ASCO 2024 GI Cancers Updates

MLS Seattle

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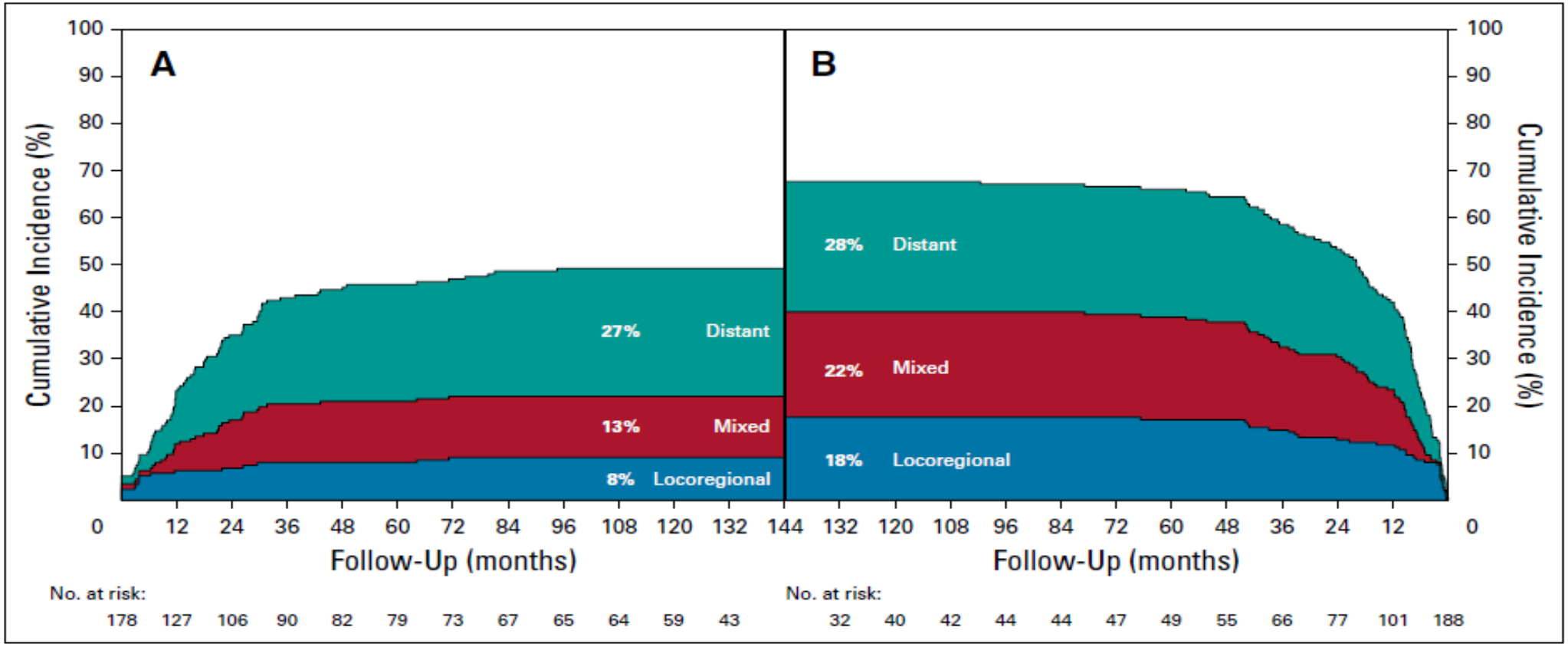
September 7, 2024

Outline

- **Gastroesophageal Cancer**
  - ESOPEC: Perioperative FLOT versus neoadjuvant chemoradiotherapy (CROSS) for resectable esophageal adenocarcinoma
- **Pancreatic Cancer**
  - RTOG 0848: Adjuvant chemotherapy +/- chemoradiation for patients with resected head of pancreatic adenocarcinoma—results of the RT + 5-FU/capecitabine randomization step
  - ECOG-ACRIN EA2186/GIANT Study: Randomized phase 2 study of gemcitabine and nab-paclitaxel compared with 5-FU/LV + nanoliposomal irinotecan in older patients with treatment-naïve metastatic pancreatic cancer
- **Hepatobiliary Cancer**
  - CheckMate 9DW: Nivolumab + ipilimumab vs lenvatinib or sorafenib as first-line treatment for unresectable hepatocellular carcinoma
- **Colorectal Cancer**
  - CheckMate 8HW: Nivolumab + ipilimumab vs chemotherapy as first-line treatment of MSI-H/dMMR metastatic colorectal cancer: expanded efficacy analysis

Gastroesophageal Cancer

Distant Relapses Remain High Despite Neoadjuvant Chemoradiation



Eyck BM et al. J Clin Oncol 2021; 39: 1995-2004

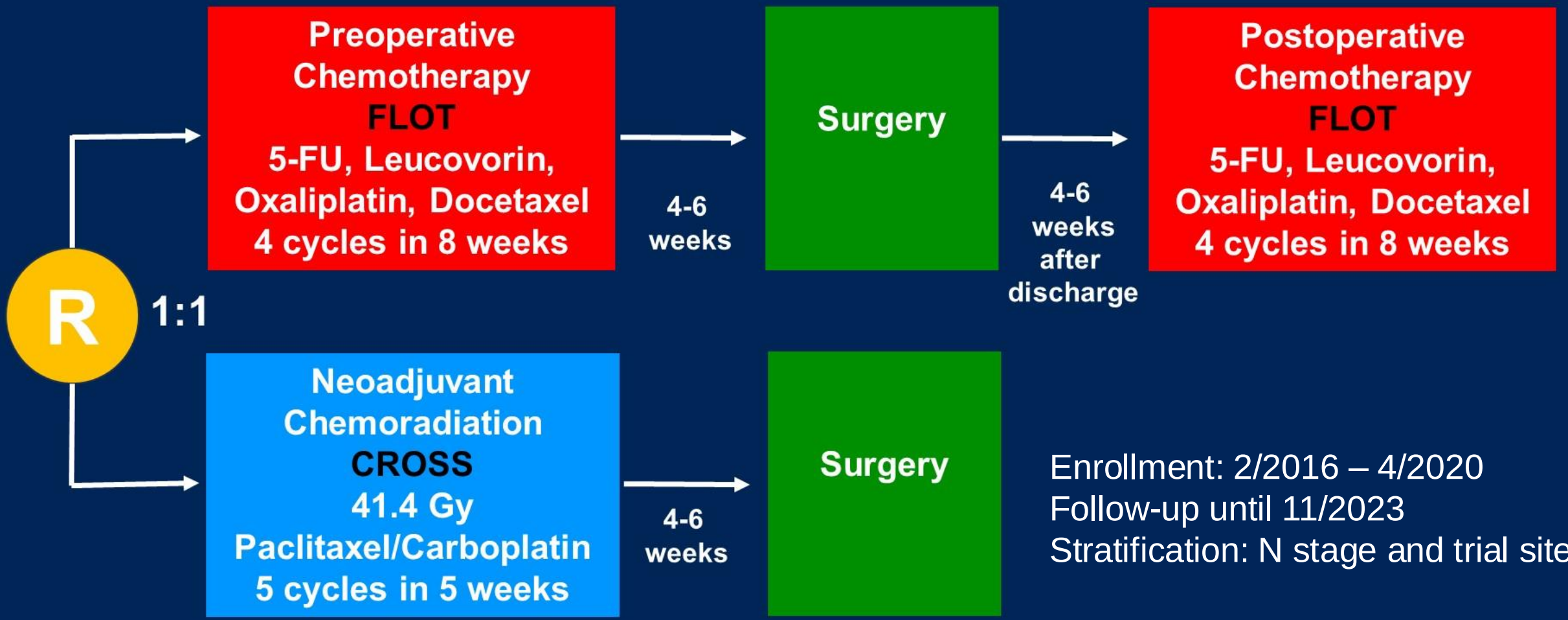
2024 ASCO® ANNUAL MEETING

Perioperative Chemotherapy (FLOT) versus Neoadjuvant Chemoradiotherapy (CROSS) for Resectable Esophageal Adenocarcinoma

The ESOPEC Trial (NCT02509286)

J Hoeppner, F Lordick, T Brunner, C Schmoor, B Kulemann, UP Neumann, G Folprecht, T Keck, F Benedix, M Schmeding, E Reitsamer, CJ Bruns, JF Lock, B Reichert, M Ghadimi, K Wille, I Gockel, JR Izbicki, S Utzolino, P Grimminger

ESOPEC Trial Scheme



Enrollment: 2/2016 – 4/2020
Follow-up until 11/2023
Stratification: N stage and trial site

Main Eligibility Criteria

Inclusion Criteria

- Histology: Adenocarcinoma
- Esophageal cancer according UICC (TNM7)[1,*]
- Clinical stage cT1N+ or cT2-4a, cN0/+, cM0

Exclusion Criteria

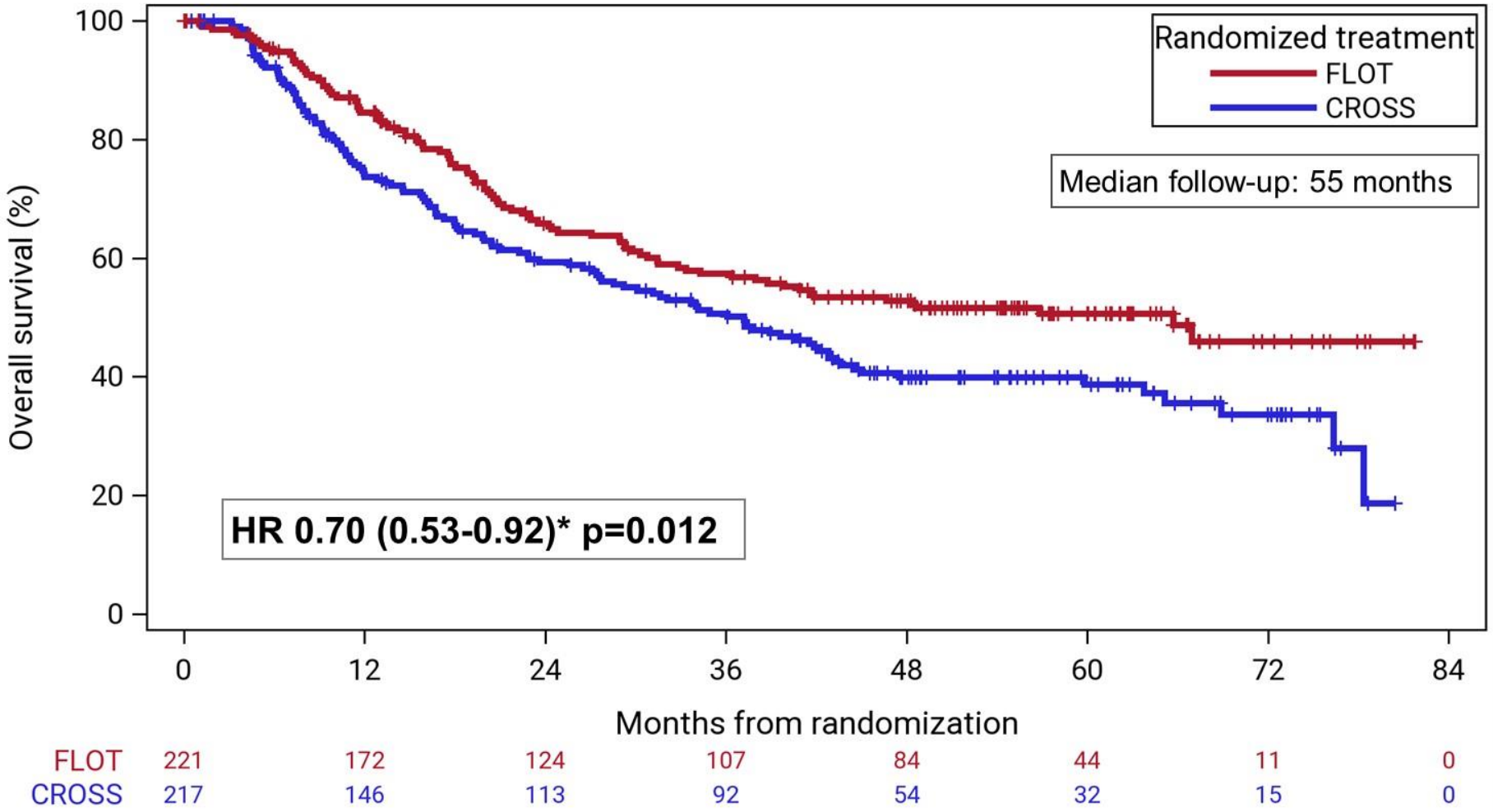
- Squamous or other non-adenocarcinoma histology
- Gastric cancer
- Clinical Stage cT1cN0 and cT4b
- Metastatic disease

*Tumors of the esophagus and tumors of which the epicenter is within 5 cm of the esophagogastric junction and also extend into the esophagus.

