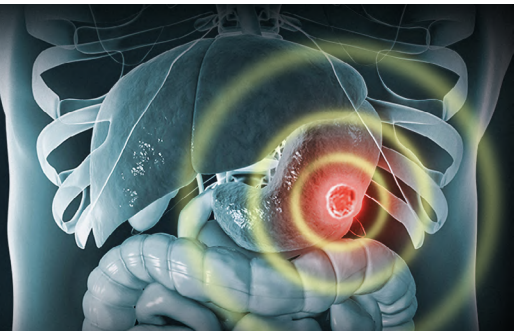
Upper GI Cancer Research Review™



Making Education Easy

Issue 11 - 2025

In this issue:

Abbreviations used in this issue:

(a)HR = (adjusted) hazard ratio; **CapeOx** = capecitabine plus oxaliplatin; **FLOT** = fluorouracil, leucovorin, oxaliplatin, docetaxel; **FOLFIRINOX** = leucovorin, fluorouracil, irinotecan, oxaliplatin; **NSCLC** = non-small cell lung cancer; **ORR** = overall response rate; **OS** = overall survival; **PDAC** = pancreatic ductal adenocarcinoma; **PFS** = progression-free survival; **RCT** = randomised controlled trial; **SBRT** = stereotactic body radiation therapy; **(TR)AE** = (treatment-related) adverse event.

Welcome to issue 11 of Upper GI Cancer Research Review.

Our first paper describes a retrospective review of nationwide US data which found that, in patients with PDAC, alterations in *KRAS* G12D and G12V are associated with poorer outcomes versus *KRAS* wild type, whereas *KRAS* G12R alterations are associated with improved outcomes; furthermore, treatment with FOLFIRINOX is associated with better outcomes than gemcitabine, regardless of *KRAS* alteration status. This is followed by a US study which confirms the clinical benefit of pemigatinib for cholangiocarcinoma a real-world setting. The next article on the SWOG S1815 trial concludes that the addition of nab-paclitaxel to gemcitabine and cisplatin is not associated with improved OS in newly diagnosed, advanced biliary tract cancer, although subgroup analyses suggest that a triplet regimen may be beneficial in gall bladder cancer and locally advanced versus metastatic disease – these trends warrant further investigation.

I hope you find these and the other articles in this review interesting and educational, and I welcome your feedback.

Kind Regards,

Dr Pei Ding
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KRAS mutation status and treatment outcomes in patients with metastatic pancreatic adenocarcinoma

Authors: Norton C et al.

Summary: This retrospective analysis of a nationwide database in the US compared the treatment outcomes of patients with pancreatic ductal adenocarcinoma (PDAC) who harboured various *KRAS* alterations. The study included 2433 patients (mean age 67.0 years; 55.1% men) from 280 US cancer clinics, covering ≈800 sites of care. Among patients with *KRAS* alterations (83.1%), those with *KRAS* G12R had the longest median OS (13.2 months; 95% CI 10.6—15.2) and the longest median time to next treatment (6.0 months; 95% CI 5.2—6.6). Compared with *KRAS* wild type, those with alterations in *KRAS* G12D and G12V had significantly greater risks of progression ([G12D HR 1.15; 95% CI 1.04—1.29; p=0.009]; [G12V HR 1.16; 95% CI 1.04—1.30; p=0.01]), and death ([HR 1.29; 95% CI 1.15—1.45; p<0.001]; [HR 1.23; 95% CI 1.09—1.39; p<0.001], respectively). Across all patients, there were lower risks of progression and death with FOLFRINOX with or without nab-paclitaxel, than with gemcitabine.

