2021 ASCO Direct Highlights at South Carolina Oncology Society Annual Conference: Gastroesophageal, Pancreatic, Hepatobiliary

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Disclosure of Conflict(s) of Interest

- Michael Morse, MD, MHS, FACP reported the following relevant financial relationships or relationships with ineligible companies of any amount during the past 24 months.

  - *Consultant; Speaker:* Genentech, Exelixis, Bayer, Eisai, Lilly, Novartis/AAA, Ipsen, Astra-Zeneca, Daiichi-Sankyo, Tersera

  - *Research support to institution:* Merck, BMS, Astra-Zeneca/Medimmune, Novartis/AAA, Ipsen, Amal

Objectives

- Review standards of care before ASCO2021
- Evaluate new data presented at ASCO2021
- Discuss implications for practice

Gastroesophageal Cancers

Esophageal squamous cell carcinoma (Advanced/Metastatic): Pre-ASCO

- 1st line
  - Fluoropyrimidine + cisplatin or oxaliplatin
  - Fluoropyrimidine + cisplatin or oxaliplatin plus pembrolizumab (PD-L1 CPS ≥10) (KEYNOTE-590)

- 2nd line
  - Nivolumab
  - Pembrolizumab for PD-L1 CPS ≥10
  - Docetaxel
  - Paclitaxel
  - Irinotecan

KEYNOTE-590

Pembrolizumab + Cisplatin and 5-Fluorouracil vs Placebo + Cisplatin and 5-Fluorouracil as First-Line Treatment in Subjects With Advanced/Metastatic Esophageal Carcinoma*

1o end points: OS in pts with ESCC PD-L1 CPS ≥10 tumors, and OS and PFS (RECIST v1.1 ; by investigator) in ESCC, PD-L1 CPS ≥10, and all pts.

	5FU/Cisplatin + pembro	5FU/Cisplatin
ESCC CPS ≥10 (mOS)	***13.9 mo (HR 0.57; 95% CI, 0.43-0.75; P < 0.0001)***	8.8 mo
ESCC (mOS)	***12.6 mo (HR 0.72; 95% CI, 0.60-0.88; P = 0.0006)***	9.8 mo
CPS ≥10 (mOS)	***13.5 mo (HR 0.62; 95% CI, 0.49-0.78; P < 0.0001)***	9.4 mo
all pts (mOS)	***12.4 mo (HR, 0.73, 95% CI, 0.62-0.86; P < 0.0001)***	9.8 mo

*Note: *73% of patients had ESCC*

ESMO 2020; LBA8_PR; Kato)

Nivolumab plus ipilimumab or nivolumab plus chemotherapy versus chemotherapy as first-line treatment for advanced esophageal squamous cell carcinoma: first results of the CheckMate 648 study

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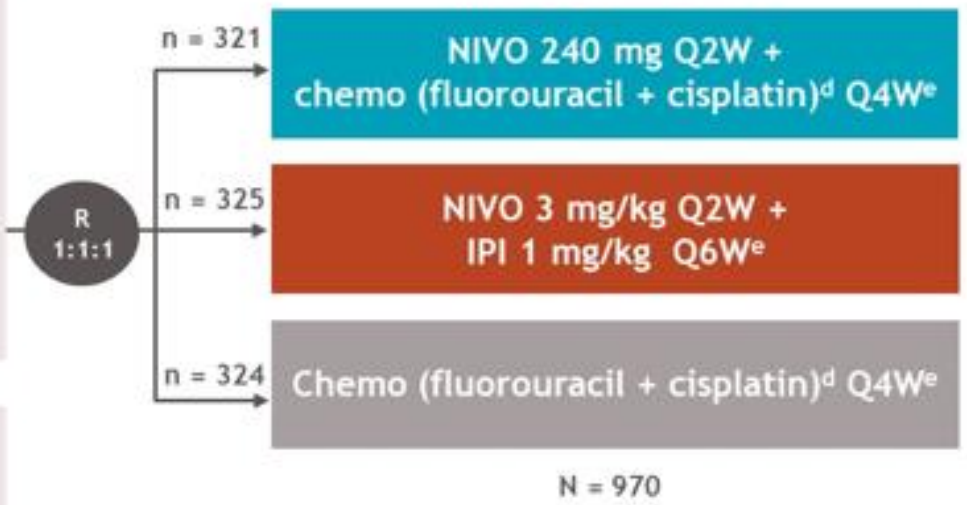
Abstract Number LBA4001

CheckMate 648 study design

- CheckMate 648 is a global, randomized, open-label phase 3 study[a]

Key eligibility criteria
- Unresectable advanced, recurrent or metastatic ESCC
- ECOG PS 0-1
- No prior systemic treatment for advanced disease
- Measurable disease

Stratification factors
- Tumor cell PD-L1 expression (≥ 1% vs < 1%[b])
- Region (East Asia[c] vs rest of Asia vs ROW)
- ECOG PS (0 vs 1)
- Number of organs with metastases (≤ 1 vs ≥ 2)



Primary endpoints:
- OS and PFS[f] (tumor cell PD-L1 ≥ 1%)

Secondary endpoints:
- OS and PFS[f] (all randomized)
- ORR[f] (tumor cell PD-L1 ≥ 1% and all randomized)

Subsequent immunotherapy[c] was received by ~ 5% of patients in the NIVO-containing arms and 16% in the chemo arm

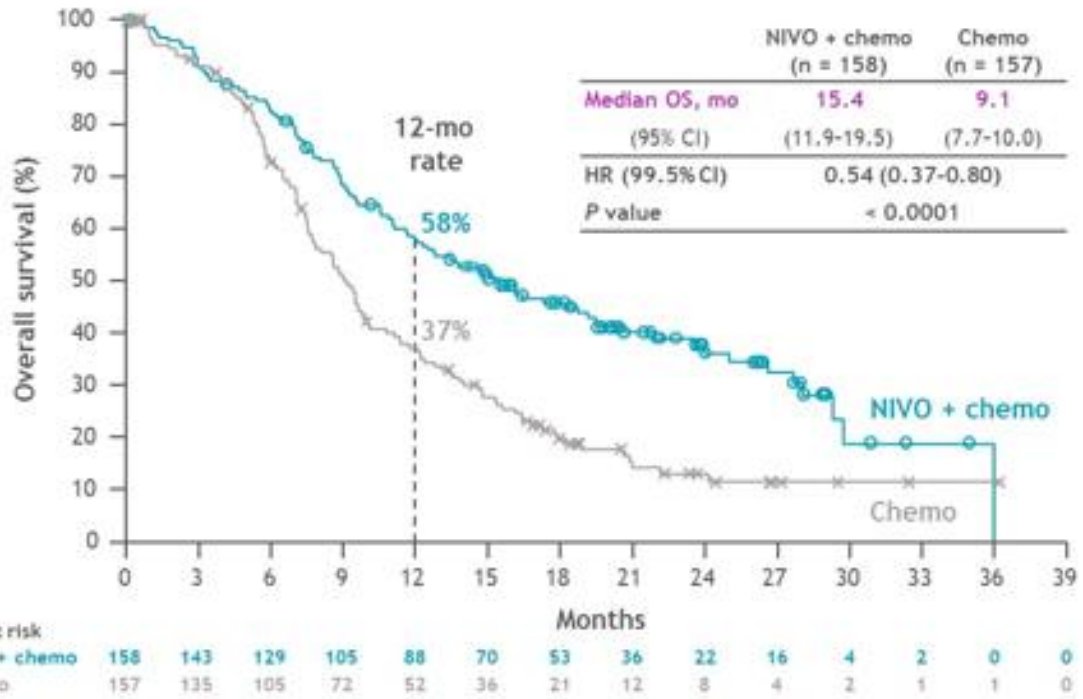
49% had tumor cell PD-L1 ≥1%

- At data cutoff (January 18, 2021), the minimum follow-up was 12.9 months[g]

[a]ClinicalTrials.gov. NCT03143153; [b]< 1% includes indeterminate tumor cell PD-L1 expression; determined by PD-L1 IHC 28-8 pharmDx assay (Dako); [c]East Asia includes patients from Japan, Korea, and Taiwan; [d]Fluorouracil 800 mg/m^2 IV daily (days 1-5) and cisplatin 80 mg/m^2 IV (day 1); [e]Until documented disease progression (unless consented to treatment beyond progression for NIVO + IPI or NIVO + chemo), discontinuation due to toxicity, withdrawal of consent, or study end. NIVO is given alone or in combination with IPI for a maximum of 2 years; [f]Per blinded independent central review (BICR); [g]Time from last patient randomized to clinical data cutoff.

Overall survival: NIVO + chemo vs chemo

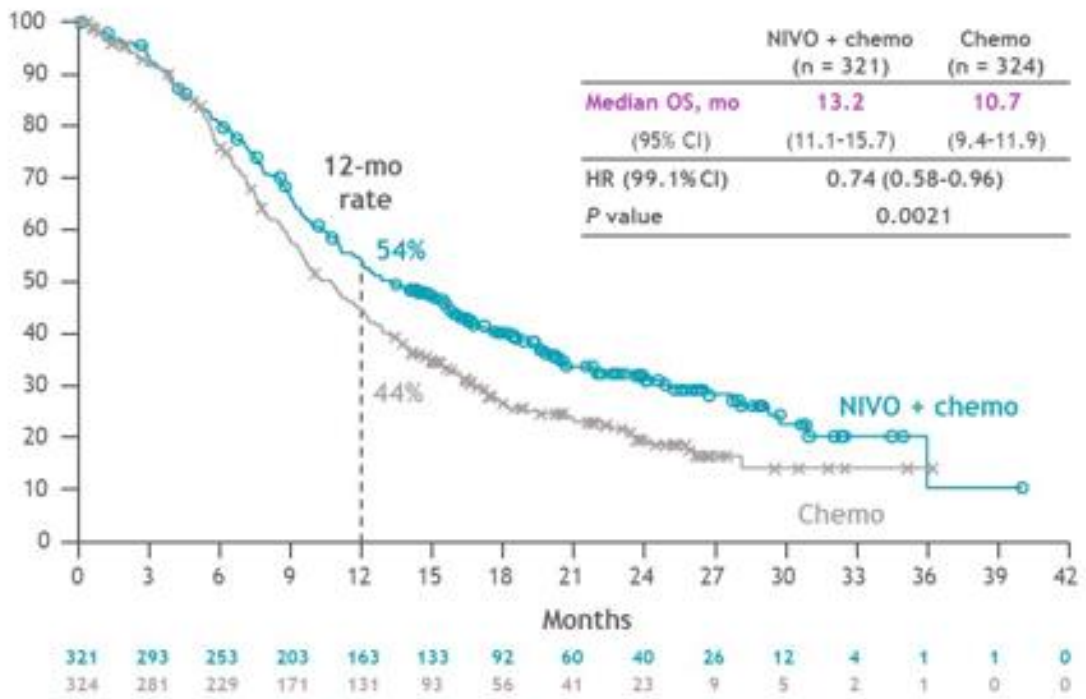
Primary endpoint (tumor cell PD-L1 ≥ 1%)[a]



	NIVO + chemo (n = 158)	Chemo (n = 157)
Median OS, mo	15.4	9.1
(95% CI)	(11.9-19.5)	(7.7-10.0)
HR (99.5% CI)	0.54 (0.37-0.80)	
P value	< 0.0001	

No. at risk														
NIVO + chemo	158	143	129	105	88	70	53	36	22	16	4	2	0	0
Chemo	157	135	105	72	52	36	21	12	8	4	2	1	1	0

All randomized[a]



	NIVO + chemo (n = 321)	Chemo (n = 324)
Median OS, mo	13.2	10.7
(95% CI)	(11.1-15.7)	(9.4-11.9)
HR (99.1% CI)	0.74 (0.58-0.96)	
P value	0.0021	

