GASTROINTESTINAL MALIGNANCIES IN 2020 AND BEYOND
Monday, July 6, and Friday, July 10, 2020
In July 2020, Aptitude Health gathered a group of clinical investigators with cross-functional expertise in gastrointestinal (GI) cancer treatment to attend a virtual expert panel meeting.

The goal of the expert panel was to discuss the latest translational and therapeutic developments in GI cancer treatment, apply these advances to dynamic and oftentimes individualized clinical decision-making, and explore how emerging research will affect ongoing clinical trials, development of new compounds, and future treatment paradigms.
Metastatic Colorectal Cancer
DAY 1 – MONDAY, JULY 6, 2020
MEET THE EXPERTS . . .

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CHEMOTHERAPY AND TARGETED THERAPIES IN METASTATIC CRC – OVERVIEW (1/2)

> How to best select first-line chemo intensity?

Overall response rates (ORR) are favorable in RAS wild-type metastatic colorectal cancer (mCRC) patients for both left-sided and right-sided tumors with chemotherapy + monoclonal antibodies (anti-epidermal growth factor receptor [EGFR]), although this does not always translate into an overall survival (OS) and progression-free survival (PFS) benefit, particularly for right-sided tumors.

- The German AIO phase II VOLFI trial showed that addition of panitumumab to FOLFOXIRI (5-fluorouracil [5-FU], leucovorin, oxaliplatin, irinotecan) in patients with mCRC improved the ORR in left- and right-sided tumors; however, it did not lead to an improvement in PFS or OS (Modest DM, et al. J Clin Oncol. 2019;37(35):3401-3411).

- Triple chemotherapy (FOLFOXIRI) vs doublet has shown improvement in OS and PFS in fit patients with mCRC, although for a select group of fit patients.

- Single-agent chemotherapy remains an option in elderly patients, as shown by data from the AVEX trial (capecitabine + bevacizumab), and now more recently by the results of the PANDA trial with 5-FU–leucovorin + panitumumab vs FOLFOX + panitumumab both meeting the primary endpoint of PFS (Lonardi S, et al. ASCO 2020, abstract 4002). Considering as well that there is a better safety profile using chemo monotherapy, the question exists of whether a doublet with an anti-EGFR antibody should be used...
Preventing metastases in rectal cancer with total neoadjuvant treatments will change the standard-of-care (SOC) paradigms in locally advanced rectal cancer (LARC) patients. In the RAPIDO trial (Hospers G, et al. ASCO 2020, abstract 4006), a lower rate of disease-related treatment failure vs SOC chemoradiation was achieved, with short-course radiotherapy then consolidation chemotherapy followed by surgery. In the PRODIGE 23 trial (Conroy T, et al. ASCO 2020, abstract 4007), neoadjuvant mFOLFIRINOX (modified regimen containing oxaliplatin, leucovorin, irinotecan, and 5-FU) then chemoradiation followed by surgery was safe, and significantly increased pathologic complete response (pCR), disease-free survival, and metastasis-free survival vs SOC chemoradiation.
Chemoradiation followed by surgery has been SOC in many European countries for the majority of patients with LARC. Experts agreed the SOC is moving toward total neoadjuvant therapy—As shown by trial data from OPRA (Garcia-Aguilar J, et al. ASCO 2020, abstract 4008), RAPIDO (Hospers G, et al. ASCO 2020, abstract 4006), and PRODIGE 23 (Conroy T, et al. ASCO 2020, abstract 4007)• The RAPIDO and PRODIGE 23 trials were especially notable for the results in "low-lying, bad-risk" rectal tumors• It was mentioned, though, that a certain level of bias is introduced, as delaying surgery due to chemotherapy allows more time for a pCR—Options now are moving toward induction chemotherapy followed by chemoradiation or preoperative short-course radiotherapy, followed by consolidating chemotherapy—However, it will be important to evaluate whether pCR also translates into an OS benefit, and it is "too early to make the choice between the different regimens"
Experts agreed the SOC is moving toward total neoadjuvant therapy (cont.)

− It will be important to understand which patients will benefit from the different approaches

− Experts agreed that with the currently available options, a triplet chemotherapy (induction chemo-intensive regimen) is not needed in the total neoadjuvant strategy, and toxicity is also reduced

− With regard to the sequence of these treatments, experts noted that when patients are symptomatic from their primary tumor, they respond to chemotherapy more rapidly than to radiotherapy

EU and US experts agreed that watch-and-wait with close follow-up is recommended in patients with "smaller, better-risk" rectal tumors that have a pCR. However, watch-and-wait is not practiced in all EU countries; for example, in Italy it is only done in the frame of a clinical trial.
mCRC

Tumor location (right- and left-sided tumors) − Tumor sidedness is an independent prognostic factor with anti-EGFR antibodies. Right-sided tumors have worse prognosis; BRAF mutations are more common, and they have a mucin-like histology.