PRESENTED BY: Jens Hoeppner MD FACS FEBS

1. Sobin LH UICC TNM 7th edition 2009

Overall Survival - ITT Population



	FLOT	CROSS
Events	97	121
Median OS time (months)	66 95% CI 36 – n.e	37 95% CI 28 – 43
3-year OS rate	57.4%	50.7%
5-year OS rate	50.6%	38.7%

*Two-sided 95% confidence interval; Cox regression adjusted for N stage and age, stratified for trial site

Pathology Results – Surgery Population

	FLOT Group	CROSS Group
N	191	180
Resection status		
No resection	0.5%	1.1%
R0	94.2%	95.0%
R1	5.2%	3.9%
Postoperative N-Stage		
ypN-	50.8%	54.4%
ypN+	48.7%	44.4%
Pathological complete remission		
ypT0 ypN0	16.8%	10.0%
Tumor regression grade (Becker[1])		
Complete regression	18.3%	13.3%
Near complete regression (<10% vital tumor)	25.1%	39.4%

per local pathology assessment

1. Becker K Cancers 2003

Take Home Points of ESOPEC Study

- **Perioperative FLOT improves OS compared to CROSS and should be considered a new standard of care**
- Neoadjuvant CROSS + adjuvant nivolumab still option for patients who may not be candidates for perioperative FLOT
- Role of neoadjuvant chemo + neoadjuvant chemoRT followed by surgery is under active investigation
- Role of immunotherapy with chemo alone in the localized disease setting remains unclear
- ESOPEC study focused on adenocarcinoma only---chemoradiation still generally preferred for esophageal SCC

Pancreatic Cancer

NRG ONCOLOGY

Advancing Research. Improving Lives.™

NRG Oncology/RTOG 0848 Trial: Adjuvant Chemotherapy +/- Chemoradiation For Patients With Resected Head of Pancreas Adenocarcinoma -

Results of the RT + 5FU/Capecitabine Randomization Step

Ross A Abrams, MD, Kathryn A Winter, MS, Karyn A Goodman, MD, William F Regine, MD, Howard P Safran, MD, Adam C Berger, MD, Chandan S Guha, MD, PhD, Lisa A Kachnic, MD, Michael T Gillin, PhD, Samantha A Seaward, MD, Abraham J Wu, MD, Jennifer J Wu, MD, Raid M Aljumaily, MD, Thomas A Dipetrillo, MD, Ravit Geva, MD, Pramila Rani Anne, MD, Jennifer Yannucci, MD, Darla K Liles, MD, Jennifer Moughan, MS, Christopher H Crane, MD

ASCO 2024

6/4/2024

NCI National Clinical Trials Network — a National Cancer Institute program

NCI Community Oncology Research Program — A program of the National Cancer Institute of the National Institutes of Health

NRG Oncology / RTOG 0848

What do we know in adjuvant RT in resected PDAC

- Mixed results, some detrimental…

EORTC

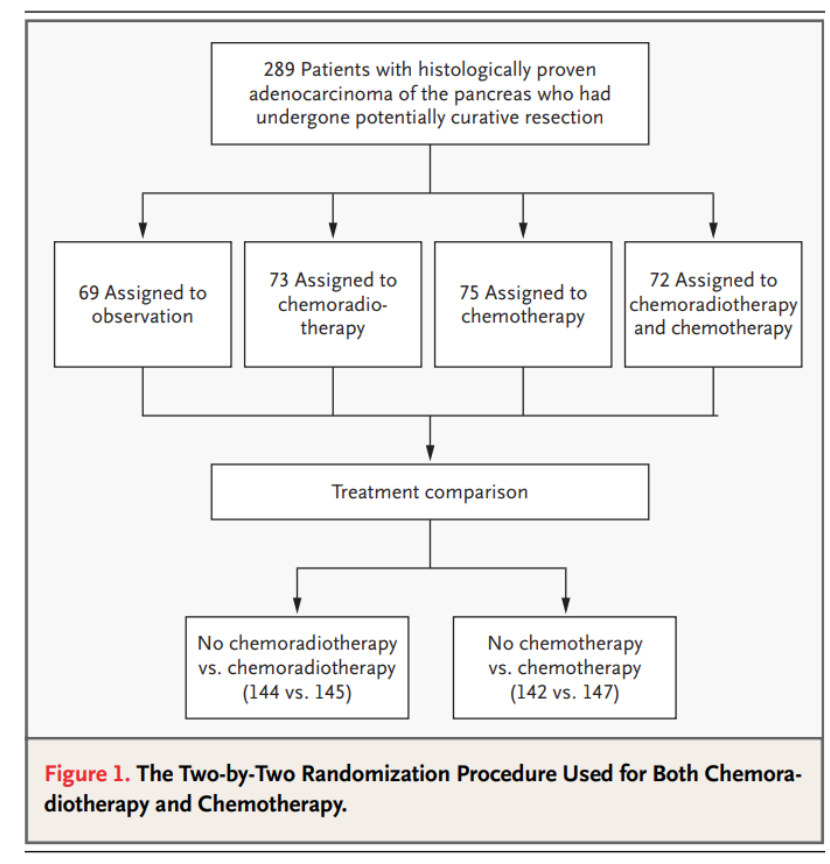
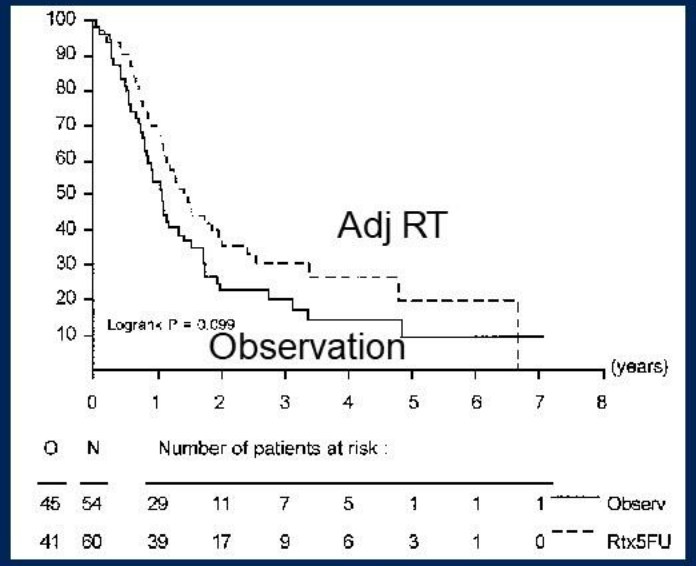
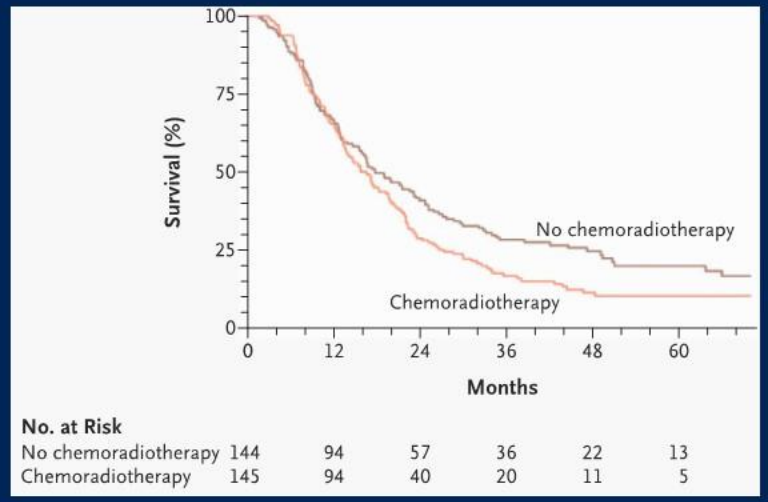


Figure 1. The Two-by-Two Randomization Procedure Used for Both Chemoradiotherapy and Chemotherapy.



Klinkenbijl *et al*. Ann Surg 1999

ESPAC-1



Neoptolemos *et al*. N Engl J Med 2004

Background

- At the time of study design in 2008, the only effective adjuvant systemic therapy for pancreatic cancer was gemcitabine
- The role of adjuvant radiotherapy was controversial (ESPAC 1)
- Recognition of early systemic failures (within 4-6 mos) following up-front surgery
- Identification of important prognostic factors requiring stratification

SCHEMA

Patients with resected pancreatic head adenocarcinomas

→ REGISTER

FIRST STEP:
ADJUVANT SYSTEMIC TREATMENT*

Arm 1:
Gemcitabine alone

Arm 2:
Gemcitabine + Erlotinib x 5 cycles (Arm 2 closed to accrual effective 4/02/14)

Abrams et al., *Am J Clin Oncol 2020;* 43:173-179

REASSESS AND IF NO PROGRESSION, THEN:

STRATIFY

Nodal Status:
1: involved
2: uninvolved

CA19-9 result:
1: ≤ 90
2: > 90 – 180

Surgical margins:
1: positive (R1)
2: negative (R0)

Adjuvant Systemic Treatment:
1. Gemcitabine alone
2. FOLFIRINOX or mFOLFIRINOX
3. Non-oxaliplatin gemcitabine combinations

RANDOMIZE

SECOND STEP:
RT RANDOMIZATION
For Non-Progressing Patients

Arm 3:
1 month of gemcitabine or combination chemotherapy

Arm 4:
1 month of gemcitabine or combination chemotherapy followed by XRT with either capecitabine or 5-FU

*Note: Up to 3 months may be initiated prior to registration.

Results: Adjuvant Systemic Treatment Received

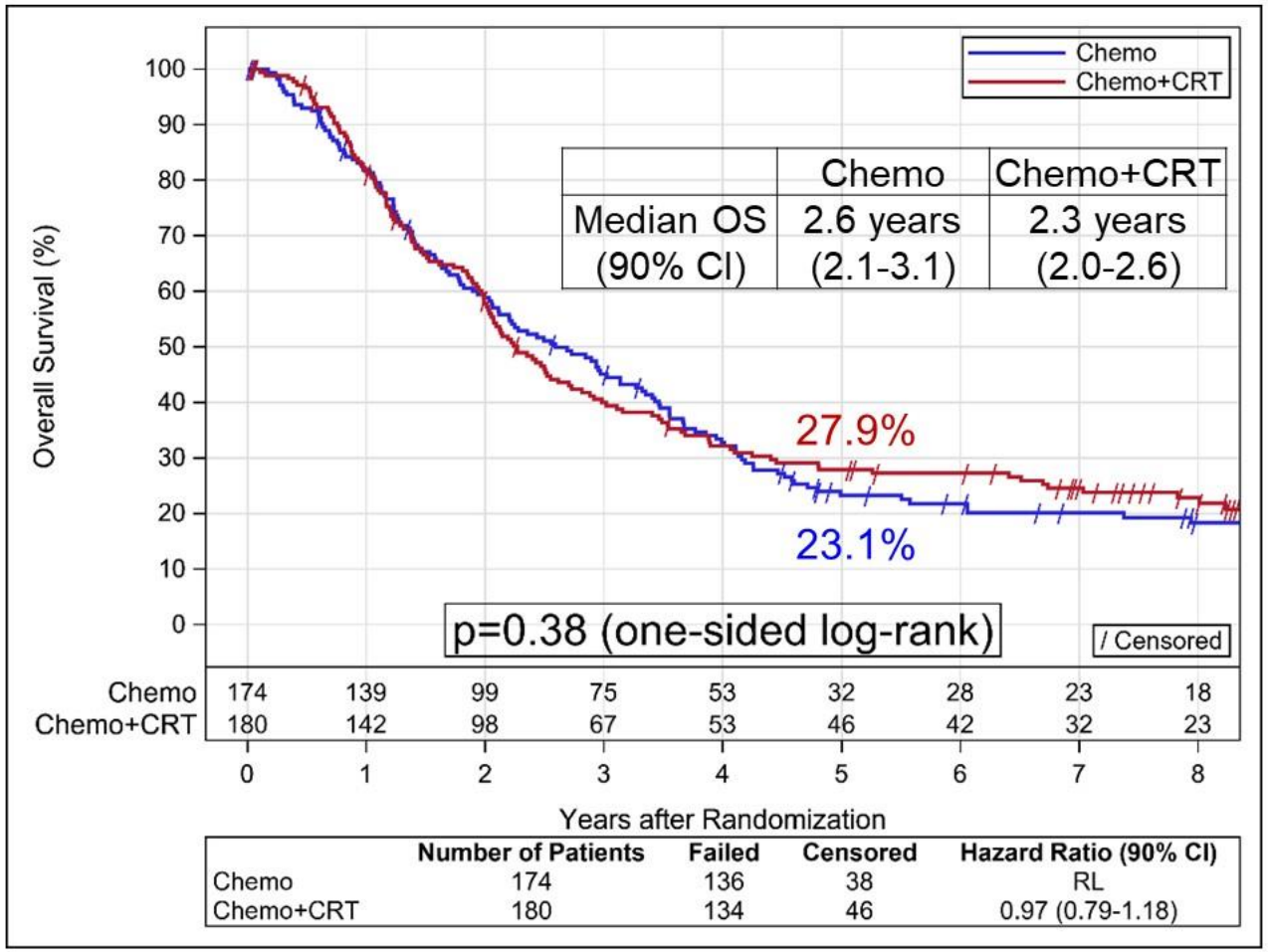
	Chemo	Chemo+CRT	Total
Enrollment Timing	174	180	354
Before June 28, 2016	148	161	309
After June 28, 2016	26	19	45
Regimen Received			
Gemcitabine	116	120	236 (67%)
Gemcitabine+Erlotinib	50	50	100 (28%)
Non Oxaliplatin Gem Combo	8	10	18 (5%)
FOLFIRINOX / mFOLFIRINOX	0	0	0 (0%)