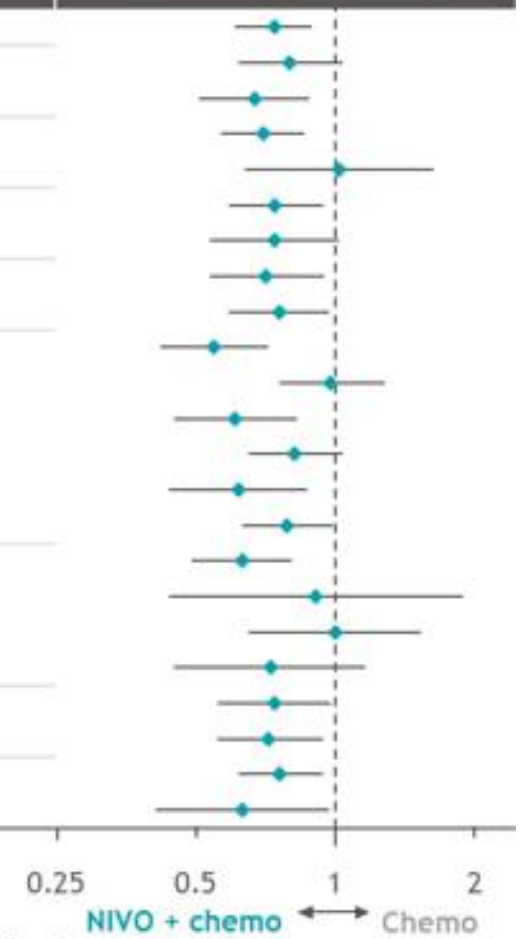
NIVO + chemo	321	293	253	203	163	133	92	60	40	26	12	4	1	0
Chemo	324	281	229	171	131	93	56	41	23	9	5	2	1	0

- Superior OS with NIVO + chemo vs chemo in tumor cell PD-L1 ≥ 1% and all randomized populations
  - Tumor cell PD-L1 ≥ 1%: 46% reduction in the risk of death and a 6.3-month improvement in median OS
  - All randomized: 26% reduction in the risk of death and a 2.5-month improvement in median OS

ASCO2021; LBA4001

Overall survival subgroup analysis: NIVO + chemo vs chemo

Category (all randomized)	Subgroup	Median OS, months		Unstratified HR for death	Unstratified HR (95% CI)
		NIVO + chemo	Chemo		
Overall (N = 645)		13.2	10.7	0.74	
Age, years	< 65 (n = 333)	11.8	10.2	0.80	
	≥ 65 (n = 312)	15.1	11.0	0.67	
Sex	Male (n = 528)	12.5	10.0	0.70	
	Female (n = 117)	15.2	14.8	1.02	
Geographic region	Asian (n = 451)	15.5	11.9	0.74	
	Non-Asian (n = 194)	10.5	8.5	0.74	
ECOG PS[a]	0 (n = 300)	17.3	12.4	0.71	
	1 (n = 344)	10.6	9.0	0.76	
Tumor cell PD-L1 expression[b]	≥ 1% (n = 314)	15.4	9.2	0.55	
	< 1% (n = 329)	12.0	12.2	0.98	
	≥ 5% (n = 235)	13.7	9.5	0.61	
	< 5% (n = 408)	12.8	11.1	0.82	
	≥ 10% (n = 199)	14.7	9.5	0.62	
	< 10% (n = 444)	12.3	10.8	0.79	
Disease status at study entry	De novo metastatic (n = 371)	13.4	9.4	0.63	
	Recurrent - locoregional (n = 46)	14.8	13.5	0.91	
	Recurrent - distant (n = 132)	12.3	12.8	1.00	
	Unresectable advanced (n = 96)	12.8	12.1	0.73	
No. of organs with metastases	≤ 1 (n = 316)	15.7	11.6	0.74	
	≥ 2 (n = 329)	11.1	9.6	0.72	
Smoking	Current or former (n = 510)	12.3	10.0	0.76	
	Never or unknown (n = 135)	15.7	11.1	0.63	

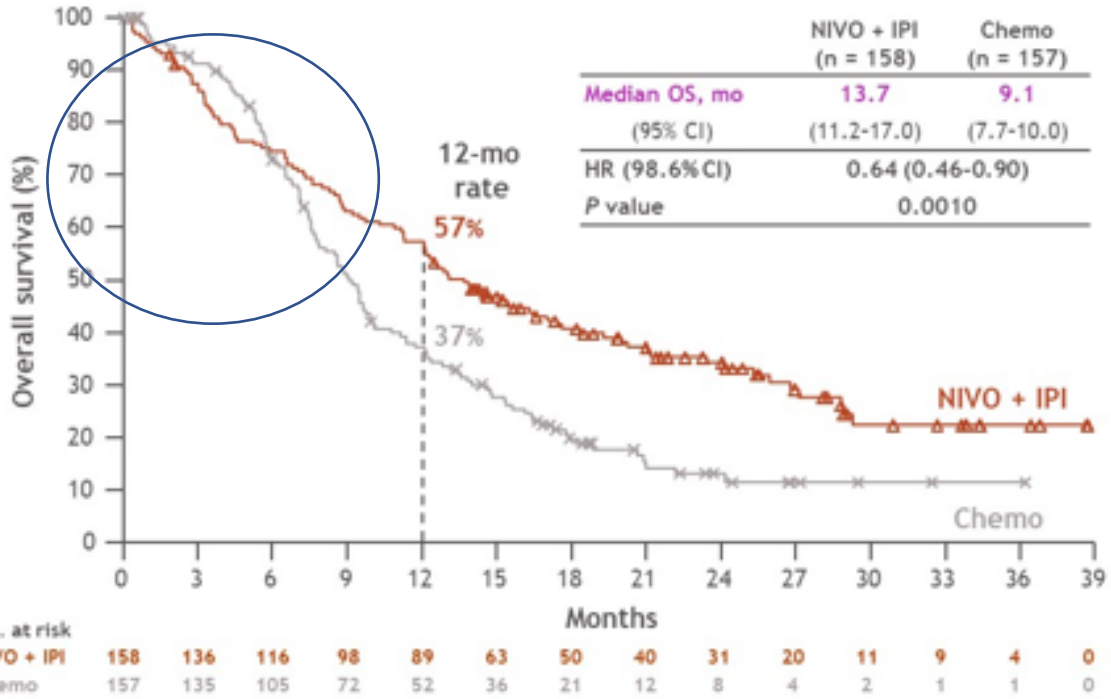


- OS favored NIVO + chemo vs chemo across most prespecified subgroups in all randomized patients

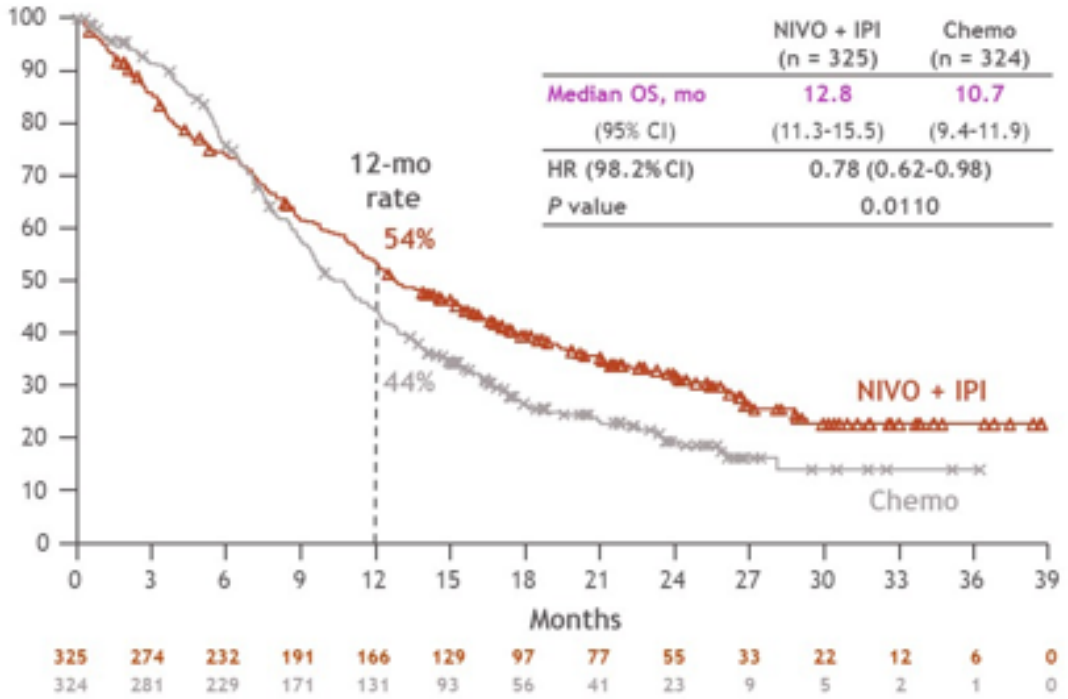
[a]Not reported in 1 patient; [b]Indeterminate, not evaluable, or missing (n = 2).

Overall survival: NIVO + IPI vs chemo

Primary endpoint (tumor cell PD-L1 ≥ 1%)[a]



All randomized[a]



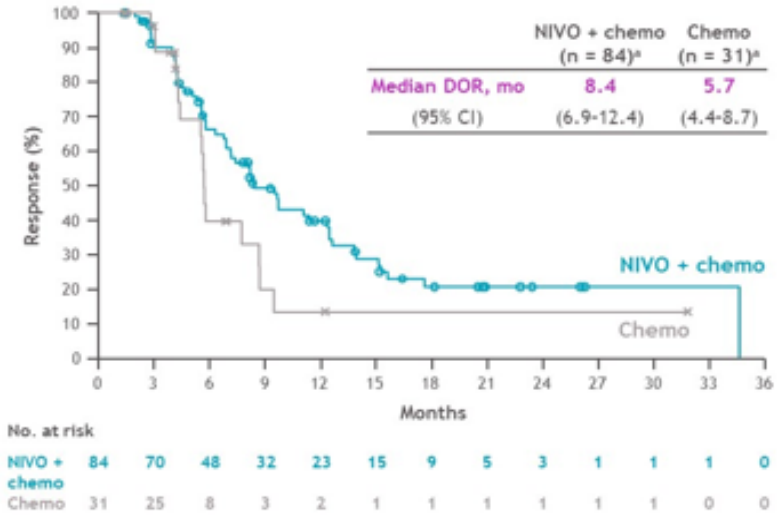
- Superior OS with NIVO + IPI vs chemo in tumor cell PD-L1 ≥ 1% and all randomized populations
  - Tumor cell PD-L1 ≥ 1%: 36% reduction in the risk of death and a 4.6-month improvement in median OS
  - All randomized: 22% reduction in the risk of death and a 2.1-month improvement in median OS

Duration of response

Nivo + chemo v chemo

Tumor cell PD-L1 ≥ 1%

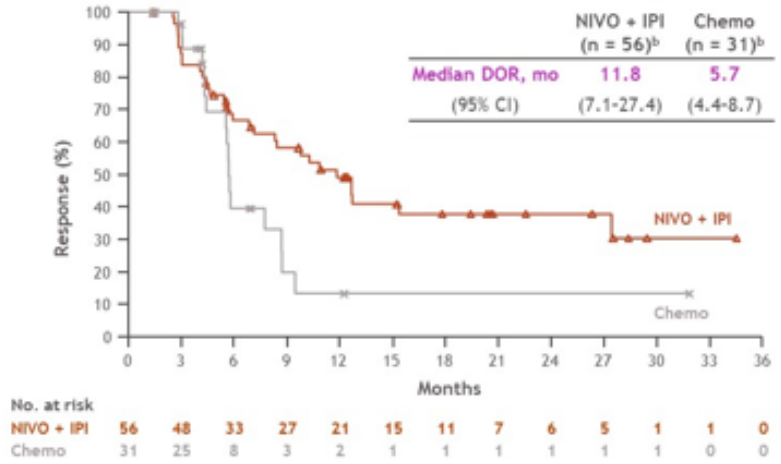
Response per BICR	NIVO + chemo (n = 158)	Chemo (n = 157)
ORR, % (95% CI)	53 (45-61)	20 (14-27)
CR	16	5
PR	37	15
SD	25	46
PD	14	15



Nivo + Ipi v chemo

Tumor cell PD-L1 ≥ 1%

Response per BICR	NIVO + IPI (n = 158)	Chemo (n = 157)
ORR, % (95% CI)	35 (28-43)	20 (14-27)
CR[a]	18	5
PR[a]	18	15
SD	27	46
PD	30	15



TRAEs

Select TRAEs[a] All treated,[b,c] n (%)	NIVO + chemo (n = 310)		NIVO + IPI (n = 322)		Chemo (n = 304)	
	Any grade	Grade 3-4[d]	Any grade	Grade 3-4[d]	Any grade	Grade 3-4
Endocrine	36 (12)	4 (1)	88 (27)	19 (6)	1 (< 1)	0
Gastrointestinal	64 (21)	7 (2)	38 (12)	5 (2)	47 (15)	7 (2)
Hepatic	32 (10)	7 (2)	42 (13)	14 (4)	12 (4)	2 (< 1)
Pulmonary	18 (6)	2 (< 1)	26 (8)	9 (3)	2 (< 1)	0
Renal	74 (24)	7 (2)	8 (2)	2 (< 1)	57 (19)	5 (2)
Skin	54 (17)	1 (< 1)	110 (34)	13 (4)	11 (4)	0

- The majority of select TRAEs were grade 1 or 2
- Grade 3-4 events occurred in ≤ 6% of patients across organ categories

Implications for practice

NIVO + chemo and NIVO + IPI each represent a new potential 1L standard of care for patients with advanced ESCC

Questions:

1) Should PD-L1 be used as a biomarker for selecting therapy?