Comment: *KRAS* mutations are the commonly identified genomic alteration in PDAC, which are seen in approximately 90% of patients. The most common *KRAS* mutations are at codon 12, with the most common being the G12D mutation (about 1/3 of all *KRAS* mutations). Multiple studies have attempted to investigate the relevance of different *KRAS* mutations to clinical outcomes. This retrospective study included over 2000 patients from 280 US cancer clinics. The study found that patients with *KRAS* G12R have the longest survival, whereas those with *KRAS* G12D and G12V have the highest risk of disease progression and death, compared with *KRAS* wild type. This is consistent with other previously published retrospective studies. This study also showed that FOLFIRINOX was efficacious, giving better clinical outcomes compared with gemcitabine with or without nab-paclitaxel, regardless of *KRAS* mutation status. *KRAS* G12D is also associated with poorer prognosis in metastatic lung cancer, which was thought to be related to a more immunosuppressive tumour microenvironment. This study did not report on the co-mutation status of the tumours, which will also likely impact on treatment outcome, as it is well known that *KEAP1* co-mutation with *KRAS* G12C was associated with early progression on *KRAS* inhibitors. Other co-mutations which are common with *KRAS* mutations such as *CKDN2A*, *SMAD4* and *PT53* could all contribute to survival and treatment outcomes, which should be investigated in future studies.

Reference: JAMA Netw Open. 2025;8(1):e2453588
Abstract

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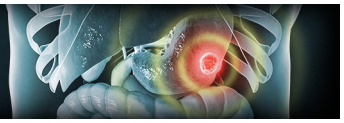

Real-world use of pemigatinib for the treatment of cholangiocarcinoma in the US

Authors: Saverno K et al.

Summary: The efficacy of pemigatinib for *FGFR*-altered cholangiocarcinoma was established in the FIGHT-202 trial. Here, researchers retrospectively evaluated medical record data on the real-world use of pemigatinib in 120 adults (median age 64.5 years; 49.2% men) who received pemigatinib for unresectable, locally advanced or metastatic cholangiocarcinoma in the US. Metastatic disease was present in 90.0% of patients at the time of prescribing. Most patients (92.5%) underwent *FGFR* testing, of whom all except one were positive; 95.5% of patients with *FGFR* alterations then underwent next-generation testing. Patients most commonly received pemigatinib as second-line therapy (94.5%), and the remainder (5.8%) were administered pemigatinib in the third line. Across a median 6.5 months of follow-up, 50% of the full cohort discontinued pemigatinib, primarily due to progression (68.3%). The overall real-world PFS was 7.4 months (95% CI 6.4—8.6), with a median ORR of 59.2% (95% CI 50.0—68.4).

Comment: FIGHT-202 study is a single arm, open-label, phase 2 study, which included patients with ECOG 0-2 whose disease progressed on at least one line of treatment for *FGFR2*-altered advanced cholangiocarcinoma, being treated with FGFR1, 2 and 3 oral inhibitor pemigatinib. It showed an ORR of 35.5% with a median PFS of 7 months, and median OS of 17.5 months. This real-world study included data from 120 patients in the US with a median real-world PFS of 7.4 months and an ORR of 59.2%. The results are very similar, with a higher ORR compared with the FIGHT-202 trial, which is likely related to differences in the methods of response assessment. This study reinforces the efficacy of pemigatinib in a real-world setting, where patients may have poor functional status with more comorbidities compared with trial patients. There were no data on TRAEs for the real-world study, which will be useful to know for future studies, especially with pemigatinib showing higher rates of grade 3/4 TRAEs (68.7% in FIGHT-202).

Reference: Oncologist. 2025;30(1):oyae204
Abstract

SWOG S1815: A phase III randomized trial of gemcitabine, cisplatin, and nab-paclitaxel versus gemcitabine and cisplatin in newly diagnosed, advanced biliary tract cancers

Authors: Shroff RT et al.

Summary: The open-label, phase 3 SWOG S1815 trial randomly assigned 441 eligible patients who were newly diagnosed with locally advanced unresectable/metastatic biliary tract cancer 2:1 to either gemcitabine-nab-paclitaxel-cisplatin, or gemcitabine-cisplatin. The study cohort included patients with intrahepatic cholangiocarcinoma (67%), extrahepatic cholangiocarcinoma (17%) and gallbladder carcinoma (16%). There were no differences between treatment arms with regard to OS (p=0.41) or PFS (p=0.32). Exploratory subset analyses suggested that patients with locally advanced disease experienced greater benefits in OS and PFS with triplet therapy than those with metastatic disease, although neither of these comparisons reached statistical significance (OS p=0.14; PFS p=0.17). Patients with gall bladder carcinoma experienced significantly longer PFS with triplet therapy than those with intrahepatic or extrahepatic cholangiocarcinomas (p=0.01), yet there was no difference in OS (p=0.28).