Results: Patient and Tumor Characteristics

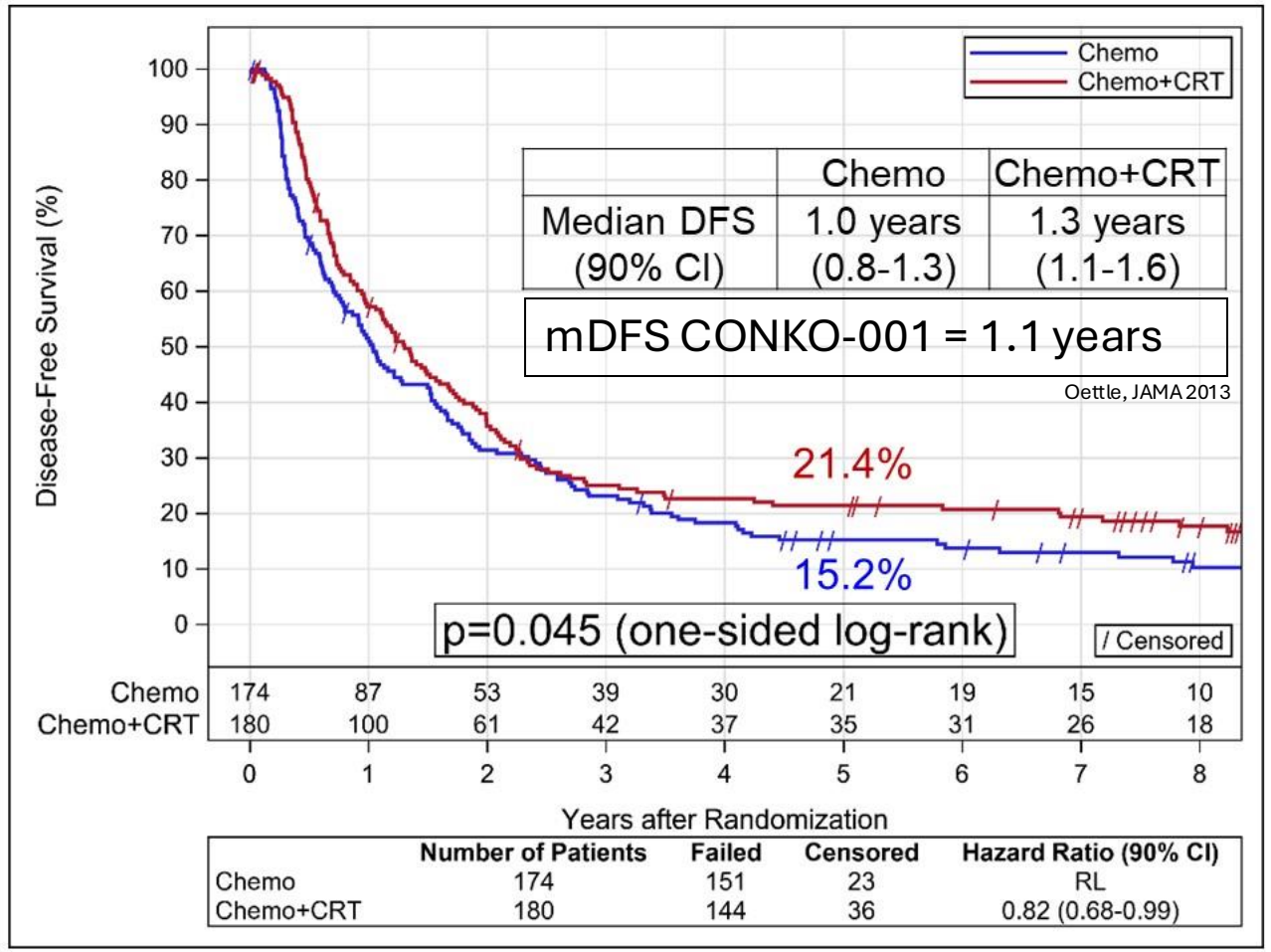
		Chemo (n=174)	Chemo+CRT (n=180)	Total (n=354)
Pathologic T stage	T1/T2	29 (17%)	37 (21%)	66 (19%)
	T3	145 (83%)	143 (79%)	288 (81%)
Pathologic N stage	N0	42 (24%)	49 (27%)	91 (26%)
	N1	132 (76%)	131 (73%)	263 (74%)
	1-3 nodes/> 3 nodes	95 (55%)/ 37 (21%)	79 (44%)/ 52 (29%)	174 (49%)/ 89 (25%)
Surgery	Classic PD	121 (70%)	139 (77%)	260 (73%)
	PPP/Other	53 (30%)	41 (23%)	94 (27%)
Surgical Margins	Negative	144 (83%)	151 (84%)	295 (83%)
	Positive	30 (17%)	29 (16%)	59 (17%)

PD: Pancreaticoduodenectomy; PPP: Pylorus preserving PD

Results: OS and DFS for All Patients

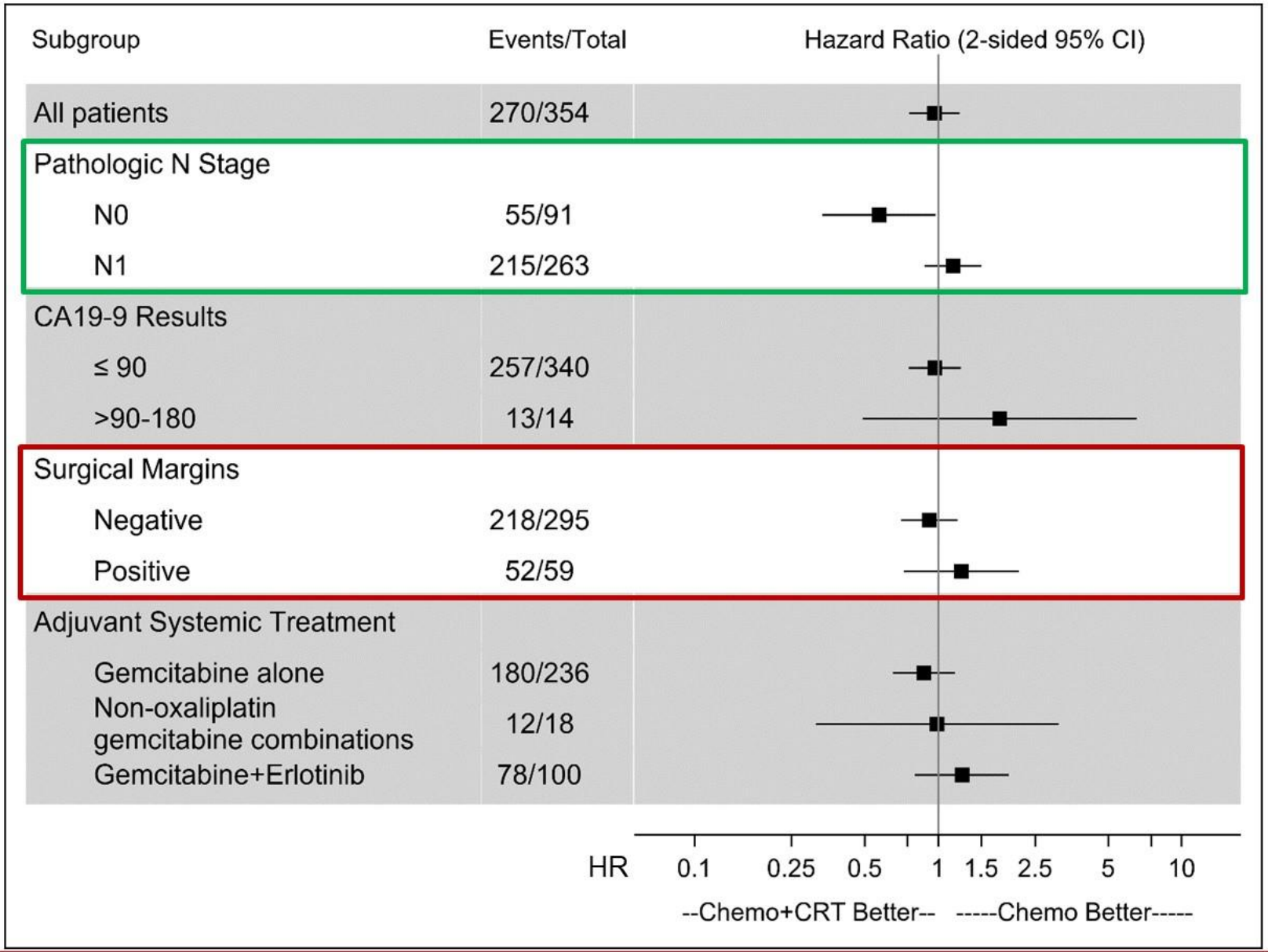


Overall Survival



Disease-Free Survival

Results: Forest Plot for OS Treatment Effect



Take Home Points of RTOG 0848

- Addition of radiation + 5-FU/capecitabine to adjuvant systemic treatment did not improve OS for all patients
- However, there was improvement in DFS for all patients
- Improved OS and DFS for NODE NEGATIVE disease
- More questions about the role of adjuvant chemoradiation in resectable pancreatic cancer

Metastatic Pancreas Cancer

1997 **Gemcitabine**
demonstrated clinical benefit over 5FU

2007 **Gemcitabine + Erlotinib**
demonstrated marginal benefit over gemcitabine

2011 **FOLFIRINOX (folinic acid, fluorouracil, irinotecan, oxaliplatin)**
improved RR, PFS, OS over gemcitabine

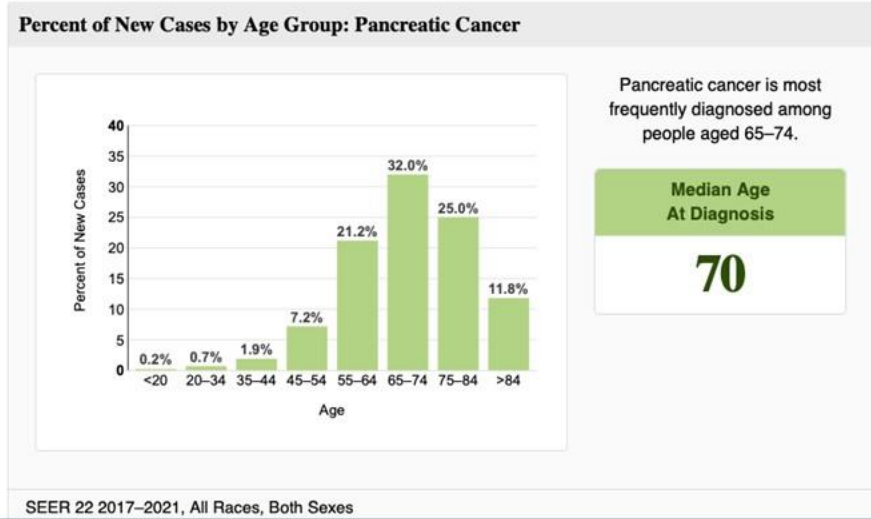
2013 **Gemcitabine + Nab-Paclitaxel**
improved RR, PFS, OS over gemcitabine

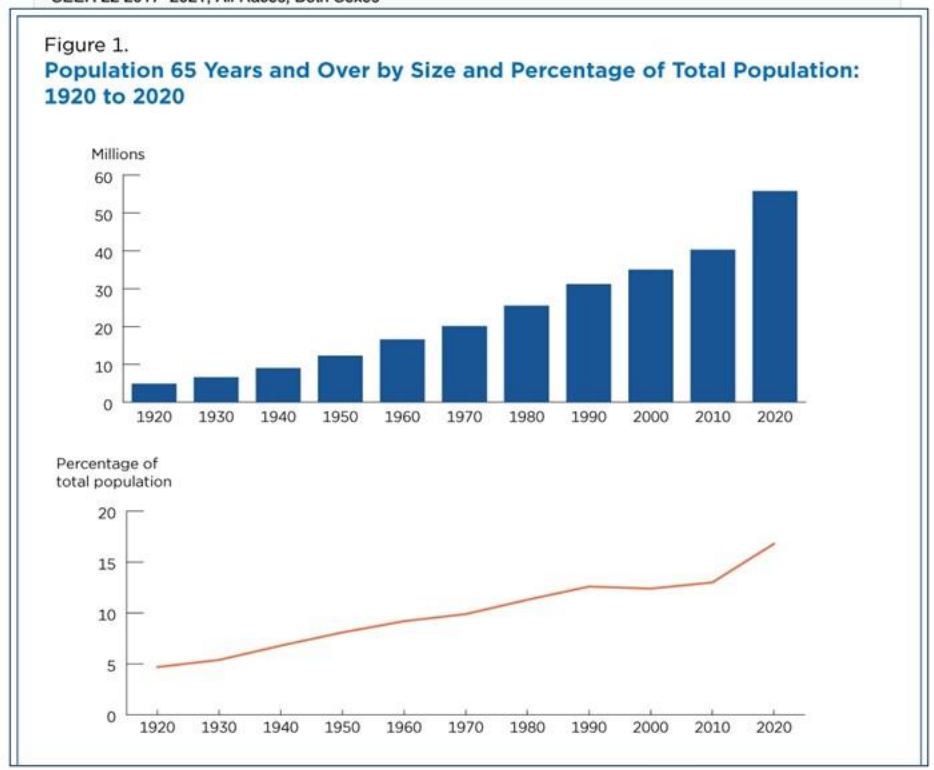
2015 **Nanoliposomal Irinotecan + fluorouracil + folinic acid**
Second Line

2023 **Nanoliposomal Irinotecan + 5FU/LV + Oxaliplatin**
First Line

Background (1)

- Older adults comprise most patients seen in clinical practice with mPDAC
- Care of older adults with cancer carries significant challenge beyond those faced by patients with mPDAC.
- Geriatric factors including co-morbidities, function, cognition, psychosocial support, and nutrition directly effect outcomes of older adults with cancer





Mohile et al. Lancet 2021; Li et al. JAMA oncology

Background (2)

Data is limited to guide the care of older adults with mPDAC, with much younger patients enrolled on prior studies.

Phase III mPDAC Studies	Median Age of enrolled patients (years)
PRODIGE	61
MPACT	62-63
NAPOLI 3	62-64

Real world data analyses shows a significant percentage of older adults remain untreated, with lower survival in those that receive therapy.

	<70y	70-79y	≥80y	P value
Overall	7.9 m	6.8m	6.2m	<0.0001
Gem +Abraxane	6.9m	6.5m	6.8m	.25
Gemcitabine	3.0m	4.0m	4.4m	.72
FOLFIRINOX	9.8m	9.6m	6.6m	.064
5FU+Liposomal Irinotecan	7.0m	6.9m	6.8m	.75

Wainberg et al. Lancet 2023; Von Hoff et al. NEJM 2013; Conroy et al. NEJM 2011; Elias et al. The oncologist 2022