There is a role for the microbiota − Microbiota ribosomal RNA profiling in the tumor or studying specific bacteria in stool can provide valuable information regarding why some tumors are more aggressive than others. Manipulating the microbiome to modulate the tumor microenvironment is an area of huge translational research potential that may impact clinical outcomes. This is an area of potential clinical research for the National Clinical Trials Network.

It is important to integrate all the factors: tumor molecular profiling, microbiome, tumor microenvironment, and merge all the information to get a more complete profile of the tumor. It was noted that the role of the tumor microenvironment in better understanding reduced responsiveness to anti-EGFR antibodies has been understudied in right-sided tumors.
The frontline treatment choices for elderly patients (70–75 years) depend on tumor and patient characteristics. "With so many options to choose, there is an educational need to realize what options there are and when to use what." Intensive chemotherapy (triplet chemotherapy) may be appropriate for selected elderly patients who are fit, starting the regimen on a reduced dose to monitor neutropenia and diarrhea. De-escalation is also an important treatment strategy for certain patients when using high-intensity chemotherapy, without impacting clinical outcomes. Otherwise, double chemotherapy + anti-EGFR (for left-sided RAS and BRAF wild-type) or doublet + bevacizumab for all other patients.
mCRC (cont.)

The frontline treatment choices for elderly patients (70–75 years) depend on tumor and patient characteristics (cont.)

- Patients who are not fit to receive doublets may receive chemo monotherapy + monoclonal antibody, as demonstrated in the following trials
  - AVEX trial: capecitabine + bevacizumab vs capecitabine
  - TASCO1 trial: trifluridine-tipiracil + bevacizumab vs capecitabine + bevacizumab (Van Cutsem E, et al. Ann Oncol. 2020;S0923-7534(20)39866-5)
  - PANDA trial: fluoropyrimidine monotherapy + panitumumab (Lonardi S, et al. ASCO 2020, abstract)

- The data from the PANDA trial in this molecularly select group of patients not fit for doublets were viewed with great interest by the experts

- Experts commented that the PANDA trial has opened the debate as to whether oxaliplatin is needed in elderly patients, particularly when bevacizumab can be added, without impacting PFS

- It is important to closely monitor increased cutaneous toxicity with anti-EGFR antibodies in elderly patients. In very few patients treatment has to be discontinued.
There is a growing number of biomarkers used for treatment decisions in mCRC. Analysis of 296 samples from the TRIBE2 patient population showed 21% of patients have targetable alterations including \( \text{BRAF} \) \( \text{V600E} \) (13%), \( \text{KRAS} \) \( \text{G12C} \) (3%), human epidermal growth factor receptor (\( \text{HER} \)) amplification (1%), \( \text{HER2} \) mutation (1%), microsatellite instability high (MSI-H; 3%; ESMO GI 2020, abstract O-018).

MSI-H tumors

Identification of MSI-H patients by immunohistochemistry (IHC) or next-generation sequencing (NGS) has shown a high concordance rate between both techniques (98.6%), per the TRIBE2 data.

MSI-H patients have a high tumor mutation load (TML).

In KEYNOTE-177 (Andre T, et al. ASCO 2020, abstract LBA4), MSI-H patients who responded to pembrolizumab in first-line treatment vs chemotherapy had "extraordinary" duration of response. It will be important to define the nonresponders by assessing TML.

\( \text{BRAF} \) \( \text{V600E} \) mutation

In the updated results of the BEACON CRC study (Kopetz S, et al. ASCO 2020, abstract 4001), the use of a RAF inhibitor (encorafenib) ± MEK inhibitor (binimetinib) + anti-EGFR inhibitor (cetuximab) showed similar median OS data between the doublet and triplet, with favorable safety profile for the doublet.

Encorafenib + cetuximab doublet has now become SOC in this patient population (received US Food and Drug Administration [FDA] approval in March 2020).
HER2-expressing tumors

In the DESTINY-CR101 trial (Siena S, et al. ASCO 2020, abstract 4000), only patients with high HER2-expressing tumors (IHC3+ or IHC2+/in situ hybridization positive) responded to trastuzumab deruxtecan (T-DXd). The drug was also active in patients pretreated with HER2 therapy.

The adverse event of special interest is interstitial lung disease, which must be closely monitored.

