Kolorektální Karcinom ASCO GI 2021

L.Petruželka

KEYNOTE-177: Phase III randomized study of pembrolizumab versus chemotherapy for microsatellite instability-high advanced colorectal cancer. Kai-Keen Shiu,et al

- **Conclusions:Pembro provided a statistically significant improvement in PFS vs chemo as first-line therapy** for patients with MSI-H/dMMR mCRC, with fewer TRAEs

KEYNOTE-177: Phase III randomized study of pembrolizumab versus chemotherapy for microsatellite instability-high advanced colorectal cancer.
Kai-Keen Shiu,et al

- **Background:**KEYNOTE-177 (NCT02563002) evaluated the antitumor activity of pembrolizumab (pembro) vs chemotherapy ± bevacizumab or cetuximab (chemo) as first-line therapy for patients with microsatellite-instability high/mismatch repair deficient (MSI-H/dMMR) metastatic colorectal cancer (mCRC). We present results of the final PFS analysis and analysis of PFS2.
- **Methods:**Patients with locally-determined MSI-H/dMMR mCRC and ECOG PS 0 or 1 were randomized 1:1 to first-line pembro 200 mg Q3W for up to 2 years or investigator's choice of mFOLFOX6 or FOLFIRI Q2W ± bevacizumab or cetuximab (chosen before randomization). Treatment continued until progression, unacceptable toxicity, patient/investigator decision to withdraw, or completion of 35 cycles (pembro only). Patients receiving chemo could crossover to pembro for up to 35 cycles after confirmed PD. Primary end points were PFS (RECIST v1.1, central review) and OS. Secondary end points included ORR (RECIST v1.1, central review) and safety. Exploratory endpoints included duration of response (DOR), PFS2 (time from randomization to progression on next line of therapy or any cause death), and health-related quality of life (HRQoL). Data cutoff was Feb 19, 2020.
- **Results:**At data cutoff a total of 307 patients were randomized (153 to pembro, 154 to chemo). Median (range) study follow-up was 32.4 mo (24.0-48.3). Pembro was superior to chemo for PFS (median 16.5 mo vs 8.2 mo; HR 0.60; 95% CI, 0.45-0.80; *P*= 0.0002). The 12- and 24-mo PFS rates were 55.3% and 48.3% with pembro vs 37.3% and 18.6% with chemo. Confirmed ORR was 43.8% vs 33.1%; median (range) DOR was not reached (2.3+ to 41.4+) with pembro vs 10.6 mo (2.8 to 37.5+) with chemo. PFS2 was longer with pembro vs chemo (median not reached vs 23.5 mo [HR 0.63; 95% CI, 0.45-0.88]). OS analysis is ongoing. Grade =3 treatment related adverse event (TRAE) rates were 22% vs 66% for pembro vs chemo. There were no grade 5 TRAEs in the pembro arm and 1 grade 5 intestinal perforation in the chemo arm. HRQoL scores were improved with pembro vs chemo.
- **Conclusions:**Pembro provided a statistically significant improvement in PFS vs chemo as first-line therapy for patients with MSI-H/dMMR mCRC, with fewer TRAEs observed. Furthermore, pembro provided a clinically meaningful improvement in PFS2 for patients with MSI-H/dMMR mCRC.

KEYNOTE-177: Phase 3 Randomized Study of Pembrolizumab Versus Chemotherapy for Microsatellite Instability-High Advanced Colorectal Cancer

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Pembrolizumab in Microsatellite-Instability–High Advanced Colorectal Cancer

T. André, K.-K. Shiu, T.W. Kim, B.V. Jensen, L.H. Jensen, C. Punt, D. Smith, R. Garcia-Carbonero, M. Benavides, P. Gibbs, C. de la Fouchardiere, F. Rivera, E. Elez, J. Bendell, D.T. Le, T. Yoshino, E. Van Cutsem, P. Yang, M.Z.H. Farooqui, P. Marinello, and L.A. Diaz, Jr., for the KEYNOTE-177 Investigators*

Pembrolizumab in MSI-H Metastatic Colorectal Cancer (mCRC)

- Microsatellite instability is detected in ~5% of patients with mCRC
- Pembrolizumab monotherapy has provided durable antitumor activity with an acceptable safety profile in patients with MSI-H mCRC[1-4]
  - Phase 2 KEYNOTE-164: ORR of 33%; DOR not reached in patients with previously treated MSI-H mCRC[1-3]
    - FDA approved pembrolizumab for adults and pediatric patients with previously treated MSI-H metastatic tumors regardless of tumor type or site[3]
  - Phase 3 KEYNOTE-177: Improved PFS versus chemotherapy as first-line therapy in MSI-H mCRC[4]
- Here we report results of analysis of PFS2 (progression-free survival on next line of therapy or death from any cause) and HRQoL in patients with MSI-H mCRC in KEYNOTE-177

1.Le DT et al. *N Engl J Med*. 2015;372:2509-20; 2 Le D et al. *J Clin Oncol* 2020;38:11-19; 3. Pembrolizumab: US Prescribing Information 2020. Merck Sharp & Dohme Corp., Whitehouse Station, NJ, USA; 4. Andre et al. *N Engl J Med*. 2020;383:2207-18; dMMR, DNA mismatch repair deficient; mCRC, metastatic colorectal cancer; MSI-H, microsatellite instability-high.

KEYNOTE-177 Study Design (NCT02563002)

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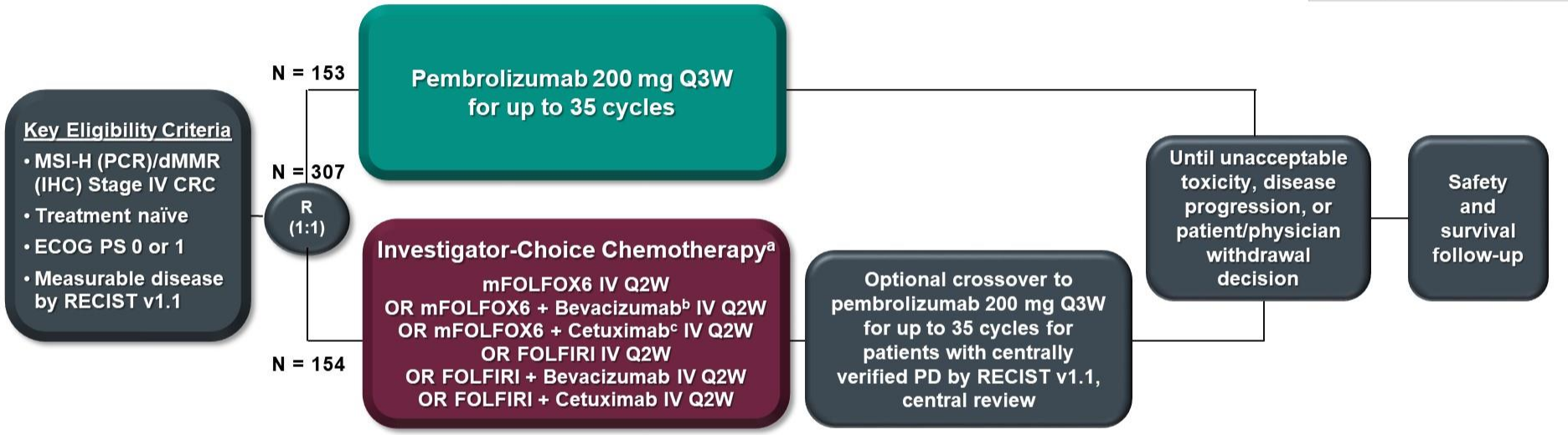

- Dual-Primary endpoints: PFS per RECIST v1.1 per blinded independent central review (BICR) and OS
- Secondary endpoints: ORR per RECIST v1.1 by BICR, safety
- Exploratory endpoints: DOR per RECIST v1.1 by BICR, PFS2, HRQoL
- Tumor response assessed at week 9 and Q9W thereafter per RECIST v1.1 by BICR

Progression-Free Survival

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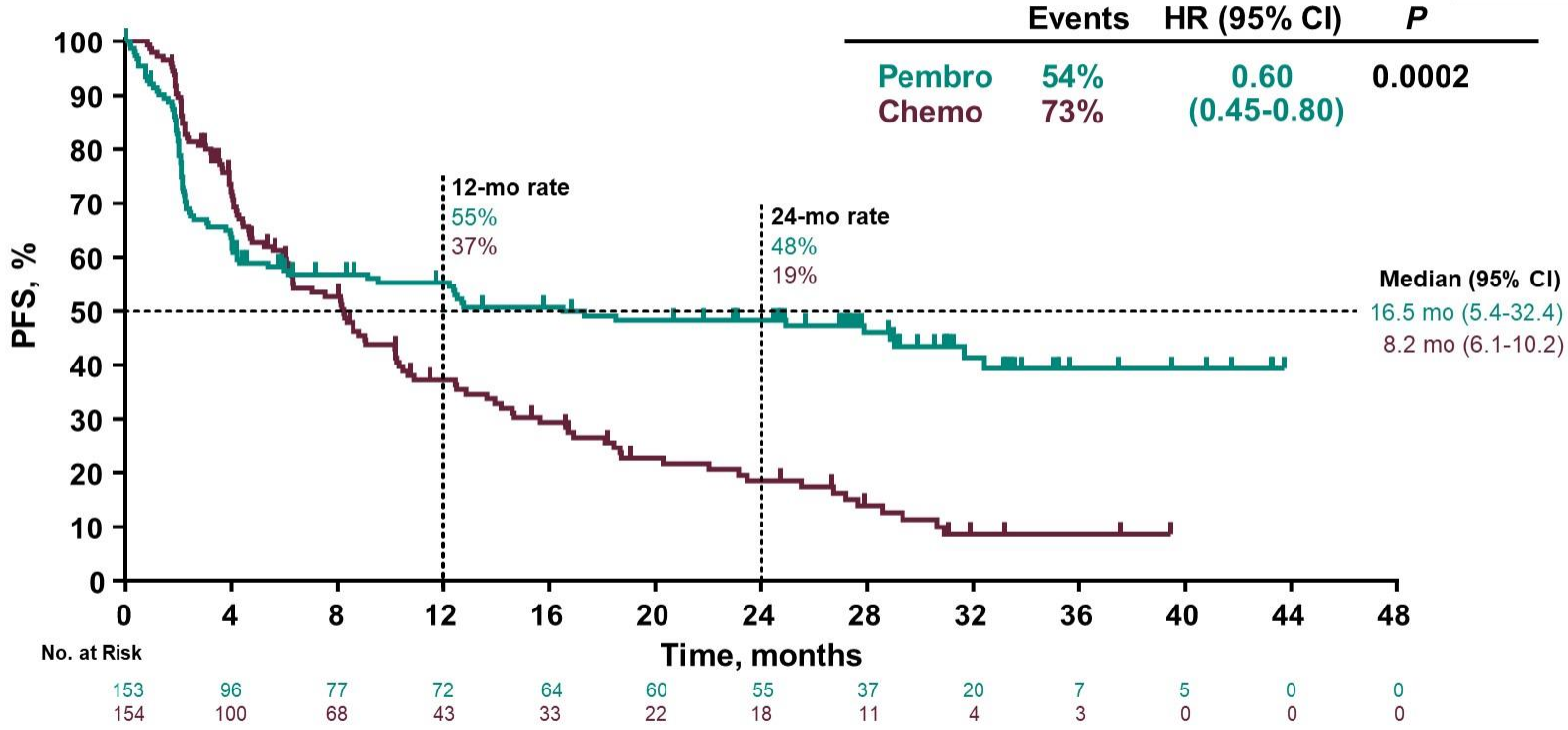
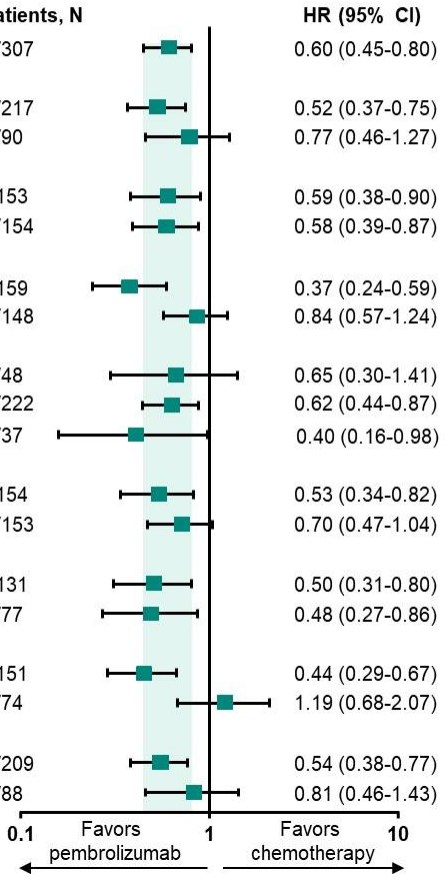


Median study follow-up: 32.4 months (range, 24.0 – 48.3); PFS (time from randomization to first documented disease progression or death) assessed per RECIST v1.1 by BICR. Superiority of pembrolizumab vs chemotherapy for PFS was demonstrated at the pre-specified one-sided $\alpha = 0.0117$; Data cut-off: 19Feb2020.

Progression-Free Survival in Key Subgroups



NA, North America; Data cut-off: 19Feb2020.

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Duration of Response

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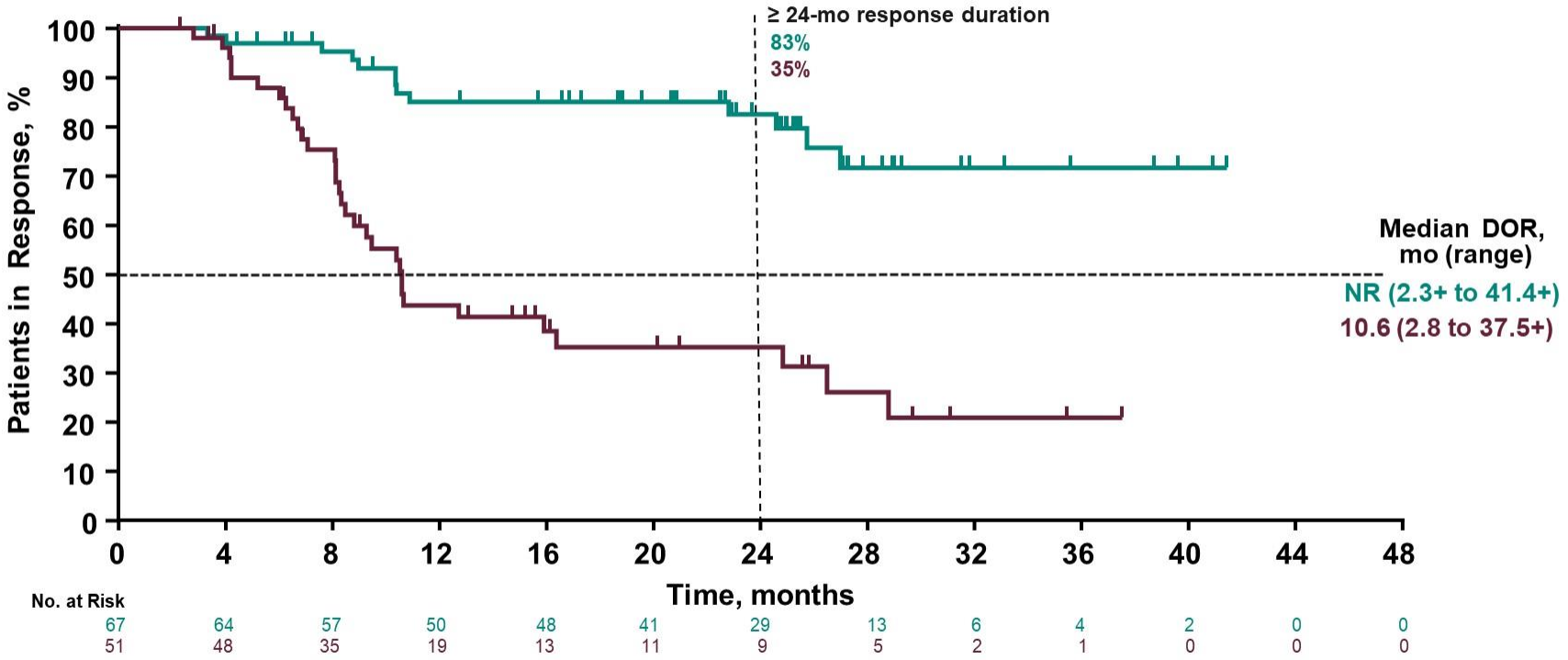


- Median time to response (range) was 2.2 mo (1.8-18.8) and 2.1 (1.7-24.9) for patients in the pembrolizumab and chemotherapy arms

Data cut-off: 19Feb2020; Duration of Response assessed per RECIST v1.1 by BICR.

