“Establishing IO Management in Gastrointestinal Cancers”

Richard Kim M.D.

Professor

Section Chief of GI Medical Oncology

Department of Gastrointestinal Oncology

Moffitt Cancer Center

Tampa, FL

Objectives

- Discuss role of IO in colorectal cancer
- Discuss role of IO in BTC
- Discuss role of IO in HCC
- Discuss role of IO in Gastroesophageal Cancer

Advanced Colorectal Cancer

Background

- In non selected colorectal cancer patients PD-1 blockade seems to be ineffective.
- Average tumor has dozens of somatic mutations.
- Mismatch repair deficient tumors harbor thousands of mutations
- Somatic mutations have the potential to generate neo-antigiens which can be recognized by immune system.

Immunotherapy in MSI-H Colorectal Cancer

- KEYNOTE-164: Phase II. ≥ 1 prior lines therapy. pembrolizumab (200mg Q3W). Primary endpoint RR.
- KEYNOTE-177: Phase III randomized. 307 pts. Pembro v. SOC chemo. Cross over permitted after PD. Primary endpoints PFS and OS.
- Checkmate-142: Phase I/II. Nivo (3 mg/kg) plus ipi (1 mg/kg) Q3W x 4, followed by nivo Q2W. Primary end point RR.

Andre. NEJM. 2020; Andre. ASCO (#3500). 2021; Le. JCO. 2020; Overman. JCO. 2018; Lenz. ASCO (#4040). 2020. Overman. Lancet Oncology. 2017; *Le. Science 2017. Le. ASCO. 2018*

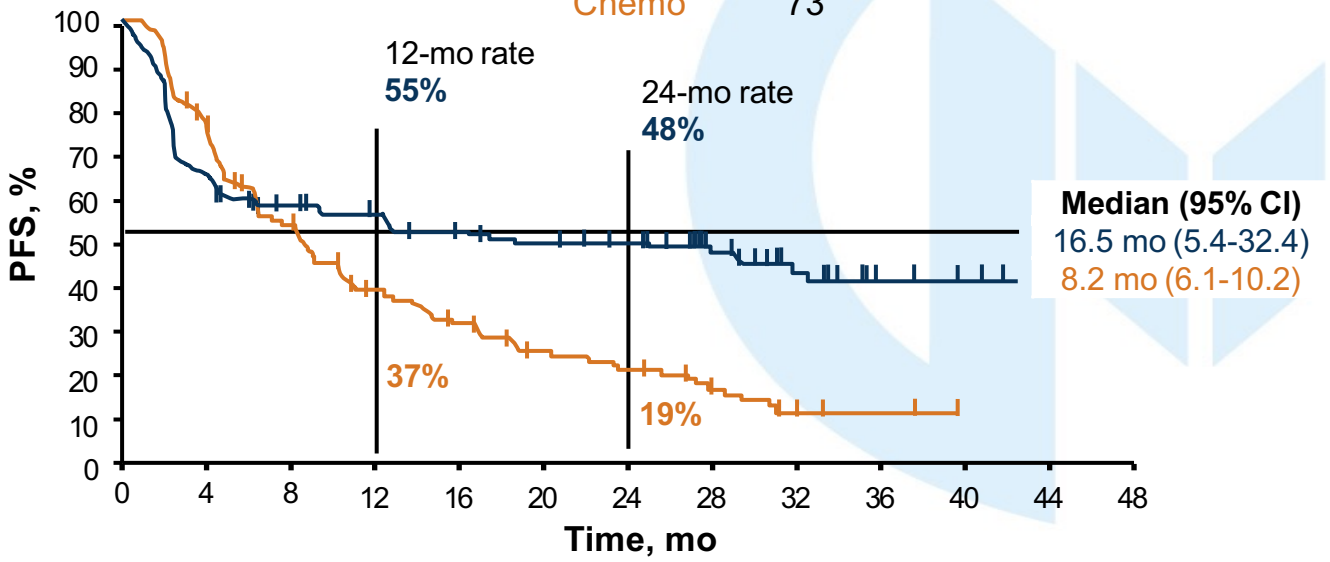
	Pembrolizumab			Nivolumab	Nivolumab + Ipilimumab	
Trial	KEYNOTE-177	KEYNOTE-164 (B)/(A)		Checkmate-142		
Population	1st L	≥2nd L	≥3rd L	≥2nd L		*1st L (cont ipi)*
Size	307 (III RCT v. chemo)	63	61	74	119	*45*
ORR	45.1% *v. 33.1%*	33%	33%	31.1%	55%	*69%*
median PFS/ 12 mo PFS %	16.5m *v. 8.2m*	41%	34%	50%	71%	*76%*
median OS/ 12 mo Surv %	NR *v. 36.7m.* HR 0.74. p=0.0359	76%	72%	73%	85%	*84%*

Andre. NEJM. 2020; Andre. ASCO (#3500). 2021; Le. JCO. 2020; Overman. JCO. 2018; Lenz. ASCO (#4040). 2020. Overman. Lancet Oncology. 2017; *Le. Science 2017. Le. ASCO. 2018*

KEYNOTE-177[1,2]