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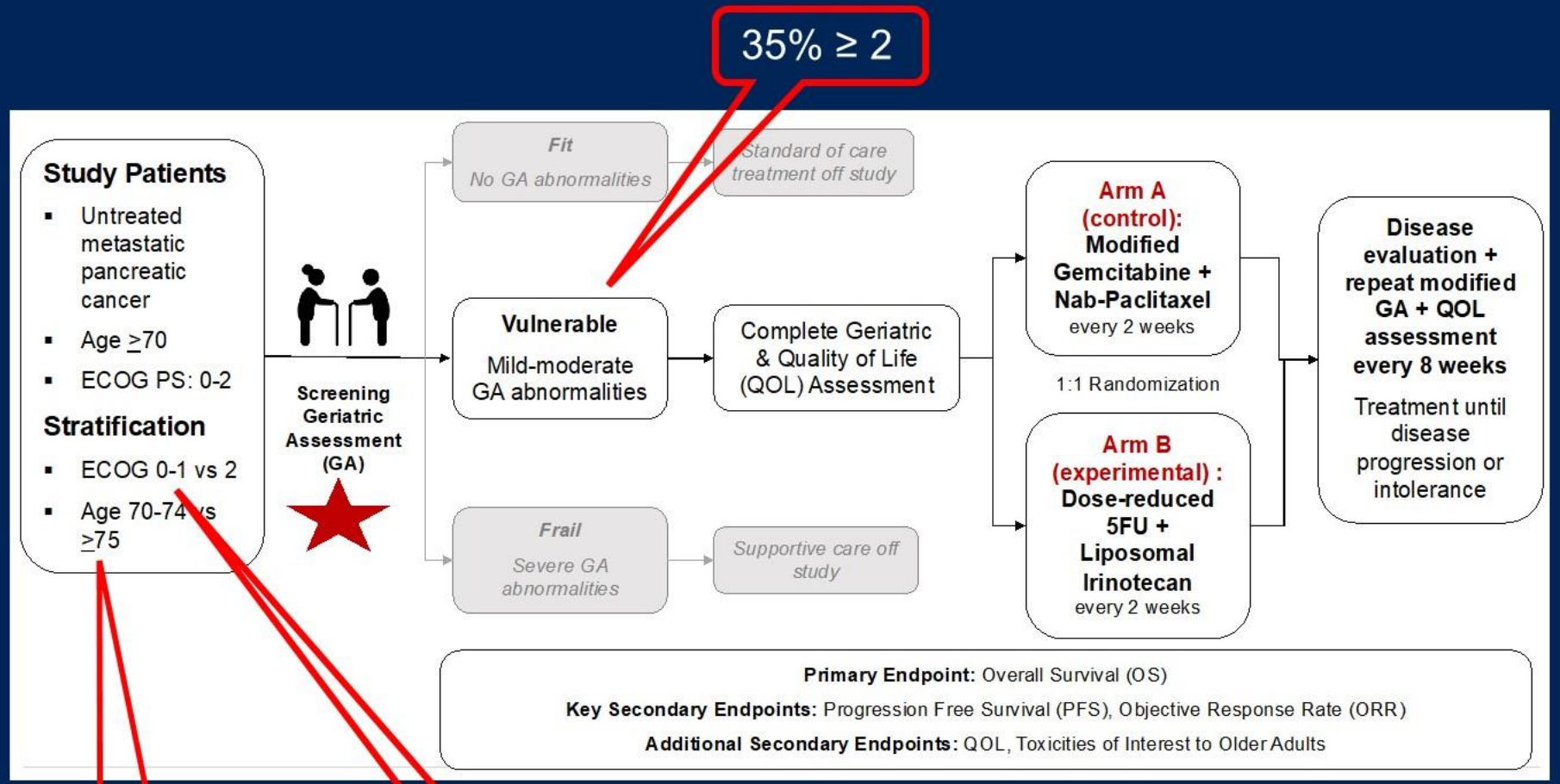
ECOG-ACRIN cancer research group

A randomized phase II study of gemcitabine and nab-paclitaxel compared with 5-fluorouracil, leucovorin, and liposomal irinotecan in older patients with treatment-naive metastatic pancreatic cancer (**GIANT**) ECOG-ACRIN EA2186

Efrat Dotan[1], Paul J. Catalano[2], Leon Lenchik[3], Robert Boutin[4], Xin Yao[5], James P. Ohr[6], Kian-Huat Lim[7], Namrata Vijayvergia[1], Sreenivasa R. Chandana[8], Aparna Kalyan[9], Richard F. Dunne[10], David B. Zhen[11], Daneng Li[12], Melissa A. Simon[9], Jordan Berlin[13], Lynne I. Wagner[3], Peter J. O'Dwyer[14].

[1]Fox Chase cancer Center, [2]Dana Farber Cancer Institute – ECOG ACRIN Biostatistics Center, [3]Wake Forest University Health Sciences, [4] Stanford University, [5]ThedaCare Regional Cancer Center, [6]UPMC Hillman Cancer Center, [7]Washington University School of Medicine, [8]Trinity Health Muskegon Hospital, [9]Northwestern University, [10]University of Rochester, [11]Fred Hutchinson Cancer Center, [12]City of Hope Comprehensive Cancer Center, [13]Vanderbilt University/Ingram Cancer Center, [14]University of Pennsylvania Abramson Cancer Center.

GIANT (ECOG-ACRIN EA2186)



Majority of participants PS 0-1, but with some vulnerability and older than 75 years old.

EA2186 (GIANT) - Screening Geriatric Assessment

Domain	Assessment Tool	Fit - no abnormalities	Vulnerable- any mild-moderate abnormalities	Frail- any severe abnormalities
Function[1]	ADL IADL (Female/Male)	6 8 /5	5 6-7/4	≤4 ≤5/≤3
Co-morbidities[2]	CIRS-G Cumulative Illness Rating Scale-Geriatric	No score 3-4 AND <5 comorbidities with a score of 2	No score 3-4 AND 5-8 comorbidities with a score of 2	≥1 score 3-4 OR >8 comorbidities with a score of 2
Cognition[3]	Blessed Orientation Memory Concentration Test	0-4	5-10	≥11
Age[2]*			≥80	
Geriatric Syndromes[4]	• Falls (>3 in 6m) • Urinary/Fecal incontinence	None	None	Presence of any of these would exclude patients

[1]Corre et al. JCO 2016 [2]Tucci et al; Leukemia and Lymphoma 2015. [3] Mohile et al; JCO 2018. [4]GrantPax study - Betge et al. BMC 2018

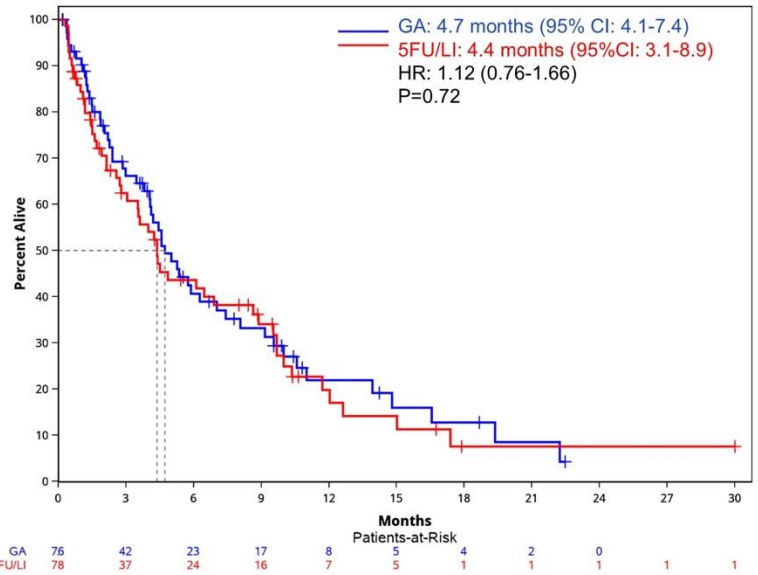
Baseline characteristics

	Gemcitabine+ Nab-Paclitaxel (N=88)	5FU+ Liposomal Irinotecan (N=88)	Total (N=176)	P-value
Age, Median (Range)	77 (70-90)	77 (70-89)	77 (70-90)	
Gender, n (%)				0.228
Female	48 (54.5%)	39 (44.3%)	87 (49.4%)	
Male	40 (45.5%)	49 (55.7%)	89 (50.6%)	
Race/Eth, n (%)				0.033
White	77 (88.5%)	64 (74.4%)	141 (81.5%)	
Black/AA	7 (8.0%)	11 (12.8%)	18 (10.4%)	
Hisp/Lat	1 (1.1%)	7 (8.1%)	8 (4.6%)	
Asian	1 (1.1%)	4 (4.7%)	5 (2.9%)	
Mult	1 (1.1%)	0 (0.0%)	1 (0.6%)	
Missing	1	2	3	
Age Stratification, n (%)				1.000
Age 70-74	33 (37.5%)	34 (38.6%)	67 (38.1%)	
Age 75+	55 (62.5%)	54 (61.4%)	109 (61.9%)	

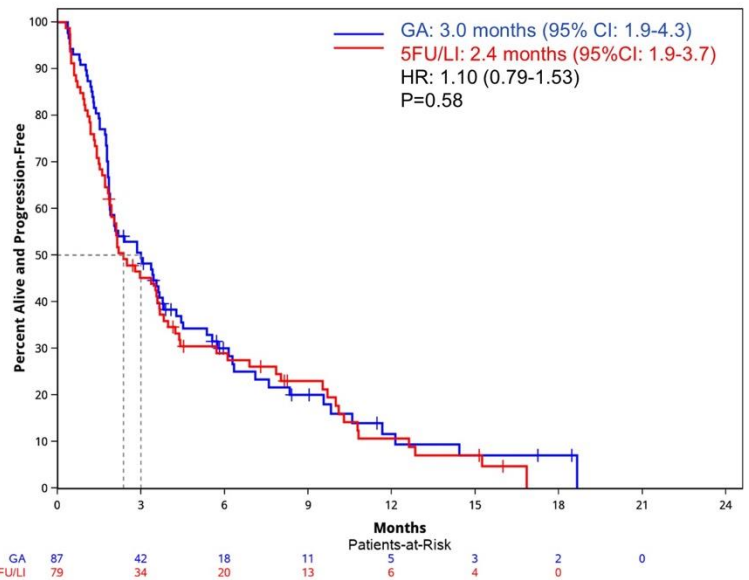
Baseline characteristics – Geriatric screening

	Gemcitabine+ Nab-Paclitaxel (N=88)	5FU+ Liposomal Irinotecan (N=88)	Total (N=176)	P-value
Performance Status, n (%)				0.974
0	20 (22.7%)	22 (25.0%)	42 (23.9%)	
1	57 (64.8%)	55 (62.5%)	112 (63.6%)	
2	11 (12.5%)	11 (12.5%)	22 (12.5%)	
Screening vulnerability, n (%)				
Age	32 (36.4%)	33 (36.4%)	64 (36.4%)	
Co-Morbidity	25 (28.4%)	32 (36.4%)	57 (32.4%)	
Cognition	36 (41.4%)	43 (49.4%)	79 (45.4%)	
Function (ADL)	5 (5.7%)	7 (8.0%)	12 (6.9%)	
Function (IADL)	18 (20.7%)	16 (18.4%)	34 (19.5%)	
# of Vulnerability Domains, n(%)				
1	53 (60.9%)	43 (49.4%)	96 (55.2%)	0.532
2	20 (23.0%)	25 (28.7%)	45 (25.9%)	
≥3	6 (6.9%)	10 (11.5%)	16 (9.2%)	

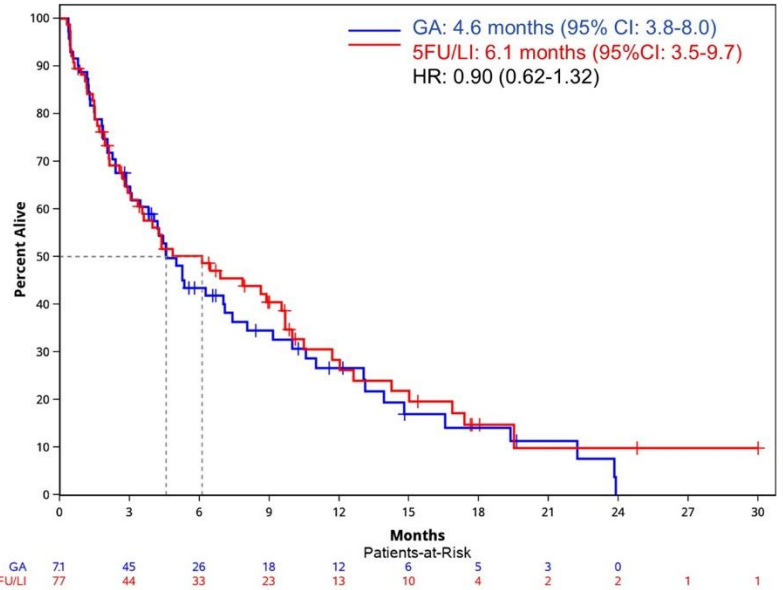
Primary end point OS - ITT



Secondary end point PFS - ITT

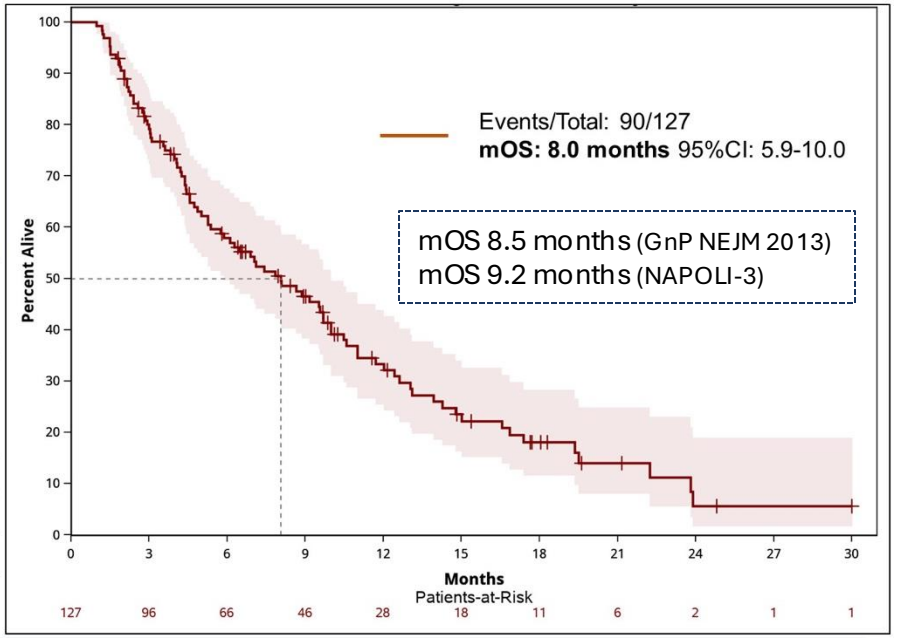


OS analysis for eligible patients

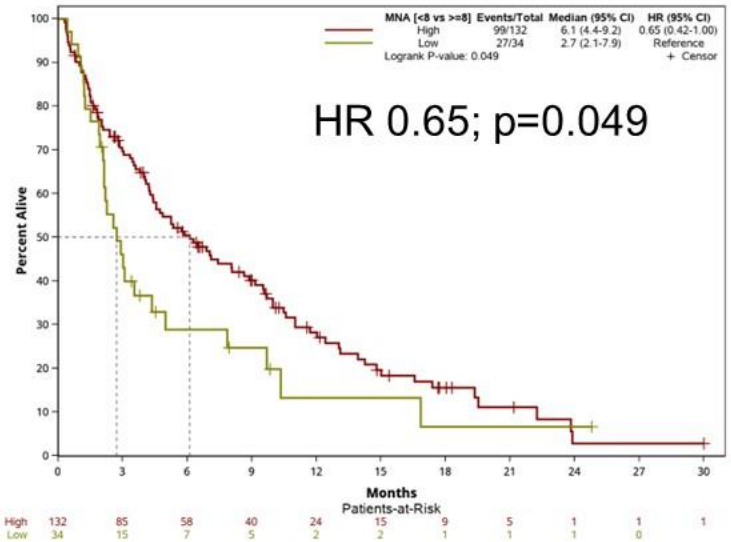


OS analysis of patients who received ≥ 4 weeks of treatment

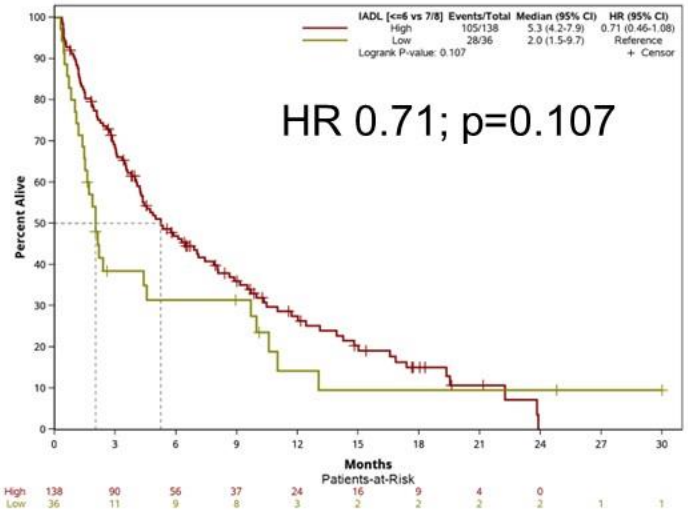
Number of chemotherapy doses	N (%)
0	22 (12.5%)
1	22 (14.3%)
≥2	127 (72%)