Cross Over and Overall Survival

- 56 of 154 (36%) patients in chemotherapy arm crossed over to receive pembrolizumab after confirmed disease progression
  - 35 additional patients received anti-PD-1/PD-L1 therapy outside of the study for an effective crossover rate of 59% in the ITT population
- Final OS analysis
  - DMC recommended reporting OS at final analysis as OS remains immature
  - Study will remain blinded for OS until 190 OS events achieved or 12 months after second interim analysis

Immune-Mediated AEs and Infusion Reactions

	Pembrolizumab N = 153		Chemotherapy N = 143	
All	31%		13%	
Grade ≥3	9%		2%	
Discontinued	7%		0	
Died	0		0	
Incidence >0%	**All**	**Grade ≥3**	**All**	**Grade ≥3**
Hypothyroidism	12%	0	2%	0
Colitis	7%	3%	0	0
Hyperthyroidism	4%	0	0	0
Pneumonitis	4%	0	1%	0
Adrenal insufficiency	3%	1%	0	0
Hepatitis	3%	3%	0	0
Infusion reactions	2%	0	8%	1%
Hypophysitis	1%	0	0	0
Myositis	1%	0	0	0
Nephritis	1%	0	0	0
Pancreatitis	1%	1%	0	0
Severe skin reactions	1%	1%	1%	1%
Thyroiditis	1%	0	0	0
Type 1 Diabetes Mellitus	1%	1%	0	0
Myocarditis	0	0	1%	0

Based on a list of terms specified by the sponsor and included by the investigator regardless of attribution to study treatment or immune relatedness; Data cutoff: 19Feb2020.

Summary and Conclusions

- Pembrolizumab provided a clinically meaningful and statistically significant improvement in PFS versus chemotherapy in patients with MSI-H mCRC
  - Median PFS: 16.5 vs 8.2 months; HR 0.60 (95% CI 0.45-0.80; *P* = 0.0002)
  - 24-month PFS rates: 48.3% vs 18.6%
- Responses were more durable with pembrolizumab versus chemotherapy
  - Overall response rate: 43.8% vs 33.1%
  - Median duration of response: not reached vs 10.6 months
- Pembrolizumab versus chemotherapy provided clinically meaningful improvement in PFS2 in patients with MSI-H mCRC
  - Median PFS2: Not reached vs 23.5 months; HR 0.63 (95% CI 0.45-0.88)
- Manageable safety profile and improved HRQoL scores with pembrolizumab versus chemotherapy
- Data support pembrolizumab as new standard-of-care for first-line therapy in patients with MSI-H mCRC

Keynote 177 Take-Home Points

- PD1-based therapy is the new standard for frontline dMMR/MSI-H metastatic colorectal cancer
- Pembrolizumab was superior to standard of care chemotherapy with regard to efficacy, toxicity, and QOL
- **Test all colorectal cancer patients for MMR/MSI**

Safety and efficacy of anti–PD-1 antibody dostarlimab in patients (pts) with mismatch repair-deficient (dMMR) solid cancers: Results from GARNET study. T.Andre et al

- Dostarlimab
  - a monoclonal antibody targeting PD-1

- **Conclusions:**Dostarlimab demonstrated durable antitumor activity in a cohort of dMMR solid tumor pts, the majority of whom had GI cancers. The safety profile was consistent with other cohorts in GARNET, with immune-related TRAEs infrequent and low grade.

GARNET Study

- **GARNET Study**
- The ongoing phase I GARNET study is evaluating dostarlimab in patients with a variety of advanced solid tumors whose disease progressed following systemic therapy.
- Findings from cohort F, which included patients with locally determined dMMR/microsatellite instability–high (MSI-H) or *POLE*-mutated nonendometrial solid tumors, the majority of which were gastrointestinal.
- Other cohorts include patients with endometrial cancer, non–small cell lung cancer, and prostate cancer. Patients received dostarlimab at 500 mg every 3 weeks for four cycles, and 1,000 mg of dostarlimab every 6 weeks thereafter for up to 2 years.

GARNET Study

Safety and efficacy findings

- Safety findings for 144 patients and efficacy findings for 106 dMMR patients, of whom 99 (93.4%) had gastrointestinal tumors, including 69 (65%) with colorectal cancer, 12 (11%) with small intestine cancer, and 8 (8%) with gastric or gastroesophageal junction cancer. The majority of patients had received two or three prior lines of treatment.
- The confirmed objective response rate was 38.7%, with a complete response rate of 7.5%. Responses were consistent across both colorectal and noncolorectal tumor types.
- For the 41 responding patients, median duration of response had not been reached after a median of 12.4 months of follow-up. The probability of maintaining a response at 12 and 18 months was 91.0% and 80.9%, respectively. Responses were durable across tumor types

GARNET Study
Safety and efficacy findings

- Treatment-related adverse events were reported in 69% of patients, of which 8% were grade ≥ 3; treatment-related serious adverse events were observed in 6% of patients, and toxicities leading to discontinuation of treatment occurred in 4%.

- "The majority of patients were enrolled with advanced disease that had progressed on prior therapy and they had limited treatment options. This represents a patient group with a high unmet need.

Circulating tumor DNA analysis for assessment of recurrence risk, benefit of adjuvant therapy, and early relapse detection after treatment in colorectal cancer patients
Tenna V Henriksen et al.

- **Conclusion:** Postoperative ctDNA positive status was associated with markedly reduced RFS compared to CEA. The study also shows that effective therapy can be curative in a portion of MRD-positive patients. In a longitudinal setting, **ctDNA analysis predicted the risk of recurrence and is a more reliable biomarker for treatment response monitoring.**

Safety and efficacy of anti–PD-1 antibody dostarlimab in patients (pts) with mismatch repair-deficient (dMMR) solid cancers: Results from GARNET study.
T.Andre et al

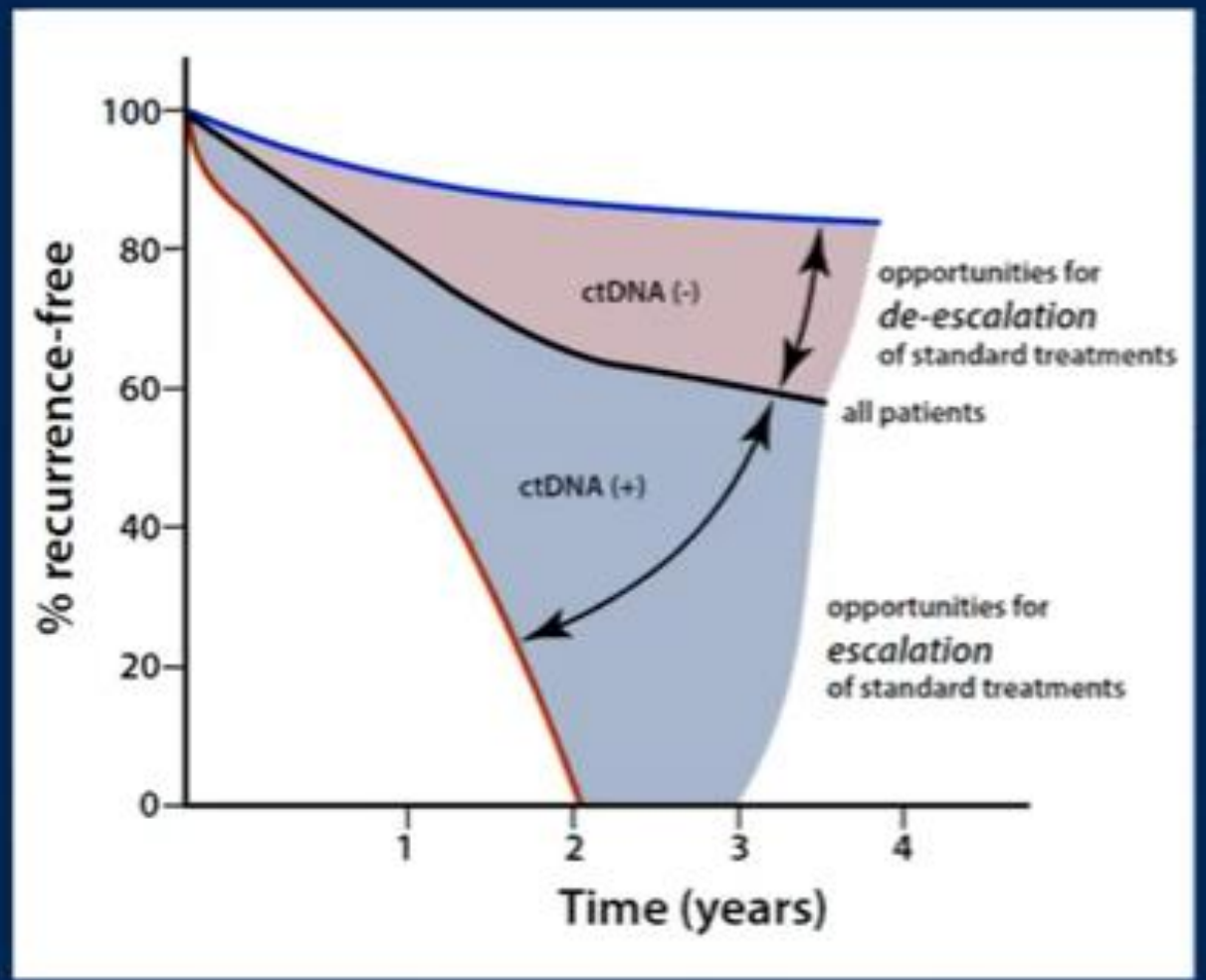
- **Background:**Dostarlimab is a humanized anti–PD-1 monoclonal antibody that binds the PD-1 receptor, blocking interaction with ligands PD-L1 and PD-L2. The ongoing phase 1 GARNET study (NCT02715284) is evaluating dostarlimab in pts with advanced solid tumors. Here we present safety and efficacy data from cohort F.
- **Methods:**Cohort F of the GARNET trial enrolled pts with dMMR or POLEmut non-endometrial solid tumors; the majority were gastrointestinal (GI) in origin. Pts must have progressed per blinded independent central review (BICR) following prior systemic therapy for advanced disease and had dMMR status by local immunohistochemistry. Pts received 500 mg dostarlimab Q3W for 4 cycles and 1000 mg Q6W until discontinuation. Objective response rate (ORR) and duration of response (DOR) were assessed by BICR per RECIST v1.1. Pts were included in the efficacy analysis if they received =1 dose of dostarlimab, had measurable disease at baseline, and 6 mo of follow up. All pts who received =1 dose were included in the safety analysis.
- **Results:**144 pts were included in the safety analysis, with 106 dMMR pts in the efficacy analysis (1 POLEmut pt with a confirmed PR was not included in this population). Of the 106 pts, 99 (93.4%) had GI tumors. Confirmed ORR in dMMR pts was 38.7% (95% CI: 29.4, 48.6), with a complete response rate of 7.5%. ORR was consistent across tumor type (**Table**). At the data cutoff, median duration of follow-up (n = 107; dMMR and POLEmut pts) was 12.4 months and median DOR was not reached. The Kaplan–Meier estimated probability of maintaining response at 12 and 18 months was 91.0% and 80.9% respectively.
- Treatment-related adverse events (TRAEs) were reported in 68.8% of pts; 8.3% of pts experienced at least 1 grade =3 TRAE. The most common was lipase increased in 2 (1.4%) pts. Treatment-related serious AEs (SAEs) were reported in 6 (5.5%) pts, and 2 pts (1.8%) discontinued dostarlimab due to a TRAE. No deaths were attributed to dostarlimab.

Circulating tumor DNA analysis for assessment of recurrence risk, benefit of adjuvant therapy, and early relapse detection after treatment in colorectal cancer patients

Tenna V Henriksen et al.

- **Background:**Timely detection of recurrence, as well as identification of patients at high risk of recurrence after surgery and after completion of adjuvant therapy, are major challenges in the treatment of colorectal cancer (CRC). Postsurgical circulating tumor DNA (ctDNA) analysis is a promising tool for the identification of patients with minimal residual disease (MRD) and a high risk of recurrence. The objective of this prospective, multicenter study was to determine whether serial postsurgical ctDNA analysis could identify the patients at high risk of recurrence, provide an assessment of adjuvant therapy efficacy and detect relapse earlier than standard-of-care radiological imaging.
- **Methods:**The cohort comprises 265 stage I-III CRC patients, the to-date largest cohort assessed for ctDNA. All patients had the tumor resected and a subset of 62.6% (166 /265) was additionally treated with ACT. Plasma samples (n = 1503) were collected at various time points for a median follow-up of 28.4 months (range: 1.2-51.0 months). Individual tumors and matched germline DNA were whole-exome sequenced and somatic single nucleotide variants (SNVs) were identified. Personalized multiplex PCR assays were designed to track tumor-specific SNVs (Signatera®, bespoke mPCR NGS assay) in each patient's plasma sample.
- **Results:** Postoperative ctDNA status prior to ACT was assessed in 218 patients, of which 9.17% (20/218) were identified to be MRD-positive and 75% (15/20) eventually relapsed. The remaining 25% (5/20) of MRD-positive patients that did not relapse, received ACT. In contrast, only 13.6% (27/198) of MRD-negative cases relapsed (HR: 11: 95% CI: 5.7-20; $p < 0.001$). Longitudinal ctDNA-positive status, post-definitive therapy (n = 202) was associated with a HR of 36 (95% CI: 16-81; $p < 0.001$). For a subset of 155 patients postoperative CEA and ctDNA measurements were compared, wherein, ctDNA-positive status was found to be significantly associated with RFS (HR, 7.1; 95% CI, 3.4-15; $P < 0.001$) compared to CEA (HR, 1.2; 95% CI, 0.46-3.1; $P = 0.73$). Serial ctDNA analysis detected MRD up to a median of 8 months (0.56 - 21.6 months) ahead of radiologic relapse.
- **Conclusion:** Postoperative ctDNA positive status was associated with markedly reduced RFS compared to CEA. The study also shows that effective therapy can be curative in a portion of MRD-positive patients. In a longitudinal setting, ctDNA analysis predicted the risk of recurrence and is a more reliable biomarker for treatment response monitoring.

ctDNA as a Biomarker for MRD



- Key assay performance depends on use:
  - De-escalation approach: High **sensitivity**
  - Escalation approach: High **specificity**

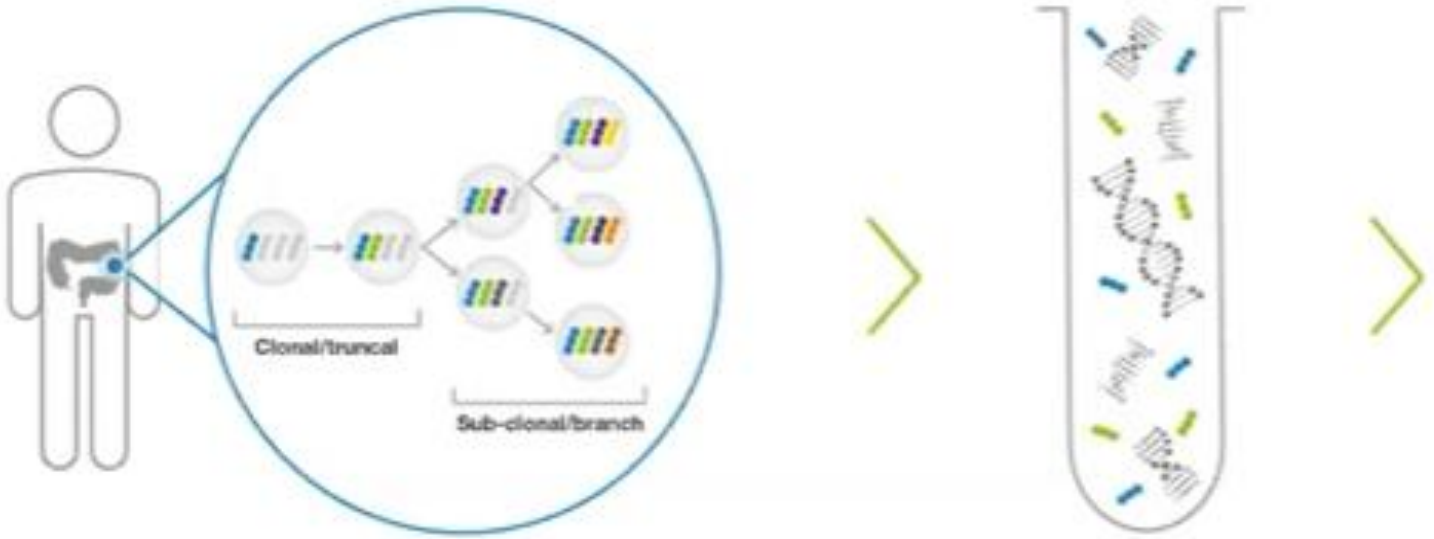
- Approaches:
  - Tumor-informed mutations
  - Panel-based (mutations, methylation…)

Please see: Emerging Tools for Precision Care session: "Circulating Tumor DNA" by Arvind Dasari

Natera tumor-informed ctDNA assay

Sequence tumor tissue to identify unique signature of tumor mutations

Custom design and manufacture personalized mPCR assay for each patient, targeting the top 16 clonal mutations found in tumor