KRAS G12C mutations

The CodeBreak 100 study (Fakih M, et al. ASCO 2020, abstract 4018) of sotorasib (AMG 510) has shown activity in heavily pretreated mCRC patients with the KRAS G12C mutation, although far less than what has been observed for non-small cell lung cancer.
“Colorectal cancer is a collection of rare diseases that can be targeted with different approaches in the first-line and later-line settings.”

KRAS mutations in mCRC are typically nondruggable targets due to their few hydrophobic pockets for allosteric inhibitors. KRAS G12C is the first druggable target for a KRAS mutation in mCRC, with the small molecule AMG 510 specifically and irreversibly binding to this mutation. On its own, clinical activity with AMG 510 in CRC is not impressive (CodeBreak 100 trial), but it offers potential to combine it with anti-EGFR antibodies, as has been demonstrated by preclinical models (in vivo xenografts). Another possibility is to explore the combination with immunotherapies, as KRAS inhibitors are known to increase the immunogenicity of the tumor microenvironment.
HER2+ mCRC

- HER2 targeting in mCRC and gastric cancer (GC) involves receptor binding-mediated cellular toxicity rather than downstream signaling inhibition, as seen in breast cancer, which may also explain the differences in activity in the different tumors. HER2-targeting activity may likely be enhanced by combination strategies in mCRC.

- DXd is "a very potent topoisomerase I inhibitor," and in an expert's view, the data for the pretreated patient population in the DESTINY-CRC01 trial are "excellent." However, pulmonary toxicity cannot be ignored.

- The challenge in Europe is that HER2 inhibitors are currently not a treatment option in HER2+ mCRC, as they are not approved (the drug has now been submitted to the European Medicines Agency [EMA] for breast cancer). An expert noted that without a comparative trial for HER2 therapies in CRC, it will be difficult to get approval from the EMA.

- The SWOG S1613 trial is underway recruiting patients comparing pertuzumab + trastuzumab with cetuximab + irinotecan.
Immunotherapy in first-line MSI-H mCRC

• Single-agent programmed cell death protein 1 (PD-1) inhibitor pembrolizumab not only doubled PFS compared with chemotherapy-based treatment, but also reduced the incidence of severe toxicities by two-thirds in the phase III KEYNOTE-177 trial (Andre T, et al. ASCO 2020, abstract LBA4)

• However, one expert pointed out that chemotherapy performs poorly in MSH-H mCRC patients, and this is also "50% of the success of pembrolizumab"

• For the non-early progressors the results are "very impressive," "unbelievable." "The people who benefit, benefit indefinitely or for quite a long time"

• It is important to molecularly characterize the tumors of the early progressors (30% of patients) on pembrolizumab at the first scan (not due to pseudoprogression), and understand their tumor mutational burden (TMB). The combination with chemotherapy may be an interesting option for these patients

• The hope in Europe is that on the basis of these data, the drug will be approved by the EMA, and if there are good quality of life data, it will also be reimbursed by the different healthcare systems

• In an expert's view, anti-PD-1 antibodies have stronger efficacy in GI malignancies than anti-PD-L1 antibodies, although data would be needed to confirm this impression
IMMUNOTHERAPY AND TARGETED THERAPIES IN METASTATIC CRC – DISCUSSION (4/5)

> Immunotherapy in first-line MSI-H mCRC

- Ipilimumab + nivolumab: the combination is a treatment option for MSI-H patients, on the basis of the CheckMate 142 trial. However, it is not clear if addition of an anti-cytotoxic T-lymphocyte antigen 4 antibody reduces the number of patients who have progression of disease compared with the combination, without adding toxicity.

- In TRIBE2 samples, IHC and NGS techniques showed very good concordance to identify MSI-H mCRC patients (Rossini D, et al. WCGI 2020, abstract O-18).

- However, it is important to recognize that IHC for determination of MSH-H mCRC patients requires highly skilled pathologists, to ensure the concordance rate with NGS remains high.

- In Italy, the standard approach is IHC + polymerase chain reaction confirmation where immunotherapy is the therapeutic choice.

Immunotherapy in first-line microsatellite-stable (MSS) mCRC

- DNA polymerase epsilon (POLE) mutated MSS mCRC patients have a high tumor mutation load. With the FDA’s recent approval of pembrolizumab in metastatic solid tumors that are tissue TMB high (≥10 mutations/megabase), in the US, POLE-mutant mCRC patients would qualify for frontline treatment with pembrolizumab.

- Experts hope that experience with immunotherapy will also allow patients who do not have actionable alterations (79% as per TRIBE2 data) to have their tumors "turned into hotter tumors" that will respond to this therapy.