2) What are second line options if anti-PD-1 is used in the first line?

Gastric, GEJ, Esophageal adenocarcinoma (Advanced/Metastatic): Pre-ASCO

- 1st line
  - Fluoropyrimidine + cisplatin or oxaliplatin (+/- docetaxel)
  - Fluoropyrimidine + cisplatin or oxaliplatin plus pembrolizumab (esophageal and Siewert type 1 GEJ)
  - Fluoropyrimidine + oxaliplatin plus nivolumab (PD-L1 CPS $\geq$5)
  - Fluoropyrimidine + cisplatin or oxaliplatin + trastuzumab for HER2 +

- 2nd line
  - Paclitaxel / ramucriumab
  - Trastuzumab deruxtecan for HER2+
  - Irinotecan
  - Docetaxel

- 3rd line
  - TAS-102
  - Pembrolizumab for PD-L1+ has been withdrawn

First-line nivolumab plus chemotherapy vs chemotherapy in advanced gastric cancer/ gastroesophageal junction cancer/esophageal adenocarcinoma: expanded efficacy and safety data from CheckMate 649

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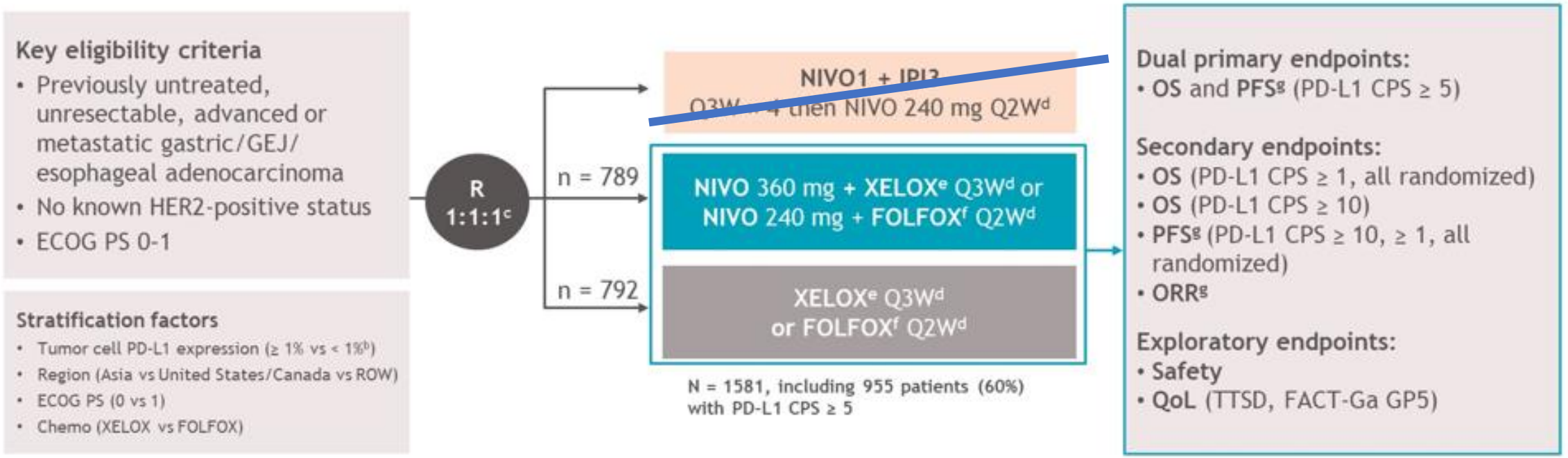
Abstract Number 4002

CheckMate 649 study design

- CheckMate 649 is a global, randomized, open-label, phase 3 study[a]

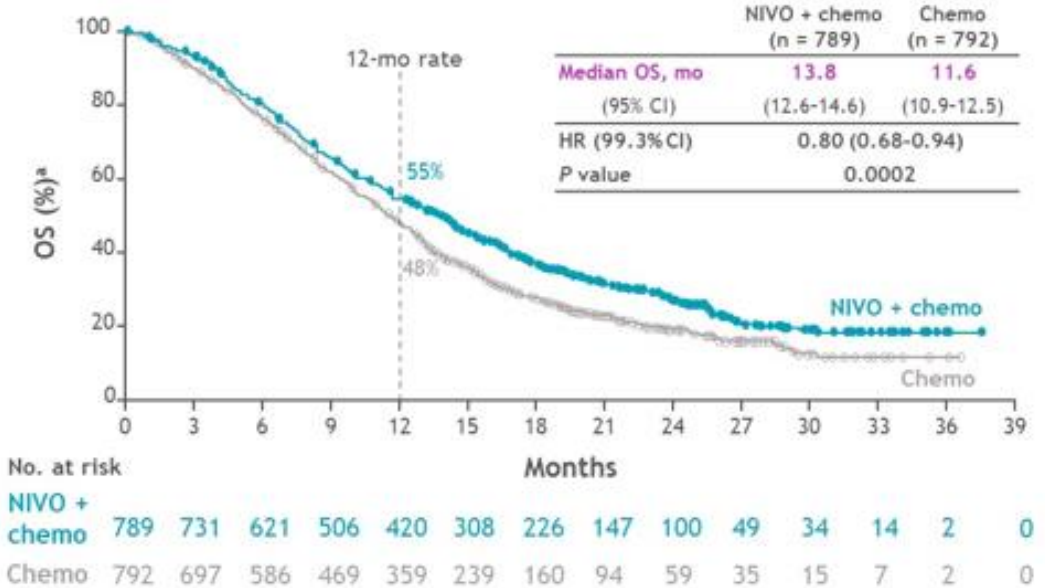


- At data cutoff (May 27, 2020), the minimum follow-up was 12.1 months[h]

[a]ClinicalTrials.gov number. NCT02872116; [b]PD-L1 < 1% includes indeterminate tumor cell PD-L1 expression; determined by PD-L1 IHC 28-8 pharmDx assay (Dako); [c]After NIVO + chemo arm was added and before new patient enrollment in the NIVO1+IPI3 group was closed; [d]Until documented disease progression (unless consented to treatment beyond progression for NIVO + chemo), discontinuation due to toxicity, withdrawal of consent, or study end. NIVO is given for a maximum of 2 years; [e]Oxaliplatin 130 mg/m^2 IV (day 1) and capecitabine 1000 mg/m^2 orally twice daily (days 1-14); [f]Oxaliplatin 85 mg/m^2, leucovorin 400 mg/m^2, and FU 400 mg/m^2 IV (day 1) and FU 1200 mg/m^2 IV daily (days 1-2); [g]BICR assessed; [h]Time from concurrent randomization of the last patient to NIVO + chemo vs chemo to data cutoff.

Overall survival and progression-free survival in all randomized patients

Overall survival

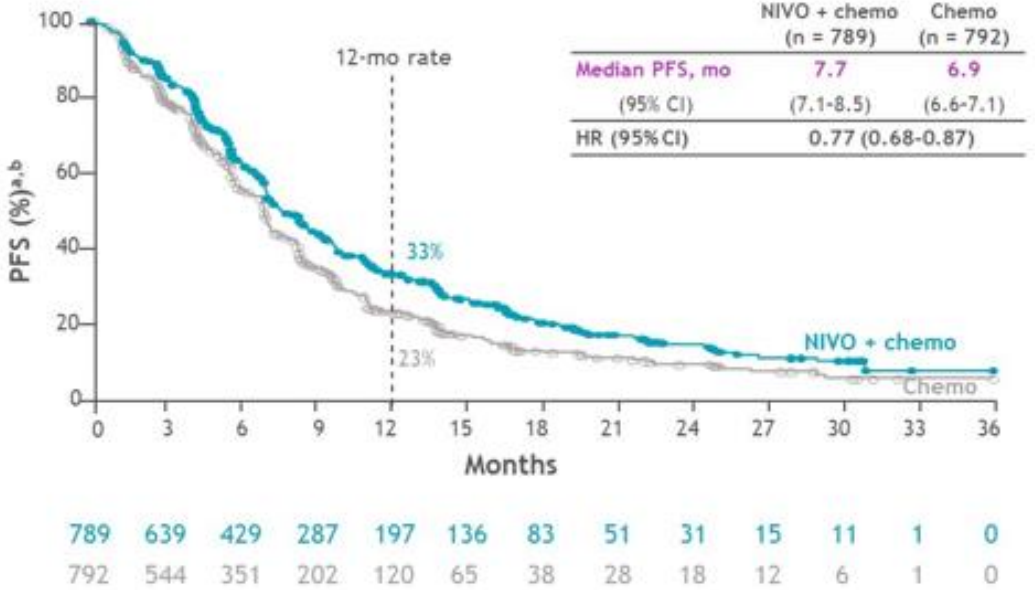


	NIVO + chemo (n = 789)	Chemo (n = 792)
Median OS, mo	13.8	11.6
(95% CI)	(12.6-14.6)	(10.9-12.5)
HR (99.3% CI)	0.80 (0.68-0.94)	
P value	0.0002	

No. at risk

NIVO + chemo	789	731	621	506	420	308	226	147	100	49	34	14	2	0
Chemo	792	697	586	469	359	239	160	94	59	35	15	7	2	0

Progression-free survival



	NIVO + chemo (n = 789)	Chemo (n = 792)
Median PFS, mo	7.7	6.9
(95% CI)	(7.1-8.5)	(6.6-7.1)
HR (95% CI)	0.77 (0.68-0.87)	

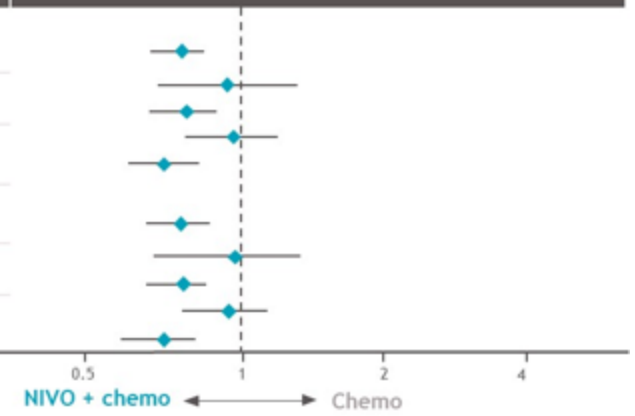
NIVO + chemo	789	639	429	287	197	136	83	51	31	15	11	1	0	
Chemo	792	544	351	202	120	65	38	28	18	12	6	1	0	

- Superior OS benefit and clinically meaningful PFS improvement in all randomized patients with NIVO + chemo vs chemo
- Median OS with NIVO + chemo vs chemo in patients with PD-L1 CPS ≥ 5 was 14.4 vs 11.1 months and median PFS was 7.7 vs 6.0 months[1]