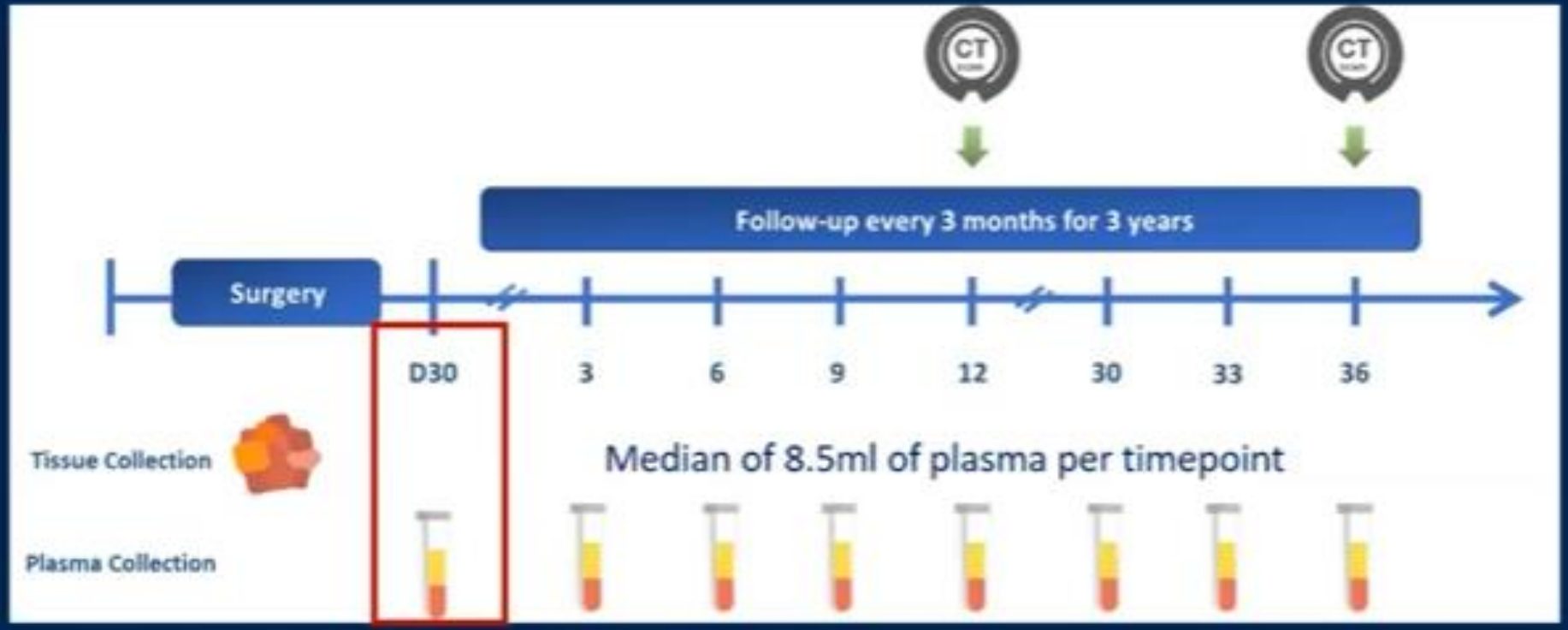


- Select clonal mutations
- Top 16 mutations used
- ≥2 variants above a set "confidence score" defines ctDNA+
- "turnaround time for timepoint 1 is less than 4 weeks"
- "Confident detection down to 0.03% VAF"

Reinert and Henriksen et al. JAMA Onc 2019
Abbosh et al. Nature 2017
Alexandrov et al. Nature 2013

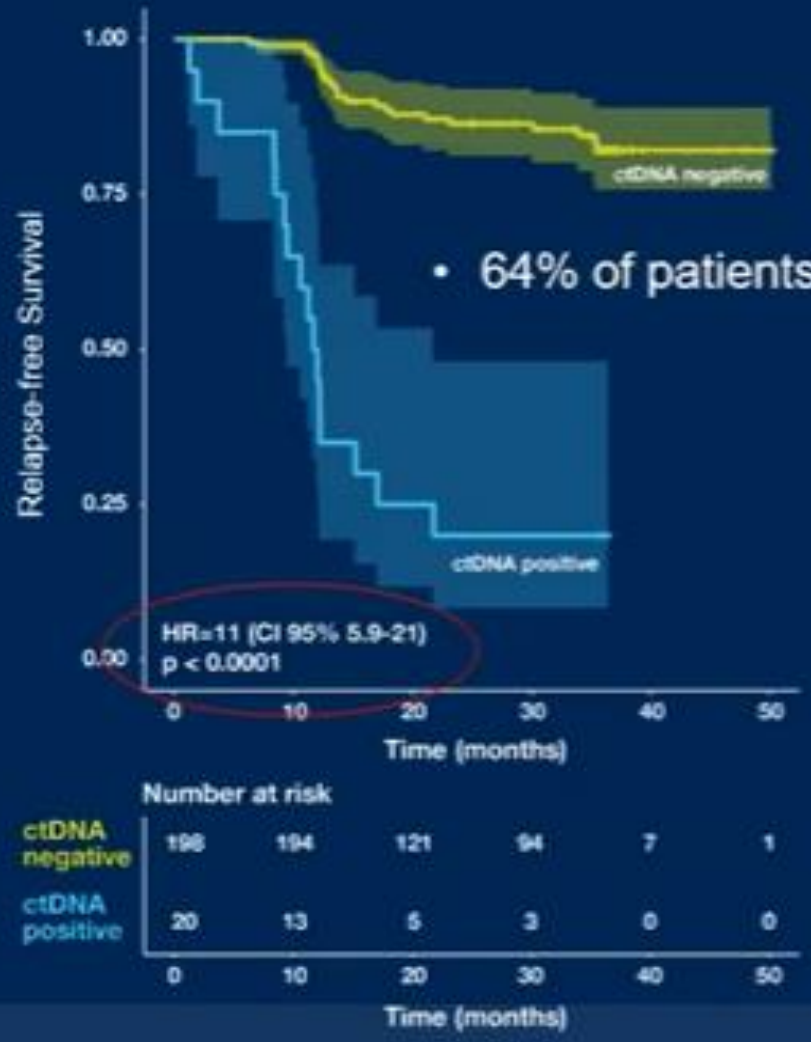
Comments on study design

- Prospective study but retrospective CEA/ctDNA analysis
  - Standard DCCG post-resection followup is a CT at 12m and 36m
  - ctDNA/CEA analysis was blinded to clinical data
  - Evaluation of time-line integration into practice was not evaluated



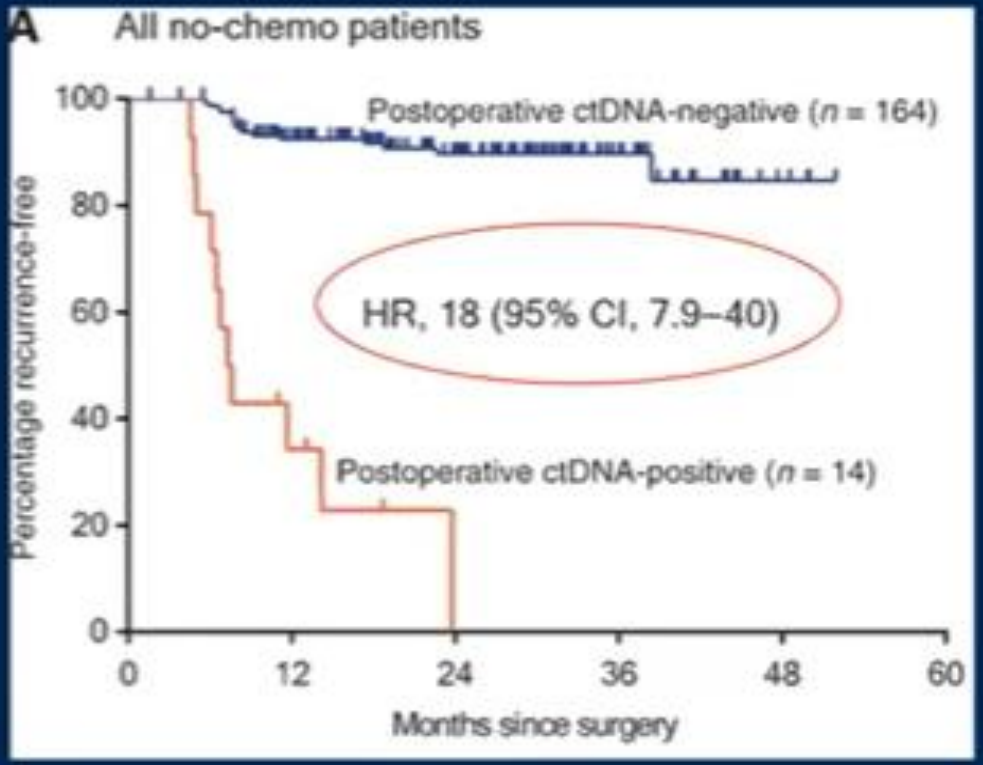
Reinert and Henriksen et al. JAMA Onc 2019

Postoperative ctDNA detection



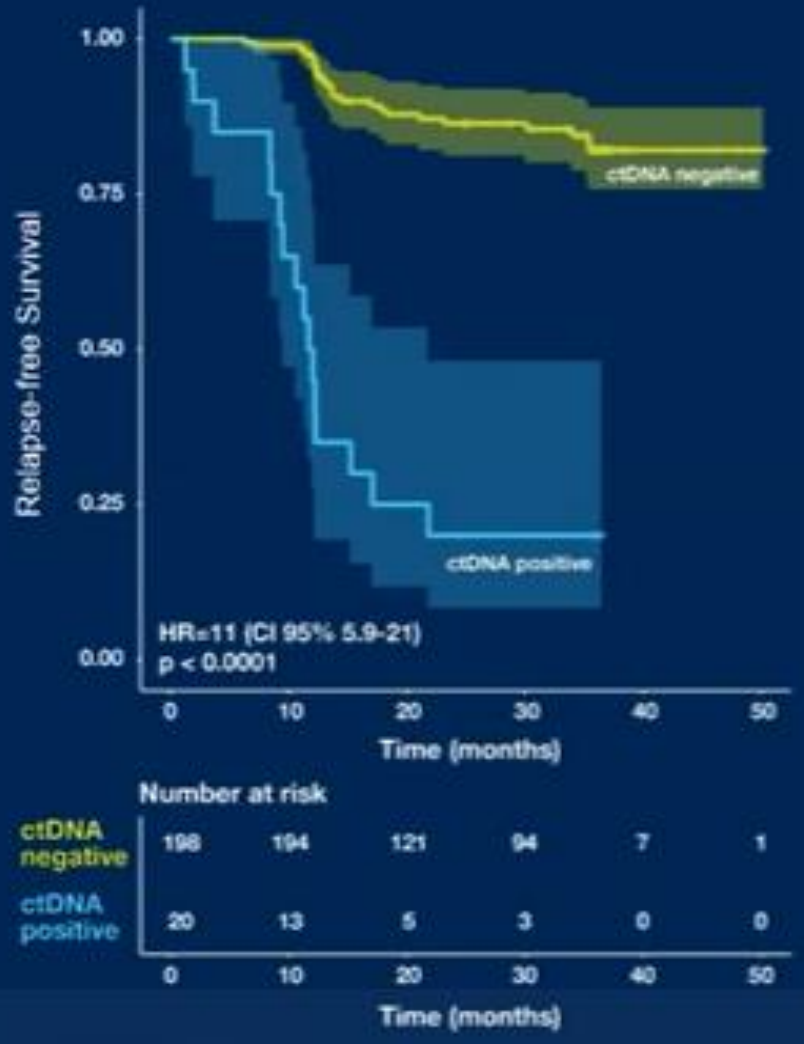
- 64% of patients were stage III

Stage II CRC Patients



Tie et al, Sci Transl Med 2016

Postoperative ctDNA detection

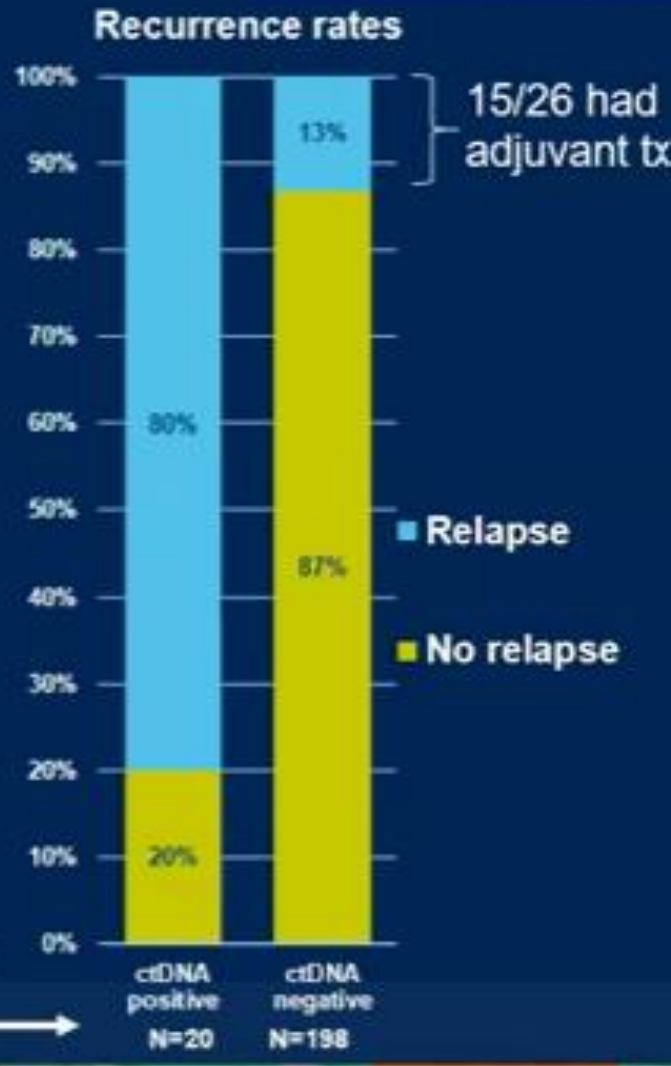


This data does not answer ctDNA as a predictive biomarker (randomized prospective studies are needed)

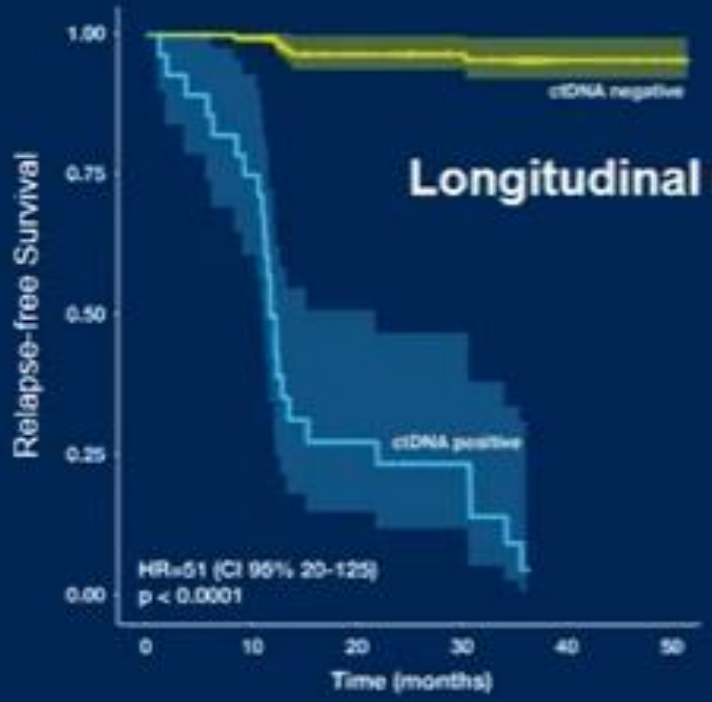
"Modified by ACT?"