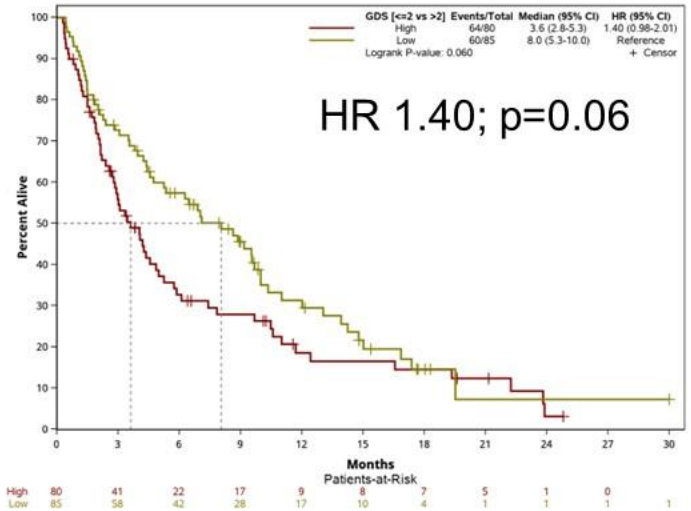
Nutrition



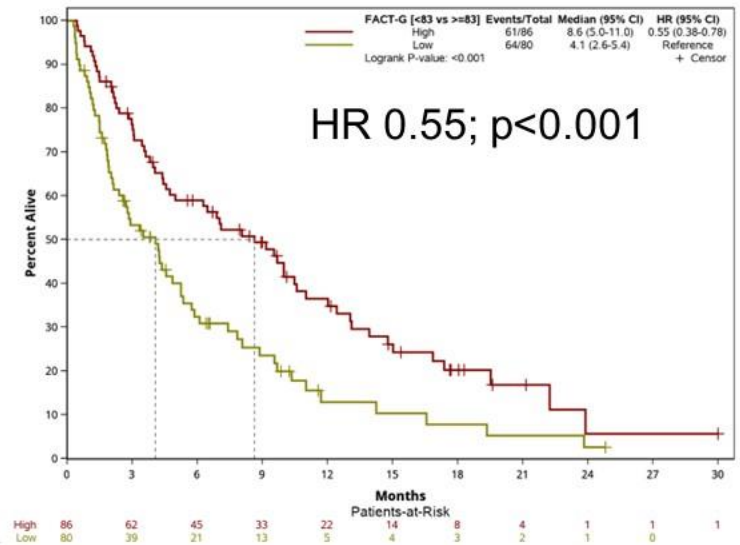
IADL



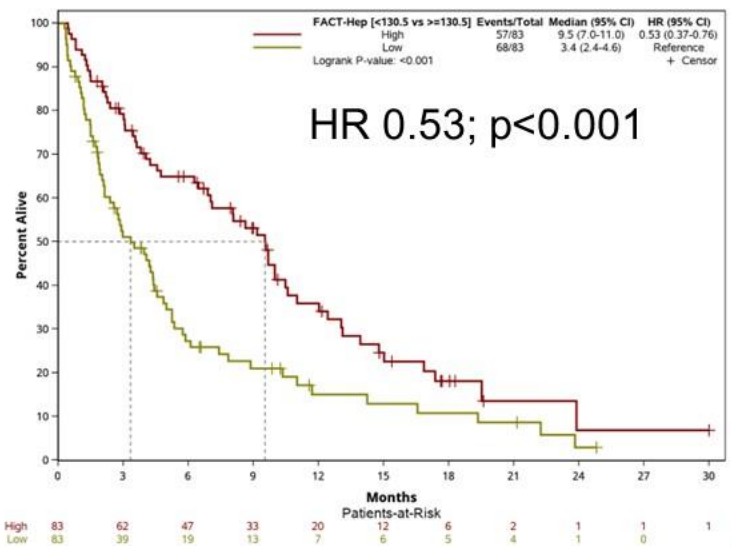
Depression



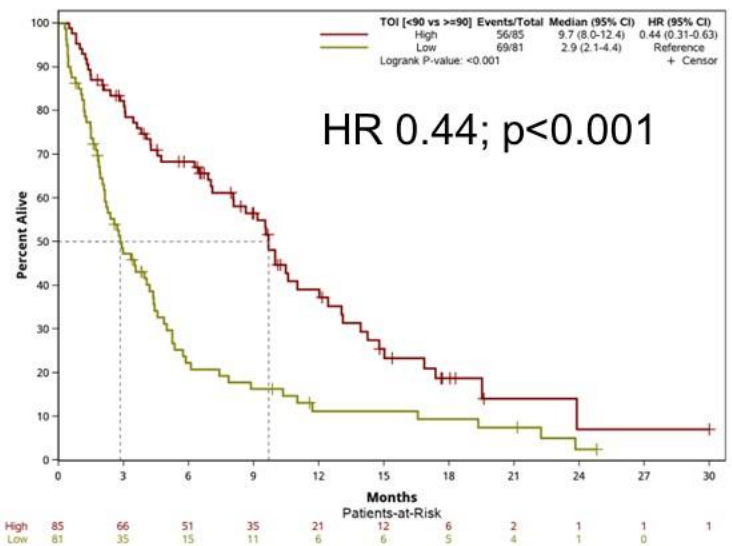
FACT- G



FACT- Hep 4



Physical/Functional well being



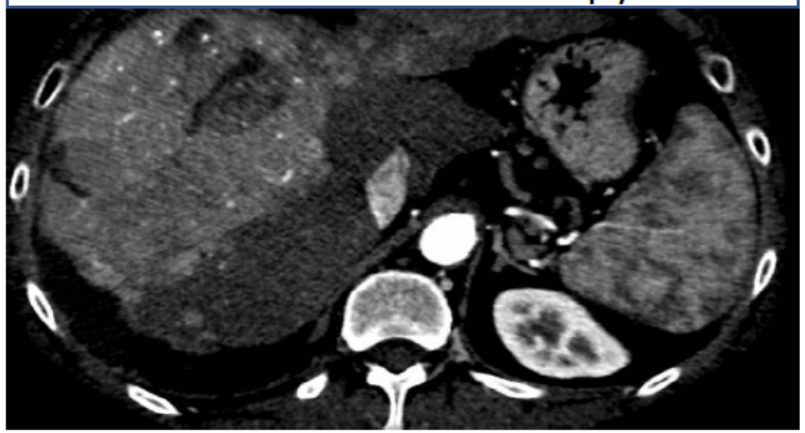
Take Home Points of EA2186/GIANT Study

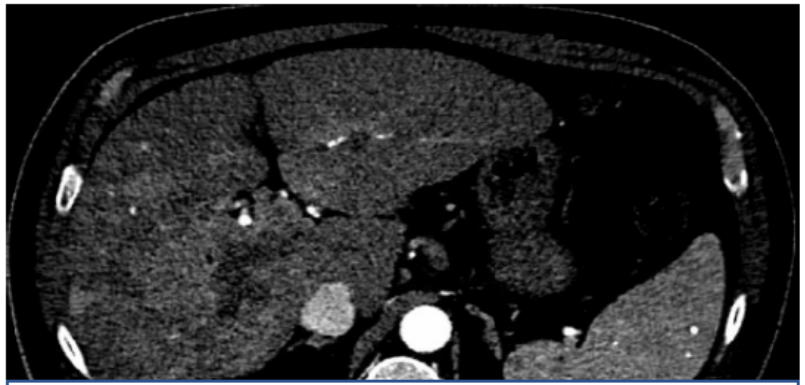
- No difference in OS between modified gemcitabine + nab-paclitaxel vs 5-FU/LV + nanoliposomal irinotecan
- OS is poor for most elderly and frail patient with metastatic pancreatic cancer
- Chemo only improves OS in those who can make it through at least 1 month of chemo
- Need better geriatric tools in clinic to help stratify patients who are most likely to benefit from chemotherapy

Hepatobiliary Cancer

Background:
Systemic Therapy for Advanced Hepatocellular Carcinoma

BCLC B (ineligible/refractory to catheter-based therapy





BCLC C (Vascular Invasion/Metastatic Disease)

FDA APPROVED AGENTS

1st Line	2nd Line	3rd Line
Sorafenib SHARP/ASIA PACIFIC	Cabozantinib CELESTIAL TRIAL	Cabozantinib CELESTIAL TRIAL
Lenvatinib REFLECT TRIAL	Regorafenib (sorafenib tolerant) RESOURCE	
Atezolizumab + Bevacizumab IMBRAVE150 TRIAL	Ramucirumab (AFP>400) REACH-2	
Durvalumab + Tremelimumab HIMALAYA TRIAL	~~Nivolumab* CHECKMATE 040~~	
	Pembrolizumab* KEYNOTE 224	
	Nivolumab + Ipilimumab CHECKMATE 040	

*Accelerated Approval based upon ORR and DOR

2024 ASCO ANNUAL MEETING

Nivolumab plus ipilimumab vs lenvatinib or sorafenib as first-line treatment for unresectable hepatocellular carcinoma: first results from CheckMate 9DW

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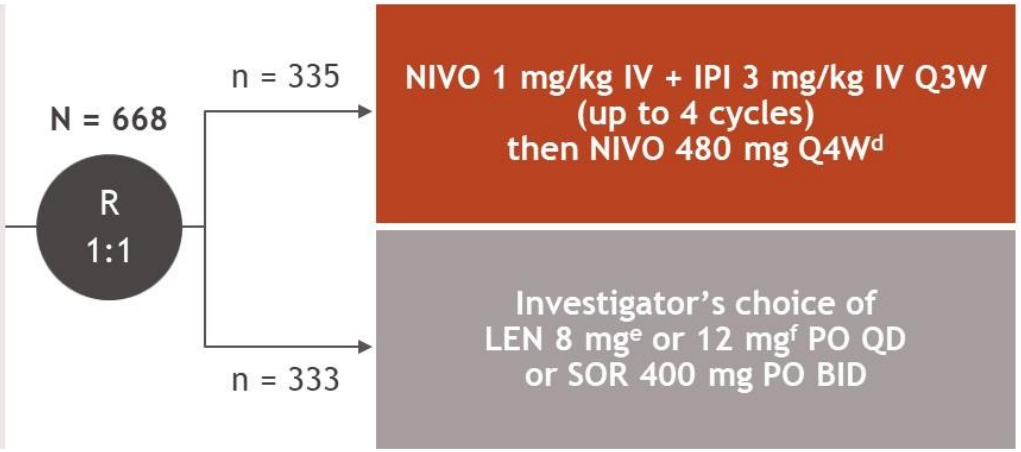
Abstract number LBA4008

CheckMate 9DW study design

- CheckMate 9DW is a global, phase 3, randomized, open-label study of NIVO in combination with IPI compared with LEN or SOR as 1L treatment in patients with unresectable HCC[a]

Key eligibility criteria
- Unresectable HCC[b]
- At least 1 measurable lesion (RECIST v1.1)
- Systemic therapy naive
- Child-Pugh score 5 or 6
- ECOG PS 0 or 1
- No main portal vein invasion (Vp4)

Stratification factors:
- Etiology (HBV vs HCV vs uninfected)[c]
- MVI/EHS (present vs absent)
- AFP (< 400 vs ≥ 400 ng/mL)



Treatment until disease progression, unacceptable toxicity, withdrawal of consent (all arms), or a maximum treatment duration of 2 years (NIVO + IPI arm only)

Among 325 patients treated with LEN/SOR:
275 (85%) received LEN and 50 (15%) received SOR

Primary endpoint:
- OS

Secondary endpoints:
- ORR and DOR by BICR per RECIST v1.1
- Time to symptom deterioration[g]

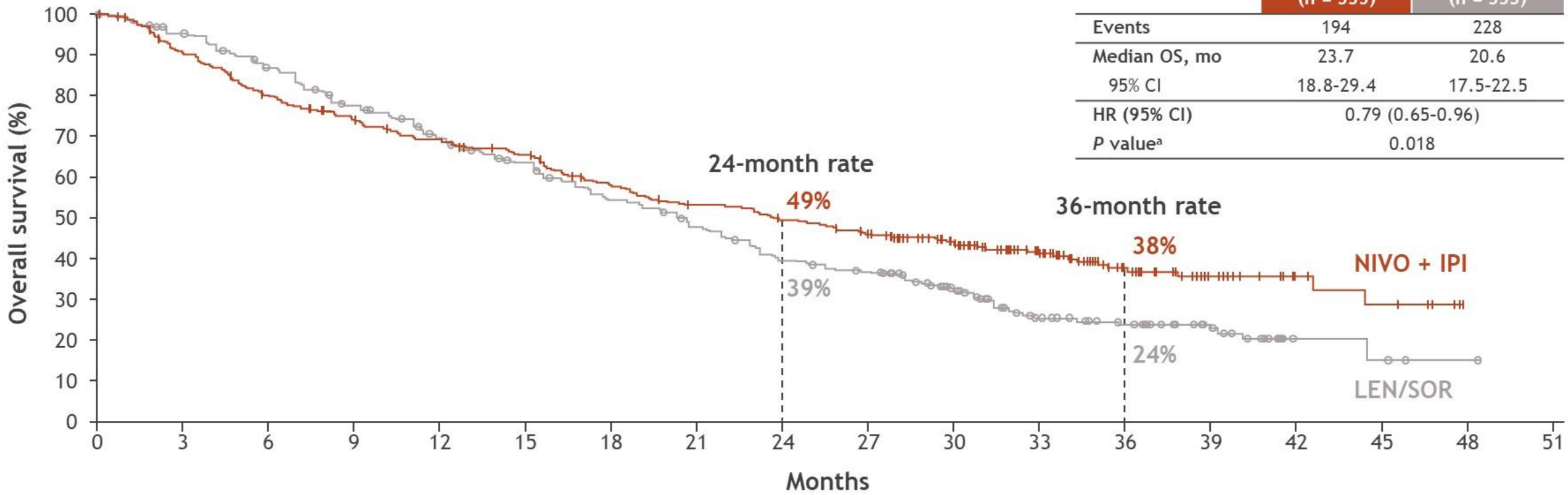
Key exploratory endpoints:
- PFS by BICR per RECIST v1.1
- Safety

Of note 85% of control arm
Was given lenvatinib

- At data cutoff (January 31, 2024), median (range) follow-up[h] was 35.2 (26.8-48.9) months

[a]ClinicalTrials.gov: NCT04039607. [b]Disease not eligible for, or progressive disease after, curative surgical and/or locoregional therapies. [c]Based on central lab serology results for stratification purpose. [d]Minimum of 1 dose of NIVO + IPI is required before proceeding to NIVO monotherapy. [e]If body weight < 60 kg. [f]If body weight ≥ 60 kg. [g]HCS subscale score of the FACT-Hep. [h]Time between randomization date and cutoff date.