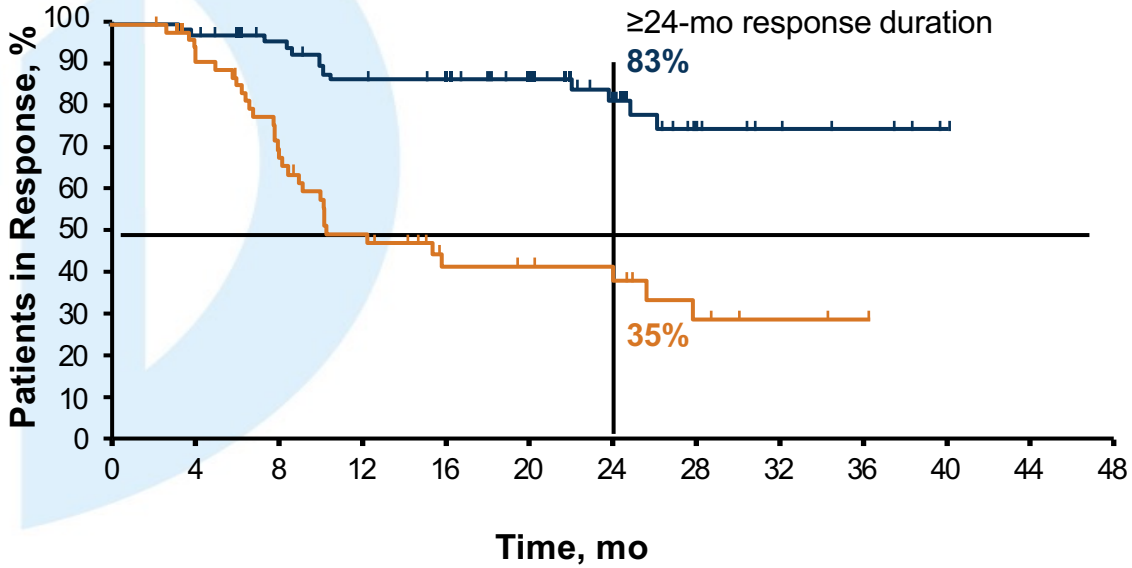
PFS

	Events, %	HR (95% CI)	*P*
Pembro	54	0.60 (0.45-0.80)	.0002
Chemo	73		



DOR

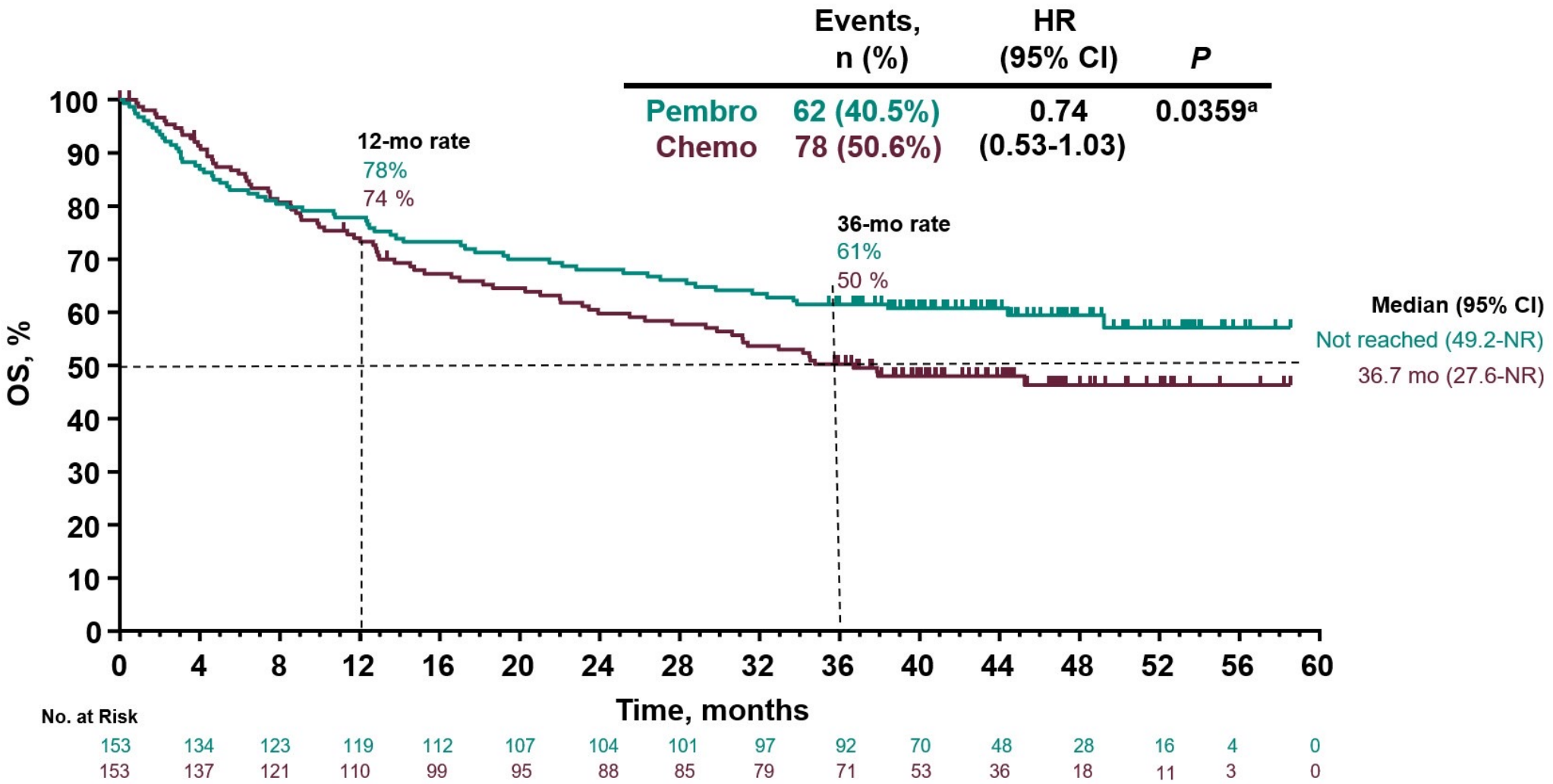
	Median DOR, mo (range)
Pembro	NR (2.3+ to 41.4+)
Chemo	10.6 (2.8 to 37.5+)



Median study follow-up: 32.4 months (range, 24-48.3): 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 *P* = .0117; data cut-off: February 19, 2020.

1. Andre T et al. ASCO 2020. Abstract LBA4. 2. Shiu K-K et al. ASCO GI 2021. Abstract 6.

KEYNOTE-177: Overall Survival



[a]**Pembrolizumab was not superior to chemotherapy for OS as one-sided α > 0.0246. Pre-specified sensitivity analyses to adjust for crossover effect by rank-preserving structure failure time model and inverse probability of censoring weighting showed OS HRs of 0.66 (95% CI 0.42-1.04) and 0.77 (95% CI 0.44-1.38).** Data cut-off: 19Feb2021.

Diaz L, et al Lancet Oncol 2022

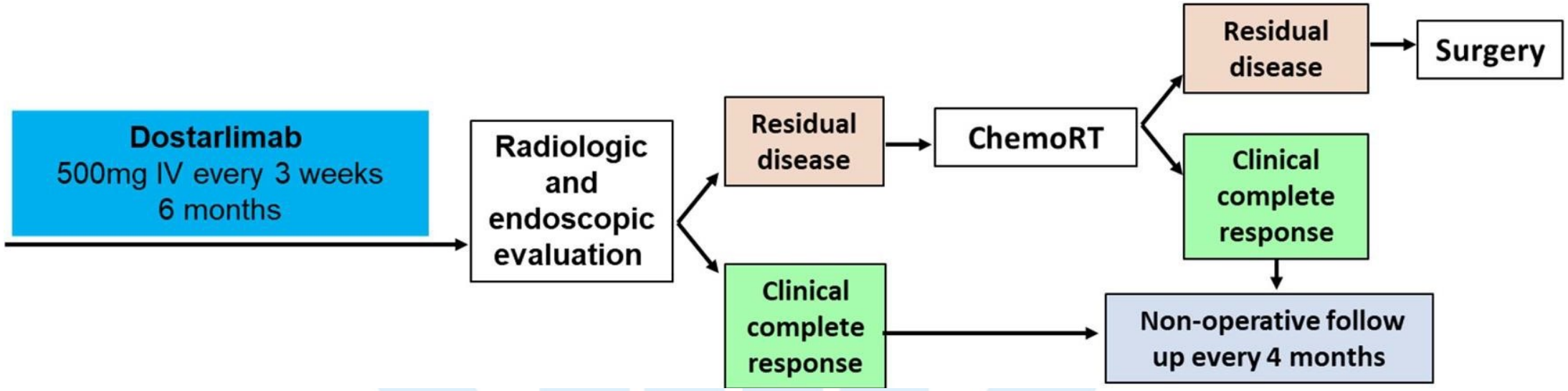
Immunotherapy in dMMR rectal cancer

ORIGINAL ARTICLE

PD-1 Blockade in Mismatch Repair–Deficient, Locally Advanced Rectal Cancer

A. Cercek, M. Lumish, J. Sinopoli, J. Weiss, J. Shia, M. Lamendola-Essel, I.H. El Dika, N. Segal, M. Shcherba, R. Sugarman, Z. Stadler, R. Yaeger, J.J. Smith, B. Rousseau, G. Argiles, M. Patel, A. Desai, L.B. Saltz, M. Widmar, K. Iyer, J. Zhang, N. Gianino, C. Crane, P.B. Romesser, E.P. Pappou, P. Paty, J. Garcia-Aguilar, M. Gonen, M. Gollub, M.R. Weiser, K.A. Schalper, and L.A. Diaz, Jr.

Study design



Patient population: stage 2 and 3 dMMR rectal cancer

Primary objectives:

- overall response rate
- pathologic or clinical complete response rate

Cercek et al, ASCO 2022

Individual responses to PD-1 blockade with dostarlimab

Patients who completed 6-months of dostarlimab

ID	Age	Stage T	Stage N	FU (months)	Digital rectal exam response	Endoscopic best response	Rectal MRI best response	Overall response 100%
1	38	T4	N+	23.8	CR	CR	CR	**cCR**
2	30	T3	N+	20.5	CR	CR	CR	**cCR**
3	61	T1/2	N+	20.6	CR	CR	CR	**cCR**
4	28	T4	N+	20.5	CR	CR	CR	**cCR**
5	53	T1/2	N+	9.1	CR	CR	CR	**cCR**
6	77	T1/2	N+	11.0	CR	CR	CR	**cCR**
7	77	T1/2	N+	8.7	CR	CR	CR	**cCR**
8	55	T3	N+	5.0	CR	CR	CR	**cCR**
9	68	T3	N+	4.9	CR	CR	CR	**cCR**
10	78	T3	N-	1.7	CR	CR	CR	**cCR**
11	55	T3	N+	4.7	CR	CR	CR	**cCR**
12	27	T3	N+	4.4	CR	CR	CR	**cCR**
13	26	T3	N+	0.8	CR	CR	CR	**cCR**
14	43	T3	N+	0.7	CR	CR	CR	**cCR**