Efficacy subgroup analysis by PD-L1 CPS in all randomized patients

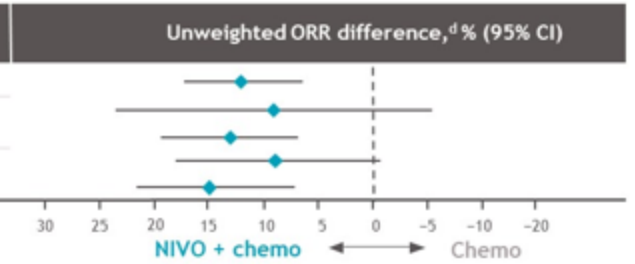
Survival

PD-L1 CPS[a]	Number of patients, n	Median, months		Unstratified HR[b]
		NIVO + chemo	Chemo	
Overall survival				
Overall (N = 1581)		13.8	11.6	0.79
< 1	265	13.1	12.5	0.92
≥ 1	1296	14.0	11.3	0.76
< 5	606	12.4	12.3	0.94
≥ 5	955	14.4	11.1	0.70
Progression-free survival				
Overall (N = 1581)		7.7	6.9	0.77
< 1	265	8.7	8.1	0.93
≥ 1	1296	7.5	6.9	0.75
< 5	606	7.5	8.2	0.93
≥ 5	955	7.7	6.1	0.69



Objective response rate

PD-L1 CPS[c]	Number of patients, n	Objective response rate, %		Unweighted ORR difference,[d] %
		NIVO + chemo	Chemo	
Overall (N = 1211)		58	46	12
< 1	178	51	41	9
≥ 1	1019	60	46	13
< 5	428	55	46	9
≥ 5	769	60	45	15

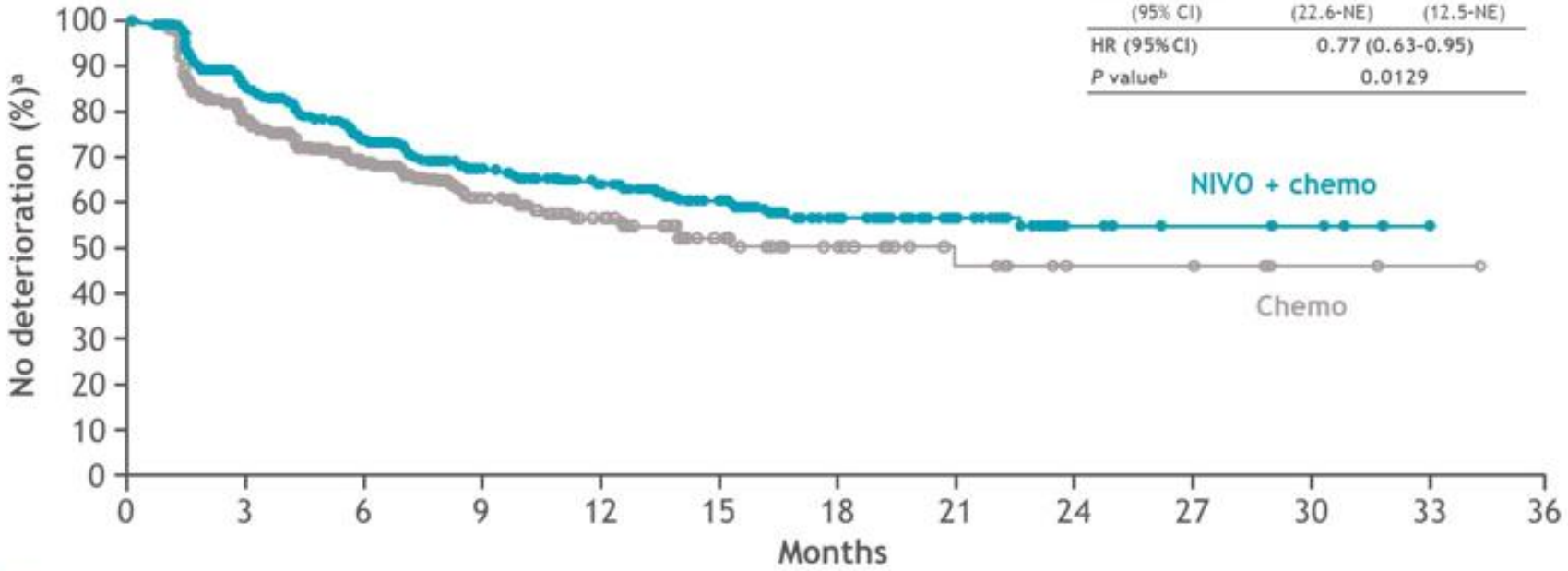


- OS and PFS benefit with NIVO + chemo was enriched at higher PD-L1 CPS cutoffs, and higher ORR was observed across all cutoffs vs chemo, including CPS < 1 and CPS < 5

[a]PD-L1 CPS expression indeterminate/unevaluable/not available, n = 20; [b]Unstratified HR for death (OS) or unstratified HR for progression or death (PFS); [c]Randomized patients who had target lesion measurements at baseline, per BICR assessment. PD-L1 CPS expression indeterminate/not available, n = 14; [d]Percentages may not reflect an exact difference due to rounding.

Time to symptom deterioration in all randomized patients

	NIVO + chemo (n = 789)	Chemo (n = 792)
Median TTD, mo	NR	21.0
(95% CI)	(22.6-NE)	(12.5-NE)
HR (95% CI)	0.77 (0.63-0.95)	
P value[b]	0.0129	



No. at risk													
NIVO + chemo	789	478	303	198	143	96	57	38	9	6	4	1	0
Chemo	792	367	211	117	63	33	19	12	5	5	2	1	0

- There was a 23% reduction in the risk of symptom worsening with NIVO + chemo vs chemo

[a]Threshold for meaningful change for time to symptom deterioration was 8.2 points on the gastric cancer subscale[1]; [b]*P* value was not formally tested.

1. Garland SN, et al. *Cancer* 2011;117:1302-1312.

Implications for practice

These data support NIVO plus chemo as a new 1L standard treatment for patients with advanced non-HER2-positive GC/GEJC/EAC

Questions:

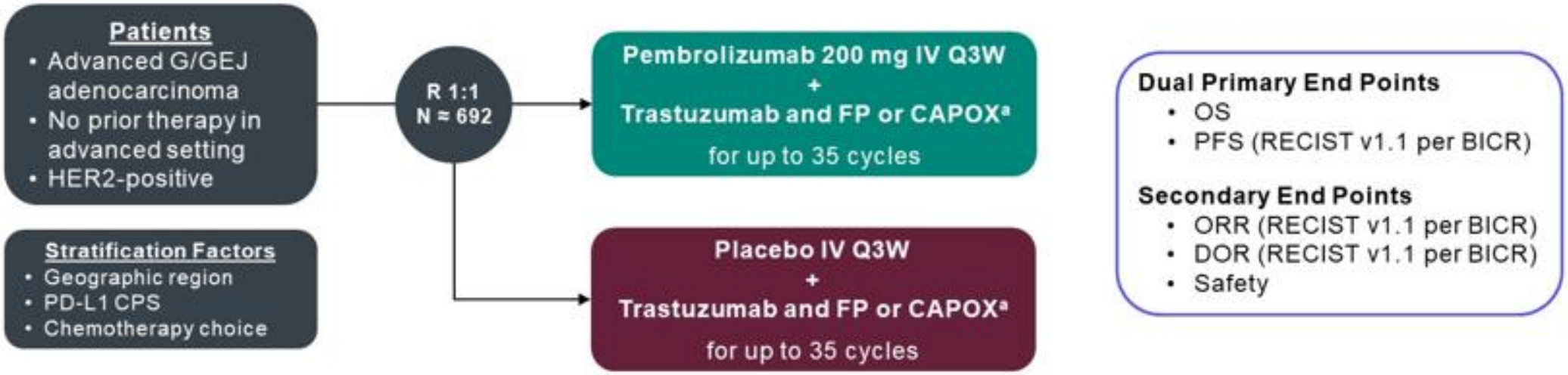
1) Use nivolumab in PD-L1 CPS≥5 (NCCN category 1) or CPS 1-4 (NCCN category 2B) or CPS < 1 (CPS not specified in FDA label)

Discussant (Dr. Cunningham)
At ASCO 2021

…And a word about adding checkpoint blockade to trastuzumab and chemotherapy in HER2+ G/GEJ adenocarcinoma

KEYNOTE-811 Global Cohort

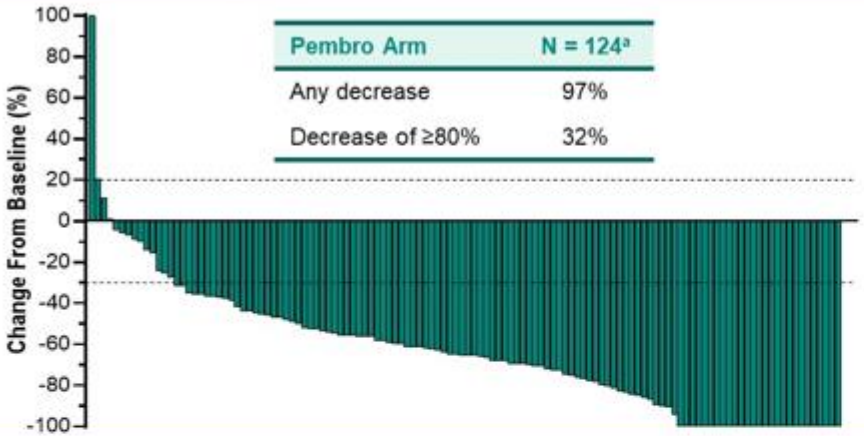
Double-Blind Phase 3 Study of Pembrolizumab + Trastuzumab and Chemotherapy vs Placebo + Trastuzumab and Chemotherapy as First-Line Therapy For HER2-Positive Unresectable or Metastatic G/GEJ Cancer (NCT03615326)



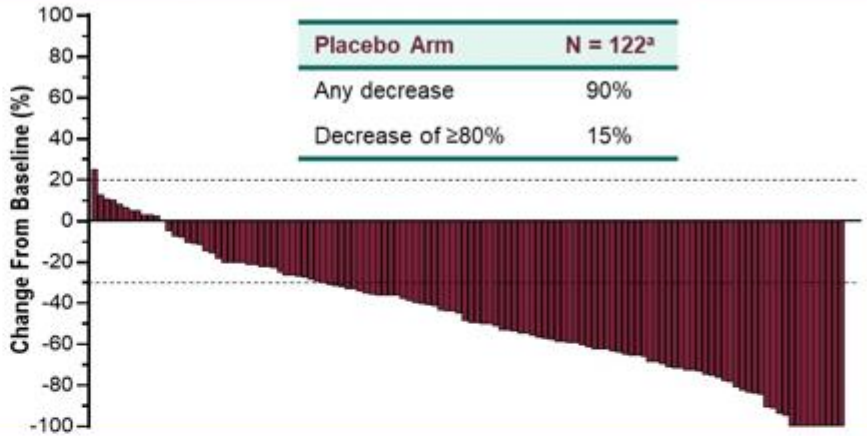
[a]Trastuzumab dose: 6 mg/kg IV Q3W following an 8 mg/kg loading dose. FP dose: 5-fluorouracil 800 mg/m² IV on D1-5 Q3W + cisplatin 80 mg/m² IV Q3W. CAPOX dose: capecitabine 1000 mg/m² BID on D1-14 Q3W + oxaliplatin 130 mg/m² IV Q3W.

