induce immune synapse formation between T cells and tumor cells, thereby promoting an antitumor response [5].

This phase I trial enrolled 64 patients with advanced, refractory, or metastatic CLDN18.2-positive PDAC who had failed standard treatments. All patients had received prior therapy with a median of 2 lines (range: 1 to 5). IBI389 was applied at varying doses (5–600 mg/kg) via intravenous administration, with a step-up dosing strategy for higher dose levels. The primary endpoint was safety, while secondary endpoints included objective response rate (ORR) and disease control rate (DCR) according to RECIST v1.1 criteria.

In this trial, claudin 18.2 expression was determined by immunohistochemistry using a validated, standardized assay. A prespecified cutoff for positivity was established based on ≥ 10% of tumor cells demonstrating moderate-to-strong membranous staining (≥ 2+ intensity).

Patients defined as having “high” claudin 18.2 expression typically met or exceeded this 10% threshold at ≥ 2+ intensity. Of the patients, 96.9% experienced treatment-related adverse events (TRAEs), whereby 54.7% were grade ≥ 3 TRAEs. The most common severe TRAEs included increased gamma-glutamyl transferase, decreased lymphocyte count, and nausea. Cytokine release syndrome was noted in 51.6%

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of patients, though none were grade ≥3. Preliminary efficacy data showed an ORR of 30.4% and a DCR of 69.6% in patients with high CLDN18.2 expression, suggesting promising antitumor activity. The median duration of response (DoR) and progression-free survival (PFS) were not reached.

IBI389 demonstrates a promising efficacy in heavily pretreated PDAC patients, particularly those with high CLDN18.2 expression. Further studies are warranted to confirm these findings and optimize dosing strategies and the management of TRAEs.

GIANT: phase II trial study comparing biweekly chemotherapy regimens in elderly PDAC patients

Previous trials have already addressed the treatment of elderly patients with advanced/metastatic PDAC, but none have prospectively compared gemcitabine and nab-paclitaxel with the 5-fluorouracil (5-FU), leucovorin, and liposomal irinotecan FOLFIRILIP regimen [6–8]. The GIANT trial, led by Dotan et al., has taken on this task and prospectively randomized these two chemotherapy regimens—both regimens applied on a biweekly basis [9].

In the GIANT trial, the study population was defined as "elderly" if patients were aged ≥70 years at the time of study entry. The study enrolled 176 elderly patients with newly diagnosed metastatic PDAC, assessing overall survival (OS) as the primary endpoint, with secondary endpoints including PFS, response rate (RR), safety, and quality of life (QOL). Median age of enrolled patients was 77 (range 70–90), 49% women, 24% ECOG-0, 64% ECOG-1 and 12% ECOG-2.

No significant difference in median OS was observed between the two arms (4.7 vs. 4.4 months; p= 0.72). Both regimens had comparable safety profiles, though the gemcitabine/nab-paclitaxel arm exhibited lower rates of grade 4 toxicity. Most common ≥grade 3 toxicities included anemia, neutropenia, fatigue in both arms, and diarrhea in arm B. The GIANT study did not find a significant difference in efficacy between the two regimens, providing valuable data to inform treatment decisions for this vulnerable patient population. These results underscore the need for comprehensive geriatric patient and individualized treatment approaches based on patient-specific factors such as comorbidities and functional status.

While the GIANT study enrolled older patients (≥70 years) with metastatic pancreatic cancer, it is important to note that nearly a quarter (24%) of participants had an ECOG performance status of 0, indicating that some patients were physiologically robust despite their advanced age. Given that the regimens were tested specifically for their tolerability and feasibility in an older population, one might question whether the "less intensive" approach could result in undertreatment for this fitter subgroup. However, the study's primary aim was to identify regimens suitable for a broad elderly cohort, including those with vulnerabilities not fully captured by ECOG performance status alone. The choice of a "friendlier" regimen may still have clinical relevance for older patients by reducing toxicity without compromising efficacy to a substantial degree, and it could serve as a more generalizable option in routine practice. Nonetheless, for select fit older patients (e.g., ECOG 0, minimal comorbidities, robust functional status), a more intensive regimen may still be considered on an individualized basis, balancing potential added benefit with the increased risk of toxicity.