Cercek et al, ASCO 2022

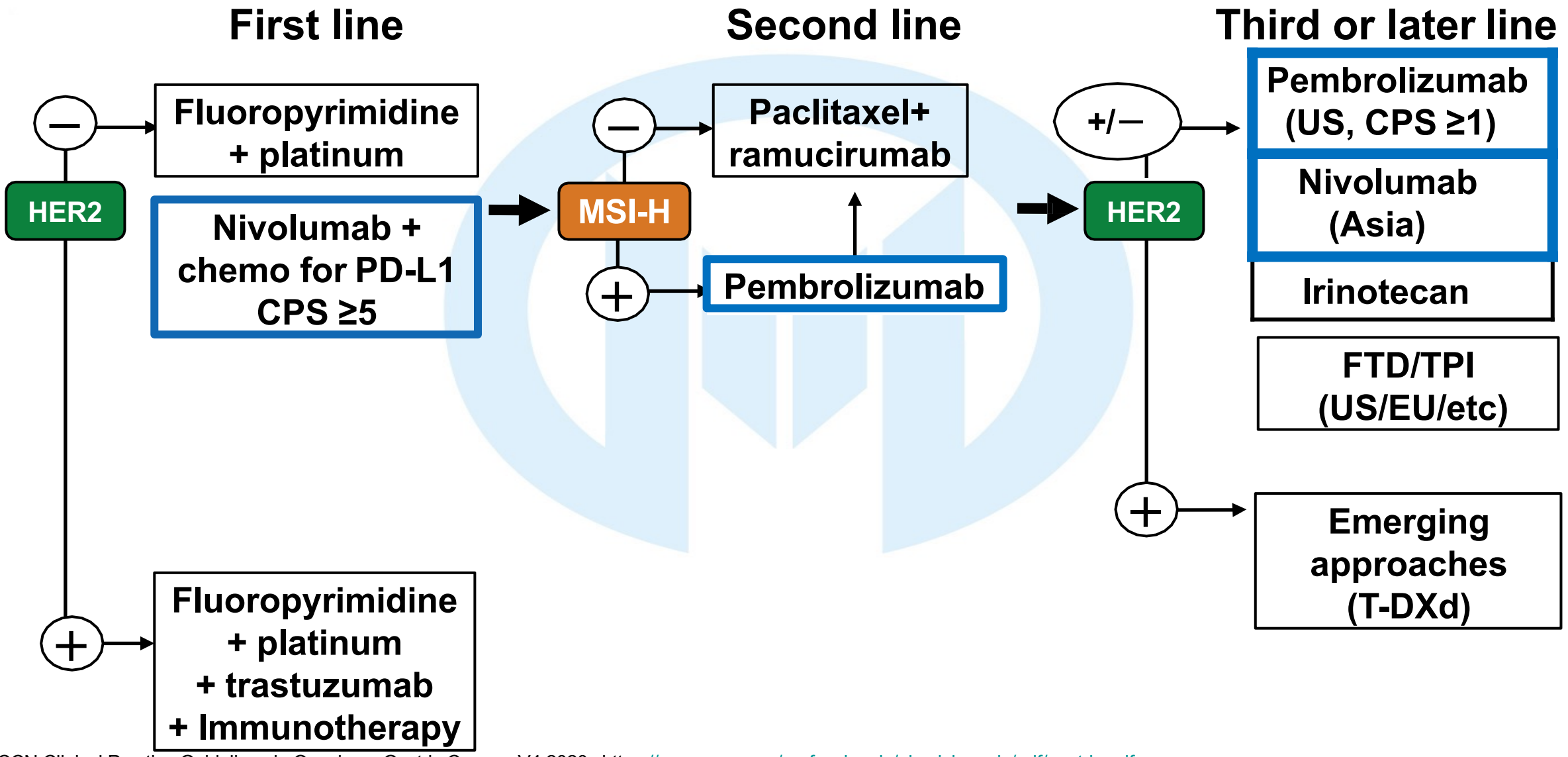
Conclusions

- NGS and mismatch repair testing is standard of care for all patients with CRC, especially those with stage IV disease
- Immune checkpoint inhibitor therapy is an important option in the first-line setting for patients with CRC and for those in the second line and beyond who have not been exposed.
- Neoadjuvant immunotherapy has the **potential** to become standard of care for patients with dMMR rectal cancer – Organ preservation for rectal cancer !!!!!
- Multiple immunotherapy approaches are being explored in mismatch repair proficient patients. To convert “cold tumor” to “ hot tumor”

MOFFITT MEDICAL GROUP

Advanced Esophagogastric Cancer

Standard Treatment for GE/Gastric Cancer[1]



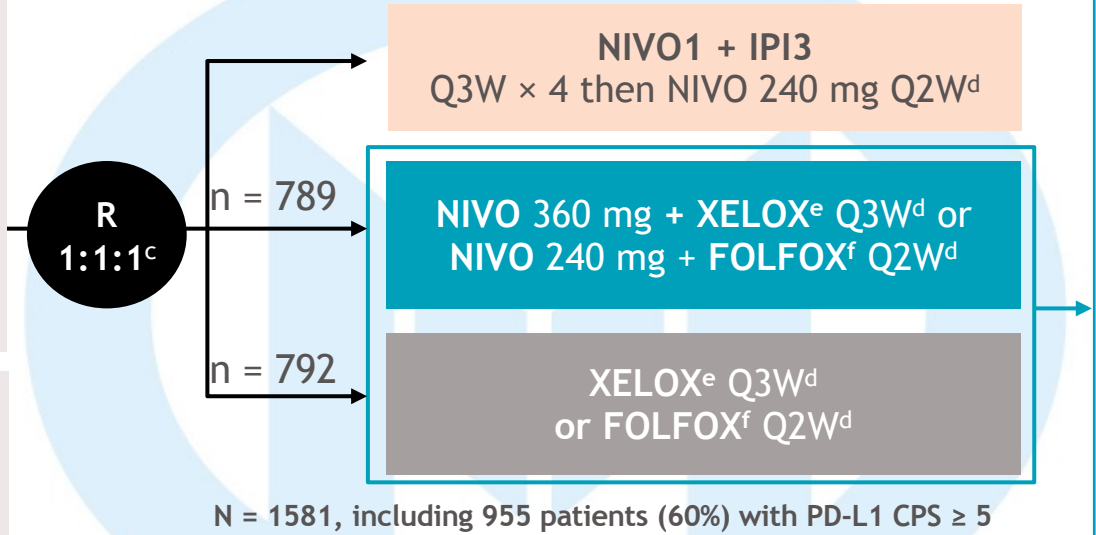
1. NCCN Clinical Practice Guidelines in Oncology. Gastric Cancer. V4.2020. https://www.nccn.org/professionals/physician_gls/pdf/gastric.pdf.

CheckMate 649 Study Design

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

Key eligibility criteria
- Previously untreated, unresectable, advanced or metastatic gastric/GEJ/ esophageal adenocarcinoma
- No known HER2-positive status
- ECOG PS 0–1

Stratification factors
- Tumor cell PD-L1 expression (≥ 1% vs < 1%[b])
- Region (Asia vs United States/Canada vs ROW)
- ECOG PS (0 vs 1)
- Chemo (XELOX vs FOLFOX)



N = 1581, including 955 patients (60%) with PD-L1 CPS ≥ 5

Dual primary endpoints:
- **OS** and **PFS**[g] (PD-L1 CPS ≥ 5)

Secondary endpoints:
- **OS** (PD-L1 CPS ≥ 1 or all randomized)
- **OS** (PD-L1 CPS ≥ 10)
- **PFS**[g] (PD-L1 CPS ≥ 10, 1, or all randomized)
- **ORR**[g]

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

[a]ClinicalTrials.gov number, NCT02872116; [b]< 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.

Janjigian YY, et al. *Lancet*. 2021;398(10294):27-40. Moehler M, et al. Presented at: ESMO; September 19-21, 2020; Virtual. Abstract LBA6.

MOFFITT MEDICAL GROUP

CheckMate -649: Global Phase 3 Registration Trial

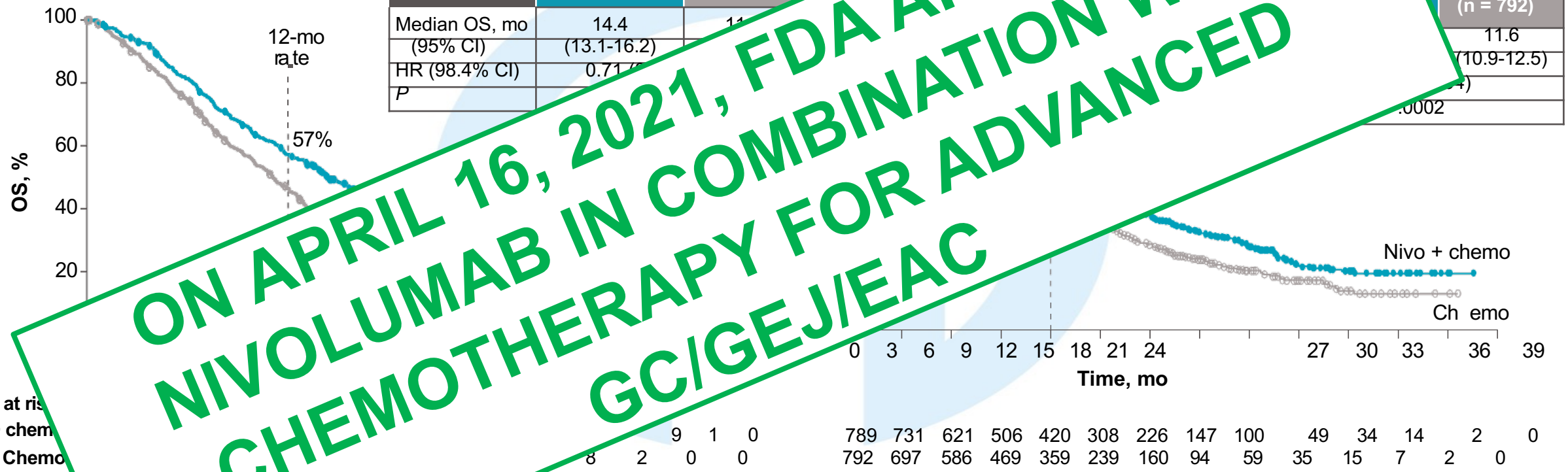
Nivolumab Plus Chemotherapy Improved Su

- FDA approved April 2021

PD-L1 CPS ≥ 5

	Nivo + Chemo (n = 473)	Chemo (n = 482)
Median OS, mo	14.4	11
(95% CI)	(13.1-16.2)	
HR (98.4% CI)	0.71	
P		