Overall survival



	NIVO + IPI (n = 335)	LEN/SOR (n = 333)
Events	194	228
Median OS, mo	23.7	20.6
95% CI	18.8-29.4	17.5-22.5
HR (95% CI)	0.79 (0.65-0.96)	
P value[a]	0.018	

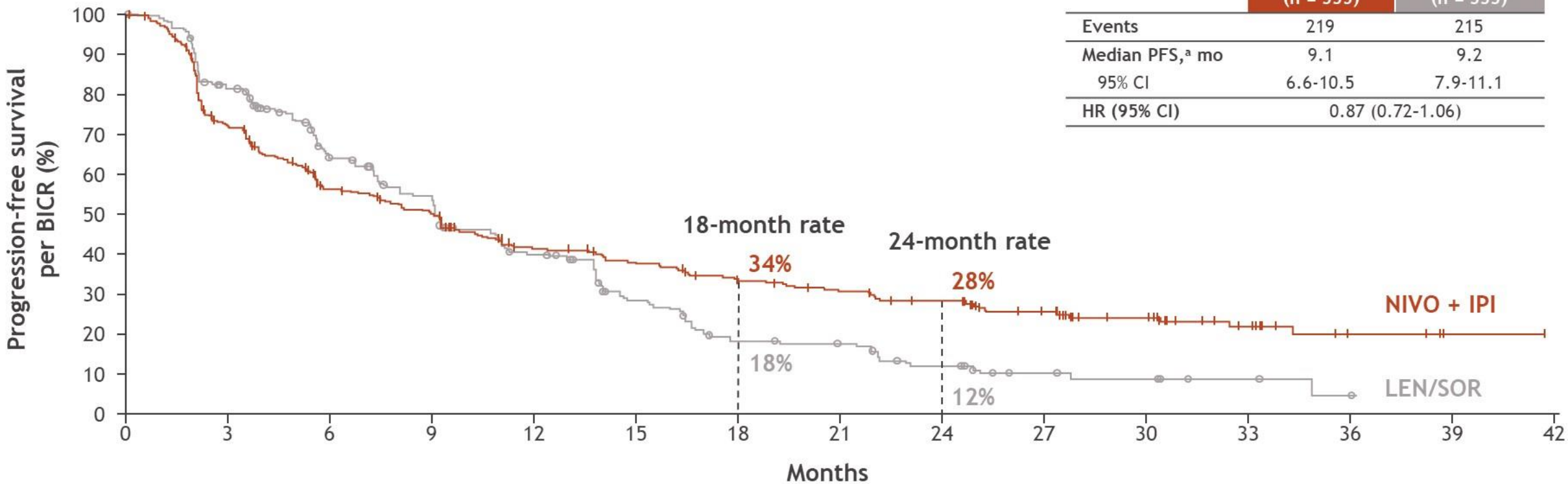
No. at risk																		
NIVO + IPI	335	300	264	239	220	206	179	162	150	137	104	71	42	24	11	8	0	0
LEN/SOR	333	310	280	245	216	194	164	144	116	106	76	44	34	20	4	3	1	0

- Statistically significant and clinically meaningful OS benefit with NIVO + IPI vs LEN/SOR
  - Longer median OS and long-term survival benefit with higher OS rates at 24 and 36 months

Median (range) follow-up, 35.2 (26.8-48.9) months. Median OS is estimated using Kaplan-Meier methodology. HR and 95% CI from stratified Cox proportional hazard model. HR is NIVO + IPI over LEN/SOR. Symbols represent censored observations. [a]Two-sided *P* value from stratified log-rank test. Boundary for statistical significance: *P* value ≤ 0.0257.

Progression-free survival

	NIVO + IPI (n = 335)	LEN/SOR (n = 333)
Events	219	215
Median PFS,[a] mo	9.1	9.2
95% CI	6.6-10.5	7.9-11.1
HR (95% CI)	0.87 (0.72-1.06)	



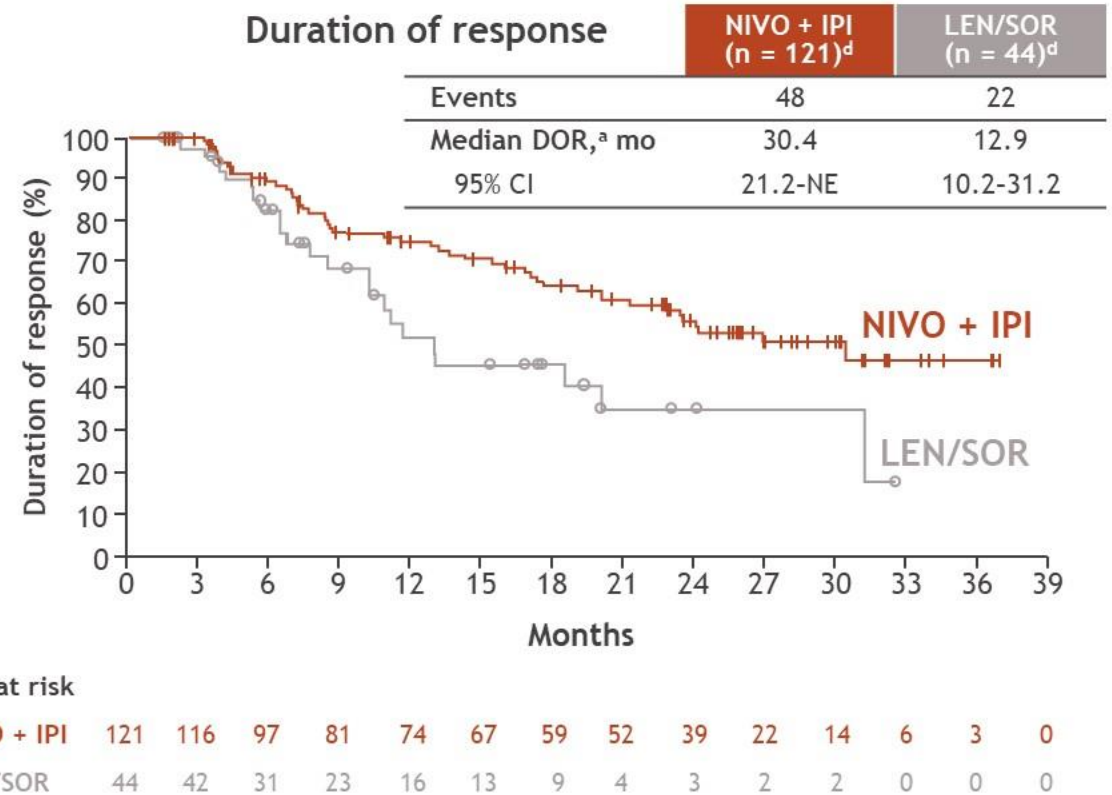
No. at risk															
NIVO + IPI	335	224	160	140	103	92	78	69	61	45	29	16	6	1	0
LEN/SOR	333	242	164	131	82	52	30	26	16	8	6	3	1	0	0

- Numerically higher PFS rates with NIVO + IPI vs LEN/SOR at 18 and 24 months

Median (range) follow-up, 35.2 (26.8-48.9) months. Median PFS is estimated using Kaplan-Meier methodology. HR and 95% CI from stratified Cox proportional hazard model. HR is NIVO + IPI over LEN/SOR. Symbols represent censored observations. [a]Assessed by BICR based on RECIST v1.1.

Response and duration of response

	NIVO + IPI (n = 335)	LEN/SOR (n = 333)
ORR,[a] %	36	13
95% CI	31-42	10-17
P value[b]	< 0.0001	
Best overall response,[a] %		
Complete response	7	2
Partial response	29	11
Stable disease[c]	32	62
Progressive disease	20	14
Not evaluable	12	11
Median TTR (range),[a] mo	2.2 (1.1-11.6)	3.7 (0.6-11.2)



- Statistically significant and clinically meaningful improvement in ORR with NIVO + IPI vs LEN/SOR, with a higher complete response rate (7% vs 2%, respectively) and durable responses

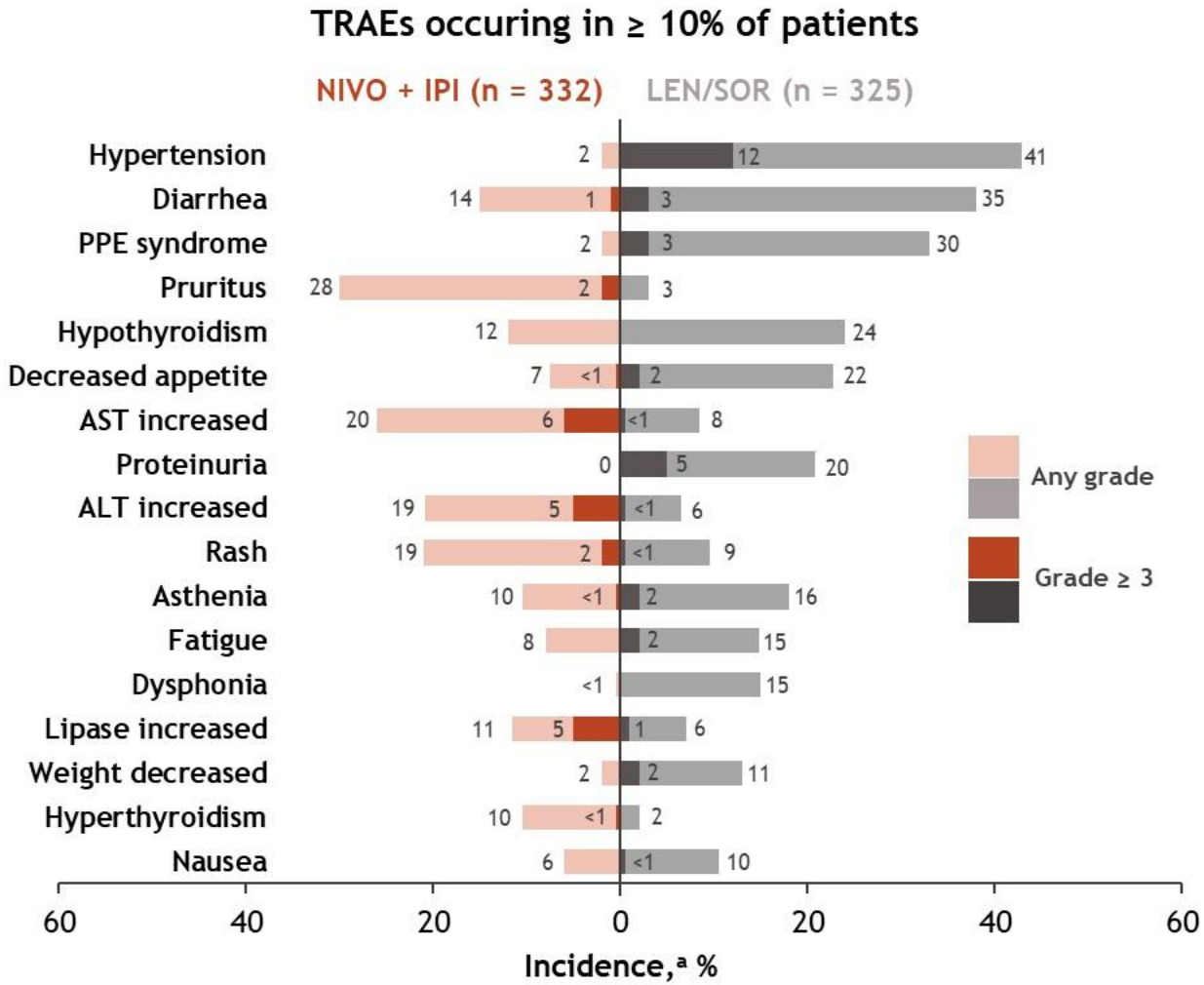
Median (range) follow-up, 35.2 (26.8-48.9) months. Symbols represent censored observations. [a]Assessed by BICR based on RECIST v1.1. [b]Two sided *P* value from stratified Cochran-Mantel-Haenszel test. Boundary for statistical significance: *P* value ≤ 0.025. [c]Includes non-CR/non-PD: NIVO + IPI, n = 6 (2%); LEN/SOR, n = 7 (2%). Non-CR/non-PD refers to patients with persistence of one or more non-target lesion(s). [d]Number of confirmed responders.