KEYNOTE-811: Deeper, more durable responses with pembrolizumab

Confirmed Response at IA1



Pembro Arm	N = 124[a]
Any decrease	97%
Decrease of ≥80%	32%



Placebo Arm	N = 122[a]
Any decrease	90%
Decrease of ≥80%	15%

ORR and DCR, % (95% CI)	Pembro Arm (N = 133)	Placebo Arm (N = 131)
ORR	**74.4% (66.2-81.6)**	**51.9% (43.0-60.7)**
ORR difference[b]	**22.7% (11.2-33.7) *P* = 0.00006**	
DCR	96.2% (91.4-98.8)	89.3% (82.7-94.0)

Best Response, n (%)	Pembro Arm (N = 133)	Placebo Arm (N = 131)
CR	**15 (11%)**	**4 (3%)**
PR	**84 (63%)**	**64 (49%)**
SD	29 (22%)	49 (37%)
PD	5 (4%)	7 (5%)
Not evaluable	0	2 (2%)
Not assessed	0	5 (4%)

Duration of Response[c]	Pembro Arm (N = 99)	Placebo Arm (N = 68)
Median[d]	10.6 mo	9.5 mo
Range	1.1+ to 16.5+	1.4+ to 15.4+
≥6-mo duration[d]	70.3%	61.4%
≥9-mo duration[d]	58.4%	51.1%

GEJ, Esophageal adenocarcinoma Neoadjuvant therapy: Pre-ASCO

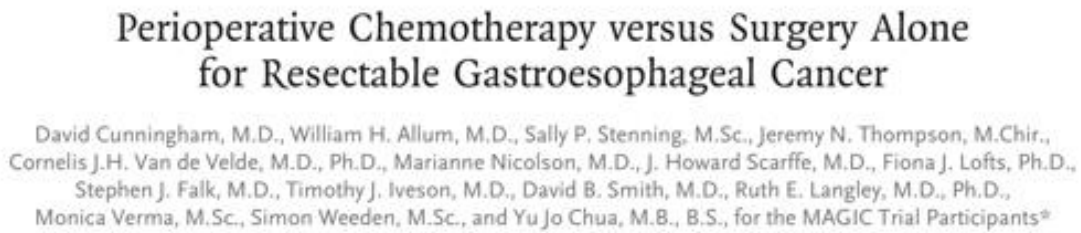
CROSS

Preoperative Chemoradiotherapy for Esophageal or Junctional Cancer

P. van Hagen, M.C.C.M. Hulshof, J.J.B. van Lanschot, E.W. Steyerberg, M.I. van Berge Henegouwen, B.P.L. Wijnhoven, D.J. Richel, G.A.P. Nieuwenhuijzen, G.A.P. Hospers, J.J. Bonenkamp, M.A. Cuesta, R.J.B. Blaisse, O.R.C. Busch, F.J.W. ten Kate, G.-J. Creemers, C.J.A. Punt, J.T.M. Plukker, H.M.W. Verheul, E.J. Spillenaar Bilgen, H. van Dekken, M.J.C. van der Sangen, T. Rozema, K. Biermann, J.C. Beukema, A.H.M. Piet, C.M. van Rij, J.G. Reinders, H.W. Tilanus, and A. van der Gaast, for the CROSS Group*

Van Hagen et al. N.Engl. J. Med. 2012; 366:2074-84

MAGIC



Perioperative Chemotherapy versus Surgery Alone for Resectable Gastroesophageal Cancer

David Cunningham, M.D., William H. Allum, M.D., Sally P. Stenning, M.Sc., Jeremy N. Thompson, M.Chir., Cornelis J.H. Van de Velde, M.D., Ph.D., Marianne Nicolson, M.D., J. Howard Scarffe, M.D., Fiona J. Lofts, Ph.D., Stephen J. Falk, M.D., Timothy J. Iveson, M.D., David B. Smith, M.D., Ruth E. Langley, M.D., Ph.D., Monica Verma, M.Sc., Simon Weeden, M.Sc., and Yu Jo Chua, M.B., B.S., for the MAGIC Trial Participants*

Cunningham D, et al. N.Engl.J.Med., 2006; 355:11-20

FLOT4

Al-Batran S. Lancet. 2019 May 11;393(10184):1948-1957. Perioperative chemotherapy with fluorouracil plus leucovorin, oxaliplatin, and docetaxel versus fluorouracil or capecitabine plus cisplatin and epirubicin for locally advanced, resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4): a randomised, phase 2/3 trial.

Adapted from Reynolds, ASCO2021

NEO-AEGIS

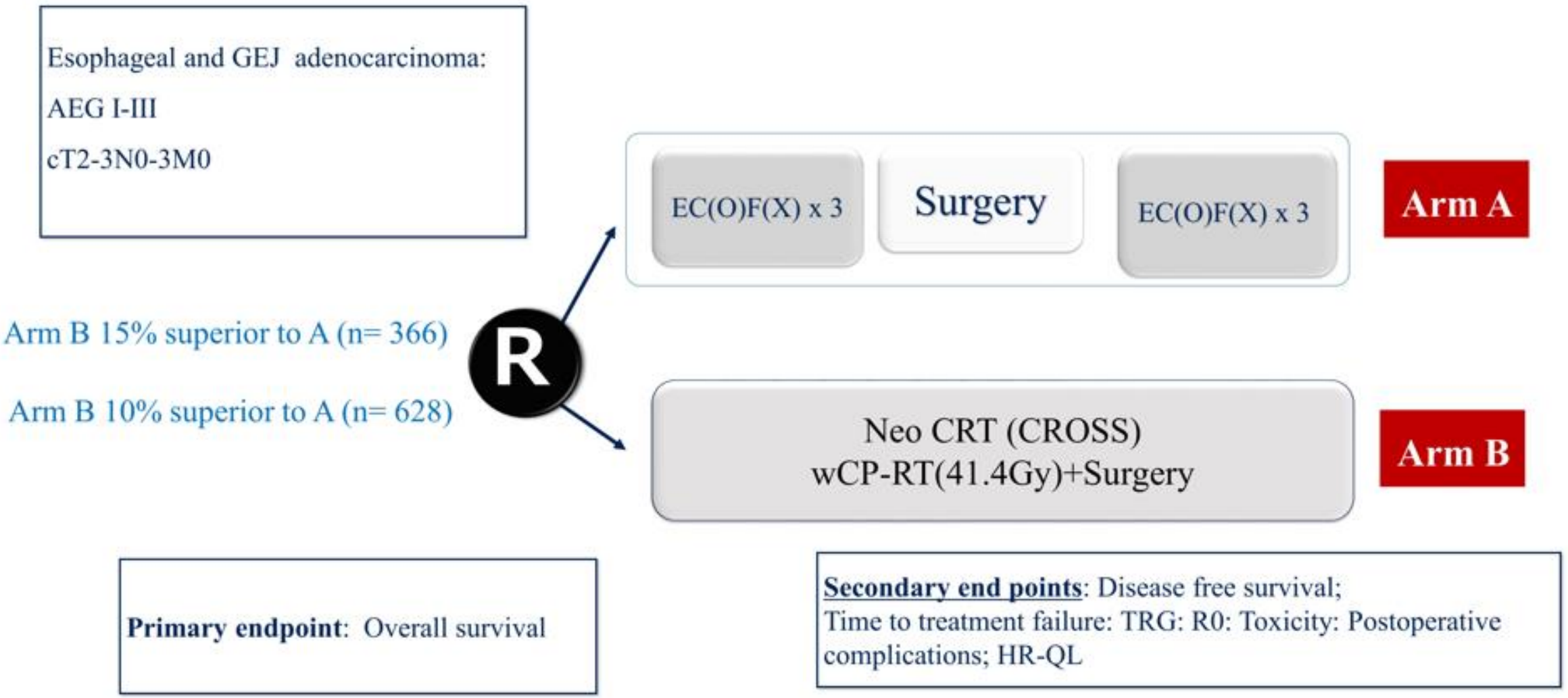
(NEOADJUVANT TRIAL IN ADENOCARCINOMA OF THE ESOPHAGUS AND ESOPHAGO-GASTRIC JUNCTION INTERNATIONAL STUDY): PRELIMINARY RESULTS OF PHASE III RCT OF CROSS VS PERI-OPERATIVE CHEMOTHERAPY(MODIFIED MAGIC OR FLOT PROTOCOL) (CTRIAL-IE 10-14) (NCT01726452)

John V. Reynolds

Cancer Trials Ireland and Trinity St. James's Cancer Institute

ASCO2021;4004

NEO-AEGIS Randomization Schema



Neo-AEGIS: FLOT Amendment June 2018

FLOT Regimen

- T docetaxel d1 50 mg/m² iv inf.
- O oxaliplatin d1 85 mg/m² iv inf.
- L leucovorin d1 200 mg/m² iv inf.
- F 5-FU d1 2.600 mg/m² iv 24h inf.

– repeated every 2 weeks

Esophageal and GEJ adenocarcinoma:

Esophageal and AEG I-III

cT2-3N0-3M0

Non-inferiority (n= 540-powered as per first futility analysis Dec 2018)

R

EC(O)F(X) x 3 or FLOT x 4 → Surgery → EC(O)F(X) x 3 Or FLOT x 4 — **Arm A**

Neo CRT (CROSS) wCP-RT(41.4Gy)+Surgery — **Arm B**

Primary endpoint: Overall survival

Secondary end points: Disease free survival; Time to treatment failure: TRG: R0: Toxicity: Postoperative complications; HR-QL

Al-Batran SE, et al. Lancet 2019; 393:1948-57

OS: 57 vs 56% (HR 1.02, 95% CI 0.74-1.42)

	Arm A (Magic/FLOT)	Arm B CROSS
R0 (negative margins)	82%	95%
ypN0	44.5%	60.1%
Tumor regression grade 1 & 2	12.1%	41.7%
Pathologic complete response	5%	16%

Results: Post operative Complications

International Consensus on Standardization of Data Collection for Complications Associated With Esophagectomy: Esophagectomy Complications Consensus Group (ECCG)

Donald E Low [1], Derek Alderson, Ivan Cecconello, Andrew C Chang, Gail E Darling, Xavier Benoit D'Journo, S Michael Griffin, Arnulf H Hölscher, Wayne L Hofstetter, Blair A Jobe, Yuko Kitagawa, John C Kucharczuk, Simon Ying Kit Law, Toni E Lerut, Nick Maynard, Manuel Pera, Jeffrey H Peters, C S Pramesh, John V Reynolds, B Mark Smithers, J Jan B van Lanschot

Specific	ARM A (Chemo) N = 157	ARM B (CROSS) N = 162	
Post op mortality	N=3 (1.9%)	N=5 (3%)	p = 0.723
Anastomotic Leaks	12%	12%	
Respiratory:			
Pneumonia	19.7%	16%	
ARDS	0.6%	4.3%	p = 0.067
Respiratory Failure	7.6%	8%	
Venous Thromboembolism	3.8%	3%	
Cardiac:			
Atrial Fibrillation	12.7%	14.2	
Sepsis	5%	5%	

Implications for practice

- Peri-operative chemotherapy was non-inferior to CRT: so clinical equipoise in decision making
- However, markers of response favor CRT
- Questions: Will patterns of recurrence explain why markers of response, while favoring CRT, did not translate into survival benefit?

GEJ, Esophageal adenocarcinoma adjuvant therapy after neoadjuvant CRT: Pre-ASCO

Phase III CheckMate-577 trial of nivolumab as an adjuvant therapy for patients with resected esophageal or gastroesophageal junction (GEJ) cancer

1) Met primary endpoint of DFS

   Treatment with Nivolumab after neoadjuvant chemoradiation therapy (CRT) and complete surgical resection showed a statistically significant improvement in DFS compared to placebo in the all-randomized population

Adjuvant nivolumab in resected esophageal or gastroesophageal junction cancer following neoadjuvant chemoradiotherapy: expanded efficacy and safety analyses from CheckMate 577

Ronan J. Kelly,[1] Jaffer A. Ajani,[2] Jaroslaw Kuzdzal,[3] Thomas Zander,[4] Eric Van Cutsem,[5] Guillaume Piessen,[6] Guillermo Mendez,[7] Josephine Feliciano,[8] Satoru Motoyama,[9] Astrid Lièvre,[10] Hope Uronis,[11] Elena Elimova,[12] Cecile Grootscholten,[13] Karen Geboes,[14] Jenny Zhang,[15] Samira Soleymani,[15] Ming Lei,[15] Prianka Singh,[15] James M. Cleary,[16] Markus Moehler[17]

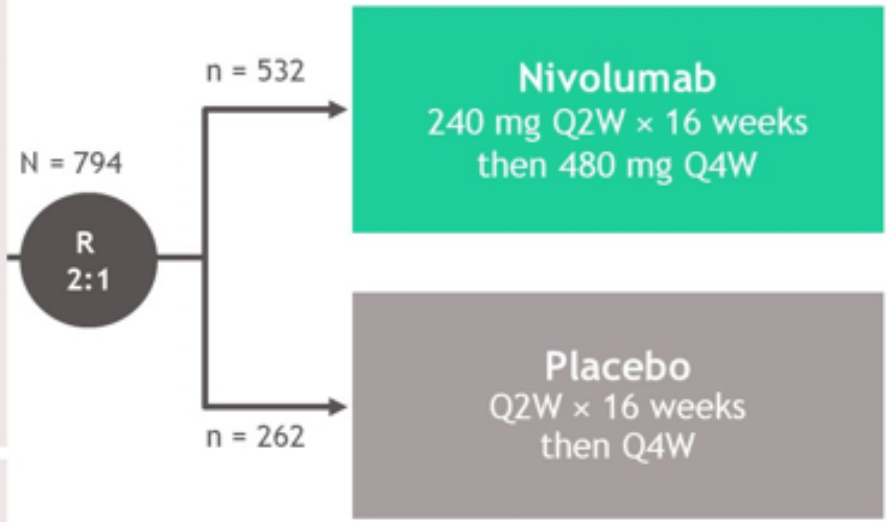
ASCO2021;4003

CheckMate 577 study design

- CheckMate 577 is a global, phase 3, randomized, double-blind, placebo-controlled trial[a]