	Chemo (n = 792)
	11.6
	(10.9-12.5)
	.0002



ON APRIL 16, 2021, FDA APPROVED NIVOLUMAB IN COMBINATION WITH CHEMOTHERAPY FOR ADVANCED GC/GEJ/EAC

- Grade … % of patients in the nivolumab + chemo arm and 44% of patients in the chemo arm
- Treatme… …ed in 16 (2%) and 4 (1%) of patients in the nivolumab + chemo and chemo arms, respectively

Adapted with permiss… …elena Y. Janjigian, MD.

1. Opdivo (nivolumab) … …scribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/125554s106lbl.pdf. 2. Janjigian YY et al. *Lancet*. 2021;398:27-40.

CheckMate 649 Update: Efficacy

Survival	All Randomized		PD-L1 CPS ≥5	
	Nivo + CT (n = 789)	**CT (n = 792)**	**Nivo + CT (n = 473)**	**CT (n = 482)**
Median OS, mo (95% CI)	13.7 (12.4-14.5)	11.6 (10.9-12.5)	14.4 (13.1-16.2)	11.1 (10.0-12.1)
▪ HR (95% CI)	0.79 (0.71-0.88)		0.70 (0.61-0.81)	
Median PFS, mo (95% CI)	7.7 (7.1-8.6)	6.9 (6.7-7.2)	8.3 (7.0-9.3)	6.1 (5.6-6.9)
▪ HR (95% CI)	0.79 (0.71-0.89)		0.70 (0.60-0.81)	
Response	**Nivolumab + CT (n = 602)**	**CT (n = 607)**	**Nivolumab + CT (n = 378)**	**CT (n = 390)**
ORR, % (95% CI)	58 (54-62)	46 (42-50)	60 (55-65)	45 (40-50)
Duration of Response	**Nivolumab + CT (n = 350)**	**CT (n = 279)**	**Nivolumab + CT (n = 226)**	**CT (n = 176)**
Median DoR, mo (95% CI)	8.5 (7.7-9.9)	6.9 (5.8-7.2)	9.6 (8.2-12.4)	7.0 (5.6-7.9)

Janjigian. ASCO GI 2023. Abstr 291.

CheckMate 649 Update: Efficacy by PD-L1 and MSI Status

Median OS, Mo	Nivo + CT	CT	Unstratified HR for Death
Overall (N = 1581)	13.7	11.6	0.78
PD-L1 CPS			
<1% (n = 265)	13.1	12.5	0.95
≥1% (n = 1297)	13.8	11.3	0.75
<5% (n = 607)	12.4	12.3	0.95
≥5% (n = 955)	14.4	11.1	0.69
<10% (n = 794)	12.4	12.5	0.91
≥10% (n = 768)	15.0	10.9	0.66

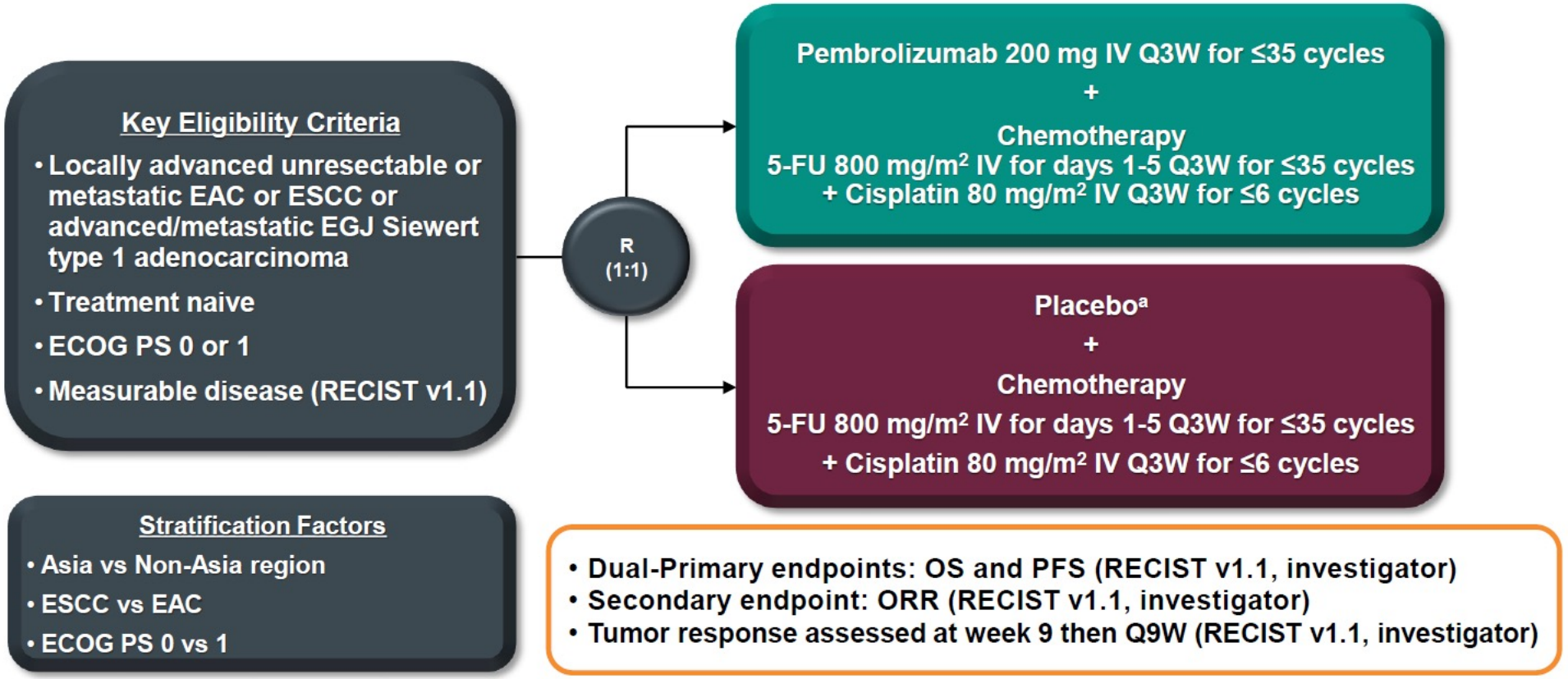
ORR, %	Nivo + CT	CT
Overall (N = 1209)	58	46
PD-L1 CPS		
<1% (n = 179)	51	41
≥1% (n = 1016)	60	46
<5% (n = 427)	56	46
≥5% (n = 768)	60	45
<10% (n = 577)	58	47
≥10% (n = 618)	59	44

OS by MSI Status	MSI-H		MSS	
	Nivo + CT (n = 23)	CT (n = 21)	Nivo + CT (n = 696)	CT (n = 682)
Median OS, mo (95% CI)	38.7 (8.4-NE)	12.3 (4.1-16.5)	13.8 (12.4-14.5)	11.5 (10.8-12.5)
▪ Unstratified HR (95% CI)	0.34 (0.16-0.74)		0.79 (0.71-0.89)	

Janjigian. ASCO GI 2023. Abstr 291.