4 ctDNA+ pts did not recur (all had adjuvant tx)

19/20 pts had adjuvant tx



CEA and longitudinal detection of ctDNA



Longitudinal monitoring

- **The greatest potential to change practice results from post-operative ctDNA testing**
- **Longitudinal monitoring potential relates to the ability to replace current post surveillance approaches (CEA and/or CT scans)**

		Univariable analysis		Multivariable analysis	
	n	HR (95% CI)	P-value	HR (95% CI)	P-value
CEA PostOP	175	1.3 (0.56-3.2)	0.524		
CEA PostACT	99	1.4 (0.44-4.2)	0.596		
CEA Longitudinal	197	4.9 (3.2-15)	<0.0001	1.8 (0.77 - 4.0)	0.184
ctDNA Longitudinal	197	95.7 (28-322)	<0.0001	80.55 (23.1 - 281)	<0.0001

ctDNA as MRD Biomarker Take-Home

- ctDNA has ability to robustly prognosticate patients post CRC surgical resection
- Multiple approaches to ctDNA detection are under investigation
- How to use ctDNA to guide therapy decisions (predictive use) is not known and many studies are underway
  - Availability is not the same as actionability
  - We must enroll patients to ctDNA guided trials to optimally learn how to utilize ctDNA in clinical practice

diskuze

NRG-GI-005 (COBRA) Study

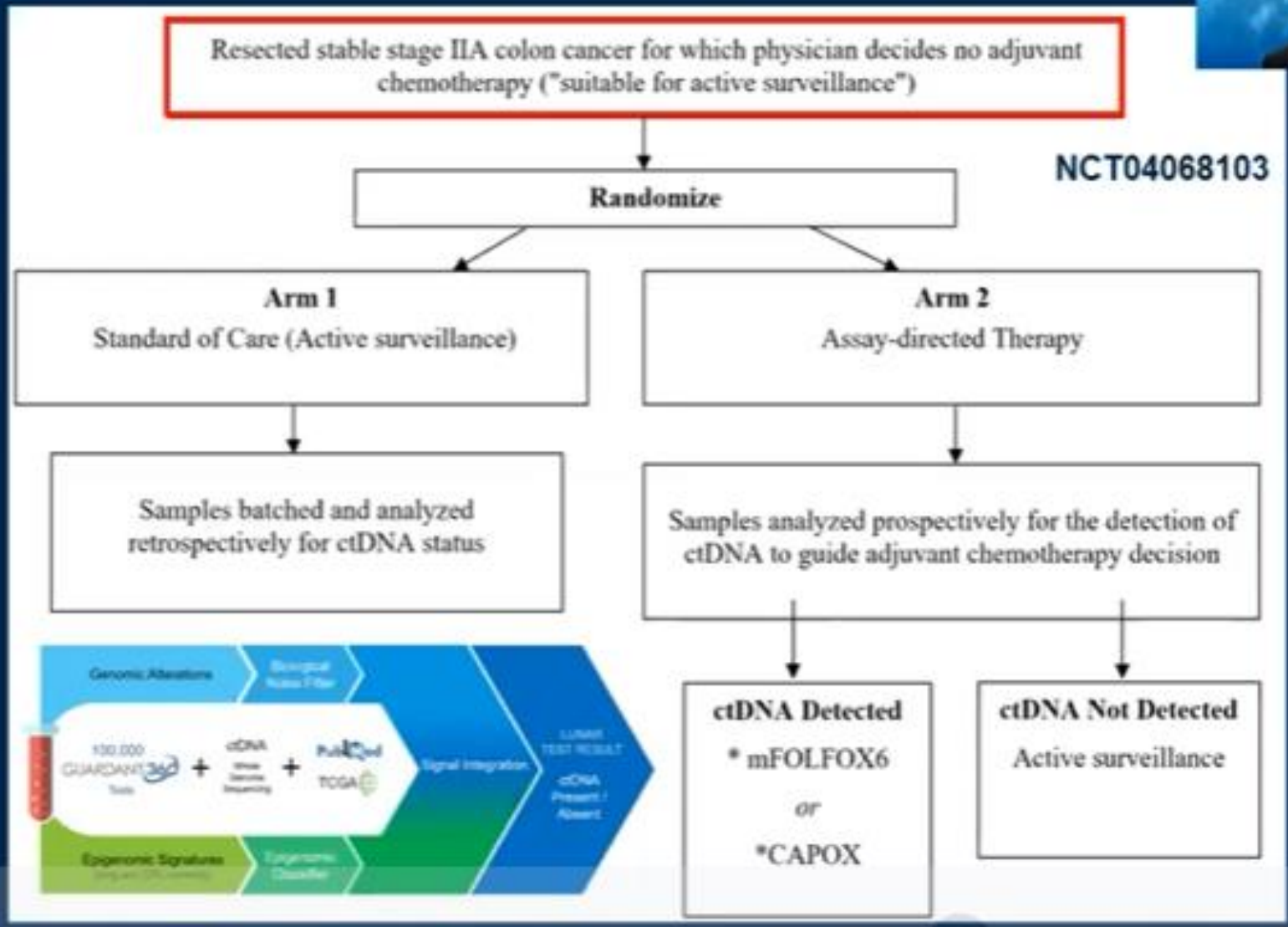
Open and Enrolling

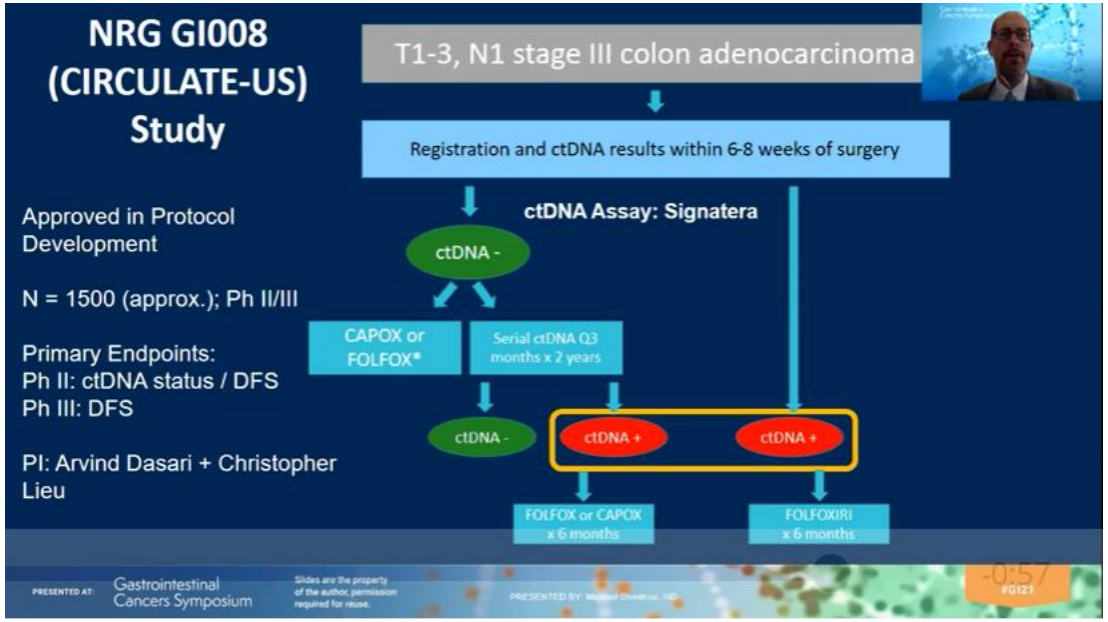
N = 1408

Primary Endpoints:
Ph II: ctDNA clearance
Ph III: RFS

PI: Van Morris

ctDNA Assay:
Guardant Lunar-1




NRG GI008 (CIRCULATE-US) Study
T1-3, N1 stage III colon adenocarcinoma
Registration and ctDNA results within 6-8 weeks of surgery
ctDNA Assay: Signatera
Approved in Protocol Development
N = 1500 (approx.); Ph II/III
Primary Endpoints:
Ph II: ctDNA status / DFS
Ph III: DFS
PI: Arvind Dasari + Christopher Lieu
ctDNA -
CAPOX or FOLFOX*
Serial ctDNA Q3 months x 2 years
ctDNA -
ctDNA +
ctDNA +
FOLFOX or CAPOX x 6 months
FOLFOXIRI x 6 months
PRESENTED AT:
Gastrointestinal Cancers Symposium
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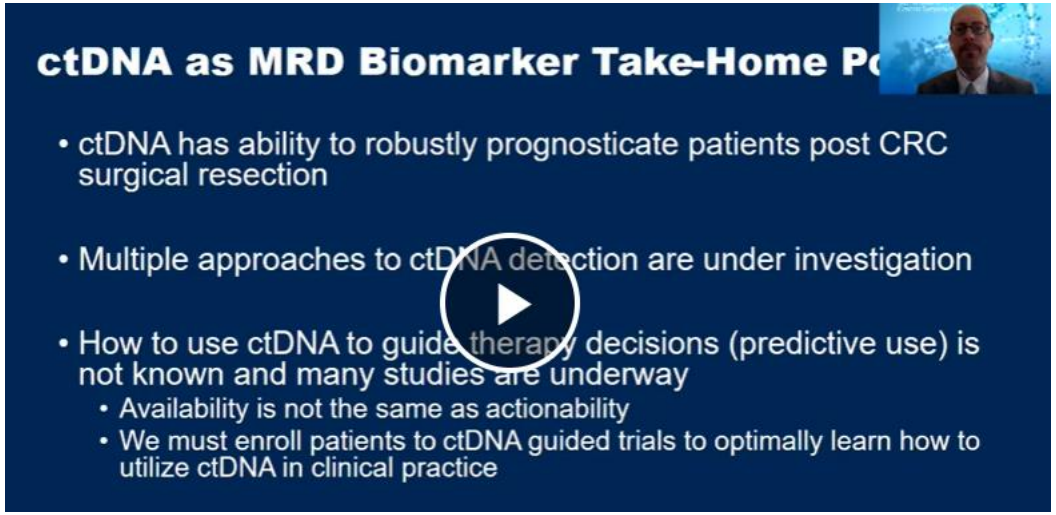

ctDNA as MRD Biomarker Take-Home Po
• ctDNA has ability to robustly prognosticate patients post CRC surgical resection
• Multiple approaches to ctDNA detection are under investigation
• How to use ctDNA to guide therapy decisions (predictive use) is not known and many studies are underway
• Availability is not the same as actionability
• We must enroll patients to ctDNA guided trials to optimally learn how to utilize ctDNA in clinical practice

- NRG-GI002: A phase II clinical trial platform using total neoadjuvant therapy (TNT) in locally-advanced rectal cancer (LARC)—Pembrolizumab experimental arm (EA) primary results.
- Osama E. Rahma et al
- **Conclusions:**
- Pembrolizumab added to chemoRT as part of TNT was safe and without unexpected short-term toxicities but failed to improve the NAR score. The secondary endpoints including PFS and OS have not been reached. Correlative analysis for both T-cell and myeloid cell populations in the tissue and blood in addition to comprehensive cytokine analysis is ongoing. NCT02921256. Support: U10CA180868, -180822; UG1-189867; U24-196067.

- **Background:**
- This NCTN multi-arm randomized phase II modular clinical trial platform utilizes TNT with parallel EAs in LARC. EAs are not intended for direct comparison, but rather to test a variety of sensitizers or hypotheses in a consistent and homogenous high-risk pt population with correlative biomarkers. Here we report the primary and available secondary endpoints (EPs).
- **Methods:**
- Stage II/III LARC pts (with ONE or more of the following: distal location [cT3-4 =5cm from anal verge, any N]; bulky [any cT4 or tumor within 3mm of mesorectal fascia]; high risk for metastatic disease [cN2]; or not a sphincter-sparing surgery [SSS] candidate) were randomized to neoadjuvant FOLFOX x 4mo ? chemoRT (capecitabine with 50.4Gy +/- pembrolizumab 200mg IV Q3 wks x 6 doses) ? surgery 8-12 wks following last dose of radiotherapy. Primary EP: Improvement in Neoadjuvant Rectal Cancer (NAR) score for EA *v* control potentially representing a 3-4% absolute OS improvement. Secondary EPs: Comparisons of OS, DFS, toxicity, pCR, cCR, therapy completion, negative surgical margins, sphincter sparing surgery (SSS), and exploratory assessments of molecular and radiographic predictors of response and distant failure. Binary EPs compared by Fisher's exact test. Reported p-values are two-sided.
- **Results:**
- From 8/2018-5/2019, 185 pts were randomized to control (n=95) or pembrolizumab (n= 90). Baseline characteristics were relatively well balanced. 137 pts were evaluable for NAR (68 control, 69 pembrolizumab). Mean NAR was 14.08 for control (95% CI: 10.7-17.4) *v* 11.53 for pembrolizumab (CI: 8.5-14.6) (p=0.26). pCR=29.4% *v* 31.9% (p=0.75); cCR=13.6% *v* 13.9% (p=0.95); and SSS=71.0% v 59.4% (p=0.15). The side effects on Arm 3 were consistent with both CRT and pembrolizumab safety profile. Grade 3/4 AEs were slightly increased on the pembrolizumab arm during and after CRT (48.2 *v* 37.3%). There were 2 deaths during FOLFOX, one on the control arm due to sepsis; the other on the EA due to pneumonia. There were no statistically significant differences in RT (fractions, dose, boost fractions, or boost dose), FOLFOX or capecitabine doses.

- Safety and efficacy of anti–PD-1 antibody dostarlimab in patients (pts) with mismatch repair-deficient (dMMR) solid cancers: Results from GARNET study.
- T.Andre et al
- **Conclusions:**Dostarlimab demonstrated durable antitumor activity in a cohort of dMMR solid tumor pts, the majority of whom had GI cancers. The safety profile was consistent with other cohorts in GARNET, with immune-related TRAEs infrequent and low grade.

- **Background:**Dostarlimab is a humanized anti–PD-1 monoclonal antibody that binds the PD-1 receptor, blocking interaction with ligands PD-L1 and PD-L2. The ongoing phase 1 GARNET study (NCT02715284) is evaluating dostarlimab in pts with advanced solid tumors. Here we present safety and efficacy data from cohort F.
- **Methods:**Cohort F of the GARNET trial enrolled pts with dMMR or POLEmut non-endometrial solid tumors; the majority were gastrointestinal (GI) in origin. Pts must have progressed per blinded independent central review (BICR) following prior systemic therapy for advanced disease and had dMMR status by local immunohistochemistry. Pts received 500 mg dostarlimab Q3W for 4 cycles and 1000 mg Q6W until discontinuation. Objective response rate (ORR) and duration of response (DOR) were assessed by BICR per RECIST v1.1. Pts were included in the efficacy analysis if they received =1 dose of dostarlimab, had measurable disease at baseline, and 6 mo of follow up. All pts who received =1 dose were included in the safety analysis.
- **Results:**144 pts were included in the safety analysis, with 106 dMMR pts in the efficacy analysis (1 POLEmut pt with a confirmed PR was not included in this population). Of the 106 pts, 99 (93.4%) had GI tumors. Confirmed ORR in dMMR pts was 38.7% (95% CI: 29.4, 48.6), with a complete response rate of 7.5%. ORR was consistent across tumor type (**Table**). At the data cutoff, median duration of follow-up (n = 107; dMMR and POLEmut pts) was 12.4 months and median DOR was not reached. The Kaplan–Meier estimated probability of maintaining response at 12 and 18 months was 91.0% and 80.9% respectively.
- Treatment-related adverse events (TRAEs) were reported in 68.8% of pts; 8.3% of pts experienced at least 1 grade =3 TRAE. The most common was lipase increased in 2 (1.4%) pts. Treatment-related serious AEs (SAEs) were reported in 6 (5.5%) pts, and 2 pts (1.8%) discontinued dostarlimab due to a TRAE. No deaths were attributed to dostarlimab.

Tumor type	N	Confirmed ORR (RECIST v1.1)	
		n (%)	95% CI*
Overall	**106**	**41 (38.7)**	**29.4–48.6**
CRC	**69**	**25 (36.2)**	**25.0–48.7**
Non-CRC			
Small Intestinal Cancer	**37**	**16 (43.2)**	
Gastric Cancer	12	4 (33.3)	
Pancreatic Carcinoma	8	3 (37.5)	
Liver Cancer	4	0	
Ovarian Cancer	2	PR, PD	
Adrenal Cortical	2	PR, SD	

Karcinom slinivky břišní

- Alliance A021501: Preoperative mFOLFIRINOX or mFOLFIRINOX plus hypofractionated radiation therapy (RT) for borderline resectable (BR) adenocarcinoma of the pancreas.
- M.Katz et al.

- **Conclusions:**Neoadjuvant mFOLFIRINOX was associated with favorable OS relative to historical data in pts with BL PDAC in this phase II NCTN trial. mFOLFIRINOX with hypofractionated RT did not improve OS compared to historical data. mFOLFIRINOX represents a reference regimen in this setting and a backbone on which to add novel agents.

Alliance A021501: Preoperative mFOLFIRINOX or mFOLFIRINOX plus hypofractionated radiation therapy (RT) for borderline resectable (BR) adenocarcinoma of the pancreas

M.Katz et al.

- **Background:**Neoadjuvant therapy has been associated with a median overall survival (OS) of 18 – 23 months (mo) in patients (pts) with BR pancreatic ductal adenocarcinoma (PDAC). To establish reference regimens to which novel treatments can be compared in future studies, we evaluated neoadjuvant mFOLFIRINOX with or without RT in BR PDAC in a phase II National Clinical Trials Network (NCTN) trial.
- **Methods:**Pts with ECOG PS 0-1 and BR PDAC confirmed by central real-time radiographic review after pre-registration were randomized to either arm A: 8 cycles of neoadjuvant mFOLFIRINOX (oxaliplatin 85 mg/m^2, irinotecan 180 mg/m^2, leucovorin 400 mg/m^2 and infusional 5-fluorouracil 2400 mg/m^2 over 46 hours), or arm B: 7 cycles of mFOLFIRINOX followed by stereotactic body RT (SBRT, 33-40 Gy in 5 fractions [fx]) or hypofractionated image guided RT (HIGRT, 25 Gy in 5 fx). Pts in either arm without disease progression underwent pancreatectomy, then 4 cycles of adjuvant mFOLFOX6 (oxaliplatin 85 mg/m^2, leucovorin 400 mg/m^2 and infusional 5-fluorouracil 2400 mg/m^2 over 46 hours). The primary endpoint, 18-mo OS rate, of each arm was compared to a historical control of 50%. Planned interim analysis mandated closure of either arm in which $\leq$11 of first 30 accrued pts underwent R0 resection.
- **Results:**155 pts pre-registered and 126 pts were enrolled to arm A (N=70; 54 randomized, 16 following closure of arm B) or arm B (N=56; closed at interim analysis, all pts randomized prior to closure). Median age (A: 63y, B: 67y), median CA 19-9 level (A: 171 U/ml, B: 248 U/ml) and ECOG PS (A: 51% PS 0, B: 57% PS 0) of registered pts were similar between arms ($p > 0.05$). Treatment detailed in Table. The 18-mo OS rate based on Kaplan Meier estimates was 67.9% (95%CI: 54.6 – 78.0) in arm A and 47.3% (95%CI: 33.7 – 59.7) in arm B. Among pts who underwent pancreatectomy, 18-mo OS rate was 93.1% (95%CI: 84.3 – 100) and 78.9% (95%CI: 62.6 – 99.6) in arm A and B, respectively. With median follow-up of 27 and 31 mo, median OS was 31.0 (95%CI: 22.2 – NE) mo and 17.1 (95%CI: 12.8 – 24.4) mo in arm A and B, respectively.