The GIANT study's adaptation of the standard gemcitabine/nab-paclitaxel schedule—omitting day 8 administration—was primarily intended to enhance tolerability in an older population. While the traditional schedule involves doses on days 1, 8, and 15, this modification reduced treatment intensity and potentially hematologic and nonhematologic toxicities. The resulting regimen can be seen as a more "elderly-adapted" approach, still providing antitumor activity, while minimizing side effects and treatment burden. In routine clinical management, this altered schedule might serve as a template for dose and schedule modifications in older or frailer patients who may not tolerate standard regimens.

GABARNANCE: phase II/III trial on neoadjuvant therapy strategy for borderline resectable PDAC

Background and objectives

Borderline resectable pancreatic cancer (BRPC) represents a challenging subset of patients who are at the cross-roads between initially resectable and locally advanced disease. Current standards often include neoadjuvant therapy to improve surgical candidacy and achieve better long-term outcomes. Neoadjuvant chemotherapy, with or without radiotherapy, aims to reduce tumor burden, increase R0 resection rates, and minimize the risk of early systemic relapse. While neoadjuvant chemotherapy alone has shown promise, the addition of radiotherapy—either conventionally fractionated or as stereotactic body radiotherapy—has been explored to further improve local control and resection quality. However, the benefit of neoadjuvant radiotherapy continues to be debated, and its optimal integration into treatment regimens is still being evaluated in prospective clinical trials [10].

The Japanese GABARNANCE trial, presented by Ikeda et al., compared neoadjuvant systemic chemotherapy versus chemoradiotherapy in patients with borderline resectable PDAC [11].

This multicenter, open-label trial randomized 112 patients to receive either gemcitabine plus nab-paclitaxel (arm A) or concurrent chemoradiotherapy with S-1 (arm B). The primary endpoint was OS, with secondary endpoints including PFS and surgical resection rates. A total of 110 patients (65 events) was re-

quired to detect a 17% difference in the 2-year OS (hazard ratio [HR] of 0.70) with a two-sided alpha level of 10% and power of 70%. In the GABARNANCE study, pathological response was defined using standardized histopathological assessment of the resected specimen following neoadjuvant therapy. Typically, this involves quantifying the extent of residual viable tumor cells relative to the pretreatment tumor volume. The Evans grading system is used for the assessment of the percentage of viable tumor cells, degree of fibrosis, and tumor regression. A strong pathological response—Evans grade IV—indicates minimal or no residual viable tumor cells, reflecting a robust tumoricidal effect of the neoadjuvant regimen [12].

The median OS was 23.1 months for the chemotherapy group and 31.5 months for the chemoradiotherapy group, though the difference was not statistically significant (HR 0.758; $p = 0.2518$). The difference in the 2-year OS between the groups was 14.6% (group A: 48.2%, group B: 62.8%) which was below the required 17%.

The tumor response rate was higher in group A (group A, 16.1%; group B, 8.9%), but the pathological response rate was higher in group B (group A, 14.3%; group B, 30.4%). Both treatments were well-tolerated with distinct toxicity profiles: neutropenia and thrombocytopenia were observed more frequently in group A, while anorexia was observed more frequently in group B. The R0 resection rate did not differ between the two groups (group A, 60.7%; group B, 57.1%).

Unlike the PREOPANC trial, the GABARANCE exclusively focused on borderline resectable PDAC and used S1 instead of gemcitabine [13]. Despite the fact that the patient population was more homogenous, the trial failed to give a clear answer to the question of whether chemoradiotherapy has a clinical value in the borderline resectable setting, warranting further investigation.

Summary and future directions

The studies presented at ASCO 2024 highlight the evolving landscape of pancreatic cancer treatment, offering new hope for improved outcomes in this challenging malignancy. The promising results from the IBI389 trial underscore the potential of novel targeted therapies targeted against CLDN18.2, while the GIANT study provides critical insights into the management of elderly and frail patients. The GABARNANCE was another large trial trying to answer the question whether neoadjuvant chemoradiotherapy is of clinical benefit; however, it did not demonstrate any significant OS difference between chemoradiotherapy and chemotherapy alone. Thus, continued research and clinical trials are essential to integrate new therapeutic strategies into standard practice.

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Conflict of interest H. Taghizadeh declares that he has no competing interests.

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