How about Siewert 1 GEJ? KEYNOTE-590

Phase 3, randomized, double-blind, placebo-controlled study to evaluate pembrolizumab plus chemotherapy versus placebo plus chemotherapy in advanced esophageal cancer in the first line



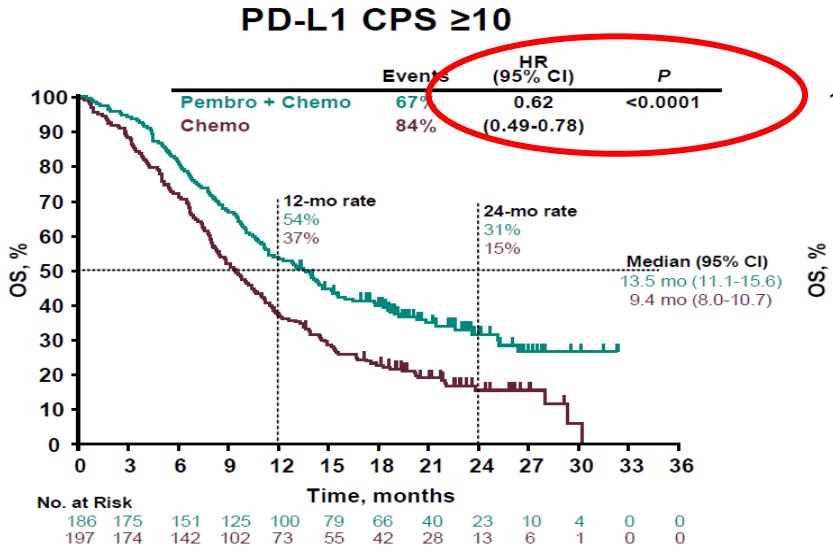
Kato et al. Annals of Oncology. 2020

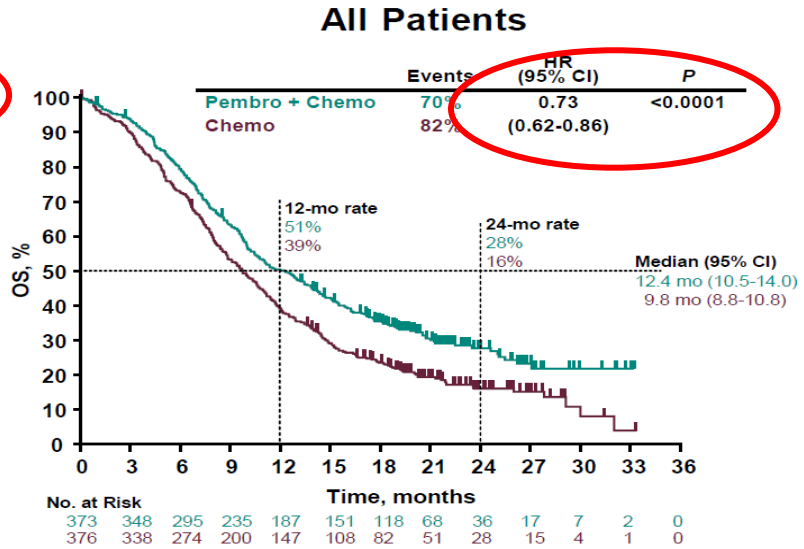
KEYNOTE-590

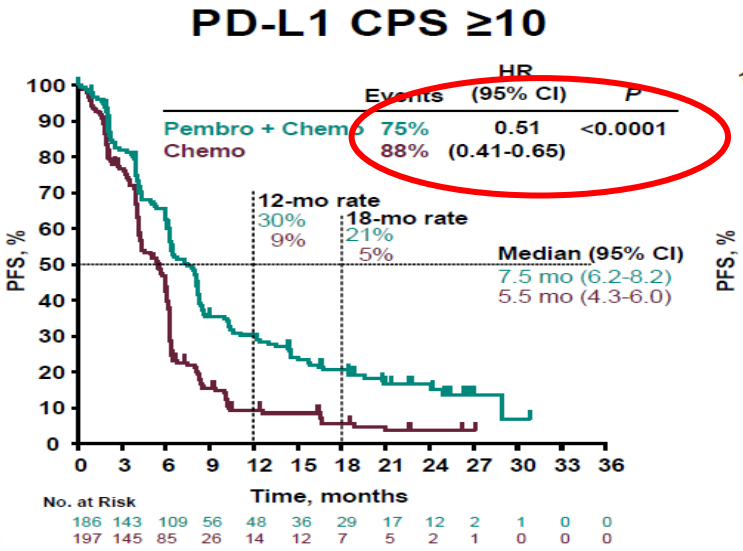
Characteristic, n (%)	Pembro + Chemo N = 373	Chemo N = 376
Median age, years (range)	64.0 (28-94)	62.0 (27-89)
≥65 years	172 (46)	150 (40)
Male	306 (82.0)	319 (84.8)
Asia Region	196 (52.5)	197 (52.4)
ECOG PS 1	223 (59.8)	225 (59.8)
Metastatic disease	344 (92.2)	339 (90.2)
Unresectable/locally-advanced	29 (7.8)	37 (9.8)
Squamous-cell carcinoma	274 (73.5)	274 (72.9)
Adenocarcinoma	99 (26.5)	102 (27.1)
Esophageal	58 (15.5)	52 (13.8)
EGJ	41 (11.0)	50 (13.3)
PD-L1 CPS ≥10[a]	186 (49.9)	197 (52.4)