Comment: This study was designed as an earlier single-arm study in 60 patients, and showed that triplet chemotherapy may provide longer median OS and PFS versus historical controls. This phase 3 RCT did not show any difference in OS or PFS in the two groups. Subgroup analyses suggested that the triplet regimen may be more efficacious in gall bladder cancer and locally advanced (vs. metastatic) disease. However, subgroup analyses results can only be taken as a 'signal' for future studies, and no definitive conclusions can be made. As expected, the triplet regimens were more toxic, with more grade 3/4 TRAEs (both haematological and non-haematological) and higher rates of dose modifications. The study opens up more questions than answers; better future trials should be designed, and the positive trend in gall bladder cancer warrants further exploration. Future study for advanced biliary tract cancer would need to take into consideration that the frontline treatment for advanced biliary tract cancers has now changed with durvalumab-cisplatin-gemcitabine being standard of care, as shown by the TOPAZ-1 study.

Reference: J Clin Oncol. 2025;43(5):536-44
Abstract

Atezolizumab plus chemotherapy with or without bevacizumab in advanced biliary tract cancer: clinical and biomarker data from the randomized phase II IMbrave151 trial

Authors: Macarulla T et al.

Summary: The IMbrave151 trial assessed whether the addition of bevacizumab (anti-VEGF) to atezolizumab (anti-PD-L1) and chemotherapy improved clinical outcomes in the first-line treatment of advanced biliary tract cancer. Eligible patients (n=162) were randomised 1:1 to either bevacizumab-atezolizumab-chemotherapy or placebo-atezolizumab-chemotherapy. There was a 0.4-month improvement in PFS with the addition of bevacizumab (8.3 vs. 7.9 months; HR 0.67; 95% CI 0.46—0.95), and no significant improvement in OS (14.9 vs. 14.6 months; HR 0.97; 95% CI 0.64—1.47). Each treatment arm had grade 3/4 AE rates of 74%. Patients with high *VEGFA* gene expression showed prolonged PFS with the addition of bevacizumab (HR 0.44; 95% CI 0.23—0.83).

Comment: IMbrave-151 is a phase 2, randomised, double-blind study of first-line treatment for advanced biliary tract cancer, investigating the role of adding bevacizumab to atezolizumab-cisplatin-gemcitabine. The study showed that adding bevacizumab led to slightly greater PFS versus standard of care (median PFS 8.3 vs. 7.9 months). OS data are still immature. The study showed that adding bevacizumab did not result in increased TRAEs. The minimal increase in 0.4 months for median PFS is far from impressive, and is not clinically meaningful. However, this study does provide an interesting signal that perhaps a subgroup of patients may benefit from the addition of bevacizumab to chemotherapy-immunotherapy, similar to NSCLC. An exploratory analysis of the APPLE study (phase 3; atezolizumab-bevacizumab-platinum chemotherapy in metastatic NSCLC) showed that patients with serum low *VEGFA* levels are likely to benefit from the addition of bevacizumab. Biomarker-directed studies or subgroup analyses for patients stratified by *VEGFA* levels will be warranted for future studies involving bevacizumab.

Reference: J Clin Oncol. 2025;43(5):545-57
Abstract

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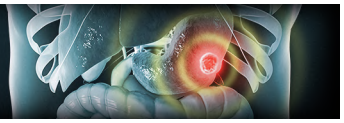

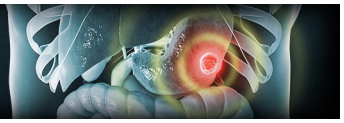

Chemotherapy dose density is prognostic for overall survival in patients with resectable pancreas cancer: A landmark analysis of SWOG 1505

Authors: Patel SH et al.