Treatment-related adverse events

All treated patients, n (%)	NIVO + IPI (n = 332)	LEN/SOR (n = 325)
Median (range) duration of treatment, mo	4.7 (< 1 to 24.4)	6.9 (< 1 to 45.8)

All treated patients, n (%)	NIVO + IPI (n = 332)		LEN/SOR (n = 325)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
TRAEs[a]				
Any TRAEs	278 (84)	137 (41)	297 (91)	138 (42)
Serious TRAEs	94 (28)	83 (25)	47 (14)	42 (13)
TRAEs leading to discontinuation	59 (18)	44 (13)	34 (10)	21 (6)
Treatment-related deaths[b]	12 (4)[c]		3 (< 1)[d]	

30% required steroid rescue



[a]Includes events reported between first dose and 30 days after last dose of study therapy. [b]Treatment-related deaths were reported regardless of time frame. [c]TRAEs leading to death in the NIVO + IPI arm included immune-mediated hepatitis (n = 4), hepatic failure (n = 3), hepatic insufficiency (n = 1), decompensated cirrhosis (n = 1), diarrhea-colitis (n = 1), autoimmune hemolytic anemia (n = 1), and dysautonomia (n = 1). [d]TRAEs leading to death in the LEN/SOR arm included hepatorenal syndrome (n = 1), ischemic stroke (n = 1), and acute kidney injury (n = 1).

Cross Trial Comparisons: Current 1L HCC Combination Options

	Atezo/Bev	STRIDE	Nivo/Ipi
OS	HR 0.58	HR 0.78	HR 0.79*
PFS	HR 0.59	HR 0.9	HR 0.87*
ORR	30% (5.5% CR)	20% (3.1% CR)	36% (7% CR)

Median OS TKI	13.2 months	13.8 months	20.6 months
Median OS Doublet	NE (updated 19 months)	16.4 months	23.7 months

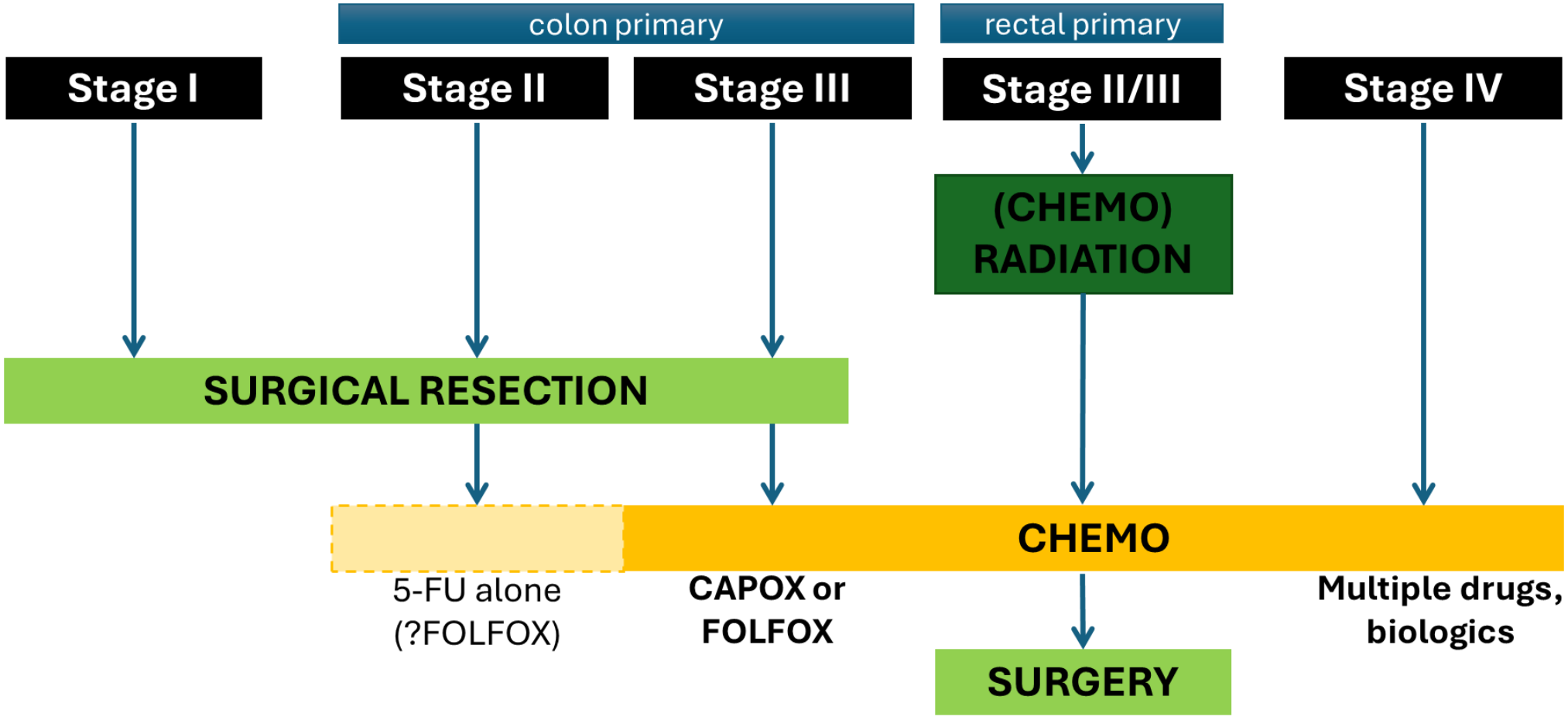
* 85% lenvatinib

Take Home Points of CheckMate 9DW

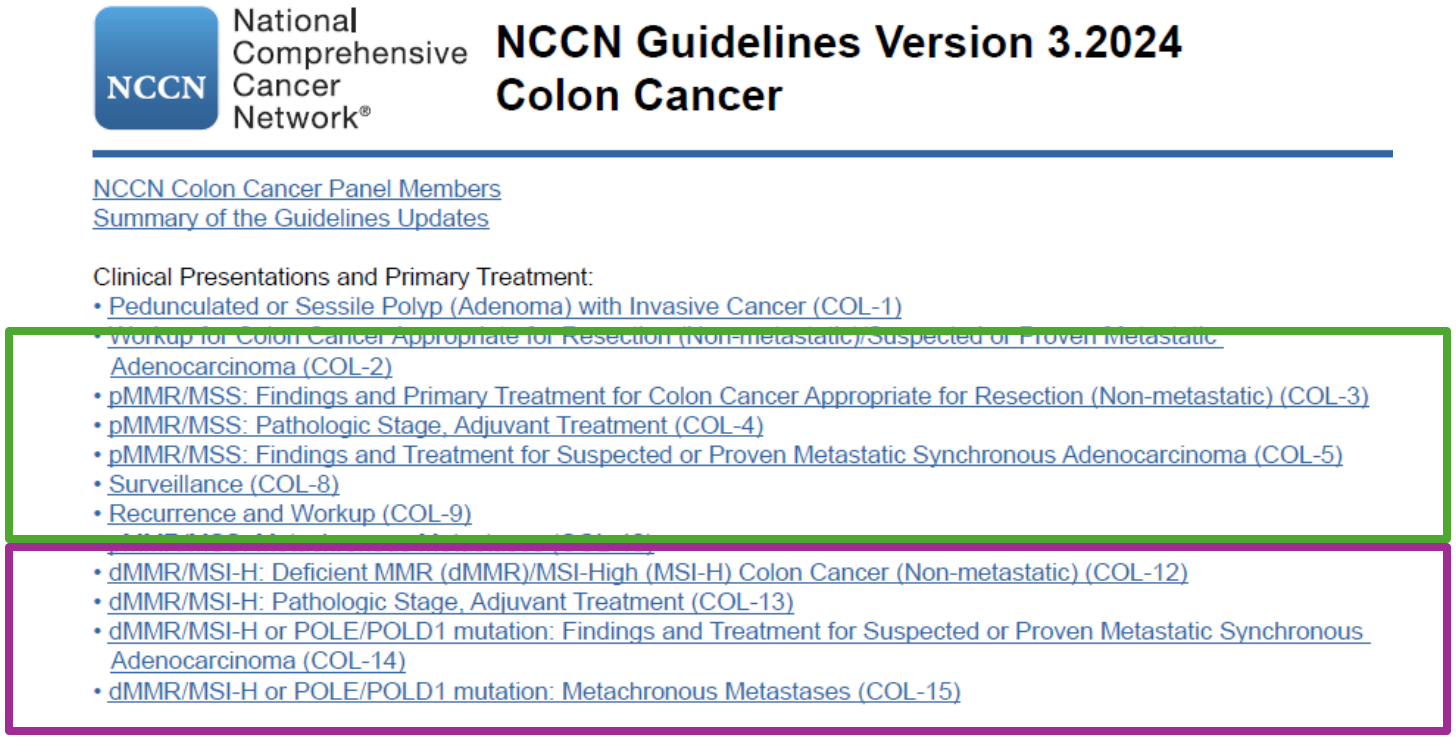
- Nivolumab + Ipilimumab will likely be approved as another 1L option for advanced HCC
- Appealing efficacy but at the expense of increased toxicity
- Might consider in patients who cannot receive atezolizumab/bevacizumab (e.g. esophageal varices) who have bulky disease and need for palliation
- Also could be an interesting option in the neoadjuvant setting
- Multiple options exist in the 1L setting for advanced HCC and multiple factors to consider when choosing therapy for patients

Colorectal Cancer (CRC)

CRC Treatment Paradigm



Paradigms vary for MSI and MSS CRC



National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2024
Colon Cancer

NCCN Colon Cancer Panel Members
Summary of the Guidelines Updates

Clinical Presentations and Primary Treatment:

- Pedunculated or Sessile Polyp (Adenoma) with Invasive Cancer (COL-1)
- Workup for Colon Cancer Appropriate for Resection (Non-metastatic)/Suspected or Proven Metastatic Adenocarcinoma (COL-2)
- pMMR/MSS: Findings and Primary Treatment for Colon Cancer Appropriate for Resection (Non-metastatic) (COL-3)
- pMMR/MSS: Pathologic Stage, Adjuvant Treatment (COL-4)
- pMMR/MSS: Findings and Treatment for Suspected or Proven Metastatic Synchronous Adenocarcinoma (COL-5)
- Surveillance (COL-8)
- Recurrence and Workup (COL-9)
- dMMR/MSI-H: Deficient MMR (dMMR)/MSI-High (MSI-H) Colon Cancer (Non-metastatic) (COL-12)
- dMMR/MSI-H: Pathologic Stage, Adjuvant Treatment (COL-13)
- dMMR/MSI-H or POLE/POLD1 mutation: Findings and Treatment for Suspected or Proven Metastatic Synchronous Adenocarcinoma (COL-14)
- dMMR/MSI-H or POLE/POLD1 mutation: Metachronous Metastases (COL-15)

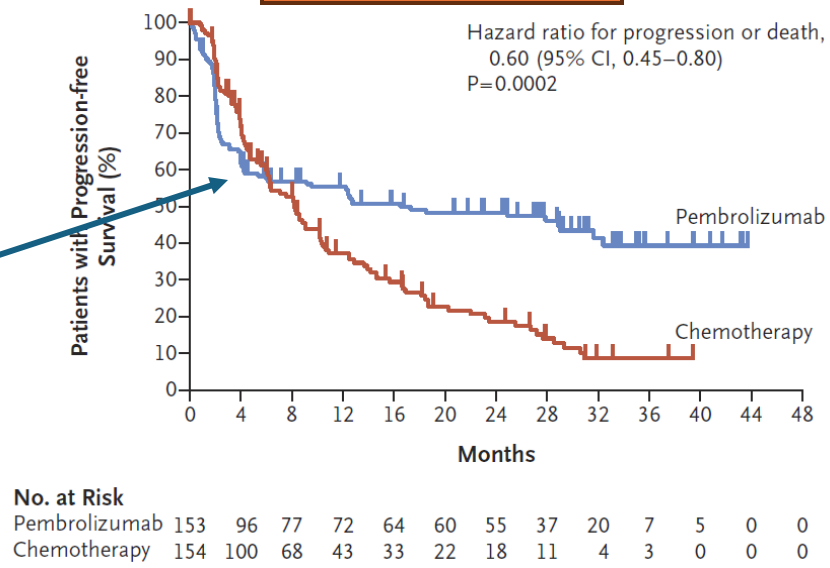
- Test all CRC!
- MSI/dMMR can…
  - Screen for Lynch syndrome
  - Prognostic
  - Predictive

Immunotherapy in 1L Metastatic CRC

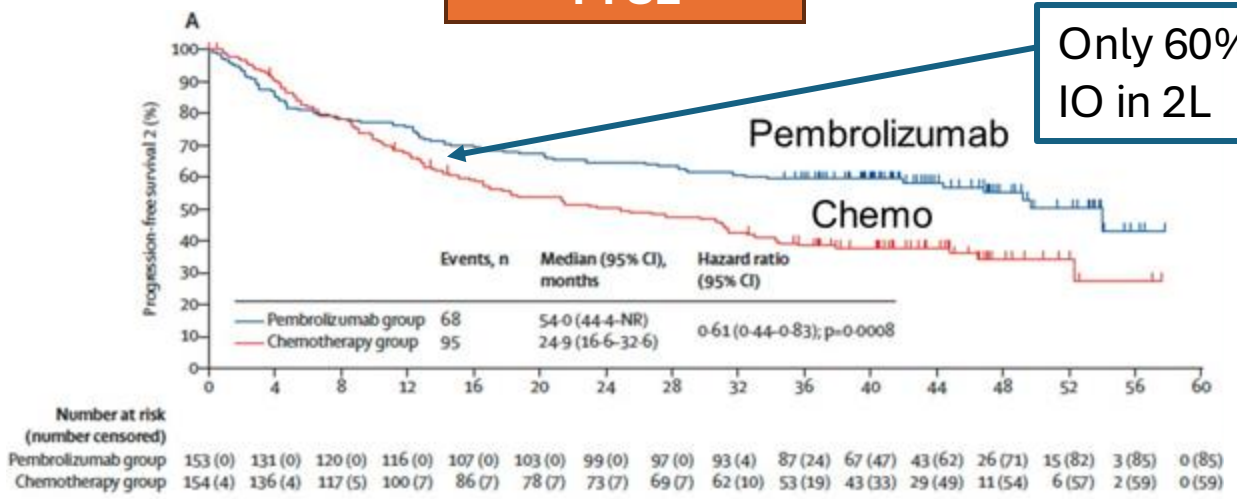
- Keynote-177: MSI CRC randomized to pembrolizumab vs. chemotherapy (any doublet ± biologic allowed)
  - Better PFS, OS, QOL for pembro