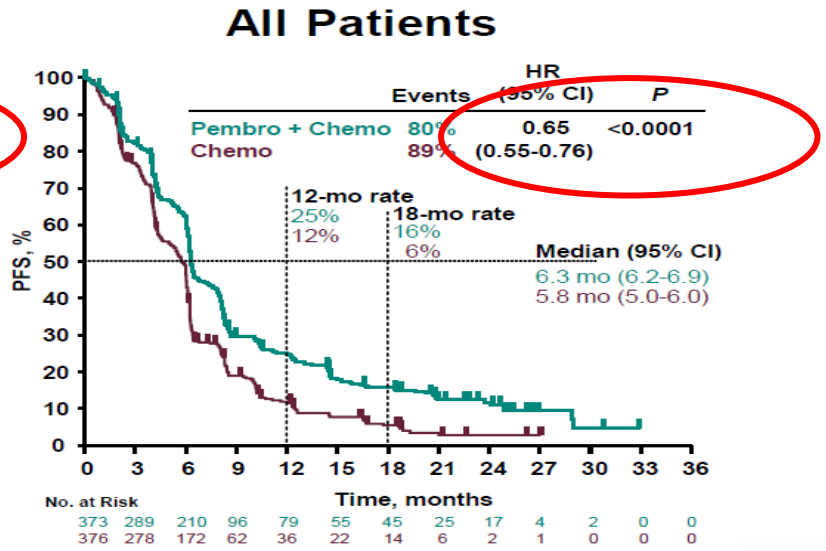
Kato et al. Annals of Oncology. 2020

KEYNOTE-590





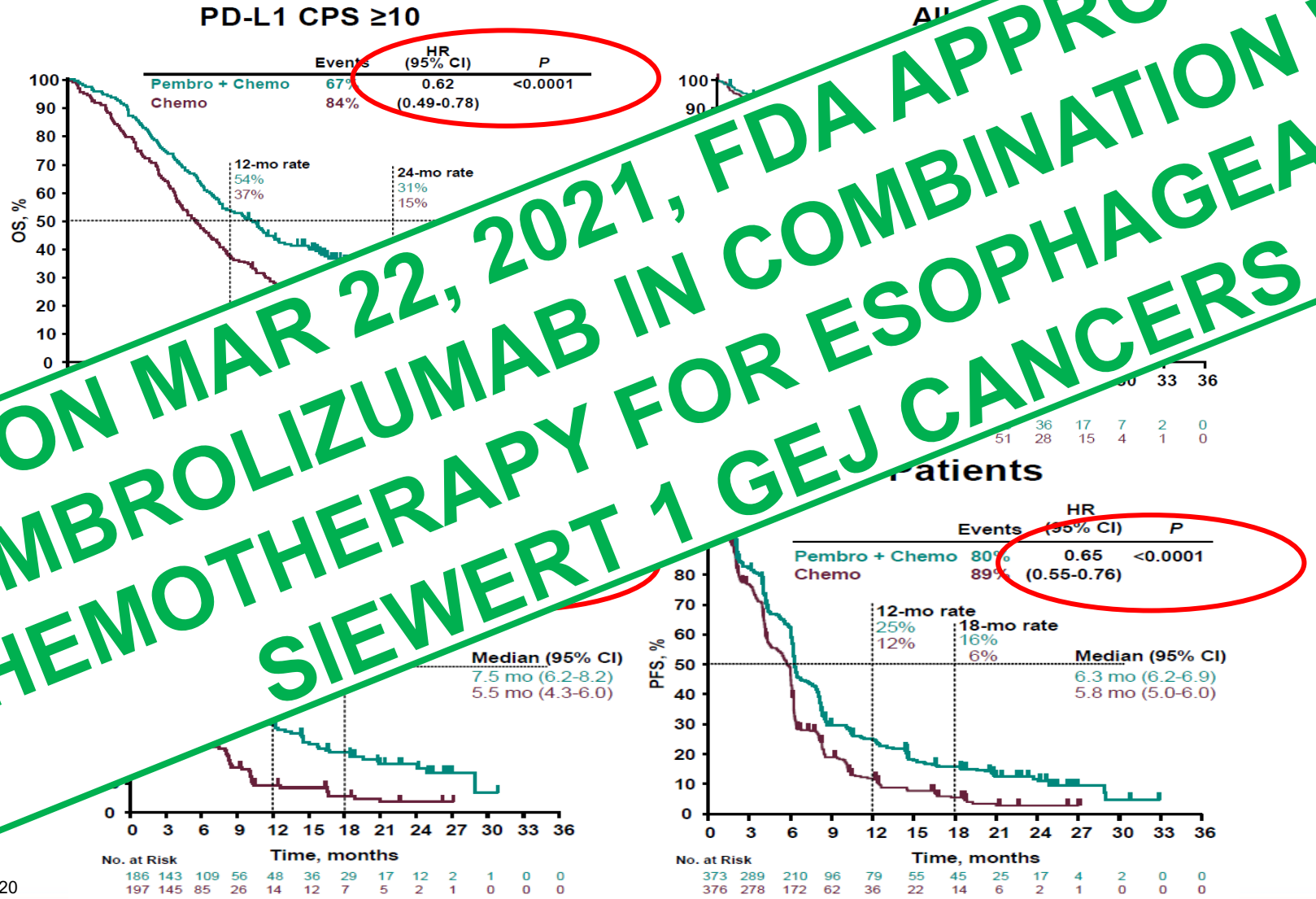




Kato et al. Annals of Oncology. 2020

MOFFITT MEDICAL GROUP

KEYNOTE-590



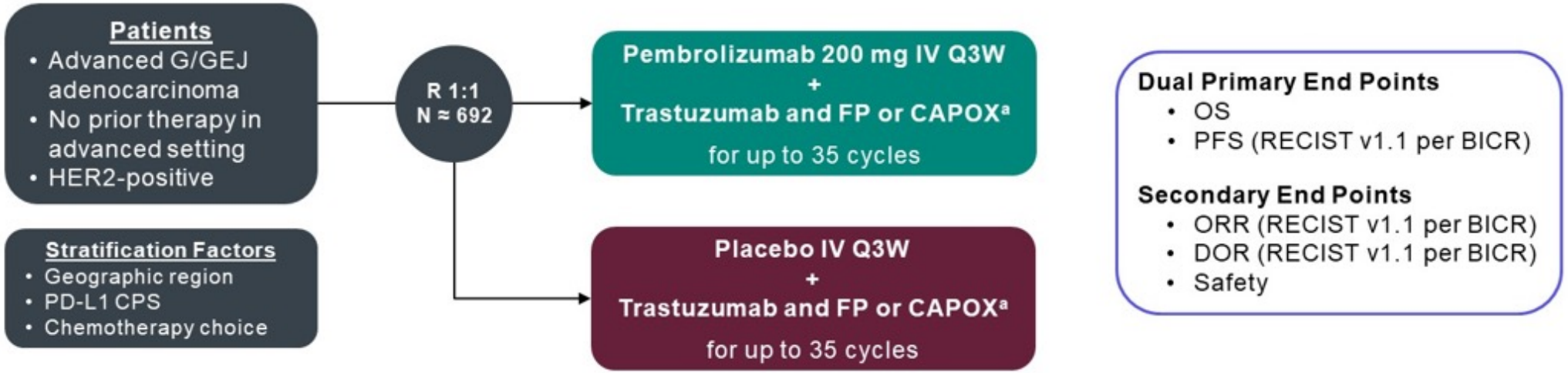
ON MAR 22, 2021, FDA APPROVED PEMBROLIZUMAB IN COMBINATION WITH CHEMOTHERAPY FOR ESOPHAGEAL AND SIEWERT 1 GEJ CANCERS

Kato et al. Annals of Oncology. 2020

KEYNOTE-811: 1L HER2-POS mGC/GEJ

KEYNOTE-811 Global Cohort

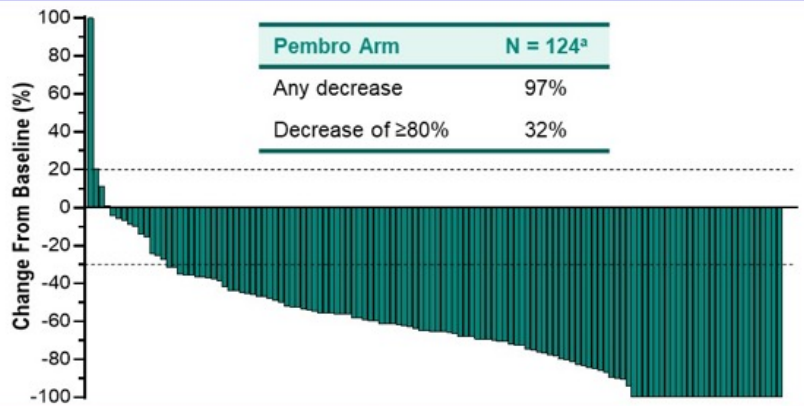
Double-Blind Phase 3 Study of Pembrolizumab + Trastuzumab and Chemotherapy vs Placebo + Trastuzumab and Chemotherapy as First-Line Therapy For HER2-Positive Unresectable or Metastatic G/GEJ Cancer (NCT03615326)

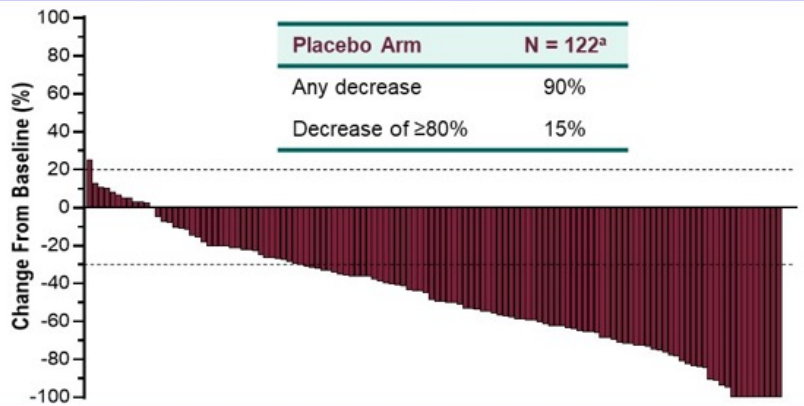


Janjigian et al. JCO. 2021

KEYNOTE-811

Confirmed Response at IA1





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%

[a]Participants with RECIST-measurable disease at baseline and ≥1 post-baseline measurement evaluable for change from baseline in target lesions. [b]Calculated using the Miettinen and Nurminen method stratified by the randomization stratification factors. [c]Calculated in participants with best response of CR or PR. [d]Kaplan-Meier estimation. The treatment regimen in both arms included trastuzumab and chemotherapy. Data cutoff date: June 17, 2020.