Summary: In this secondary analysis of SWOG 1505, investigators explored the impacts of chemotherapy dose density on OS in patients with resectable PDAC. The study included 102 enrolled patients, of whom 71% underwent surgery, with a median preoperative chemotherapy dose density of 89%. OS was significantly longer in those who received ≥85% dose density versus <85% (38.1 vs. 17.2 months; p=0.039). Of the 82 patients who were alive at 40 weeks after randomisation, 67 underwent surgery, with a mean perioperative chemotherapy dose density of 67%. Perioperatively, OS was significantly longer in those who received ≥70% versus <70% (32.2 vs. 14.0 months; p=0.017). There were no associations between perioperative dose density and lymph node negativity, pathologic response or margin status.

Comment: Perioperative chemotherapy is a vital part of treatment for PDAC, but optimal duration and dose of chemotherapy were determined by seminal clinical trials. The effect of dose delay, dose reduction and omission on the outcome of resectable PDAC was not clear, with some retrospective analyses showing that reduced dose density could have a negative impact on survival. This study used phase 2 randomised study data (SWOG 1505) to assess the prognostic value of reduced dose density on survival for patients included in SWOG 1505 with resectable PDAC. It showed that patients with ≥85% dose density had higher OS versus those with <85% dose density, but perioperative dose density was not associated with pathological response or lymph node negativity, which is consistent with the perceived larger role of perioperative chemotherapy in eliminating micro-metastatic disease rather than local disease. However, association does not always imply causation. Therefore, clinical trials with randomisation for different chemotherapy dosages and schedules will be needed to confirm the findings.

Reference: Cancer. 2025;131(4):e35759
Abstract

A phase III randomized trial of integrated genomics and avatar models for personalized treatment of pancreatic cancer: The AVATAR trial

Authors: Sarno F et al.

Summary: The phase 3 AVATAR trial randomised 125 eligible patients with PDAC 1:2 to receive physician's choice of conventional treatment (n=44) or first-line conventional treatment plus comprehensive precision medicine (n=81). Those in the precision medicine arm provided a tumour biopsy, and 80.3% of these underwent whole-exome sequencing. The biopsy was also used to create avatar mouse models (patient-derived xenografts), in which mice were implanted with malignant tumour tissue, as well as patient-derived organoids. Phenotypic drug screening was performed on patient-derived xenografts and organoids, to identify personalised treatments. Experimental models were generated for 19.8% of those in the precision medicine arm. Potentially actionable alterations were identified in 21.5% of patients in the precision medicine arm who underwent whole-exome sequencing. Although 39/81 patients in the precision medicine arm received second-line therapy, only four (10.2%) were able to receive personalised treatment, due to study result delays, rapid clinical worsening or lack of actionable targets. There was no difference in OS between the control and precision medicine arms (primary objective; 8.7 vs. 8.6 months; p=0.849) or in PFS (3.8 vs. 4.3 months; p=0.563). However, OS was substantially longer among the four patients who were administered personalised treatment (19.3 months).

Comment: This is an interesting study conducted in Spain, which is the first prospective randomised study to assess the efficacy and feasibility of a personalised medicine approach in the treatment of patients with metastatic pancreatic cancer. The standard arm received chemotherapy or clinical trial drugs at the discretion of the treating physician. The personalised treatment arm patients also received first-line treatment at the discretion of investigator, but underwent a biopsy with tissue submitted to next-generation sequencing to generate patient-derived organoids and mouse avatar models. Genomic data were analysed to select the most promising agents to undergo efficacy testing in the PDO models, and drugs that showed the greatest efficacies were tested on avatar mouse models. These generated efficacy and toxicity results, with consensus treatment recommendations made for patients at the time of progression. The team should be applauded for designing this study, which is highly time-consuming, requiring input from multiple teams to generate patient-derived organoid and xenograft models. A total of 125 patients were randomised, with 81 patients randomised to the experimental arm. Although the personalised strategy did not improve OS, it showed the real-world challenges of implementing integrated medicine in PDAC due to the lengthy process. The majority of patients did not receive second-line treatment; for those who started second-/subsequent-line treatment, 10% received a molecularly-matched therapy, with longer OS. The AVATAR trial showed that a small subset of PDAC patients with a less rapid course of disease may benefit from patient-derived organoid and xenograft models to establish and inform personalised treatment decisions. With advancements of technology in this area, and with shorter turnaround times for personalised treatment decisions, hopefully more patients will benefit from this approach in the future.