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Circulating tumor (ct)DNA

- Minimal residual disease (MRD) assessment will be a "game changer" in how patients are treated in the adjuvant and advanced disease settings.
- In the early setting (e.g., stage II CRC), a patient with MRD-positive ctDNA may now be considered for adjuvant chemotherapy, whereas this likely would not have been considered before. This raises the potential of using ctDNA clearance as an endpoint for adjuvant studies.
- In the advanced setting, MRD positivity has "such an important prognostic weight" that it will impact treatment approaches in resected CRC patients in all stages of disease. In one expert's view, MRD should be integrated into the American Joint Committee on Cancer classification of CRC tumors, as has been done with BRAF, KRAS, and RAS mutations.
- Additionally, ctDNA will be a valuable tool to identify acquired resistance mechanisms to anti-EGFR antibodies, and this will influence treatment decisions in clinical practice.
- The challenge currently remains determining the best assays (blood based, tissue based) that provide the highest sensitivity for MRD detection.

Importantly, the future should integrate the molecular characterization of the tumor with the assessment of ctDNA, to get a better understanding of the disease state.
Hepatocellular and Biliary Tract Cancers, Gastroesophageal Cancers, Pancreatic Cancer

DAY 2 – FRIDAY, JULY 10, 2020
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The gold standard for liver cancer staging is the Barcelona Clinic Liver Cancer (BCLC) method (stage 0, stage A, B, C, and D). BCLC stage C patients are the primary candidates for systemic therapy.

Immunotherapy:
- There are several FDA approvals in immunotherapy (nivolumab, pembrolizumab, ipilimumab + nivolumab).
- Combination with anti-vascular endothelial growth factor (VEGF) is very promising, as demonstrated by the IMbrave150 study (Finn RS, et al. *N Engl J Med.* 2020;382(20):1894-1905).
  - Atezolizumab + bevacizumab vs sorafenib SOC
  - OS at 12 months was 67.2% with atezolizumab + bevacizumab and 54.6% with sorafenib. Median PFS was 6.8 months and 4.3 months in the respective groups (hazard ratio [HR]; *P* < .001).
  - Treatment with atezolizumab + bevacizumab delayed deterioration of patient-reported quality of life (median time to deterioration, 11.2 months with atezolizumab + bevacizumab vs 3.6 months with sorafenib; HR 0.63).
- Study 22 of tremelimumab and durvalumab (Kelley RK, et al. ASCO 2020, abstract 4508).
  - Tremelimumab was studied at 300 mg and 75 mg in combination with durvalumab.
  - Median OS was 18.7 months for the combination arm vs 13.6 for the durvalumab and 15.1 months for the tremelimumab arms. The tremelimumab 300 mg + durvalumab arm had the highest confirmed ORR (duration of response: not reached) and longest OS.
  - The phase III HIMALAYA trial of the combination regimen is ongoing.
The recent FDA approval of atezolizumab + bevacizumab in first line will replace sorafenib and lenvatinib, the current SOC.

Other ongoing trials in first line:
- CheckMate 9DW: nivolumab + ipilimumab vs sorafenib or lenvatinib
- COSMIC-312: atezolizumab + cabozantinib vs sorafenib or cabozantinib
- LEAP-002: pembrolizumab + lenvatinib vs lenvatinib (recently denied FDA approval)

Biliary cancer:
- There is a multitude of targets in biliary tract cancer, depending on anatomic location: intrahepatic cholangiocarcinoma, perihilar cholangiocarcinoma, or distal cholangiocarcinoma + gall bladder.
- The SWOG S1815 is ongoing, studying gemcitabine and cisplatin with or without nab-paclitaxel.
  - Median follow-up was 17.8 months; 35.5% of patients with FGFR2 fusions or rearrangements achieved an objective response (3 complete responses and 35 partial responses).
- Another ongoing trial is FIGHT-203 with pemigatinib vs gemcitabine + cisplatin in first line.
- Ivosidenib in IDH1–mutated cholangiocarcinoma (pending FDA approval) was studied in the phase III ClarIDHy study (Abou-Alfa GK, et al. Lancet Oncol. 2020;21(6):796-807). PFS was significantly improved with ivosidenib vs placebo (median 2.7 months vs 1.4 months; HR 0.37; P < .0001).
HEPATOCELLULAR AND BILIARY TRACT CANCERS – DISCUSSION (1/5)

> Sequencing


- However, it is important to select the right patients. For example, in IMBrave150 (atezolizumab + bevacizumab vs sorafenib), patients with esophageal and/or gastric varices at risk of bleeding were excluded. A better first-line option in patients with esophageal varices and portal hypertension who need treatment to prevent bleeding may be sorafenib or lenvatinib, to prevent treatment delays.