Key eligibility criteria
- Stage II/III EC/GEJC
- Adenocarcinoma or squamous cell carcinoma
- Neoadjuvant CRT + surgical resection (R0,[b] performed within 4-16 weeks prior to randomization)
- Residual pathologic disease
  - ≥ ypT1 or ≥ ypN1
- ECOG PS 0-1

Stratification factors
- Histology (squamous versus adenocarcinoma)
- Pathologic lymph node status (≥ ypN1 versus ypN0)
- Tumor-cell PD-L1 expression (≥ 1% versus < 1%[c])



Primary endpoint:
- DFS[e]

Secondary endpoints:
- OS[f]
- OS rate at 1, 2, and 3 years

Exploratory endpoints included:
- Safety
- DMFS[g]
- PFS2[h]
- QoL

- Median follow-up was 24.4 months (range, 6.2-44.9)[i]
- Geographical regions: Europe (38%), United States and Canada (32%), Asia (13%), rest of the world (16%)

Kelly, ASCO2021;4003

Baseline characteristics

	Nivolumab (n = 532)	Placebo (n = 262)
Median age (range), years	62 (26-82)	61 (26-86)
Male, %	84	85
Race,[a] %		
White	81	82
Asian	16	13
ECOG PS, %		
0	58	60
1	42	40
Disease stage at initial diagnosis,[b] %		
II	34	38
III	66	62
Tumor location, %		
EC	60	59
GEJC	40	41
Histology,[c] %		
Squamous cell carcinoma	29	29
Adenocarcinoma	71	71
Pathologic lymph node status ≥ ypN1, %	57	58
Tumor-cell PD-L1 expression,[d,e] %		
≥ 1%	17	15
< 1%	70	75
Time from complete resection to randomization, %		
< 10 weeks	34	28
≥ 10 weeks	66	72

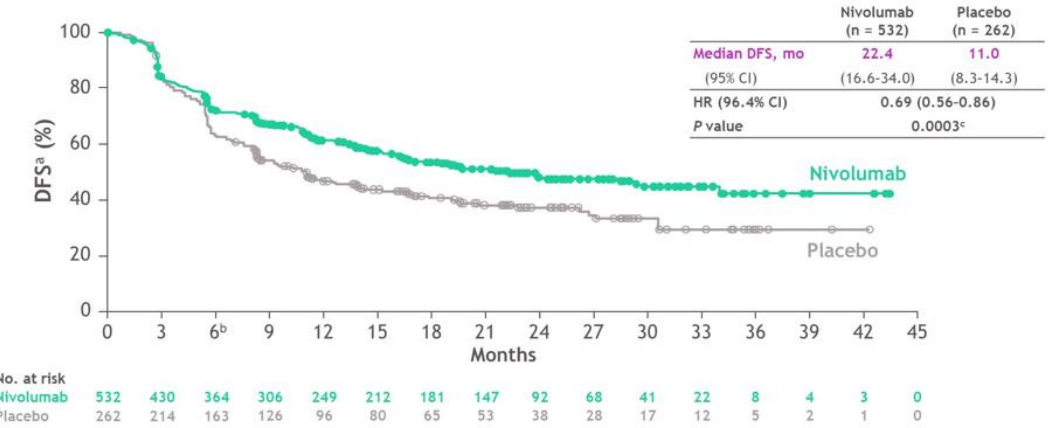
- In a post hoc analysis, a baseline PD-L1 CPS of 5 or higher was observed in 246 of 435 patients (57%) in the nivolumab arm and in 125 of 231 patients (54%) in the placebo arm

[a]Other races not shown; [b]< 1% not reported in the nivolumab arm; [c]< 1% had other histology in the nivolumab arm; [d]PD-L1 expression determined from tumor tissue specimen by the PD-L1 IHC 28-8 pharmDx assay (Dako), which for most patients, was obtained after completion of chemoradiotherapy; [e]13% and 10% of patients had PD-L1 indeterminate or nonevaluable in the nivolumab and placebo arms, respectively.

Kelly RJ, et al. *N Engl J Med* 2021;384:1191-1203.

Kelly, ASCO2021;4003

Disease-free survival (DFS)

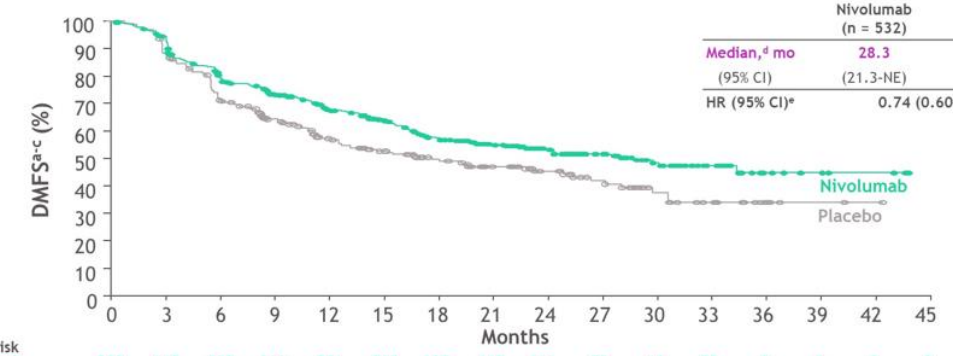


	Nivolumab (n = 532)	Placebo (n = 262)
Median DFS, mo	22.4	11.0
(95% CI)	(16.6-34.0)	(8.3-14.3)
HR (96.4% CI)	0.69 (0.56-0.86)	
P value	0.0003[c]	

No. at risk																
Nivolumab	532	430	364	306	249	212	181	147	92	68	41	22	8	4	3	0
Placebo	262	214	163	126	96	80	65	53	38	28	17	12	5	2	1	0

- Nivolumab provided superior DFS with a 31% reduction in the risk of recurrence or death and a doubling in median DFS versus placebo

Distant metastasis–free survival (DMFS)



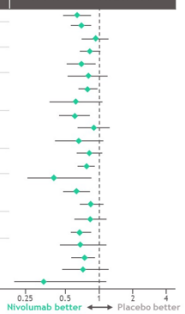
	Nivolumab (n = 532)	Placebo (n = 262)
Median,[d] mo	28.3	17.6
(95% CI)	(21.3-NE)	(12.5-25.4)
HR (95% CI)*	0.74 (0.60-0.92)	

No. at risk																
Nivolumab	532	449	392	332	276	235	195	160	102	75	44	23	8	4	3	0
Placebo	262	226	180	142	113	93	77	64	46	33	21	14	5	2	1	0

- Nivolumab showed a 26% reduction in the risk of distant recurrence or death versus placebo
- Distant (29% versus 39%) and locoregional (12% versus 17%) recurrences were less frequent with nivolumab versus placebo, respectively

Disease-free survival subgroup analysis

Category	Subgroup	Median DFS, mo		Unstratified HR	Unstratified HR (95% CI)
		Nivolumab	Placebo		
Overall	N = 794	22.4	11.0	0.70	
Tumor location at initial diagnosis	Esophagus (n = 462)	24.0	8.3	0.61	
	Gastroesophageal junction (n = 332)	22.4	20.6	0.87	
Histologic type	Adenocarcinoma (n = 563)	19.4	11.1	0.75	
	Squamous cell carcinoma (n = 230)	29.7	11.0	0.61	
Tumor cell PD-L1 expression[a]	≥ 1% (n = 129)	19.7	14.1	0.75	
	< 1% (n = 570)	21.3	11.1	0.73	
	Indeterminate/nonevaluable (n = 95)	Not reached	9.5	0.54	
PD-L1 CPS expression[a,b]	≥ 5 (n = 371)	29.4	10.2	0.62	
	< 5 (n = 295)	16.3	11.1	0.89	
	Missing/nonevaluable (n = 128)	Not reached	10.8	0.61	
Pathologic lymph node status	ypN0 (n = 336)	Not reached	27.0	0.74	
	≥ ypN1 (n = 457)	14.8	7.6	0.67	
Pathological tumor status	ypT0 (n = 47)	34.0	5.2	0.35	
	ypT1 or ypT2 (n = 308)	28.3	9.3	0.60	
	ypT3 or ypT4 (n = 436)	18.9	14.1	0.84	
Time from complete resection to randomization	< 10 weeks (n = 256)	24.0	14.1	0.84	
	≥ 10 weeks (n = 538)	21.4	10.8	0.66	
Radiotherapy dosage[b,c]	< 41.4 Gray (n = 92[b])	19.7	13.8	0.69	
	41.4-50.4 Gray (n = 504)	24.0	11.1	0.73	
	> 50.4 Gray (n = 152)	21.4	8.3	0.72	
	Not reported (n = 41)	14.4	6.1	0.41	



- Disease-free survival benefit was observed with nivolumab versus placebo across multiple subgroups

Adjuvant nivolumab demonstrated an acceptable safety profile and maintained QoL

- TRAEs with potential immunologic etiology resolved for most patients with the use of established management algorithms
- Similar trends in QoL improvement were observed with nivolumab and placebo during treatment and were maintained post-treatment

Kelly, ASCO2021;4003

Implications for practice

These results provide further support for adjuvant nivolumab as a new standard of care for patients with resected EC/GEJC who received neoadjuvant CRT with residual pathologic disease

Kelly, ASCO2021;4003

Pancreatic cancer

Not a big pancreatic year at ASCO

- 4016: Preoperative chemoradiotherapy to improve overall survival in pancreatic cancer: Long-term results of the multicenter randomized phase III PREOPANC trial.
  - OS (ITT), DFS, LF improved after preoperative CRT compared with immediate surgery
  - Gemcitabine/RT regimen used not the current standard

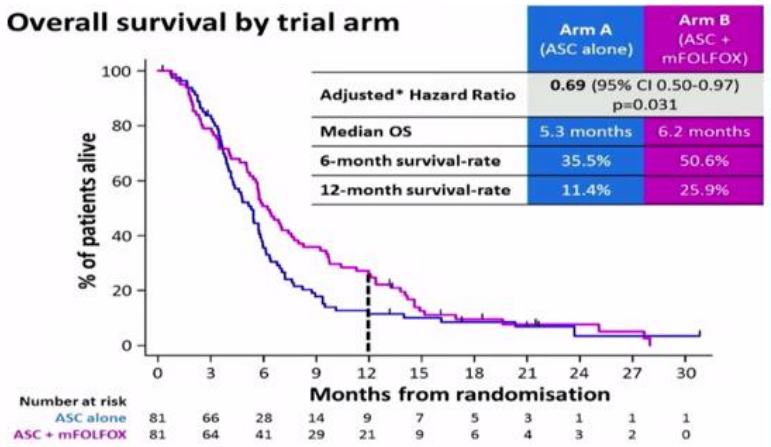
- 4017: Randomized phase II study of modified FOLFIRINOX versus gemcitabine plus nab-paclitaxel combination therapy for locally advanced pancreatic cancer (JCOG1407)
  - 1-year OS in GnP was better than mFOLFIRINOX, but mFOLFIRINOX achieved longer 2-year OS. Similar GR3/4 AE rate between the arms.

- 4018: Masitinib plus gemcitabine as first-line treatment of pancreatic cancer with pain: Results from phase 3 study AB12005.
  - In unresectable LAPC with pain, better mOS with MAS-GEM (13.0 mo (97.5% CI [11.0;18.0]) vs 11.2 months (97.5% CI [7.4;13.0]); p = 0.007. The HR was 0.46 (97.5% CI [0.2;0.9], p = 0.0047). BUT no difference in the group with metastases.