Alliance A021501

Quality control
Imaging, RT, Surgery, Pathology

Patient with BLR PDAC (Intergroup Definition)

PREREGISTER → CENTRAL REVIEW → REGISTER / RANDOMIZE

Arm A

mFOLFIRINOX [1] 4 cycles → RESTAGE → mFOLFIRINOX [1] 4 cycles → RESTAGE → SURGERY [3] → RESTAGE → FOLFOX [4] 4 cycles

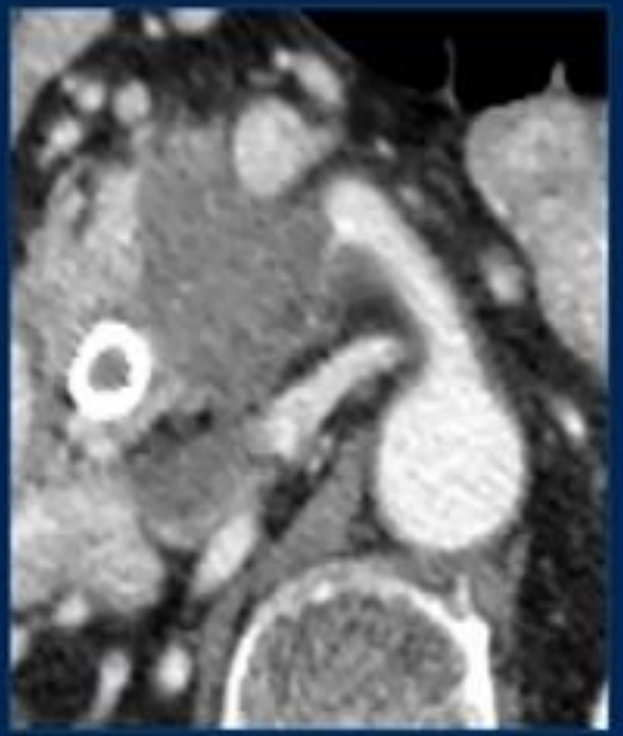
Arm B

mFOLFIRINOX [1] 4 cycles → RESTAGE → mFOLFIRINOX [1] 3 cycles → RADIATION [2] → RESTAGE → SURGERY [3] → RESTAGE → FOLFOX [4] 4 cycles

[1] Oxaliplatin 85 mg/m², irinotecan 180 mg/m², leucovorin 400 mg/m² and infusional 5-fluorouracil 2400 mg/m² over 46 h
[2] Stereotactic Body RT, 33-40 Gy in 5 fx or hypofractionated image guided RT, 25 Gy in 5 fx
[3] Segmental pancreatectomy with regional lymphadenectomy +/- vascular resection
[4] Oxaliplatin 85 mg/m², leucovorin 400 mg/m² and infusional 5-fluorouracil 2400 mg/m² over 46 h

Eligibility

- Biopsy-proven pancreatic adenocarcinoma
- One or more centrally-reviewed radiographic criteria
  - Interface with SMV or PV ≧ 180°
  - Short-segment occlusion of SMV-PV, amenable to reconstruction
  - Interface (of any degree) with HA, amenable to reconstruction
  - Interface with SMA or CA < 180°
- Age ≧ 18, PS 0-1
- Normal physiologic parameters including bilirubin ≦ 2 mg/dL
- M1 to distant nodes or organs; ascites; prior treatment excluded



SMV/PV ≧ 180° + SMA < 180°

Statistics

- **Primary Endpoint**
  - Binary 18-month OS rate
- **Secondary Endpoints**
  1. EFS: Time from randomization to first of: progression, R2 resection, recurrence following resection, death
  2. AE rates during preoperative therapy, 90-day perioperative window, adjuvant therapy
  3. R0 resection rate
  4. pCR rate

- **Interim futility analysis**
  - Closure of either arm in which ≦ 11 (37%) of first 30 patients underwent R0 resection
- **Final efficacy analysis**
  - Sample size: 62 patients/arm to detect an improvement in the 18-month OS rate of 13% over historical rate of 50%
  - 82% power at one sided alpha 0.07
  - Either arm which reached full accrual and in which at least 36 patients alive 18 months after randomization declared efficacious
  - If both arms successfully pick the winner

Trial logistics

Enrollment targets, sites, and activation/closure dates

Characteristic	Trial	Arm A mFOLFIRINOX	Arm B mFOLFIRINOX → RT
Enrollment target, N	134	67	67
Activation date	12/01/2016		
Interim analysis (R0 in first 30 pts)	8/1/2018 †	17 (57%)	10 (33%)
Closure date	5/31/2019	5/31/2019	8/13/2018
Actual enrollment, N *	126	70	56

* 50 sites accrued ≧ 1 patient
† Alliance DSMB released the interim analysis data

CONSORT

Pre-registered
N = 155

Registered
N = 126

	Arm A n = 70, first 54 randomized	Arm B n = 56, all randomized	
	mFOLFIRINOX c1 65	mFOLFIRINOX c1 55	
AE (1) Progression (1) Other (3)			AE (1)
	mFOLFIRINOX c8 47 (72%)	RT † 40 (73%)	
AE (8*) Progression (3) Physician choice (2) Other (5)			AE (5) Progression (3) Physician choice (2) Other (5)
	Surgery 38 (58%)	Surgery 28 (51%)	
AE (1) Progression (3) Physician choice (4) Other (1)			Progression (6) Physician choice (4) Other (2)
	Pancreatectomy 32 (49%)	Pancreatectomy 19 (35%)	
Unresectable (4) Metastasis (2)			Unresectable (4) Metastasis (5)
	FOLFOX 22 (34%)	FOLFOX 13 (24%)	
AE (4) Progression (2) Other (4)			AE (2) Progression (2) Other (2)
	Completed therapy 20 (31%)	Completed therapy 10 (18%)	
AE (1) Progression (1)			AE (1) Progression (1) Other (1)

* 1 AE-related death

† SBRT (35), HIGRT (5)

Baseline profile

Baseline clinicodemographic profile of all treated patients

Characteristic	Arm A mFOLFIRINOX (n = 65)	Arm B mFOLFIRINOX → RT (n = 55)
Age, yr, median (range)	62 (37 – 83)	64 (40 – 80)
Female gender, n (%)	32 (49)	28 (51)
White race, n (%)	54 (83)	50 (91)
ECOG 0, n (%)	33 (51)	32 (58)
CA 19-9, U/ml, median (range)	167 (1 – 13,220)	260 (0 – 14,010)

Preoperative treatment-related toxicity

Adverse events (at least possibly related) during each preoperative treatment modality

AE during treatment, n (%)	Arm A mFOLFIRINOX (n = 65)	Arm B mFOLFIRINOX → RT (n = 55)
Experienced ≧ 1 grade 3+ AE	37 (57)	35 (64)
During mFOLFIRINOX	37 (57)	35 (64)
During RT*	–	5 (13)
Experienced ≧ 1 grade 4+ AE	11 (17) †	5 (9)
During mFOLFIRINOX	11 (17)	5 (9)
During RT*	–	0 (0)

* 40 patients received RT
† 1 patient experienced a grade 5 AE (sepsis)

Surgery and pathology

Surgery and pathology outcomes

Characteristic, n (%)	Arm A mFOLFIRINOX (n = 32)	Arm B mFOLFIRINOX → RT (n = 19)
Pancreatoduodenectomy	30 (94)	18 (95)
SMV/PV resection	12 (38)	6 (32)
Hepatic artery resection	1 (3)	2 (11)
R0, n (%)	28 (88)	14 (74)
N0, n (%)	15 (47)	9 (47)
pCR	0	2 (11) *

* < 5% viable cancer cells: Arm A 4 (13%); Arm B 5 (26%)

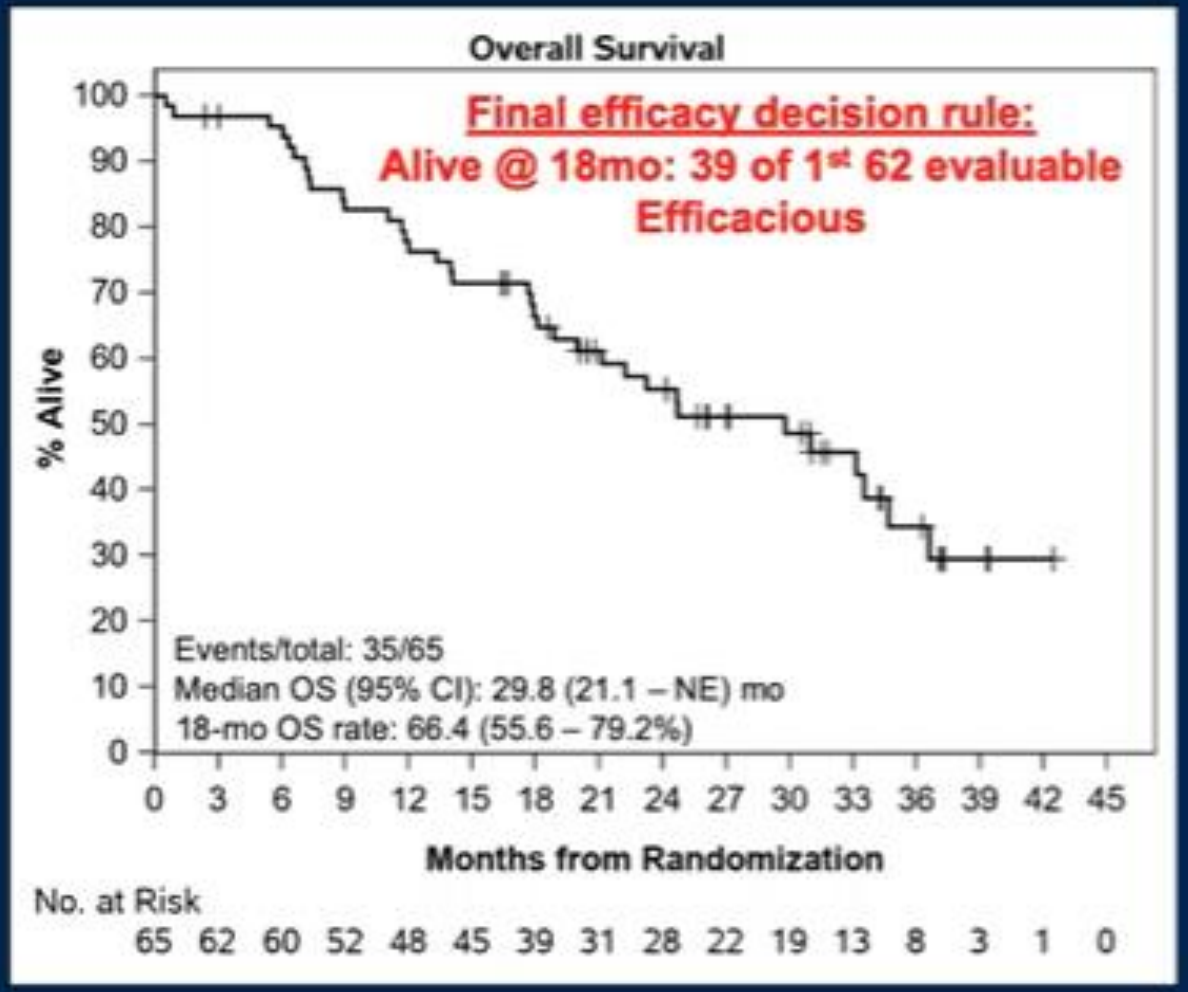
Surgical Adverse Events

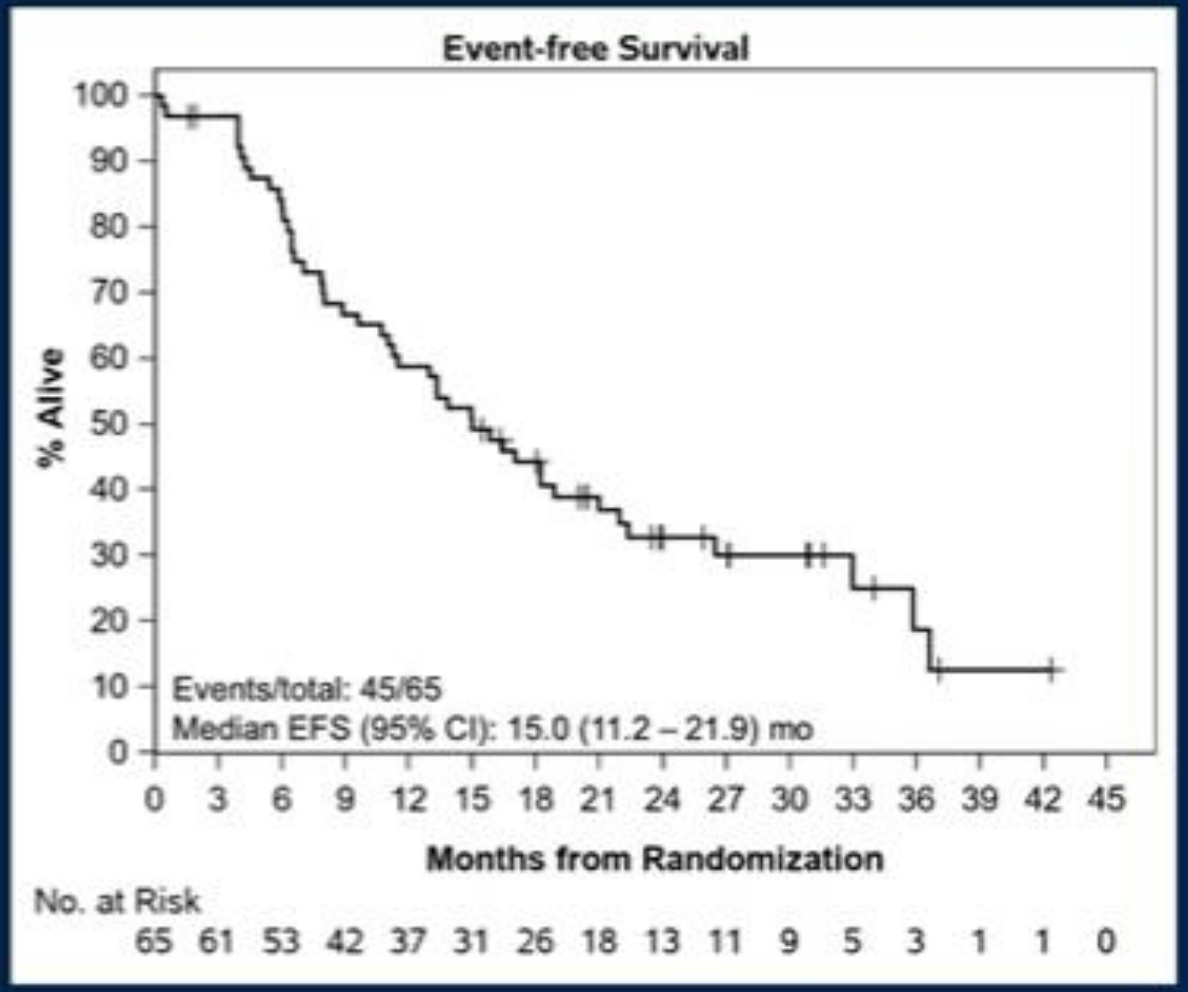
Perioperative adverse events

AE, n (%)	Arm A mFOLFIRINOX (n = 32)	Arm B mFOLFIRINOX → RT (n = 19)
Weight Loss (Grade 3+) *	3 (11)	1 (8)
Anemia (Grade 3+) *	1 (4)	2 (17)
Pancreatic fistula or intra-abdominal abscess	3 (9)	3 (16)
Wound infection	2 (6)	3 (16)
Readmission	5 (16)	8 (42)
Reoperation	4 (13)	1 (5)
Death	1 (3)	2 (11)

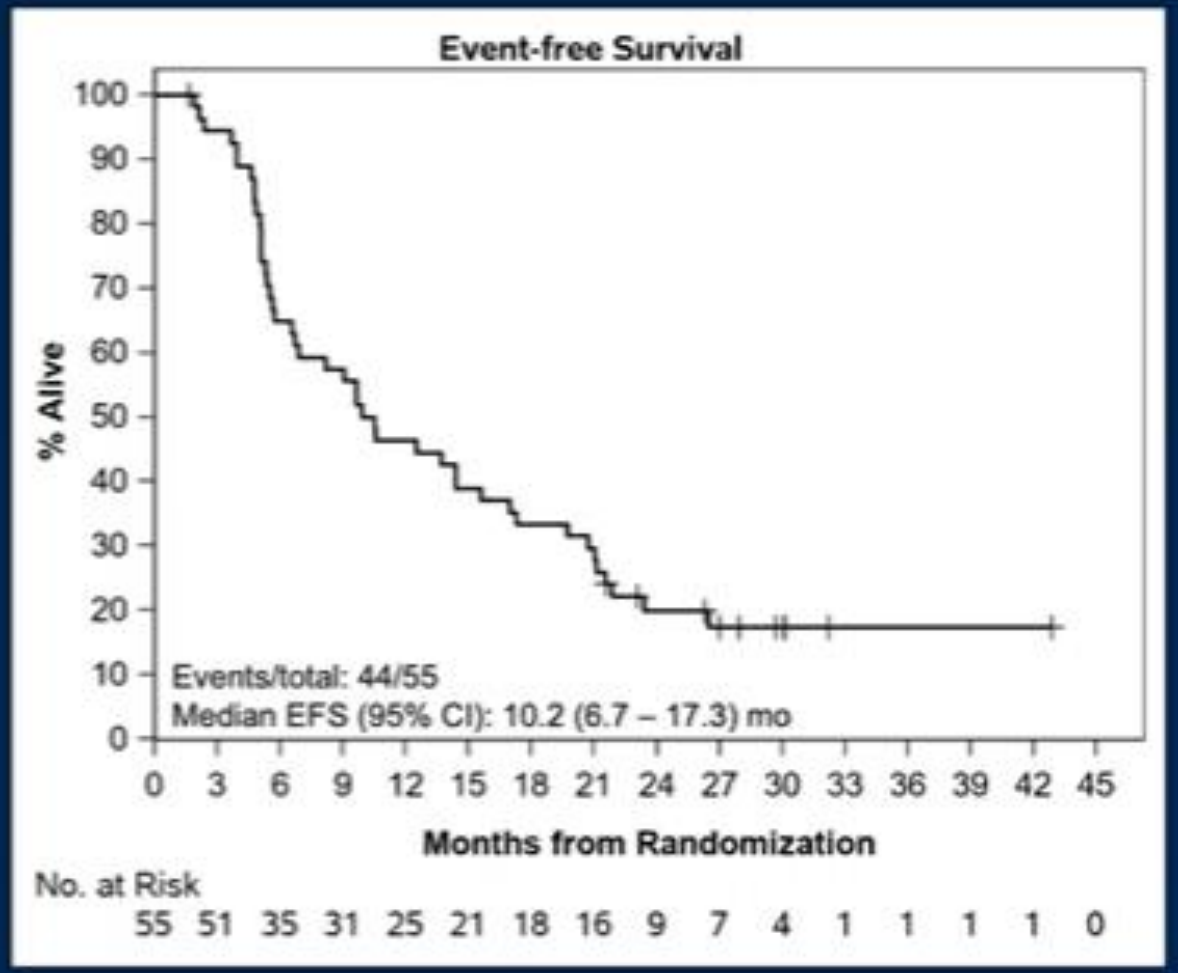
* Most common perioperative AEs (related to treatment)