Janjigian et al. JCO. 2021

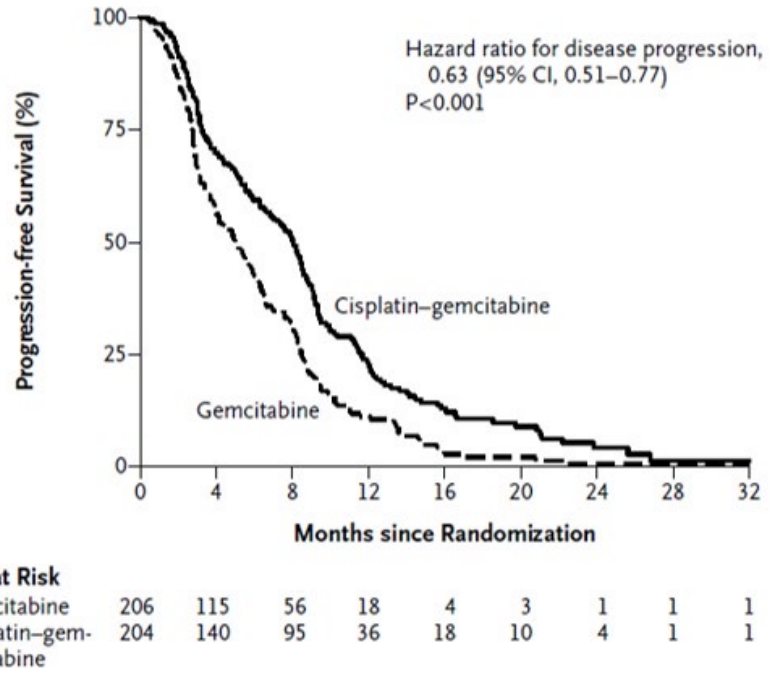
Summary

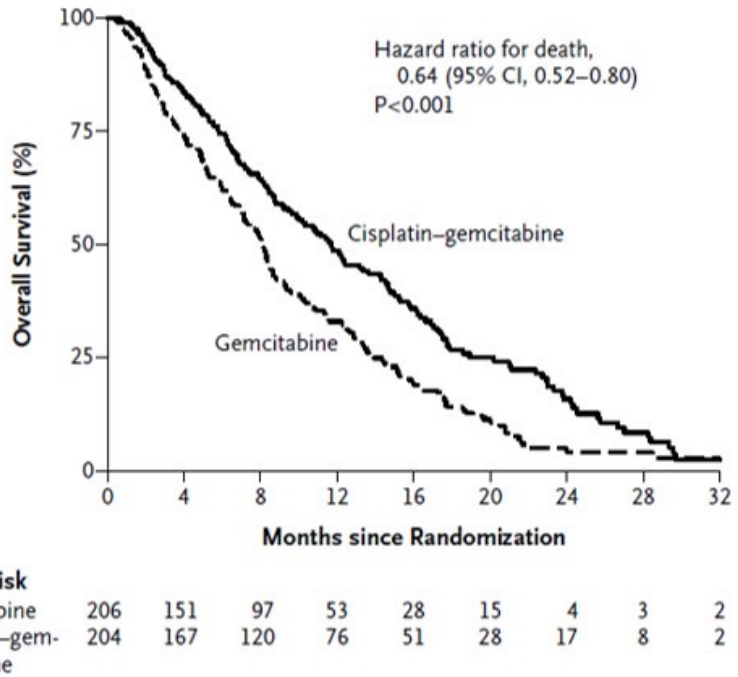
- Nivolumab in combination with chemotherapy is standard of care for patients with advanced/metastatic disease esophagogastric cancer
- Pembrolizumab in combination with chemotherapy is standard of care option for patients with esophageal cancer adenocarcinoma or SCC.
- Pembrolizumab in combination with chemotherapy and trastuzumab is standard of care for patients with HER2+ gastric, GEJ adenocarcinoma
- Patients with MSI high advanced disease benefit from immunotherapy or immunotherapy with chemotherapy

Advanced Biliary Tract Cancer

Standard first-line treatment option for Biliary tract cancers

Randomised phase 3 studies in advanced/metastatic bile duct cancer – gemcitabine ± cisplatin





		PFS (months)		OS (months)	
Study	**Reference**	**Gem**	**CisGem**	**Gem**	**CisGem**
ABC-02	Valle *NEJM* 2010[1]	5.0	8.0	8.1	**11.7**
BT-22	Okusaka *BJC* 2010[2]	3.7	5.8	7.7	**11.2**

1. Valle J, et al. *N Engl J Med.* 2010;362:1273–81.
2. Okusaka T, et al. *Br J Cancer*. 2010;103:469–74.

ABC-02: Conclusions

Cisplatin and gemcitabine significantly improves overall survival compared with gemcitabine monotherapy (11.7 vs. 8.3 months)

Benefit gained with no clinically significant added toxicity

Gem/Cis is recommended as a worldwide standard of care and the backbone for further studies

Caution required in patients with PS $\geq$ 2

Phase 3 TOPAZ-1 Trial: First-Line Immunotherapy Plus Chemotherapy in Patients With Advanced Biliary Cancers[1,2]

Key Eligibility Criteria

- Aged ≥18 years
- Previously untreated biliary cancer, including cholangiocarcinoma (intrahepatic or extrahepatic) and gallbladder carcinoma, if unresectable or metastatic at initial diagnosis or recurrent disease >6 mo after curative surgery or completion of adjuvant therapy)
- WHO/ECOG PS of 0 or 1
- N = 685

R

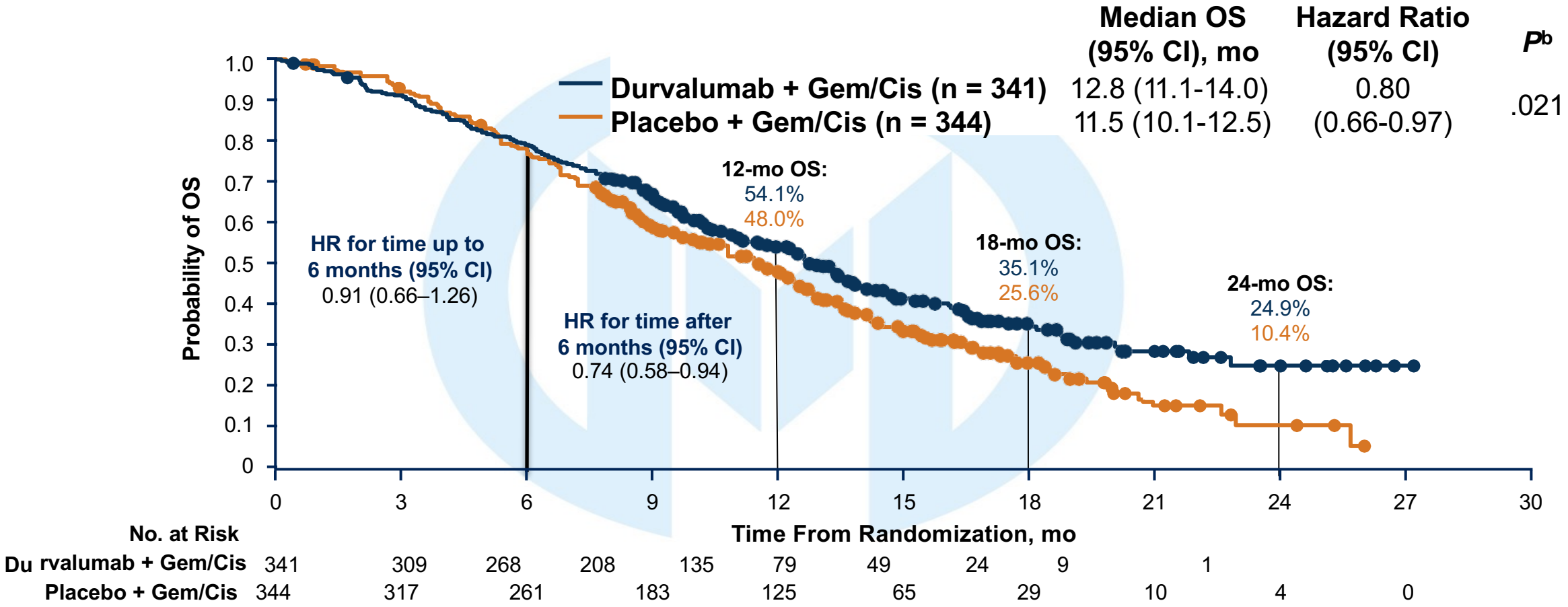
Durvalumab IV every 3 wk with gemcitabine + cisplatin up to 8 cycles followed by monotherapy every 4 wk until disease progression or other discontinuation criteria (n = 344)

Placebo IV every 3 wk with gemcitabine + cisplatin up to 8 cycles followed by monotherapy every 4 wk until disease progression or other discontinuation criteria (n = 341)

- **Stratification:** disease status and primary tumor location
- **Primary endpoint:** OS
- **Second endpoints:** PFS, ORR, and DOR by investigator assessment using RECIST v1.1

1. https://clinicaltrials.gov/ct2/show/NCT03875235. 2. Oh D-Y et al. *Ann Oncol*. 2019;30:319.