Biliary Tract Malignancies

Biliary tract (Advanced/Metastatic): Pre-ASCO

- 1st line
  - Gemcitabine/Cisplatin (category 1) (ABC-02)
- 2nd line
  - FOLFOX (preferred) (ABC-06)



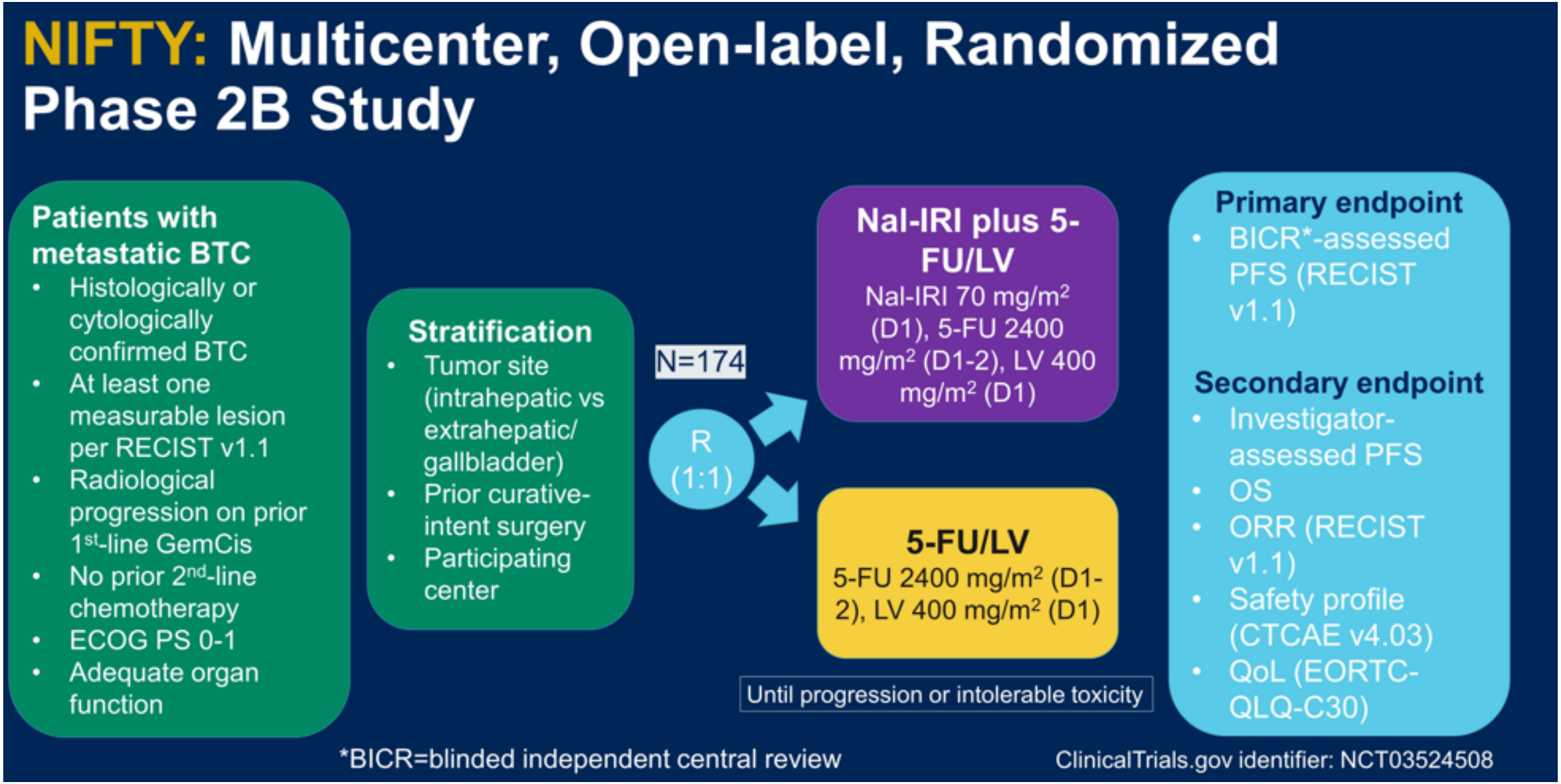
- 2nd line specific circumstances
  - Pemigatinib, infigratinib (FGFR2 fusion/rearrangement) (Update of FIGHT-202, abstr 4086)
  - Ivosidenib (IDH-1 mutation) (Update of ClarIDHy trial, abstr 4069)
  - Dabrafenib/trametinib (BRAF V600E mutated)

Liposomal Irinotecan (nal-IRI) in combination with Fluorouracil (5-FU) and Leucovorin (LV) for Patients (pts) with Metastatic Biliary Tract Cancer (BTC) after Progression on Gemcitabine plus Cisplatin (GemCis): Multicenter Comparative Randomized Phase 2B study (NIFTY)

Changhoon Yoo[1], Kyu-pyo Kim[1], Ilhwan Kim[2], Myoung Joo Kang[2], Jaekyung Cheon[3], Byung Woog Kang[4], Hyewon Ryu[5], Jae Ho Jeong[1], Ji Sung Lee[6], Kyung Won Kim[7], Baek-Yeol Ryoo[1]

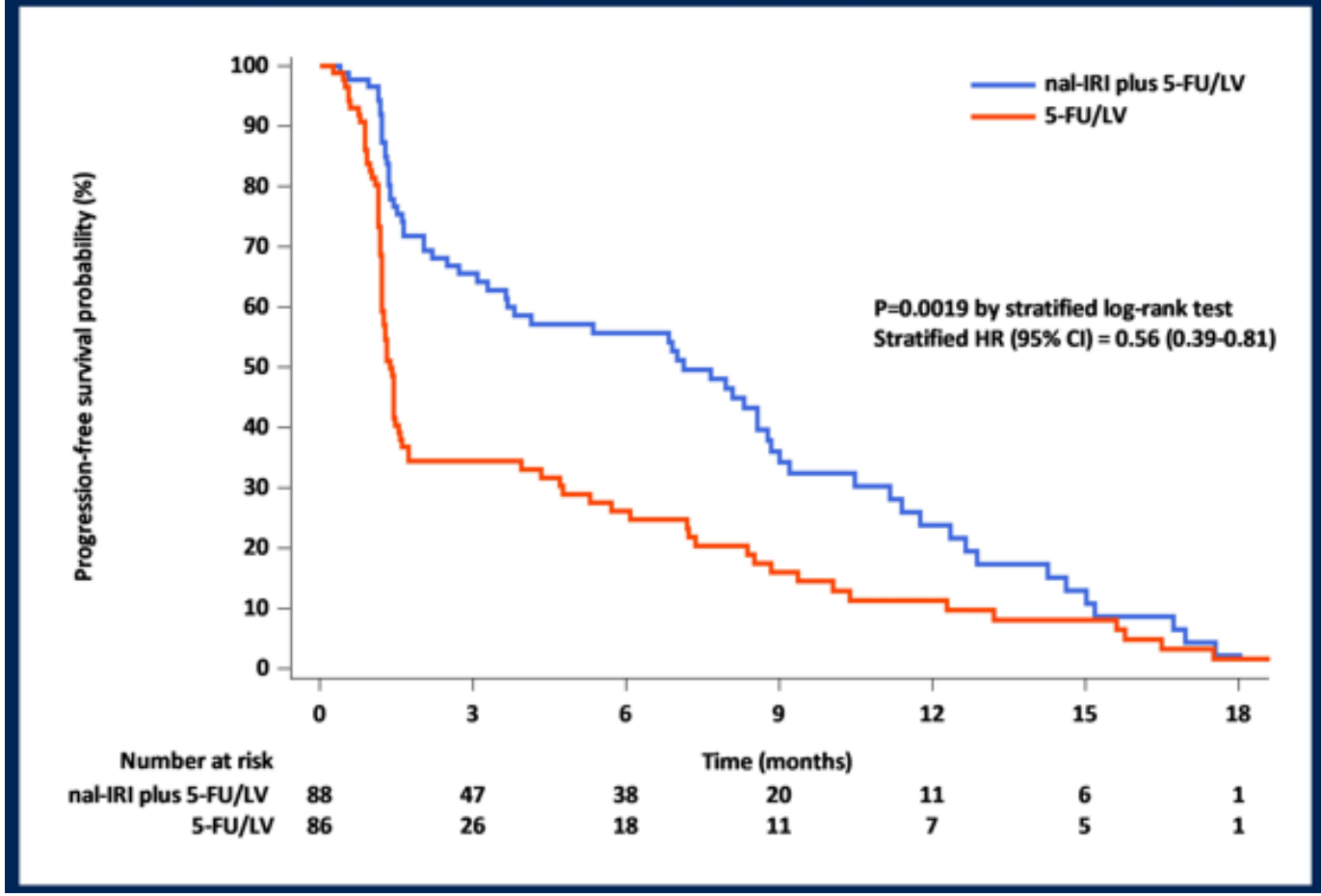
ASCO2021;4006

NIFTY: Multicenter, Open-label, Randomized Phase 2B Study



ASCO2021;4006

Primary Endpoint: BICR-Assessed PFS

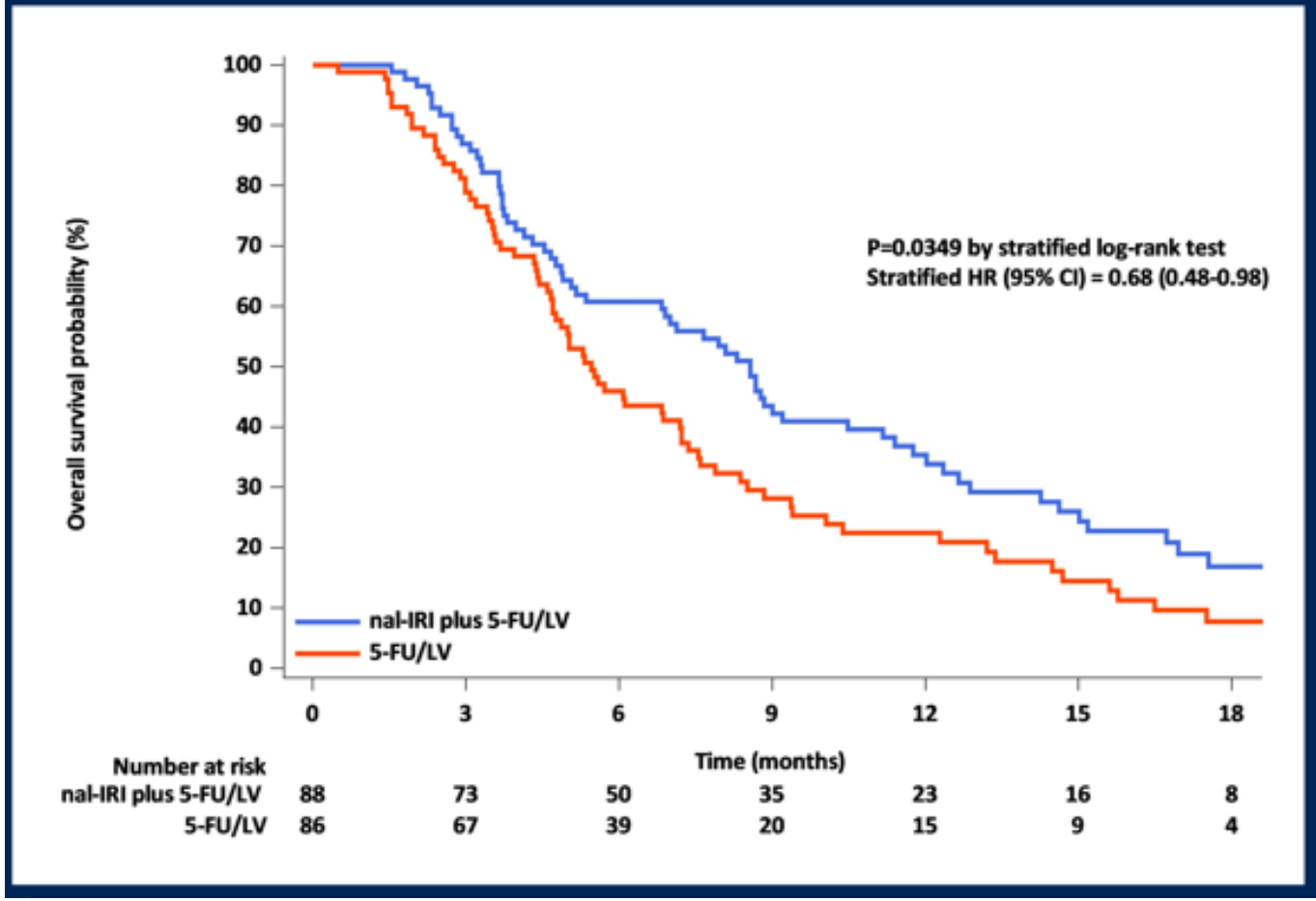


Median follow-up period: 11.8 months (IQR 7.7-18.7)