Arm A: mFOLFIRINOX





Arm B: mFOLFIRINOX → RT



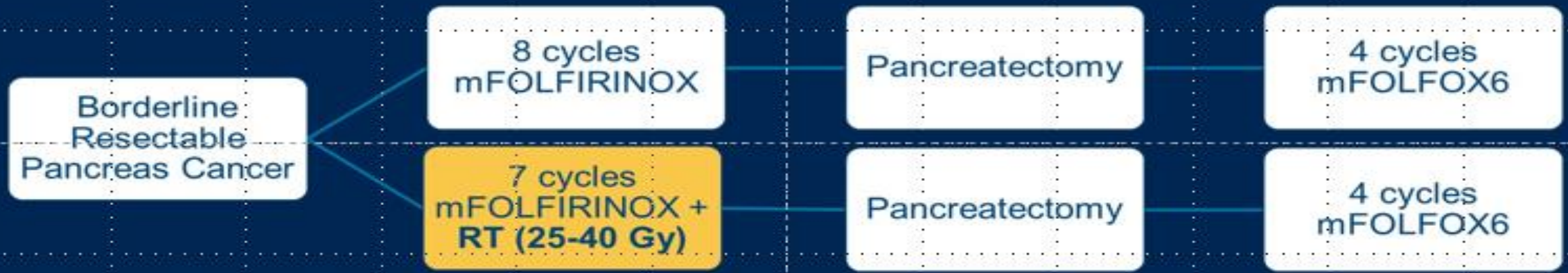
Summary

Arm A: mFOLFIRINOX Efficacious	Arm B: mFOLFIRINOX → RT Did not meet requirements to conclude efficacy
18-month OS rate (KM) 66.4%	**18-month OS rate (KM) 47.3%**
EFS: 15.0 months	EFS: 10.2 months
Resection rate: 49%	Resection rate: 35%
pCR rate: 0%	pCR rate: 11%
Preoperative 3+ AE rate: 57%	Preoperative 3+ AE rate: 64%

Conclusion/Takeaway

- Preoperative mFOLFIRINOX was associated with favorable OS relative to historical data in patients with BR PDAC
- mFOLFIRINOX → RT met the predefined futility boundary for R0 resection at interim analysis
- mFOLFIRINOX represents a reference preoperative regimen for patients with borderline resectable PDAC

Alliance A021501



Interim analysis:
R0 resection
10/30 (33%)

cholangio

- Final results from a phase II study of infigratinib (BGJ398), an FGFR-selective tyrosine kinase inhibitor, in patients with previously treated advanced cholangiocarcinoma harboring an *FGFR2* gene fusion or rearrangement.
- MM.Javle et al

- **Conclusions:**Infigratinib is associated with promising anticancer activity and a manageable AE profile in patients with advanced, refractory CCA with an *FGFR2* gene fusion or rearrangement. A phase III study of infigratinib versus gemcitabine/cisplatin is ongoing in the front-line setting (NCT03773302).

- **Background:**Treatment options for cholangiocarcinoma (CCA) after progression on first-line gemcitabine-based therapy are limited. Fibroblast growth factor receptor 2 (*FGFR2*) gene fusions occur in 13–17% of intrahepatic CCA. A single-arm, phase II study (NCT02150967) evaluated infigratinib, an ATP-competitive FGFR1–3-selective oral tyrosine kinase inhibitor, in previously-treated advanced CCA with *FGFR* fusions/rearrangements.
- **Methods:**Adult patients with advanced/metastatic CCA with progression on =1 line of systemic therapy received infigratinib 125 mg orally for 21 days of each 28-day cycle until unacceptable toxicity or disease progression. All patients received prophylaxis with the oral phosphate binder sevelamer. Primary endpoint: objective response rate (ORR) by independent central review per RECIST v1.1, with duration of response (DOR). Secondary endpoints: progression-free survival (PFS), disease control rate, overall survival, safety, pharmacokinetics. Approximately 160 patients are planned (120/20/20 patients in Cohorts 1/2/3). This analysis focuses on Cohort 1 (patients with *FGFR2* gene fusions or rearrangements without receiving a prior FGFR inhibitor).
- **Results:**As of 31 March 2020, 108 patients, including 83 (77%) with *FGFR2* fusions, received infigratinib: median age 53 years (range 23–81 years); 54% had received =2 prior treatment lines. Median follow-up was 10.6 months (range 1.1–55.9 months). 96 patients (88.9%) discontinued treatment (12 ongoing). Centrally reviewed ORR was 23.1% (95% CI 15.6–32.2) including 1 CR and 24 PRs; median DOR was 5.0 months (range 0.9–19.1 months). Among responders, 8 (32.0%) patients had a DOR of =6 months. Median PFS was 7.3 months (95% CI 5.6–7.6 months). Prespecified subgroup analysis: ORR was 34% (17/50) in the second-line setting and 13.8% (8/58) in the third-/later-line setting (3–8 prior treatments). Most common treatment-emergent adverse events (TEAEs, any grade) were hyperphosphatemia (76.9%), eye disorders (67.6%, excluding central serous retinopathy/retinal pigment epithelium detachment [CSR/RPED]), stomatitis (54.6%), and fatigue (39.8%). CSR/RPED occurred in 16.7% of patients (including 1 G3 event; 0 G4). Other common grade 3/4 TEAEs were stomatitis (14.8%; all G3), hyponatremia (13.0%; all G3), and hypophosphatemia (13.0%; 13 G3, 1 G4).

ivosidenib (IVO)

- Final results from ClarIDHy, a global, phase III, randomized, double-blind study of ivosidenib (IVO) versus placebo (PBO) in patients (pts) with previously treated cholangiocarcinoma (CCA) and an isocitrate dehydrogenase 1 (*IDH1*) mutation.
- AX Zhu et al

- **Conclusions:**IVO was well tolerated and resulted in a favorable OS trend vs PBO despite a high rate of crossover. These data – coupled with statistical improvement in PFS, supportive quality of life data, and favorable safety profile – demonstrate the clinical benefit of IVO in advanced m*IDH1* CCA.

- **Background:**CCA is a rare cancer for which there are limited effective therapies. *IDH1* mutations occur in ~20% of intrahepatic CCAs, resulting in production of the oncometabolite D-2-hydroxyglutarate, which promotes oncogenesis. IVO (AG-120) is a first-in-class, oral, small-molecule inhibitor of mutant *IDH1* (m*IDH1*). ClarIDHy aimed to demonstrate the efficacy of IVO vs PBO in pts with unresectable or metastatic m*IDH1* CCA. The primary endpoint was met with significant improvement in progression-free survival (PFS) by independent radiology center (IRC) with IVO vs PBO (hazard ratio [HR] = 0.37, $p < 0.0001$). Objective response rate (ORR) and stable disease for IVO were 2.4% (3 partial responses) and 50.8% (n = 63) vs 0% and 27.9% (n = 17) for PBO. IVO pts experienced significantly less decline in physical and emotional functioning domains of quality of life at cycle 2 day 1 vs PBO pts (nominal $p < 0.05$).
- **Methods:**Pts with m*IDH1* CCA were randomized 2:1 to IVO (500 mg PO QD) or matched PBO and stratified by prior systemic therapies (1 or 2). Key eligibility: unresectable or metastatic m*IDH1* CCA based on central testing; ECOG PS 0–1; measurable disease (RECIST v1.1). Crossover from PBO to IVO was permitted at radiographic progression. Primary endpoint: PFS by IRC. Secondary endpoints included overall survival (OS; by intent-to-treat), ORR, PFS (by investigator), safety, and quality of life. The planned crossover-adjusted OS was derived using the rank-preserving structural failure time (RPSFT) model.
- **Results:**As of 31 May 2020, ~780 pts were prescreened for an *IDH1* mutation and 187 were randomized to IVO (n = 126) or PBO (n = 61); 13 remain on IVO. Median age 62 y; M/F 68/119; 91% intrahepatic CCA; 93% metastatic disease; 47% had 2 prior therapies. 70% of PBO pts crossed over to IVO. OS data were mature, with 79% OS events in IVO arm and 82% in PBO. Median OS (mOS) was 10.3 months for IVO and 7.5 months for PBO (HR = 0.79; 95% CI 0.56–1.12; one-sided $p = 0.093$). The RPSFT-adjusted mOS was 5.1 months for PBO (HR = 0.49; 95% CI 0.34–0.70; $p < 0.0001$). Common all-grade treatment emergent adverse events (TEAEs, = 15%) in the IVO arm: nausea 41%, diarrhea 35%, fatigue 31%, cough 25%, abdominal pain 24%, decreased appetite 24%, ascites 23%, vomiting 23%, anemia 18%, and constipation 15%. Grade = 3 TEAEs were reported in 50% of IVO pts vs 37% of PBO pts, with grade = 3 treatment-related AEs in 7% of IVO pts vs 0% in PBO. 7% of IVO pts experienced an AE leading to treatment discontinuation vs 9% of PBO pts. There were no treatment-related deaths.

NSCLC

- Outcomes to first-line pembrolizumab in patients with PD-L1-high (≥50%) non-small-cell lung cancer and a poor performance status
- Joao Victor Machado Alessi et al

- **Conclusions:**Although a subset of patients with an ECOG PS of 2 can respond first-line pembrolizumab, clinical outcomes in this population are poor, and use of second-line systemic therapy is infrequent.

- **Background:**Patients with non-small cell lung cancer (NSCLC) and a poor Eastern Cooperative Oncology Group performance status (ECOG PS) have been excluded from immunotherapy clinical trials. We sought to evaluate clinical outcomes to first-line pembrolizumab in patients with advanced NSCLC, a PD-L1 tumor proportion score (TPS) of ≥50%, and an ECOG PS of 2.**Methods:**We performed a multicenter retrospective analysis of patients with metastatic NSCLC and a PD-L1 tumor proportion score (TPS) of ≥50% (negative for genomic alterations in *EGFR* and *ALK*) who received treatment with first-line commercial pembrolizumab. Clinical outcomes were compared in patients based on ECOG PS.**Results:**Among 234 patients, 83.3% (N = 195) had an ECOG PS of 0 or 1, and 16.7% (N = 39) had an ECOG PS of 2. The baseline clinicopathological characteristics were balanced between the ECOG PS 0-1 vs 2 groups in terms of age, sex, tobacco use, histology, *KRAS* mutation status, presence of other potentially targetable driver mutations (*BRAF*, *MET*, *HER2*, *RET*), history of central nervous system (CNS) disease, and PD-L1 TPS distribution. Compared to patients with an ECOG PS of 0-1, patients with an ECOG PS of 2 had a significantly lower objective response rate (ORR 43.1% vs 25.6%; P = 0.04), a numerically shorter median progression free survival (mPFS 6.6 months vs 4.0 months; P = 0.09), and a significantly shorter median overall survival (mOS 20.3 months vs 7.4 months; P < 0.001). Upon disease progression, patients with an ECOG PS of 2 were significantly less likely to receive second-line systemic therapy compared to patients with an ECOG PS of 0-1 (55.5% vs 14.3%, P < 0.001).**Conclusions:**

History of cancer immunotherapy

- Paul Ehrlich (1908) first conceived the idea that tumor cells can be recognized as “foreign” and eliminated by the immune system.
- Sir Macfarlane Burnet (1960) formalizes concept by developing idea of “immune surveillance”

- Over the last decade, we have made some progress in advanced disease. FOLFIRINOX (5-fluorouracil, leucovorin, irinotecan, and oxaliplatin) and gemcitabine with nab-paclitaxel are the standards of care, both demonstrating an improvement in overall survival (OS) compared with gemcitabine alone.[2,3] In the second-line setting, prospective data have shown modest results, with response rates to chemotherapy generally less than 20%, including second-line FOLFIRINOX or 5-fluorouracil with nanoliposomal irinotecan.[4,5]

- In the last decade, there has been a movement toward precision oncology through comprehensive genomic profiling of tumor specimens' revealing potential targets for therapeutic intervention.
- Unfortunately, thus far, success in identifying targets for pancreatic adenocarcinoma has been limited. The notable genomic heterogeneity of pancreatic adenocarcinoma only partly explains the complexities in therapeutic development.

- Several molecular profiling studies have demonstrated that up to 25% (from 12% to 25%) of pancreatic cancers harbor actionable molecular alterations, with actionability defined as a molecular alteration for which there is clinical or strong preclinical evidence of a predictive benefit from a specific therapy (in any cancer type).[6,7]

- The first targeted therapy approved by the U.S. Food and Drug Administration (FDA) for pancreatic cancer was erlotinib, a tyrosine kinase inhibitor targeting the EGFR pathway. Since most pancreatic cancers overexpress EGFR, the National Cancer Institute of Canada Clinical Trials Group coordinated a large, randomized phase III clinical trial comparing gemcitabine alone with gemcitabine plus erlotinib. The combination showed a very modest improvement in median OS (6.24 vs. 5.91 months, HR 0.82), and, based on this, the FDA approved the regimen as a standard treatment for patients with advanced pancreatic cancer. With that said, this combination is not very popular given the nominal improvement in OS and notable toxicities of fatigue, rash, and diarrhea.[8,9]

PARP Inhibitors

- The largest proportion of actionable alterations in pancreatic cancer comes from mutations in the DNA damage response pathway, especially the *BRCA-FANC* family of genes. Genes with homologous recombination DNA damage response and repair deficiency include *BRCA1, BRCA2, PALB2, ATM, ATR, ATRX, BAP1, BARD1, BRIP1, CHEK1, CHEK2, RAD50, RAD51, RAD51B, FANCA, FANCC, FANCD2, FANCE, FANCF, FANCG*, or *FANC*.[6-8]
- The most common germline mutations associated with familial pancreatic cancer include *BRCA1/2* and *PALB2*. *BRCA2* mutations increase the risk of pancreatic cancer by 3.5-fold and account for up to 17% of familial cases.[10,11] *BRCA1* and *BRCA2* are tumor-suppressor genes involved in the repair of DNA. Their protein products form the complex necessary to repair DNA double-strand breaks. In the setting of *BRCA* mutations, the PARP of the base excision repair pathway is used for DNA repair, making it an excellent therapeutic target (Figure).[12] Studies indicate that patients with homologous recombination gene mutations may have improved outcomes when treated with platinum-based chemotherapies.[13]

- Further, advanced pancreatic adenocarcinoma associated with germline *BRCA1/2* mutations has shown response to the PARP inhibitors.[14] Phase II trials investigating rucaparib have had promising results. In the RucaPanc trial (NCT02042378), patients with refractory, advanced PDAC and a *BRCA* germline or somatic mutation received rucaparib until disease progression (Table).[15]

Table. Clinical Trials Investigating The Efficacy of PARP Inhibitors in PDAC

Drug	Trial	Population	Comparison	Pts.	RR	PFS
Rucaparib (15)	RUCAPANC Phase II (NCT02042378),	Refractory, advanced PDAC with *BRCA* germline or somatic mutation; Until disease progression		19	16.0%	
Olaparib (16)	POLO Phase III (NCT02184195).	Germline *BRCA1/2*-positive metastatic PDAC, sensitive to first-line platinum-based chemotherapy. Maintenance therapy	Placebo	154	23.0%	7.4 mos vs. 3.8 mos
Rucaparib (17)	Phase II	Platinum-sensitive, advanced PDAC with *BRCA* or *PALB2* mutations. Maintenance therapy		24	36.0%	
Veliparib (18)	Phase II	Advanced PDAC with *BRCA1/2* or *PALB2* mutations. In combination with gemcitabine and cisplatin	Cisplatin and gemcitabine	50	74.1%	10.1 mos vs. 9.7 mos