Reference: Clin Cancer Res. 2025;31(2):278-87
Abstract

Impact of neoadjuvant therapy on oncological outcomes of patients with distal pancreatic adenocarcinoma

Authors: Chopra A et al.

Summary: This retrospective cohort study examined the impacts of neoadjuvant therapy on outcomes in 141 patients (median age 69.8 years; 51.8% women) with resectable and borderline-resectable distal PDAC who were treated at a single centre in the US between 2012-20. Neoadjuvant therapy was administered to 50.4% of all patients, while 49.6% underwent upfront surgery. Those who received neoadjuvant therapy had a higher rate of borderline-resectable disease than those in the surgery first group (31% vs. 4.3%; p<0.05) and were significantly younger (65.9 vs. 72.6 years; p<0.05). Multivariate analysis revealed that patients with distal PDAC who underwent neoadjuvant therapy were more likely to experience improved PFS (HR 0.64; 95% CI 0.42—0.96; p=0.031) and improved OS (HR 0.60; 95% CI 0.39—0.93; p=0.021).

Comment: Patients with distal (body or tail) pancreatic cancer have worse outcomes than patients with pancreatic head cancer, due to the majority being detected at an advanced stage, with other studies showing that the biology of the cancer is different from pancreatic head cancers. Due to this, distal PDAC patients were excluded from neoadjuvant therapy trials, resulting in limited data and understanding of the benefits of neoadjuvant therapy for resectable distal PDAC. This retrospective study showed that neoadjuvant therapy is associated with better survival (both PFS and OS) versus upfront surgery. Future RCTs looking at the role of neoadjuvant therapy should include patients with distal PDAC in order to confirm this finding.

Reference: J Surg Oncol. 2024;130(8):1579-88
Abstract

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Comparison of metastasectomy and stereotactic body radiation therapy for pulmonary oligometastasis from hepatocellular carcinoma

Authors: Shin YS et al.

Summary: These investigators conducted a retrospective, propensity score-weighted analysis of 209 patients with hepatocellular carcinoma and pulmonary oligometastasis who underwent metastasectomy (n=150; 241 lesions) or stereotactic body radiation therapy (SBRT; n=59; 81 lesions) between 2008-18. At a median follow-up of 39.8 months, following adjustments, there were no between-group differences in 2-year overt systemic PFS (50.8% vs. 52.7%; p=0.396), 2-year PFS (23.0% vs. 24.7%; p=0.478) or 2-year OS (72.6% vs. 83.0%; p=0.428). Multivariate analysis revealed that significant prognostic factors for PFS and OS were viable intrahepatic lesions and number of previous liver-directed treatments, and OS was significantly associated with duration of time between diagnosis and development of metastases.

Comment: Metastasectomy has been considered to be the most effective for local control, and therefore the widely accepted treatment for pulmonary oligometastasis, with limited data on SBRT, which is gaining more acceptance as a surgical alternative for primary lung tumours or metastatic lung disease. The non-invasive nature of SBRT allows for less interruptions to systemic therapy, with many non-randomised studies showing SBRT to be safe and effective with a high local control rate. There are limited data for the use of SBRT in the treatment of pulmonary oligometastatic disease in hepatocellular carcinoma. This retrospective study directly compares surgery with SBRT for oligometastasis in the lung for patients with hepatocellular carcinoma. It showed that there were no differences in PFS or OS between arms after adjustment. Randomised trials will be useful to know whether these strategies are indeed equivalent. Whether these data can be extrapolated to other tumour types is unclear, and should be further investigated.

Reference: Int J Radiat Oncol Biol Phys. 2025;121(2):432-41
Abstract

Neoadjuvant chemotherapy in relation to long-term mortality in individuals cured of gastric adenocarcinoma

Authors: Leijonmarck W et al.