30-40% have primary resistance

PFS



PFS2



Only 60% got IO in 2L

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Nivolumab plus ipilimumab vs chemotherapy as first-line treatment for microsatellite instability-high/mismatch repair-deficient metastatic colorectal cancer: expanded efficacy analysis from CheckMate 8HW

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Abstract number 3503

CheckMate 8HW Schema

NOT reported yet

Key eligibility criteria:
- Histologically confirmed unresectable or metastatic CRC
- MSI-H/dMMR status by local testing
- ECOG PS 0 or 1

85% confirmed

Stratification factors:
- Prior lines of treatment (0 vs 1 vs ≥ 2)
- Primary tumor location (right vs left)

R 2:2:1

1L setting: n = 202

1L setting: n = 101

NIVO 240 mg Q2W for 6 doses, followed by NIVO 480 mg Q4W[b]

NIVO 240 mg + IPI 1 mg/kg Q3W for 4 doses, followed by NIVO 480 mg Q4W[b]

Investigator's choice chemo[c] (mFOLFOX6 or FOLFIRI ± bevacizumab or cetuximab)

Treatment until disease progression, unacceptable toxicity, withdrawal of consent (all arms), or a maximum treatment duration of 2 years (NIVO and NIVO + IPI arms only)

Dual primary endpoints in patients with centrally confirmed MSI-H/dMMR status[d]:
- PFS by BICR[e] (NIVO + IPI vs chemo in the 1L setting)
- PFS by BICR[e] (NIVO + IPI vs NIVO across all lines)

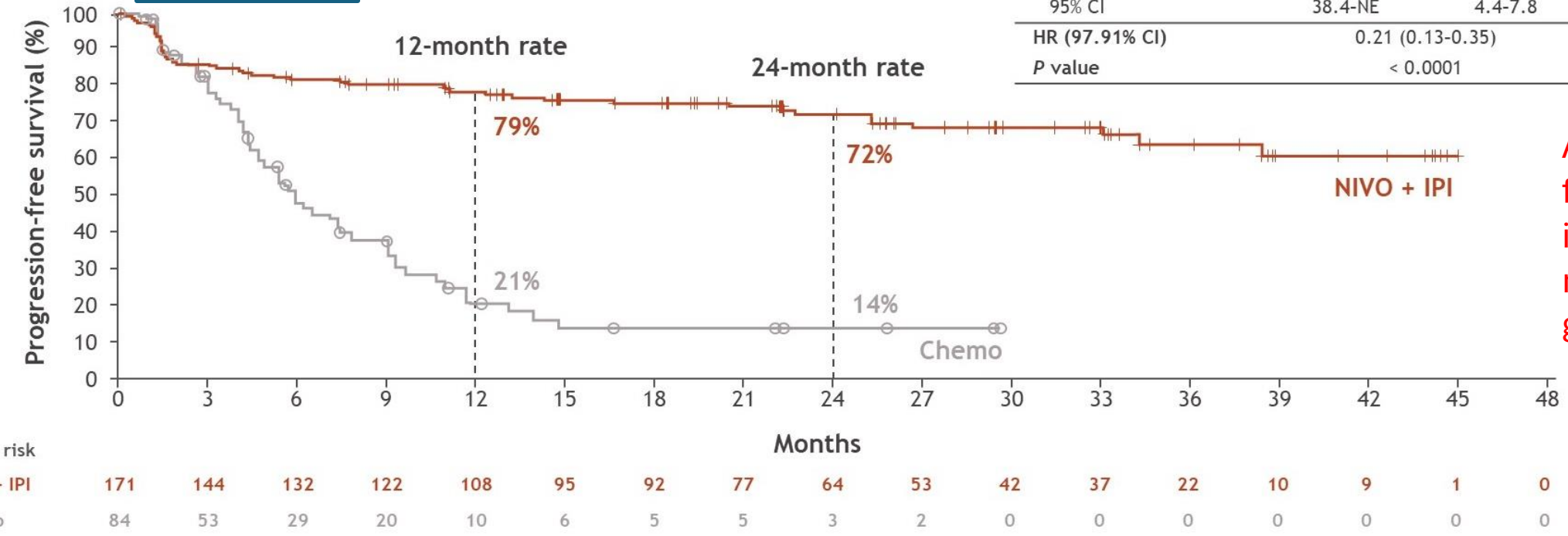
Other select endpoints:
- Safety
- OS; PFS2 by investigator[e]; ORR by BICR[e]; PROs

Cross-over permitted: 67% had subsequent IO

- At data cutoff (October 12, 2023), the median follow-up[f] was 31.5 months (range, 6.1-48.4)

Progression Free Survival

15% have primary resistance



1L centrally confirmed MSI-H/dMMR	NIVO + IPI (n = 171)	Chemo (n = 84)
Median PFS,[a,b] mo	NR	5.9
95% CI	38.4-NE	4.4-7.8
HR (97.91% CI)	0.21 (0.13-0.35)	
P value	< 0.0001	

No. at risk																	
NIVO + IPI	171	144	132	122	108	95	92	77	64	53	42	37	22	10	9	1	0
Chemo	84	53	29	20	10	6	5	5	3	2	0	0	0	0	0	0	0

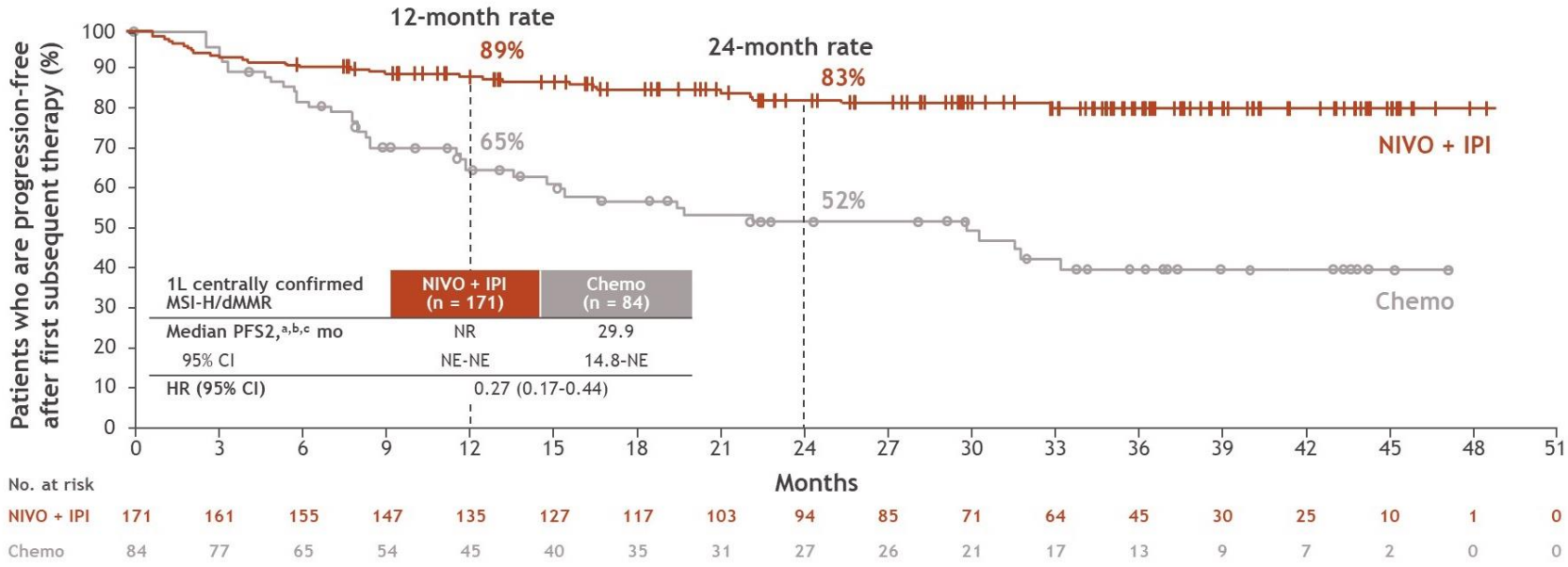
All sub-groups favored nivo/ipi, including liver metastases and germline Lynch

PFS2 (After Change in Therapy)

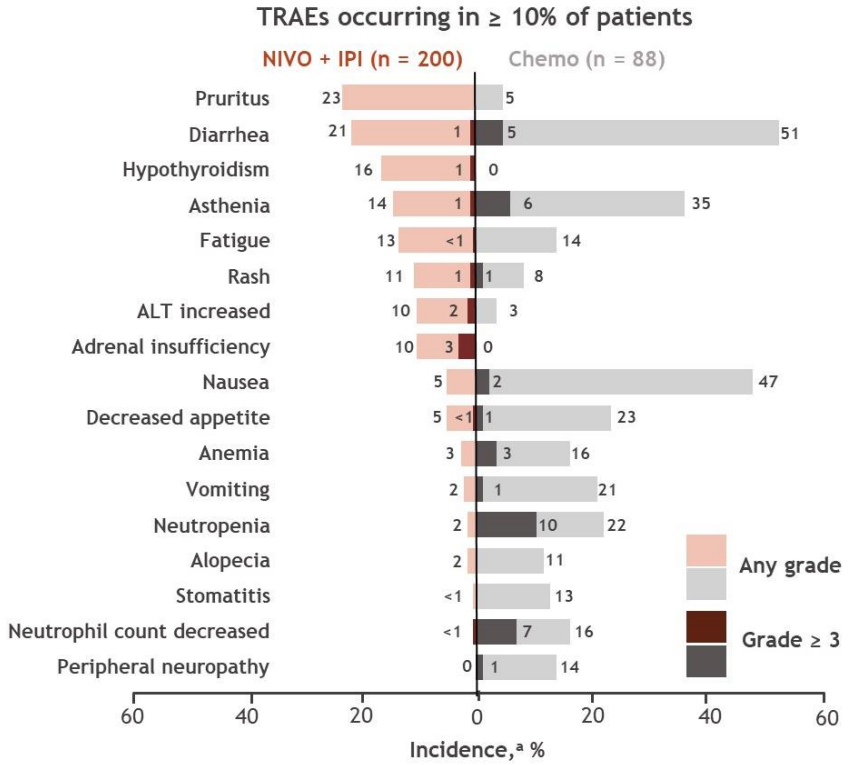
Subsequent therapy (1L centrally confirmed MSI-H/dMMR),[a]	NIVO + IPI (n = 171)	Chemo (n = 84)
Any subsequent therapy	26 (15)	58 (69)
Radiotherapy	1 (< 1)	1 (1)
Surgery	5 (3)	4 (5)
Systemic therapy	20 (12)	57 (68)
Immunotherapy	7 (4)	56 (67)
On-study crossover to NIVO + IPI	0	39 (46)
Non-study immunotherapy	7 (4)	17 (20)
EGFR inhibitors	5 (3)	1 (1)
Platinum compounds	8 (5)	
VEGFR targeted therapy	5 (3)	
MEK, *NRAS*, and *BRAF* inhibitors	2 (1)	
Other systemic anticancer therapy	12 (7)	

- 67% of chemo arm got subsequent IO (46% on study)

- Excellent responses to IO observed



Not Without Toxicity



1L all treated patients	NIVO + IPI (n = 200)		Chemo (n = 88)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
TRAEs,[a] n (%)				
Any TRAEs	160 (80)	46 (23)	83 (94)	42 (48)
Serious TRAEs	38 (19)	32 (16)	17 (19)	14 (16)
TRAEs leading to discontinuation	33 (17)	23 (12)	28 (32)	9 (10)
Treatment-related deaths, n (%)	2 (1)[b]		0 (0)[c]	

- Any-grade and grade 3/4 TRAEs were less frequent in the NIVO + IPI arm than in chemo arm
- The most common any-grade TRAEs occurring in ≥ 10% of patients were:
  - NIVO + IPI: pruritis (23%), diarrhea (21%), and hypothyroidism (16%)
  - Chemo: diarrhea (51%), nausea (47%), and asthenia (35%)

[a]Includes events reported between first dose and 30 days after last dose of study therapy. [b]Includes 1 event each of myocarditis and pneumonitis. [c]One death (acute myocarditis) was related to crossover treatment.

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- Most tolerated nivolumab + ipilimumab well
- BUT, 3 deaths from (2 in 1L, 1 in cross-over)
  - 2 were myocarditis (no predictive risk factors)

Take Home Points of CheckMate 8HW

- Initial results demonstrate superior PFS and PFS2 (permitting cross-over) from combination nivolumab/ipilimumab compared to chemotherapy
- Results from the single-agent nivolumab arm are yet to be reported (so the need for ipilimumab remains unclear)
- For stage 4 MSI-H CRC, nivolumab/ipilimumab is a more powerful first-line combination compared to chemotherapy (but unknown compared to pembro)

Summary

- **Gastroesophageal Cancer**
  - ESOPEC: Perioperative FLOT versus neoadjuvant chemoradiotherapy (CROSS) for resectable esophageal adenocarcinoma → Evolving paradigm of perioperative chemotherapy for esophageal adenocarcinoma
- **Pancreatic Cancer**
  - RTOG 0848: Adjuvant chemotherapy +/- chemoradiation for patients with resected head of pancreatic adenocarcinoma—results of the RT + 5-FU/capecitabine randomization step → Only node negative patients benefit from adjuvant RT but question of the relevance of this study with outdated chemo regimens
  - ECOG-ACRIN EA2186/GIANT Study: Randomized phase 2 study of gemcitabine and nab-paclitaxel compared with 5-FU/LV + nanoliposomal irinotecan in older patients with treatment-naïve metastatic pancreatic cancer → Need better tools to select elderly and frail patients who would benefit from palliative chemo chemo
- **Hepatobiliary Cancer**
  - CheckMate 9DW: Nivolumab + ipilimumab vs lenvatinib or sorafenib as first-line treatment for unresectable hepatocellular carcinoma → Another efficacious 1L therapy for patients with HCC
- **Colorectal Cancer**
  - CheckMate 8HW: Nivolumab + ipilimumab vs chemotherapy as first-line treatment of MSI-H/dMMR metastatic colorectal cancer: expanded efficacy analysis → Another efficacious 1L therapy for patients with MSI-H CRC

Fred Hutch Cancer Center

Thank you

Acknowledgments:

- ASCO 2024 Authors, Presenters, Patients, Caregivers
- FHCC GI Oncology
  (Drs. Stacey Cohen, Andrew Coveler, William Harris, Ronan Hsieh)

UW Medicine