- Subsequently, the phase III POLO trial was designed to evaluate the efficacy of olaparib as maintenance therapy in patients with germline *BRCA1/2*–positive metastatic PDAC that is sensitive to first-line platinum-based chemotherapy (NCT02184195). This double-blind, placebo-controlled study, in which patients were randomly assigned to receive maintenance olaparib or placebo. Based on these data, the FDA has approved olaparib as a maintenance treatment for adult patients with *BRCA*–mutated metastatic pancreatic adenocarcinoma whose disease has not progressed on at least 16 weeks of a first-line platinum-based chemotherapy regimen.[16]

- Several phase II clinical trials investigating the efficacy and safety of other PARP inhibitors, including veliparib and rucaparib, are in progress (Table). Rucaparib is also being evaluated as maintenance therapy in patients with platinum-sensitive, advanced PDAC with *BRCA* or *PALB2* mutations.[17] A randomized phase II trial evaluating veliparib in combination with gemcitabine and cisplatin, in patients with PDAC who have *BRCA1/2* or *PALB2* mutations, was recently published.[18] The authors concluded that patients with these germline mutations should be considered for gemcitabine and cisplatin chemotherapy in the frontline setting.[19]

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- Further studies will aim to inform the sequencing of PARP inhibitor treatment, resistance mechanisms, and the role of maintenance treatment. Beyond *BRCA1* and *BRCA2*, the clinical significance of other *BRCA-FANC* family genes remains unclear, but alterations in this pathway often have a common mutational profile referred to as "*BRCA*ness" and are associated with defects in DNA double-strand break repair. Studies have shown that alterations in genes within the *BRCA-FANC* family, other than *BRCA1* and *BRCA2*, have similar response rates to platinum-based therapy as *BRCA1* and *BRCA2* mutational carriers.[13]

Other Potential Treatment Targets

- Importantly, there are several well-defined driver genes that are important in the tumorigenesis and progression of pancreatic adenocarcinoma. In fact, *KRAS*, *TP53*, *CDKN2A*, and *SMAD4* are the most frequently altered genes in pancreatic adenocarcinoma. The most frequently mutated gene in pancreatic cancer is *KRAS*, seen in approximately 90% to 95% of all pancreatic cancer cases. It most frequently involves a mutation at codon 12 (i.e., G12A/C/D/F/L/R/S/V), which accounts for 98% of mutations, with G12D being most common (51%), followed by G12V (30%), G12R (12%), G12A/C/S (2% each), and G12L/F (< 1%). Less frequent (< 1%) mutations are also observed at codon 13 (i.e., G13C/D/P/S) and codon 61 (Q61H/K/R).[7,20-22]

- For more than 3 decades, there have been multiple attempts to target *RAS*, most of which have been unsuccessful. Multiple studies have demonstrated various agents' inability to effectively bind to the small binding pockets, coupled with a highly competitive guanine triphosphate concentration, rendering the KRAS protein undruggable to date. This problem is coupled with canonical signaling of downstream targets of KRAS—RAF, MEK, and subsequently ERK—creating bypass pathways for *RAS* targeting.[12,22,23]

- Recently, the novel compound sotorasib has worked by occupying the His95 groove near the cysteine pocket to maintain a high level of inactive KRAS. Even though the initial results are encouraging for cancers that harbor *KRAS G12C* mutations (e.g., lung cancers), their utility for PDAC is limited, with only approximately 2% *KRAS G12C* mutations seen. Hopefully, these studies will lead to drug discovery initiatives targeting *KRAS G12D* and *KRAS G12V* mutations, which constitute about 80% of the *KRAS* mutations in PDAC.[21,22,24]
- The PI3K/PTEN/Akt/mTORC1 is another key pathway activated in pancreatic cancer, likely because of its association with KRAS.[25] Monotherapy targeting of PI3K, AKT, and mTOR has not been successful in *RAS*-mutant pancreatic cancer. Dual PI3K pathway inhibition with RAF-MEK-ERK inhibition is currently under investigation, which could prove to be an effective strategy.[12] A randomized phase II study evaluating selumetinib, a MEK inhibitor, and MK-2206, an AKT inhibitor, failed to show any benefit compared with modified FOLFOX in patients who failed gemcitabine-based therapy.[22,26-28] Currently, there are multiple ongoing clinical trials with MEK1/2 inhibitors such as cobimetinib and trametinib in PDAC, and it will be important to assess their outcomes before considering the clinical utility of MEK1/2 inhibitors for PDAC.[29,30]

- Kinase fusion genes are the most frequent driver alterations in *KRAS* wild-type PDACs. There are reports of activity of ALK inhibitors in pancreatic adenocarcinoma with ALK fusions. In addition to *ALK*, other kinase fusions found in *KRAS* wild-type PDACs include *BRAF*, *FGFR2*, *RAF*, *RET*, *MET*, *NTRK1*, *ERBB4*, and *FGFR3*. Although these kinase fusions and corresponding treatments have been described in other neoplasms, limited data are currently available regarding their efficacy in PDAC.[7,31]
- *BRAF* mutations are significantly and inversely correlated with *KRAS* alterations. The most common *BRAF* alteration, V600E mutation, is mutually exclusive with *KRAS* mutations. Clinical trials targeting *BRAF* alterations are in progress.[32] BrafPanc is an ongoing phase II trial of binimetinib and encorafenib for the treatment of pancreatic cancer in patients with a somatic *BRAF*V600E mutation (NCT04390243).
- The neuronal membrane protein sortilin is emerging as an important regulator in cancer cell development. In a study published by Gao et al, scientists were the first to report sortilin expression and function in human pancreatic cancer. The results highlight an increased sortilin protein level in pancreatic cancer cells compared with normal pancreatic epithelial cells. Sortilin was found to contribute to pancreatic cancer invasion in vitro, through potentially upregulating the FAK signaling pathway. AF38469 is a novel selective bioavailable pharmacologic inhibitor of sortilin and inhibits pancreatic cancer cell adhesion and invasion, thereby reducing phosphorylation of FAK. This study suggests sortilin as a potential therapeutic target in pancreatic cancer, and further studies are clearly needed.[33]

- Microsatellite instability–high (MSI-H) and tumor mutational burden–high tumors are relatively infrequent findings in PDAC, with a reported prevalence of 1%. Immune checkpoint blockade with pembrolizumab is an effective FDA-approved therapeutic strategy for patients with MSI-H and/or tumor mutational burden–high tumors.[34] Le et al reported a 62% response rate and 75% disease control rate for eight patients with MSI-H PDAC after treatment with pembrolizumab.[35] *NTRK* and *ROS1* gene fusions are rare in pancreatic cancer. Anecdotal data suggest that entrectinib, a central nervous system–active, potent, and selective TRK and ROS1 inhibitor, has substantial clinical activity in patients with PDAC.[36]

- Pancreatic adenocarcinoma is no longer considered one entity. Although it remains an aggressive cancer, newer cancer therapeutics are bringing much hope and enthusiasm.

- **Conclusion**
- Pancreatic adenocarcinoma is no longer considered one entity. Although it remains an aggressive cancer, newer cancer therapeutics are bringing much hope and enthusiasm. A retrospective analysis of the Know Your Tumor registry trial demonstrated that the ability of patients with pancreatic cancer to undergo tumor molecular profiling or receive targeted therapies remains a challenge in the U.S. healthcare system. Even though about 25% of patients have actionable alterations, less than 5% are able to receive targeted therapies because of either the aggressiveness of the disease or logistical and economic issues. Results show that patients who have actionable molecular alterations can derive considerable benefit from receiving a matched therapy, with median OS in these patients being 1 year longer than those with actionable alterations who receive unmatched therapy, or those without actionable alterations.[6] These findings give hope that targeted genomic profiling and novel therapeutic agents can provide a new path forward in the treatment of advanced PDAC.

- **Conclusion**
- Pancreatic adenocarcinoma is no longer considered one entity. Although it remains an aggressive cancer, newer cancer therapeutics are bringing much hope and enthusiasm. A retrospective analysis of the Know Your Tumor registry trial demonstrated that the ability of patients with pancreatic cancer to undergo tumor molecular profiling or receive targeted therapies remains a challenge in the U.S. healthcare system. Even though about 25% of patients have actionable alterations, less than 5% are able to receive targeted therapies because of either the aggressiveness of the disease or logistical and economic issues. Results show that patients who have actionable molecular alterations can derive considerable benefit from receiving a matched therapy, with median OS in these patients being 1 year longer than those with actionable alterations who receive unmatched therapy, or those without actionable alterations.[6] These findings give hope that targeted genomic profiling and novel therapeutic agents can provide a new path forward in the treatment of advanced PDAC.

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Alliance A021501: Preoperative mFOLFIRINOX or mFOLFIRINOX plus hypofractionated radiation therapy (RT) for borderline resectable (BR) adenocarcinoma of the pankreas Matthew H. G. Katz et al.

- **Methods:**Pts with ECOG PS 0-1 and BR PDAC confirmed by central real-time radiographic review after pre-registration were randomized to either arm A: 8 cycles of neoadjuvant mFOLFIRINOX (oxaliplatin 85 mg/m^2, irinotecan 180 mg/m^2, leucovorin 400 mg/m^2 and infusional 5-fluorouracil 2400 mg/m^2 over 46 hours), or arm B: 7 cycles of mFOLFIRINOX followed by stereotactic body RT (SBRT, 33-40 Gy in 5 fractions [fx]) or hypofractionated image guided RT (HIGRT, 25 Gy in 5 fx). Pts in either arm without disease progression underwent pancreatectomy, then 4 cycles of adjuvant mFOLFOX6 (oxaliplatin 85 mg/m^2, leucovorin 400 mg/m^2 and infusional 5-fluorouracil 2400 mg/m^2 over 46 hours). The primary endpoint, 18-mo OS rate, of each arm was compared to a historical control of 50%. Planned interim analysis mandated closure of either arm in which $\leq$11 of first 30 accrued pts underwent R0 resection

- **Results:**155 pts pre-registered and 126 pts were enrolled to arm A (N=70; 54 randomized, 16 following closure of arm B) or arm B (N=56; closed at interim analysis, all pts randomized prior to closure). Median age (A: 63y, B: 67y), median CA 19-9 level (A: 171 U/ml, B: 248 U/ml) and ECOG PS (A: 51% PS 0, B: 57% PS 0) of registered pts were similar between arms ($p > 0.05$). Treatment detailed in Table. The 18-mo OS rate based on Kaplan Meier estimates was 67.9% (95%CI: 54.6 – 78.0) in arm A and 47.3% (95%CI: 33.7 – 59.7) in arm B. Among pts who underwent pancreatectomy, 18-mo OS rate was 93.1% (95%CI: 84.3 – 100) and 78.9% (95%CI: 62.6 – 99.6) in arm A and B, respectively. With median follow-up of 27 and 31 mo, median OS was 31.0 (95%CI: 22.2 – NE) mo and 17.1 (95%CI: 12.8 – 24.4) mo in arm A and B, respectively.

- **Conclusions:**Neoadjuvant mFOLFIRINOX was associated with favorable OS relative to historical data in pts with BL PDAC in this phase II NCTN trial. mFOLFIRINOX with hypofractionated RT did not improve OS compared to historical data. mFOLFIRINOX represents a reference regimen in this setting and a backbone on which to add novel agents.

Therapy by treatment arm (N = 126), (n [%])

	Arm A (mFOLFIRINOX) n = 70	Arm B (mFOLFIRINOX + RT) n = 56
Initiated preop treatment	66	55
Started cycle 8 ctx or RT*	47 (71)	40 (73)
Surgery	38 (58)	28 (51)
Pancreatectomy	32 (48)	19 (35)
R0 pancreatectomy	28 (42)	14 (25)
Initiated postop ctx	22 (33)	13 (24)
Completed all treatment	20 (30)	10 (18)

Ctx, chemotherapy

*SBRT (n = 35); HIGRT (n = 5)

Neoadjuvant mFOLFIRINOX Established as Reference Standard in Borderline Resectable PDAC

- Patients with borderline resectable pancreatic ductal adenocarcinoma (PDAC) who received neoadjuvant therapy with modified FOLFIRINOX (mFOLFIRINOX) had an 18-month overall survival (OS) rate of 66.4% in a prospective phase II study conducted by the National Clinical Trials Network
- This rate exceeded the prespecified historical control of 50%, establishing mFOLFIRINOX as efficacious
- In contrast, neoadjuvant treatment with mFOLFIRINOX plus hypofractionated radiation therapy (RT) failed to exceed the 50% OS threshold at 18 months. This arm had to be closed early due to the low number of patients who proceeded to pancreatectomy.

- “Based on the results of this study, mFOLFIRINOX represents a reference preoperative regimen for patients with borderline resectable pancreatic adenocarcinoma.”

- Gomez-Roca C, Yanez E, I S-A, et al. LEAP-005: a phase II multicohort study of lenvatinib plus pembrolizumab in patients with previously treated selected solid tumors—results from the colorectal cancer cohort.

- Presented at: Gastrointestinal Cancers Symposium; January 15-17, 2020. Abstract 94.

Lenvatinib Plus Pembrolizumab Safe, Effective in non-MSI-H/pMMR CRC

- Lenvatinib plus pembrolizumab demonstrated promising antitumor activity with a manageable safety profile in patients with previously treated advanced non–microsatellite instability-high (MSI-H)/mismatch repair proficient (pMMR) colorectal cancer (CRC), according to results from the CRC cohort of the LEAP-005 study, presented at the 2021 Gastrointestinal Cancers Symposium.

- The LEAP-005 trial's (ClinicalTrials.gov identifier: NCT03797326) CRC cohort included 32 individuals (median patient age, 56 years) with histologically/cytologically confirmed metastatic and/or unresectable non-MSI-H/pMMR disease who received prior oxaliplatin and irinotecan. LEAP-005 investigators administered lenvatinib at 20 mg once daily plus 200 mg of pembrolizumab every 3 weeks for up to 35 cycles of pembrolizumab therapy (~2 years). The median time from first dose to data cutoff (April 10, 2020) was 10.6 months (range, 5.9-13.1).

- Iyer RV, Li D, Dayyani F, et al. DEDUCTIVE: a study of tivozanib in combination with durvalumab in subjects with untreated advanced hepatocellular carcinoma; phase Ib results.

- Presented at: Gastrointestinal Cancers Symposium; January 15-17, 2021. Abstract 294.

- Combination treatment with the VEGFR inhibitor tivozanib plus the anti-PD-L1 antibody durvalumab was found to be well-tolerated in patients with advanced hepatocellular carcinoma (HCC) who had not received prior therapy for their disease, according to the results of the phase 1b DEDUCTIVE trial presented at the Gastrointestinal Cancers Symposium.

- The phase 1b portion of the study (ClinicalTrials.gov identifier: NCT03970616), which determined the recommended phase 2 dose (RP2D) to be 1 mg of oral tivozanib on days 1 through 21 plus 1500 mg of intravenous durvalumab on day 1 of each 28-day cycle, enrolled 7 patients with newly diagnosed, treatment-naïve, advanced HCC. The primary end point was establishment of the RP2D and assessment of the doublet therapy's safety and tolerability in this patient population.

- All patients were classified as Child-Pugh Class A. Patients were excluded if they had hepatitis B or C virus or significant organ dysfunction. At baseline, the median age was 75 years; 6 patients were male.
- Of the 7 patients enrolled, 2 achieved a partial response and 3 had stable disease. Progressive disease was reported in 2 patients.
- One patient had mild elevation of LFTs, did not complete the 21-day course of tivozanib, and was subsequently replaced. Regarding toxicities, no patient experienced a grade 3 or higher adverse event (AE) in cycle 1. However, 1 patient developed a serious AE (grade 3 gastrointestinal hemorrhage).

- The most common adverse drug reactions included cough, diarrhea, fatigue, hypertension, and palmar-plantar erythrodysesthesia. Each event was observed in 2 of 7 patients.
- Existing data have validated the viability of combined VEGF and PD-L1 blockade. For example, bevacizumab plus atezolizumab was recently found to result in improved overall survival and progression-free survival vs sorafenib. The phase Ib findings add to the pool of available data on this approach.

- The rationale for coadministering tivozanib and durvalumab derives from evidence demonstrating both therapies' single-agent activity in the HCC arena. Of note, tivozanib selectively inhibits 3 different VEGFRs and therefore may provide an additional benefit.
- A phase 2 trial to further evaluate this combination is now enrolling and aims to accrue an additional 30 patients.

- Rha SY, Lee C-K, Kim HS, et al. A multi-institutional phase Ib/II trial of first-line triplet regimen ([embrolizumab, trastuzumab, chemotherapy) for HER2-positive advanced gastric and gastroesophageal junction cancer (PANTHERA trial): molecular profiling and clinical update.

- Presented at: 2021 Gastrointestinal Cancers Symposium; January 15-17, 2021. Abstract 218.

- Frontline pembrolizumab, trastuzumab, and chemotherapy demonstrated “promising efficacy” in HER2-positive advanced gastric and gastroesophageal junction (GEJ) cancer irrespective of PD-L1 status, according to updated clinical and molecular profiling data from the phase 1b/2 PANTHERA trial presented at the 2021 Gastrointestinal Cancers Symposium.

- At a median follow-up of 18.2 months, PANTHERA’s primary end point analysis showed that the overall response rate among the 43 patients who received the triplet therapy was 76.7% (95% CI, 61.4-88.2). More than half of patients (56.6%) had a reduction in tumor burden greater than 50%. The disease control rate was 97.7% (95% CI, 87.7-99.9).