Summary: The aim of this nationwide, population-based cohort study from Sweden was to determine whether neoadjuvant chemotherapy influences long-term survival in patients who are deemed to be 'cured' of gastric adenocarcinoma. The analysis included 613 patients who underwent gastrectomy for gastric adenocarcinoma between 2006-15 and survived for ≥5 years. Patients who received neoadjuvant chemotherapy (43.9%) demonstrated a reduction in crude mortality (HR 0.66; 95% CI 0.46—0.96), although this association was no longer statistically significant after adjustments for all confounders (aHR 0.83; 95% CI 0.56—1.23) and adjustments for age and comorbidities only (aHR 0.82; 95% CI 0.56—1.20). It was concluded that neoadjuvant chemotherapy did not reduce long-term survival in these gastric adenocarcinoma survivors.

Comment: This is an interesting population-based cohort study which used a large, unselected cohort of patients with early gastric cancer who received surgery ± neoadjuvant chemotherapy, and were considered cured from the disease. The hypothesis of this study is that neoadjuvant chemotherapy influences long-term survival in gastric adenocarcinoma survivors. The results showed that the receipt of neoadjuvant chemotherapy was associated with a lower mortality rate, but the association became non-significant after adjusting for confounders (i.e., age and comorbidities). It was found from this study that survivors who received neoadjuvant chemotherapy were a select group who were younger and fitter with less comorbidities, and therefore had better chances of long-term survival. It is reassuring that potential known long-term sequelae from neoadjuvant chemotherapy did not reduce long-term survival for gastric cancer survivors in this study.

Reference: Gastric Cancer. 2025;28(1):96-101
Abstract

Short-term outcomes of a phase II trial of perioperative capecitabine plus oxaliplatin therapy for advanced gastric cancer with extensive lymph node metastases (OGSG1701)

Authors: Kimura Y et al.

Summary: The efficacy and safety of perioperative capecitabine plus oxaliplatin (CapeOx) for advanced gastric cancer with extensive lymph node metastases was assessed in this phase 2, multicentre trial. Between 2017-22, patients with gastric adenocarcinoma (n=30) with para-aortic lymph node metastases and/or bulky lymph node metastases located at the celiac axis, common hepatic artery and/or splenic artery were administered preoperative CapeOx, followed by postoperative CapeOx after gastrectomy. The ORR was 66.7% (complete response n=0, partial response n=20; stable disease n=8; progressive disease n=1). There was a preoperative chemotherapy completion rate of 96.7%, and a curative resection rate of 93.3%. It was noted that CapeOx had an acceptable safety profile in this patient population; the grade 3 AEs observed with preoperative chemotherapy included anorexia (10.0%), anaemia (6.7%) and neutropenia (3.3%).

Comment: This study was conducted in Japan, where CapeOx is the standard of care after gastrectomy for advanced gastric cancer and first-line treatment for unresectable or recurrent gastric cancer. This single-arm, prospective, multicentre phase 2 trial evaluated the efficacy and safety of CapeOx (3 pre-op cycles and 5 post-op cycles) in patients with advanced gastric cancer with extensive lymph node metastases who couldn't be resected without neoadjuvant therapy. The study showed that CapeOx provided a promising pre-op treatment regime with an ORR of 66.7% and a tolerable AE profile, and a high curative resection rate of 93.3%. Being a single-arm study with a small number of patients (n=30), the results should be treated with caution, and survival data are pending. Nonetheless, the study provided signals that the CapeOx regimen may be an acceptable regimen compared to FLOT, which may be worth further investigations.

Reference: Gastric Cancer. 2025;28(1):112-21
Abstract

Independent commentary by Dr Pei Ding

Dr. Pei Ding underwent medical oncology training at Liverpool and St Vincent's hospital in Sydney and completed her fellowship and PhD study in lung cancer liquid biopsy research at the Ingham Institute of Applied Medical Research and Western Sydney University. She is now a medical oncologist at Nepean and Westmead hospitals with clinical expertise in managing lung cancers and gastrointestinal cancers. She is also a senior clinical lecturer at the University of Sydney.