- It was noted that it will be difficult to outperform bevacizumab + anti–PD-1 with a tyrosine kinase inhibitor (TKI) + anti–PD-1, as TKIs are generally more toxic.

- There are high expectations for the HIMALAYA trial (dual immunotherapy of durvalumab + tremelimumab vs sorafenib), especially in patients with a greater risk of bleeding.
Sequencing

Second-line treatment: it is still unclear what the best option is after atezolizumab + bevacizumab, and there is confusion in the medical community about the right choice after this in first line. Options include regorafenib, cabozantinib, or ramucirumab (although there are fewer data for the latter). However, an expert pointed out that besides regorafenib, “there is no real information on safety for all other agents.”

Knowledge of the tumor microenvironment in HCC is crucial to understand the possible continuation of immunotherapy in second-line.

The third-line treatment choice would be cabozantinib.

In general, before deciding on the treatment beyond first line, it is very important to select the right patients and check for comorbidities.
HEPATOCELLULAR AND BILIARY TRACT CANCERS – DISCUSSION (3/5)

> General considerations

− When the benefit is there, systemic therapies in HCC should be prioritized before interventional radiologic strategies
− Patients should be screened for esophageal varices prior to initiating systemic therapy
− It was pointed out by an expert that delaying the pattern of disease progression may be more important than measuring response rate in HCC trials, particularly when treating with antiangiogenics

Child-Pugh B patients

− One expert pointed out that Child-Pugh classification "has no real value in liver disease." Rather, it is important to look at whether the patient has compensated or decompensated liver disease. Patients in the latter group have very little tolerance to treatments and have very poor prognosis
− This patient population is highly heterogeneous, and there are currently no data available to support the use of novel agents (immunotherapy or TKIs) in treating this patient population
BCLC stage C patients: local therapy (to prime the tumor to respond better to

Experts commented that the perioperative setting in clinical trials is likely to be more relevant in these patients than the adjuvant setting.

Biomarker development is a significant unmet need in HCC for patient selection. In particular, biomarkers for immunotherapy, rather than for TKIs or anti-VEGFs.

- Biomarkers for angiogenesis vary tremendously in HCC tissue depending on when the sampling was done (e.g., if the patient was lying down for a long period, or standing for a long period, or if the patient had a heavy meal).
- In the IMBrave150 trial, it would be interesting to study the molecular differences, if any, between the patients who have durable responses without disease progression vs the patients who relapse very quickly. This information can also help in deciding what to do in second-line treatment.

The challenge remains that the tissue is highly heterogeneous in HCC, and lymphocytes in the microenvironment may show more promise in the search for biomarkers.
Biliary tract cancer

- This is a rare disease, although the incidence is rising worldwide
- In Europe, the SOC remains platinum agents + gemcitabine
- Experts agreed that molecular profiling is done in all patients prior to treatment
  - Tissue availability remains a challenge. Liquid biopsies are currently not optimal, as the FGFR gene fusions are missed. Additionally, turnaround times for results can delay treatment (up to 4 weeks)
- Immunotherapy after first line
  - Monotherapy in second line and beyond has shown little activity. It is possible the results will improve in combination with chemotherapy, and there are two phase III trials ongoing (chemotherapy ± immunotherapy)
  - High PD-L1 staining does not appear to be a contributing factor to the activity of immunotherapy
Globally, in gastroesophageal cancers, 5-year survival is achieved in approximately 60% of localized cases; SOC is perioperative chemotherapy or postoperative chemotherapy in 20% of locally advanced cases; SOC is preoperative chemotherapy, radiochemotherapy, or palliative chemotherapy in <5% of metastatic cases; first-line fluoropyrimidine + platinum salts ± trastuzumab, second-line taxane + ramucirumab, third-line trifluridine + tipiracil.

Large gains in survival have occurred over the past several decades, but 5-year survival remains poor.

First-line treatment in mGC:
- There has been an evolution in the chemotherapy regimens in the last 20 years in first line
  - Platinum + fluoropyrimidine-based doublet regimens are generally used
  - Triplet regimens containing taxanes are also an evidence-based option
  - FLOT (5-FU, leucovorin, oxaliplatin, and docetaxel) and FOLFIRI may be used in selected patients
- There have been several failed first-line phase III trials with EGFR, VEGF, or MET inhibitors. Anti-HER2 targeted therapies have also been disappointing with anti-HER2/3 antibodies, TKIs, or trastuzumab emtansine.
Second-line treatment in mGC

- Chemotherapy with a taxane (docetaxel, paclitaxel) or irinotecan, or ramucirumab as single agent or in combination with paclitaxel, is recommended for patients with performance status 0–1.
  - As shown in the phase III RAINBOW trial, where patients treated with ramucirumab + paclitaxel had a statistically significant and clinically meaningful improvement in OS compared with those treated with paclitaxel alone (median OS 9.6 months vs 7.4 months, respectively).
  - However, ramucirumab is not available in all countries.