- Clinical features including PD-L1 status and metastatic organ or baseline tumor burden “were not related to survival,” Sun Young Rha, MD, PhD, of Yonsei Cancer Center in Seoul, South Korea, said during the presentation. Combined positive score (CPS) analysis at indicated that 39.5% of patients had a CPS of less than 1%, 48.8% had a CPS of 1% or more, 11.6% had a CPS of 10% or greater, and 11.6% were not evaluated for CPS at diagnosis.
- PANTHERA’s secondary end points included progression-free survival (PFS), overall survival (OS), duration of response, safety, and predictive biomarker analysis by targeted next-generation sequencing. The median PFS was 8.6 months (7.2-16.4), and the median OS, 19.3 months (95% CI, 16.5-not reached).

- Biomarker analyses betrayed varying survival benefits. For example, patients with HER2 amplification per next-generation sequencing (≥ 4 copy number) were associated with a statistically significant survival benefit vs those without HER2 amplification (median PFS, 22.0 months vs 7.7 months; *P* =.0275). This trend extended to patients with RTK/RAS pathway alterations compared with those with wild-type RTK/RAS (median PFS, 13.8 months vs 4.9 months; *P* = .001).
- Though the correlative biomarkers derived from the PANTHERA trial "need to be validated through ongoing trials," according to Rha, the first-line regimen demonstrated anticancer activity and may therefore be a viable strategy for the treatment of HER2-positive advanced gastric and GEJ cancer. The biomarkers identified in PANTHERA will be validated in the phase 3 KEYNOTE-118 study (ClinicalTrials.gov identifier: NCT03615326), which is testing pembrolizumab plus trastuzumab in combination with standard-of-care chemotherapy vs trastuzumab and chemotherapy in individuals with advanced HER2-positive gastric or GEJ cancer.

- Chin K, Kato K, Cho BC, et al. Three-year follow-up of ATTRACTION-3: a phase III study of nivolumab (nivo) in patients with advanced esophageal squamous cell carcinoma (ESCC) that is refractory or intolerant to previous chemotherapy.

- Presented at Gastrointestinal Cancer Symposium; January 15-17, 2021. Abstract 204.

- Nivolumab continued to show improved overall survival (OS) compared with chemotherapy in patients with unresectable advanced or recurrent advanced esophageal squamous cell carcinoma (ESCC), according to research reporting results of the randomized, open-label phase 3 ATTRACTION-3 study.

- At last data cut-off, 3 years after the last patient was enrolled, the median overall survival was 10.91 months with nivolumab compared with 8.51 months with taxane chemotherapy (HR, 0.79; 95% CI, 0.64-0.97), reported Keisho Chin, of The Cancer Institute Hospital of JFCR, Japan, and colleagues at the 2021 Gastrointestinal Cancers Symposium.

- The study included 419 patients with unresectable advanced, recurrent/refractory disease, or disease intolerant to 1 prior fluoropyrimidine/platinum-based chemotherapy. The patients were randomly assigned to receive nivolumab (n=210) or chemotherapy (n=209). The primary end point was OS.
- The rate of OS at 24 months was 20.2% for nivolumab and 13.5% for chemotherapy; at 36 months it was 15.3% and 8.7%, for nivolumab vs chemotherapy, respectively.

- The researchers also looked at OS by best overall response and found that nivolumab showed a longer median OS compared with chemotherapy, regardless of the best overall response. Median OS in patients who had complete or partial response were 19.91 and 15.41 months for nivolumab and chemotherapy (HR, 0.84; 95% CI, 0.46-1.54). In patients with stable disease, the median OS was 17.38 and 9.36 months for nivolumab and chemotherapy, respectively (HR, 0.45; 95% CI, 0.26-0.78).
- The researchers reported no new safety signals during the 3-year study follow-up.

- Evans TRJ, Cutsem EV, Prenen H, et al. Phase I study of the novel pro-drug MIV-818 in patients with hepatocellular carcinoma, intra-hepatic cholangiocarcinoma or liver metastases.

- Presented at: Gastrointestinal Cancers Symposium; January 15-17, 2021. Abstract 309

- MIV-818, a nucleoside analogue prodrug, induced antitumor activity with an acceptable safety profile in patients with hepatocellular carcinoma (HCC), hepatic cholangiocarcinoma (CCA), or liver metastases from solid tumors, according to the results of a phase 1a study presented at the 2021 Gastrointestinal Cancers Symposium.
- Because MIV-818 is a prodrug, its conversion to the nucleoside analogue troxacitabine in the liver results in liver-targeted DNA breaks and ultimately, cell death. The aim of this phase 1a study was to determine the safety and efficacy of investigational agent, as well as an optimal dose.

- Investigators of the phase 1a study (ClinicalTrials.gov identifier: NCT03781934) treated 9 patients (2 with advanced HCC, 1 with CCA, and 6 with liver metastases) with MIV-818 at doses up to 60 mg. All patients had received prior treatment for their disease.
- Primary end points included safety and tolerability and establishing the starting dose for the inter-patient dose-escalation phase 1b study. Secondary objectives included overall response rate (ORR) and pharmacokinetic and dynamic effects.

- At baseline, the median age of patients was 57 years (range, 50-84). Patients had an Eastern Cooperative Oncology Group performance status of 0 or 1. The median number of lines of prior therapies was 2 (range, 1-5).
- Preliminary data indicated that MIV-818 was delivered to the liver with low plasma levels. DNA damage was observed in tumor cells of liver biopsies, suggesting “clear signs of a tumor-selective effect,” according to T.R. Jeffry Evans, FRCP, MBBS, MD, who presented the findings. Additional efficacy outcomes were not reported.
- The majority of treatment-related adverse events (AEs) were grade 1 at doses below 50 mg. Nausea, elevations in liver enzymes, and fatigue were among the most common AEs. Hematologic AEs were observed with doses of 50 mg or higher.
- The starting dose selected for the ongoing phase 1b trial was 40 mg. To date, 1 dose-limiting toxicity of rash has been observed in the phase 1b setting, which resolved with a dose reduction to 30 mg.

- Morse M, Halperin DM, Uronis HE, et al. Phase Ib/II study of pembrolizumab with lanreotide depot for advanced, progressive gastroenteropancreatic neuroendocrine tumors (PLANET).

- Presented at: Gastrointestinal Cancers Symposium; January 15-17, 2021. Abstract 369.

- Results from the phase 1b/2 PLANET study showed that lanreotide synergized with pembrolizumab to yield a stable disease rate of 40.9% in patients with advanced well- or moderately differentiated gastroenteropancreatic neuroendocrine tumors (GEP-NETs).

- at a median follow-up of 15 months, the median progression-free survival (PFS) was 5.4 months with the combination therapy (95% CI, 2.7-8.3). The median overall survival (OS) had not been reached.
- There were no partial or complete responses. Overall, 54.5% of patients had progressive disease; 4.5% were not evaluable for response assessment.

- The PLANET trial (ClinicalTrials.gov identifier: NCT03043664) included 22 patients with progressive, advanced or metastatic GEP-NETs who received lanreotide plus pembrolizumab. Six of these patients were treated in a safety cohort. The primary end point was overall response rate (ORR). Secondary end points included PFS, OS, and safety.
- At baseline, the median patient age was 60.9 years and the median time since diagnosis was 5.3 years. The NET was located within the gastrointestinal track among 63.6% of patients, with the remaining 36.4% in the pancreas. The median Ki67 was 5%.

- Data from previous studies have demonstrated an ORR of 3.7% to 12% with pembrolizumab in patients with low-grade NETs. Somatostatin analogues (SSAs) such as lanreotide can be an effective treatment for NETs and may modulate immunity through the reduction of serotonin. The aim of the PLANET study was to determine whether lanreotide and pembrolizumab would be synergetic in patients with low- to intermediate-grade GEP-NETs.
- Regarding toxicities, no new safety signals were identified in the PLANET trial. Serious pembrolizumab-related adverse events occurred in 9 patients and included hyperglycemia, colitis, pneumonitis, and abdominal pain. Treatment discontinuation due to AEs occurred in 13.6% of patients. There were no grade 5 events.
- “Further studies to identify other approaches to increase the immunogenicity of well/moderately-differentiated GEP-NETs are required,” concluded Michael Morse, MD, who presented the findings.

- Kasi PM, Jordan E, Jahreiss L. Deploying an AI-based online search tool to increase patients' access to and understanding of solid tumor GI clinical trials.

- Presented at: Gastrointestinal Cancers Symposium, January 15-17, 2021. Abstract 456.

- A novel, artificial intelligence (AI)-based search tool was found to simplify gastrointestinal (GI) cancer clinical trial identification, improve understanding of study-related information, and clarify the steps involved in trial enrollment, according to data presented at the 2021 Gastrointestinal Cancers Symposium.
- These results derive from a 20-minute survey that compared the ClinicalTrials.gov clinical trials registry with CancerTrialSearch.gov, an AI-powered tool that matches patients with GI malignancies to clinical trials based on 7 factors: tumor type, cancer stage, across solid tumors, mutation profile, prior treatment status, trial sponsor, and trial phase. A 5-point Likert scale was used to rank user experience with each website.

- The findings, presented by Pashtoon Kasi, MD, MS, showed that CancerTrialSearch.gov made it easier for patients to select studies (3.7±0.9) than did ClinicalTrials.gov (2.7±1.3). Respondents also reported an improvement in their ability to understand the information presented with CancerTrialSearch.gov compared with ClinicalTrials.gov (3.8±1.1 vs. 2.6±1.3). The newer website provided more clarity on the next steps of trial enrollment (4.2±0.8 vs. 3.7±1.4), translating to higher patient satisfaction (3.4±1.1 vs. 2.3±0.5).
- “Patients have limited access to and understanding of clinical trials and the online search tools that we have available can be very hard to navigate, not only for patients but also for providers, which makes it very difficult to find clinical trials,” Kasi said of the new tool, which uses AI to restructure trial information across 6 supported GI cancer types.

- Edeline J, Cattan S, Merle P, et al. Landmark analysis of overall survival (OS) by objective response (OR) in previously treated patients (pts) with advanced hepatocellular carcinoma (aHCC): post-hoc analysis of the randomized, phase III KEYNOTE-240 study.

- Poster presented at: Gastrointestinal Cancers Symposium; January 15-17, 2021. Abstract 318.

- In the KEYNOTE-240 trial, findings from a landmark analysis showed that OR was prognostic of longer OS in those who received the ICI. The purpose of this post hoc analysis was to determine whether OR at landmark is prognostic of prolonged survival after landmark.
- In the post hoc analysis, the landmark evaluation of OS was conducted at 6, 12, and 18 weeks after randomization for the pembrolizumab group (n=270), and stratified by OR. Responders at each landmark time point were defined as those who achieved a partial or complete response before the landmark. All other patients with a response assessment of stable or progressive disease or who were not evaluable were deemed nonresponders.

- At baseline, the median patient age was 70 years and 66 years among responders (n=51) and nonresponders (n=219), respectively. Nearly all patients were classified as Child Pugh class A. BCLC stage varied by responders and nonresponders. Stage B disease was present in 11.8% of responders and 22.8% nonresponders. Stage C disease was present in 88.2% and 77.2% of responders and nonresponders, respectively.
- At a median follow-up of 21.2 months, the OR rate was 18.3%. At each landmark analysis, OR was found to be significantly associated with prolonged OS.
- At 6 weeks, median OS was not reached in the responder group compared with 12.1 months in the nonresponder group (HR, 0.37; 95% CI, 0.18-0.75). At 12 weeks, the median OS was 20.4 months and 10.8 months in the responder and nonresponder subpopulations, respectively (HR, 0.39; 95% CI, 0.23-0.66). At Week 18, median OS was not reached among responders compared with 10.8 months among nonresponders (HR, 0.37; 95% CI, 0.21-0.63).

- The authors concluded that “these results support the association between OR to pembrolizumab and OS observed in KEYNOTE-224.” They noted that additional prospective studies with larger sample sizes are needed to further validate this relationship.

- Kato K, Doki Y, Ura T, et al. Nivolumab in advanced esophageal squamous cell carcinoma (ATTRACTION-1/ONO-4538-07): minimum of five-year follow-up.

- Poster presented at Gastrointestinal Cancer Symposium; January 15-17, 2021. Abstract 207.

- Results from a long-term survival analysis of the ATTRACTION-1 study demonstrated nivolumab’s enduring efficacy in patients with advanced esophageal squamous cell carcinoma (ESCC), according to data based on a minimum of 5 years of follow-up presented at the 2021 Gastrointestinal Cancers Symposium.

- A total of 65 patients with advanced ESCC who were either refractory to or could not tolerate fluoropyrimidine-, platinum-, and taxane-based therapy enrolled on the phase 2 ATTRACTION-1 trial between February 25, 2014 and November 14, 2014, and 64 were evaluated for treatment efficacy. At the final database lock for long-term follow-up analysis on August 6, 2020, 17.2% of patients were found to have an objective response by central assessment (95% CI, 9.9-28.2), reported Ken Kato, MD, PhD, of National Cancer Center Hospital in Japan.

- The median overall survival (OS) was 10.8 months (95% CI, 7.4-13.9), and the estimated 5-year OS rate was 6.3% (95% CI, 2.0-14.0). The median progression-free survival (PFS) wasn1.5 months (95% CI, 1.4-2.8). The estimated 5-year PFS rate was 6.8% (95% CI, 2.2-15.1). These findings represent the longest follow-up of patients with advanced ESCC treated with nivolumab, according to Kato, who added that “long-term survivors tended to show [a] deeper response.”
- Importantly, no new safety signals were identified during the longer follow-up period. The most common treatment-related adverse events (frequency of >10%) were diarrhea and rash.

- The findings, which are consistent with those for nivolumab in other disease settings, build on 2-year follow-up data from ATTRACTION-1, which previously demonstrated nivolumab’s capacity to induce antitumor activity with a manageable safety profile.

- Abou-Alfa GK, Meyer T, Zhang J, et al. Evaluation of neratinib, pembrolizumab, everolimus and nivolumab in patients with fibrolamellar carcinoma.
- Presented at: Gastrointestinal Cancers Symposium; January 15-17, 2021. Abstract 310.

- Several neratinib-based combination regimens demonstrated antitumor activity in patients with fibrolamellar carcinoma (FLC) who experienced disease progression during or after immune checkpoint inhibitor (ICI) therapy, according to study data presented at the 2021 Gastrointestinal Cancers Symposium.
- Effective treatment options for patients with FLC are limited, and surgical resection is typically “used extensively with non-curative intent,” according to Ghassan K. Abou-Alfa, MD, of Memorial Sloan Kettering Cancer Center in New York, New York. Although HER2 has been identified as an upregulated signaling pathway in this disease, HER2 inhibitors have not yet been systematically evaluated in FLC. The purpose of this small trial was to evaluate the role of neratinib, both as a monotherapy and in combination with other agents, in patients with FLC.

- The study included 15 patients from the SUMMIT basket trial (FLC cohort; ClinicalTrials.gov identifier: NCT01953926). Two patients were treated via compassionate use.
- Patients in the FLC cohort received neratinib monotherapy; the remaining 2 patients were treated with neratinib plus an ICI (pembrolizumab or nivolumab) with or without everolimus. Five patients in the FLC cohort crossed over to receive the compassionate use regimen after experiencing disease progression on single-agent neratinib.

- Among patients in the FLC cohort, the median patient age at baseline was 27.9 years, and 60% of patients were male. The median time from initial diagnosis to study enrollment was 2.5 years. Eighty percent of patients had prior surgery, and 60% had previously received an anticancer medication. FLC was found to be metastatic or locally advanced in 33% of patients.
- “Neratinib had limited benefit as a single agent,” Abou-Alfa noted. The clinical benefit rate was 13.3% among patients who received neratinib monotherapy.
- Regarding patient characteristics of the individuals treated with neratinib combination therapy, including those who crossed-over from the FLC cohort, the median age at baseline was 26 years and 57% were male. The median number of prior systemic therapies was 0 (range, 4-0).
- “The triplet combination of neratinib plus pembrolizumab plus everolimus led to prolonged stable disease,” Abou-Alfa said. In addition, 1 patient achieved a partial response with neratinib plus pembrolizumab.
- Overall, the neratinib-based combinations were considered tolerable, with no treatment-related grade 4 or 5 events reported.
- Abou-Alfa concluded that although “these are case-limited observations,” they “are critical and worth evaluating further in upcoming clinical trials, given the continued lack of a standard care therapy for patients with FLC.”

- Results showed that the objective response rate—the study's primary end point—was 22% (95% CI, 9-40). There were no complete responses and 7 partial responses.
- Secondary end points included the disease control rate (DCR), duration of response (DOR), progression-free survival (PFS), and overall survival (OS). The DCR was 47% (95% CI, 29-65), and the DOR had not been reached at the time of the data cutoff. The median PFS with the doublet regimen was 2.3 months (95% CI, 2.0-5.2); the median OS, 7.5 months (95% CI, 3.9-not reached).

- Forty-seven percent of patients reported a grade 3 or 4 treatment-related adverse event (TRAE) and 50% of patients experienced grade 3 to 5 TRAEs, which led to treatment discontinuation in 3 patients. Of the 3 patients who discontinued therapy, 1 patient had a grade 2 ischemic stroke; 1 patient had grade 3 increased liver transaminases; and 1 patient had grade 5 intestinal perforation.
- The 5 most common AEs (all-grade, affecting ≥5% of patients) were hypertension (47%), hepatotoxicity (34%), proteinuria (34%), and hypothyroidism (28%), and hemorrhage (22%).
- Based on these data, enrollment in the CRC cohort has been expanded to 100 patients, according to Carlos Alberto Gomez-Roca, MD, who presented the findings.