	Nal-IRI + 5-FU/LV (n=88)	5-FU/LV (n=86)
No. of events, n (%)	64 (72.7%)	79 (91.9%)
mPFS, months (95% CI)	7.1 (3.6-8.8)	1.4 (1.2-1.5)
	HR, 0.56 95% CI, 0.39-0.81 *P*=0.0019	
6-month PFS rate, % (95% CI)	55.7% (44.7-66.6)	26.2% (16.6-35.8)

ASCO2021;4006

Secondary Endpoint: Overall Survival



	Nal-IRI + 5-FU/LV (n=88)	5-FU/LV (n=86)
No. of events, n (%)	64 (72.7%)	74 (86.0%)
mOS, months (95% CI)	8.6 (5.4-10.5)	5.5 (4.7-7.2)
	HR, 0.68 95% CI, 0.48-0.98 *P*=0.0349	
6-month OS rate, % (95% CI)	60.7% (50.3-71.2)	45.9% (35.3-56.5)
1-year OS rate, % (95% CI)	35.4% (24.9-45.9)	22.4% (13.1-31.7)

ASCO2021;4006

Response rate

Response per RECIST v1.1	BICR-assessed response		Investigator review-assessed response	
	Nal-IRI+5-FU	5-FU/LV	Nal-IRI+5-FU	5-FU/LV
Objective response	**14.8%**	**5.8%**	**19.3%**	**2.3%**
	***P*=0.0684**		***P*=0.0002**	
CR	0	0	0	0
PR	14.8%	5.8%	19.3%	2.3%
SD	50.0%	29.1%	53.4%	47.7%
PD	29.5%	64.0%	21.6%	48.8%
Not evaluable	5.7%	1.2%	5.7%	1.2%

ASCO2021;4006

Adverse Events Occurring in >10% of Patients

	Nal-IRI plus 5-FU/LV (n=88)		5-FU/LV (n=86)	
	Any grade (%)	Grade 3-4 (%)	Any grade (%)	Grade 3-4 (%)
With at least one AE	87 (98.9)	68 (77.3)	74 (86.0)	29 (33.7)
Hematological				
Anemia	13 (14.8)	8 (9.1)	5 (5.8)	3 (3.5)
Febrile neutropenia	2 (2.3)	2 (2.3)	0 (0)	0 (0)
Neutropenia	29 (33.0)	21 (23.9)	3 (3.5)	1 (1.2)
Thrombocytopenia	3 (3.4)	0 (0)	1 (1.2)	1 (1.2)
Non-hematological				
Nausea	22 (25.0)	5 (5.7)	14 (16.3)	1 (1.2)
Vomiting	9 (10.2)	0 (0)	4 (4.7)	1 (1.2)
Abdominal pain	22 (25.0)	4 (4.5)	14 (16.3)	3 (3.5)
Constipation	26 (29.5)	0 (0)	19 (22.1)	0 (0)
Diarrhea	20 (22.7)	4 (4.5)	9 (10.5)	0 (0)
Dyspepsia	20 (22.7)	0 (0)	12 (14.0)	0 (0)
Stomatitis	14 (15.9)	2 (2.3)	10 (11.6)	0 (0)
Fatigue/Asthenia	27 (30.7)	11 (12.5)	17 (19.8)	3 (3.5)
Pyrexia	15 (17.0)	0 (0)	8 (9.3)	1 (1.2)
Decreased appetite	24 (27.3)	1 (1.1)	16 (18.6)	0 (0)

Implications for practice

Fluorouracil/leucovorin plus nanoliposomal irinotecan may become an option for treatment of biliary tract malignancies following gemcitabine/cisplatin (in patients without targetable molecular alterations)

Hepatocellular carcinoma

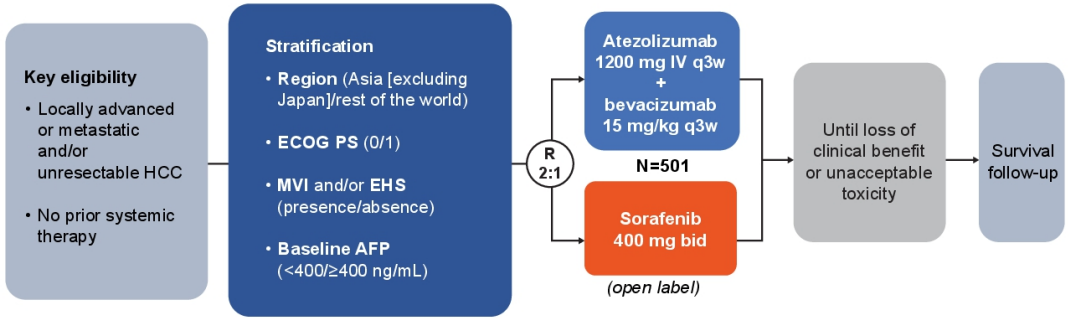
Not a big HCC year at ASCO

- 4007: Hepatic arterial infusion chemotherapy of oxaliplatin plus fluorouracil versus sorafenib in advanced hepatocellular carcinoma: A biomolecular exploratory, randomized, phase 3 trial (The FOHAIC-1 study)
  - Population had large tumors (11.7 cm, and >80% had macrovascular invasion)
  - mOS with HAIC-FO was 13.9 mo (95%CI 10.6-17.2), compared with 8.2 month for sorafenib

- 4008: Neoadjuvant transarterial infusion chemotherapy with FOLFOX could improve outcomes of resectable BCLC stage A/B hepatocellular carcinoma patients beyond Milan criteria: An interim analysis of a multi-center, phase 3, randomized, controlled clinical trial.
  - 3 yr OS (63.5 vs 46.3%) and 18 mo PFS (47.4 vs 34.8%) were statistically higherfor neoadjuvant group than for the operative alone group. RFS was numerically but not statistically better for the neoadjuvant therapy group.

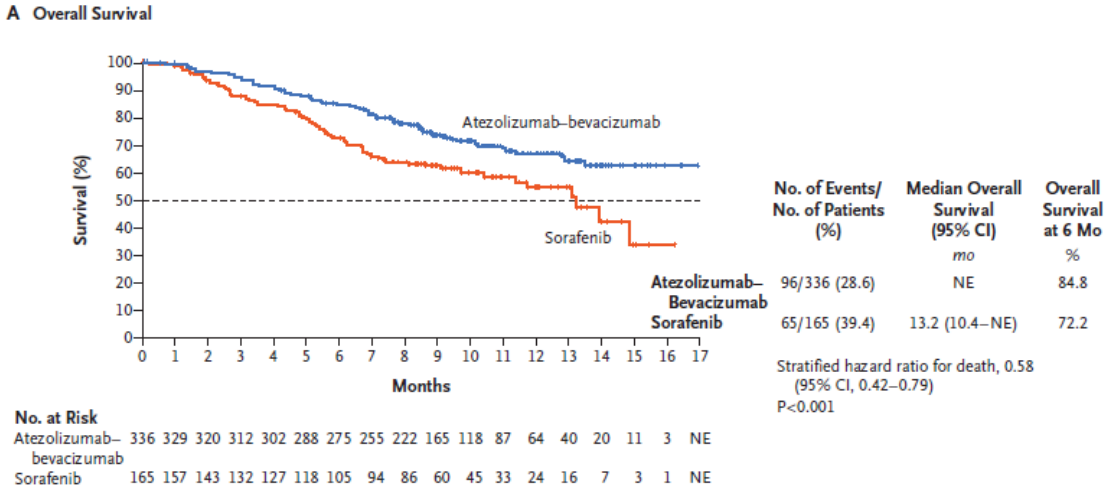
- 4070 Adjuvant nivolumab for hepatocellular carcinoma (HCC) after surgical resection (SR) or radiofrequency ablation (RFA) (NIVOLVE): A phase 2 prospective multicenter single-arm trial and exploratory biomarker analysis
  - 1 yr RFSR and RFS were 76.6% and 26.0 months, respectively. (May give insight into 9DX study)

Association of response and outcome in IMBRAVE150 study

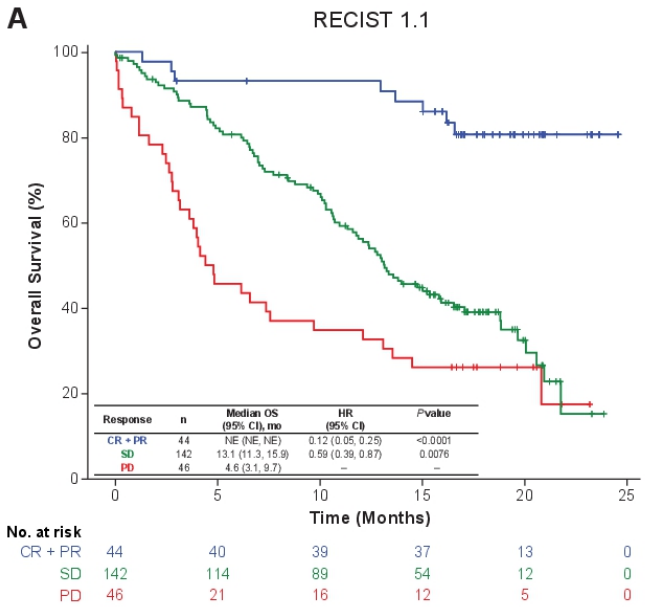


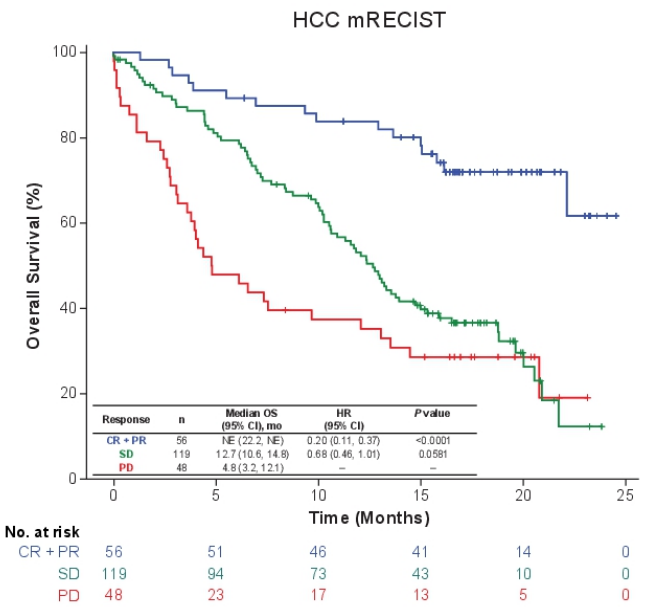
Co-primary endpoints:
- OS
- IRF-assessed PFS per RECIST 1.1

Key secondary endpoints
- IRF-assessed ORR per RECIST 1.1
- IRF-assessed ORR per HCC mRECIST



N Engl J Med 2020;382:1894-905.





Summary from ASCO 2021

- Advanced ESCC: Nivolumab + chemo or nivolumab + ipilimumab represent new standard for 1L
  - Chemotherapy plus pembrolizumab also has survival benefit in this group (CPS≥10)
- Advanced adenocarcinoma of stomach, GE junction, esophagus: nivolumab plus chemotherapy has improved survival compared with chemotherapy alone
  - Chemotherapy plus pembrolizumab has survival benefit in the Siewert 1 GEJ/esophagus group
- Esophageal adeno/GEJ: Peri-operative chemotherapy was non-inferior to CRT (CROSS) but markers of response better with CRT
- Resected GEJ/esophageal: Adjuvant Nivolumab is a new standard if residual disease
- Pancreatic cancer: No major studies reported
- Biliary: Nanoliposomal irinotecan plus fluorouracil/leucovorin may be an option for gemcitabine/cisplatin pretreated advanced disease
- Hepatocellular carcinoma: No major studies reported