- Rechallenge may be appropriate in patients with disease progression >3 months after first-line chemotherapy.

Treatment beyond second line in mGC is a real unmet need.

- In the phase III TAGS study with trifluridine-tipiracil vs placebo, trifluridine-tipiracil significantly improved OS vs placebo, with a median OS of 5.7 months in the trifluridine-tipiracil group and 3.6 months in the placebo group (HR 0.69, two-sided P = .00058).

- Trifluridine-tipiracil represents an effective treatment option with a manageable safety profile for patients with heavily pretreated mGC.

- There are ongoing trials in second line with immunotherapy:
  - ATTRACTION-2, KEYNOTE-059, and CheckMate 032 have shown promise in this field.
  - However, there have also been several failures (JAVELIN Gastric 300, KEYNOTE-061).

- Patients who respond better to immunotherapy are MSI-H, Epstein-Barr virus (EBV) positive, or PD-L1 positive.
Treatment beyond second line in mGC is a real unmet need (cont.)

- T-DXd has shown authentic promise in heavily pretreated mGC HER2+ patients, with the results of the DESTINY-Gastric01 trial (Shitara K, et al. ASCO 2020, abstract 4513). Median OS was significantly prolonged with T-DXd vs chemotherapy (12.5 vs 8.4 months, respectively; HR 0.59; P = .0097).

Biomarkers

- There are currently few targeted therapies for GC, and the many molecular biomarkers that have shown potential efficacy as diagnostic and prognostic tools require further validation.
> Biopsies and biomarkers in GC

- Experts agreed that upfront MSI and HER2 testing should be standard, but for other biomarkers samples are often limited and of poor quality to do further testing.
- In France, all other biomarkers remain limited to young, fit patients with no possibility beyond the line in which they start.
- In major cancer centers in the US, molecular profiling is done by NGS in all newcomers. It was noted, though, that in community hospitals there is an educational need regarding molecular testing and treatment options.
- It was noted that generally, rebiopsy may be valuable but it is not commonly done for HER2.
- There was agreement that liquid biopsies are complex in HER2+ GC, as they cannot detect all HER2 amplifications, but the field should be explored further.
Biomarkers beyond HER2 and MSI

Combined Positive Score is not considered a strong predictive biomarker for immunotherapy.

High TMB appears promising.

CLDN18.2 monoclonal antibody, targeting the tight-junction protein claudin-18, is "particularly interesting" in diffuse GC, which is not responsive to chemotherapy and has poor prognosis.

There is an ongoing phase III trial of zolbetuximab + epirubicin, oxaliplatin, capecitabine (EOX) in first-line advanced CLDN18.2 positive GC. If the trial is positive, it would be interesting to see this combination move to the perioperative setting, as patients with diffuse GC "do particularly badly."

It was noted, though, that expression of claudin-18 may not be as common as hoped for.

There are geographic variations in the use of first-line treatments:

- In the UK, patients do not receive triple chemo regimens, to avoid adding toxicity.
- In France, patients pretreated perioperatively with FLOT may now start receiving FOLFIRI as first line.
- In the US, very high-TMB patients (>25–30 mutations/megabase) and MSI-H GC patients may receive PD-1 inhibitors (in large academic centers).
Immunotherapy

− It is still not clear what is the right positioning of immunotherapy in the treatment landscape of patients with GC. It may be "reserved to last line" in selected patients (MSI-H, EBV positive), and could be interesting to evaluate in the maintenance setting (despite failure of the JAVELIN 300 trial).

− GC is not "an immunologic hot tumor"; therefore, the role of immunotherapy needs to be explored in selected patients and in combination regimens.

− Combination with TKIs is considered of interest by the experts.

• A phase II study of cabozantinib and pembrolizumab (NCT04164979) in metastatic GC is now recruiting patients.

• The response rates of the single-arm phase II trial (Kawazoe A, et al. Lancet Oncol. 2020;S1470-2045(20)30271-0) of lenvatinib + pembrolizumab were "really good." However, these data are viewed with caution, as the study was done in Japan and experts noted the Asian population generally responds better to TKIs and anti–PD-1s than the Caucasian population. A planned phase III study will shed light on this question.

• There are also ongoing clinical studies of ramucirumab in combination with immunotherapy, and in the maintenance setting this regimen may also be of interest.

− Combination with chemotherapy does not appear to add benefit. In KEYNOTE-062, patients receiving pembrolizumab + chemotherapy did not respond better vs patients receiving pembrolizumab alone or chemotherapy alone. The data from the CheckMate-649 (nivolumab + ipilimumab or nivolumab + chemo vs chemo alone) will also provide further answers regarding efficacy of combination immunotherapies, and the added benefit of oxaliplatin to single-agent immunotherapy.

− Combination of TKI + chemotherapy or TKI + immunotherapy + chemotherapy is regarded as a "very toxic" regimen in first line and not favored by the experts.
> HER2+ GC

The synergy of immunotherapy + HER2-targeted agents is being investigated. 

- Phase III KEYNOTE-811 of first-line pembrolizumab + trastuzumab (Chung HC, et al. ASCO GI 2020, abstract TPS463) is ongoing.

- Phase I/IIb of first-line margetuximab + pembrolizumab in pretreated HER2+ patients (Catenacci DVT, et al. Lancet Oncol. 2020;S1470-2045(20)30326-0) is looking very promising, and now there is an ongoing phase III trial.

In these combination studies, it remains to be seen if the combination enhances responses in PD-L1–positive patients vs the PD-L1–negative patients.

- The antibody-drug conjugate (ADC) T-DXd (DESTINY-Gastric01) is a “very exciting drug” in HER2+ refractory GC patients (particularly those for whom prior trastuzumab failed) and has shown to significantly improve their outcomes. However, it is more toxic than direct HER2 inhibitors, and this cannot be neglected in the COVID-19 environment (particularly the concern with pneumonitis).

- It would be interesting to evaluate the ADC in the perioperative setting, as it would be given for a limited period of time, thus allowing better control of pneumonitis. However, it was also noted that FLOT is a very effective regimen in this setting; therefore, it would be hard to “give it up.”

- An option to explore would be T-DXd in the adjuvant setting in patients with borderline resectable tumors that are locally advanced, MRD positive, would likely recur and be resistant to FLOT.
Other considerations

- Trial design should take geographic variations into consideration, particularly in trials with immunotherapy. "If we understand better the biology, we will be able to overcome these significant variances."
LOCALLY ADVANCED/METASTATIC PANCREATIC CANCER – OVERVIEW (1/3)

> Median survival for this disease has not gone above 1 year, and chemotherapy is the mainstay of systemic therapies.

Chemotherapy regimens:
- No difference was observed between the use of FOLFIRINOX vs gemcitabine-nab-paclitaxel (Patel T, et al. ASCO 2020, Abstract 769).
- In the phase I/II trial using nab-IRI + 5-FU/LV + oxaliplatin (NALIRIFOX) (Wainberg Z, et al. WCGI 2020, Abstract LBA), efficacy was similar to other regimens (gemcitabine/nab-paclitaxel or FOLFIRINOX), but safety appeared more manageable.
- It may be interesting to see if this regimen moves to localized disease like perioperative or adjuvant.

In the last 5 years, there have been plenty of negative trials for targeted compounds and immunotherapy, particularly as single agents.

Molecular profiling: 90% of pancreatic adenocarcinomas have RAS mutations but currently they are not druggable.

DNA repair abnormalities in pancreatic cancer represent a therapeutic opportunity:
- Olaparib (PARP inhibitor) has become part of the standard of care in patients with germline BRCA1/2 mutations based on the results of the phase III POLO study. However, there has been a debate around the trial data as the PFS benefit did not translate into an OS benefit with olaparib as maintenance following 1L platinum-based chemotherapy.
- It will be important to investigate mutations beyond germline BRCA, e.g., PALB2, ATM.
- Exploring combinations will be interesting, e.g., targeting DNA damage response at multiple points or combining with immunotherapy.
LOCALLY ADVANCED/METASTATIC PANCREATIC CANCER – OVERVIEW (2/3)

> Exploring novel pathways

- Combination of MEK/ERK inhibitor and autophagy as a treatment approach for pancreatic cancer is being considered.
  - CPI-613, targets the mitochondrial tricarboxylic acid cycle, an indispensable process essential to tumor cell multiplication and survival, selectively in cancer cells. The clinical activity in combination with FOLFIRINOX was shown in a phase I study, and has lead to a phase II trial (NCT03699319).
- Eryaspase (L-asparaginase) is designed to target the modified asparagine and glutamine metabolism of cancer cells, and is being studied in the 2L setting in the Trybeca-1 trial comparing the drug + chemotherapy vs chemotherapy alone.
- Studying and modifying the microenvironment will shed light into further treatment options.
  - APX005M (tCD40 agonist) + gemcitabine-nab-paclitaxel ± nivolumab is being investigated in a phase I/II trial (NCT03214250).
  - Cabiralizumab targets the tumor-associated macrophages and is being investigated in several clinical trials with chemotherapy ± immunotherapy (eg, NCT03336216).
Immunotherapy combination

The SWOG 2001 trial will investigate olaparib ± pembrolizumab as maintenance therapy in metastatic pancreatic cancer patients with germline BRCA1/2 mutations.

RAS wild-type patients comprise about 10% of the patients. RAS wild-type disease is significantly more enriched with targetable alterations (e.g., BRAF, ALK, ROS1, NRG1, MSI-H) as compared with KRAS mutant tumors, suggesting potential benefit of targeted therapies.

TMB and MSI tend to be higher in KRAS wild-type tumors, suggesting unique immune treatment strategy.

There is a huge research interest in modeling pancreatic cancer with organoids—in which cells are cultured in 3D under conditions intended to mimic those in the body—to understand response to treatment. However, there can be a turnaround time of 4 months, which would delay start of treatment.

There is a great opportunity for using the neoadjuvant chemotherapy platform to develop new drugs.
Conventional cytotoxic therapy remains the mainstay of systemic therapy. Molecular profiling may help in a select group of patients. Genetic counselling is done in all patients who will get genetic tests in EU and US. BRCA mutations are evaluated, and experts agreed that BRCA and MSI testing is performed in academic centers in Europe, although quality and quantity of tissue may be sometimes be a challenge. In the US, ATM mutation is also evaluated. Experts agreed that patients with germline BRCA mutations receive 1L platinum-based regimens such as FOLFIRINOX, with gemcitabine-cisplatin being a good alternative. The field of somatic BRCA mutations and its definition or role in pancreatic cancer is evolving. Experts noted that in the US, patients with somatic mutations will also be treated. ATM mutations respond very well to platinum and to irinotecan. KRAS wild-type tumors have gene fusions (NGFR1 or FGFR) and BRAF mutations. Patients with the NGFR1 fusions may have an option with afatinib, which seems to be relatively active.
PARP inhibitors

PARP inhibitors work by causing synthetic lethality in a specific mismatch repair pathway, and they do not work in all those other DNA repair deficiencies; as Dr Philip noted, "I don't understand why people keep thinking it's going to work for them when it's really specific for PARP defect".

The only evidence for PARP inhibitors in pancreatic cancer is in patients with BRCA1/2 mutations.

It was also noted that "a single-agent PARP inhibitor has very little effect in this disease".

POLO trial: The experts do not consider olaparib after 1L platinum-based chemo in patients with a germline BRCA1/2 mutation, as a maintenance regimen (as it is referred to in the clinical trial), but rather as a "treatment switch". They were not impressed by the trial design "set up definitely not to lose," although it did show "a proof of principle" in a disease where chemotherapy is the main treatment. Experts agreed there is a degree of activity from olaparib that qualifies it for further investigation to understand the right sequence or combination strategy.

It was noted that in Europe and in some centers, as screening for BRCA1/2 mutations would delay the start of treatment, patients start on FOLFIRINOX "because they're saying if there is indeed a BRCA mutation, they are started on oxaliplatin".
Immunotherapy in pancreatic cancer

Pancreatic cancer is "an incredibly cold tumor, but there might be some hope" with immunotherapy in combination strategies in a subset of patients.

- Immunotherapy may be a good option in patients who are MSI-high, but not in non-MSI-high patients, where immunotherapy remains a challenge.

The phase IIa COMBAT trial, investigating BL-8040 (a CXCR4 antagonist) + pembrolizumab + chemotherapy, was considered interesting (Bockorny B, et al. Nat Med. 2020;26:878-885). The disease control rate was 34.5% in the evaluable population, including 9 patients (31%) with stable disease and 1 patient (3.4%) with partial response.

Importantly, the focus should be on altering the tumor microenvironment; "we have to get off the mindset of PD-L1/PD-1, especially in this disease".

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Resectable or borderline resectable disease

- Foremost, it is important to provide a standard definition of borderline resectable disease and "to what degree has a patient been staged"
- Neoadjuvant chemotherapy is favored by the experts prior to resection; this is also favored by the surgeons, although there are currently no trial data available in support of this and "maybe we are going a bit too fast"
- In the US, a trial will be initiated of perioperative vs adjuvant using FOLFIRINOX, 4 months of preoperative chemotherapy, and 2 months of adjuvant vs 6 months of adjuvant
- In the US, in clearly resectable disease, patients do not receive radiation. For borderline and locally advanced disease, radiation may be used. In community hospitals, however, in the view of the experts, radiation is used more often than what is needed.

Experts confirmed it is still too early to shed any light on the role of the microbiome in pancreatic cancer.

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