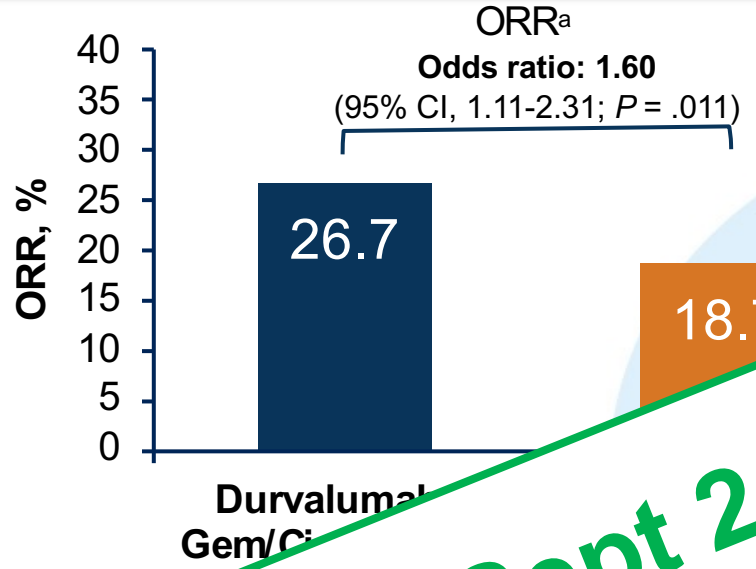
Phase 3 TOPAZ-1 Trial: OS[1,a]

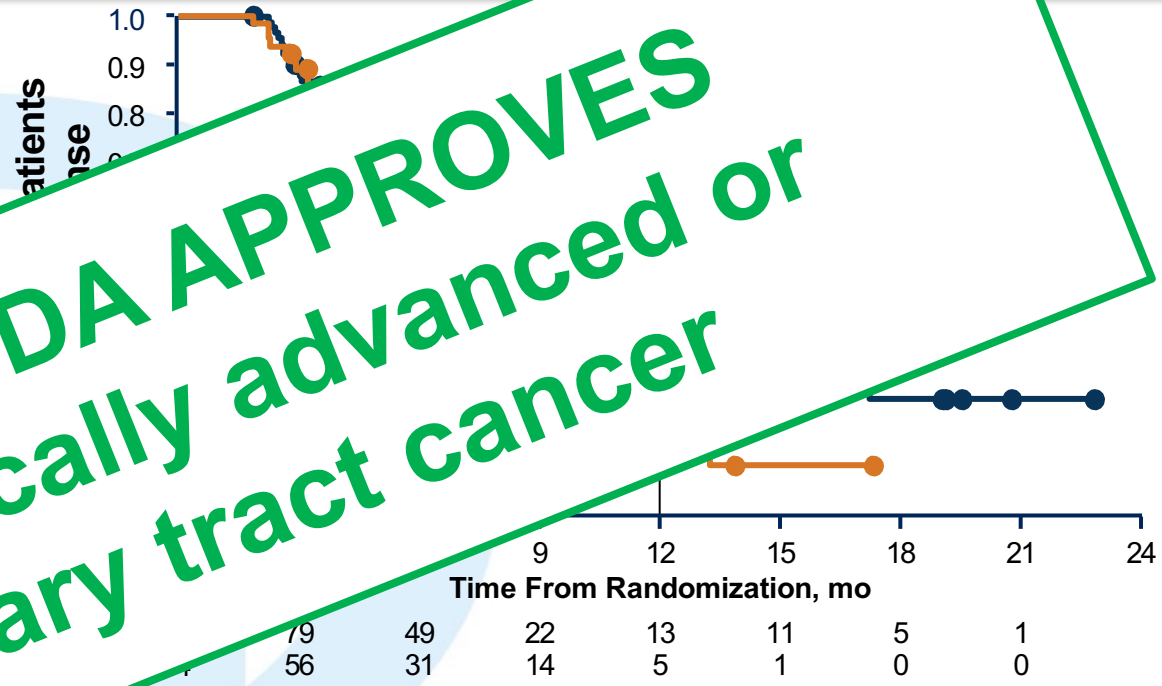


[a] Median duration of follow-up (95% CI) was 16.8 (14.8-17.7) months with durvalumab + gemcitabine/cisplatin and 15.9 (14.9-16.9) months with placebo + gemcitabine/cisplatin. [b] Statistical significance cut-off for OS: $P = .03$.

1. Oh D-Y et al. ASCO GI 2022. Abstract 378.

Phase 3 TOPAZ-1 Trial: Tumor Resp[illegible]e[1]





On Sept 2, 2022, FDA APPROVES durvalumab for locally advanced or metastatic biliary tract cancer

	Durvalumab + Gem/Cis (n = 91)	Placebo + Gem/Cis (n = 64)
Median DOR (quartile 1-3), mo	6.4 (4.6-17.2)	6.2 (3.8-9.0)
Median time to response (quartile 1-3), mo	1.6 (1.3-3.0)	2.7 (1.404.1)

[a] By investigator a[illegible]using RECIST v1.1 based on patients in the final analysis set who had measurable disease at baseline. [b] Analysis of DOR was based on patients in the full a[illegible]is set who had an objective response and measurable disease at baseline. [c] Analysis of DCR was based on all patients in the full analysis set.

1. Oh D-Y et al. ASCO GI 2022. Abstract 378.

Conclusions

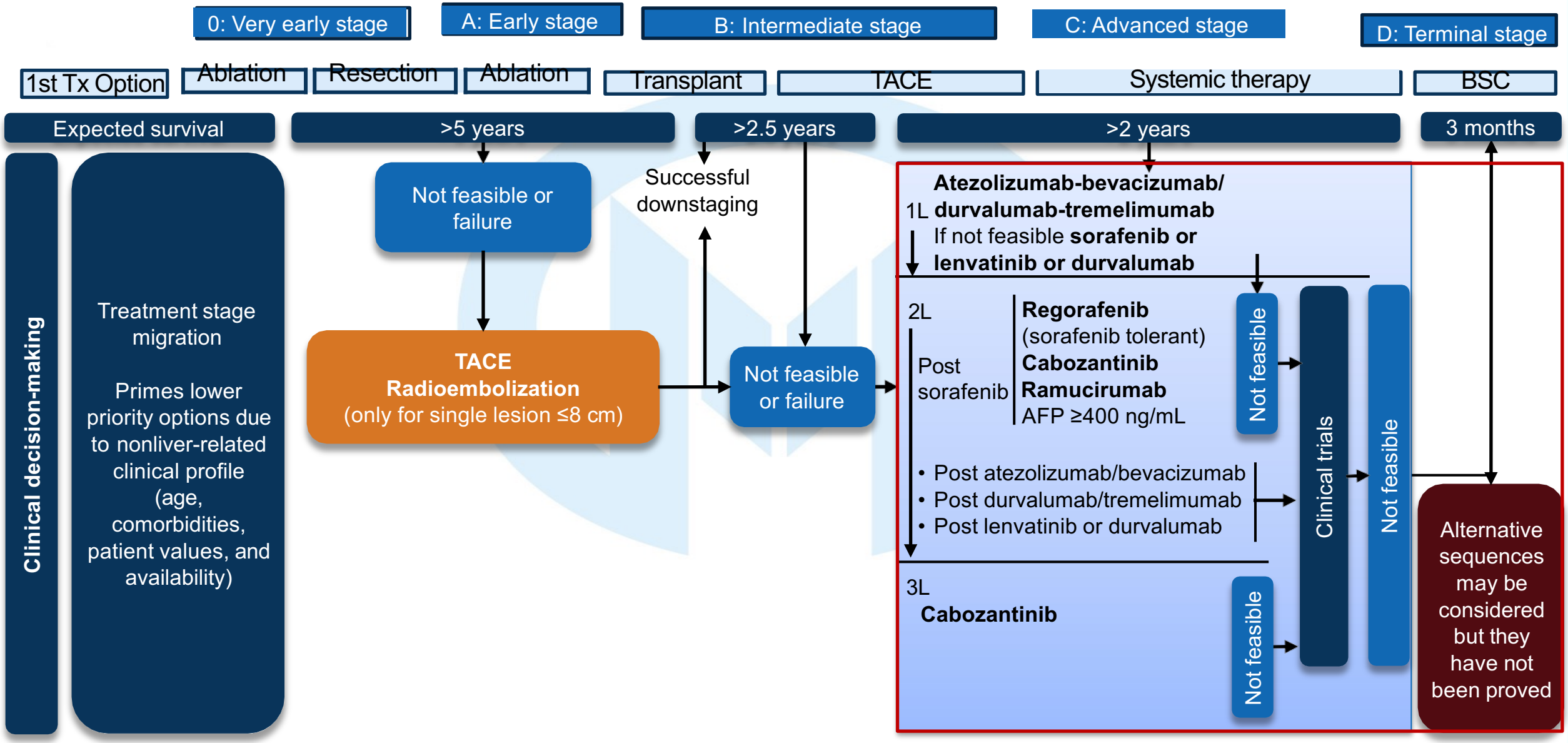
- Combination GemCis + durvalu
  ORR) over GemCis alone
  tract cancers in T
  - Benef
    gions of patients
    as a new standard for first-
- A
  ongoing studies of GemCis ± pembrolizumab
  (KL

Jan 25, 2023. Press Release. Pembrolizumab incombination with standard of care chemotherapy (gemcitabine and cisplatin) demonstrated a statistically significant and clinically meaningful improvement in overall survival (OS) versus chemotherapy alone for the first-line treatment of patients with advanced or unresectable biliary tract cancer (BTC)

Last but not least..

Advanced Hepatocellular carcinoma

BCLC

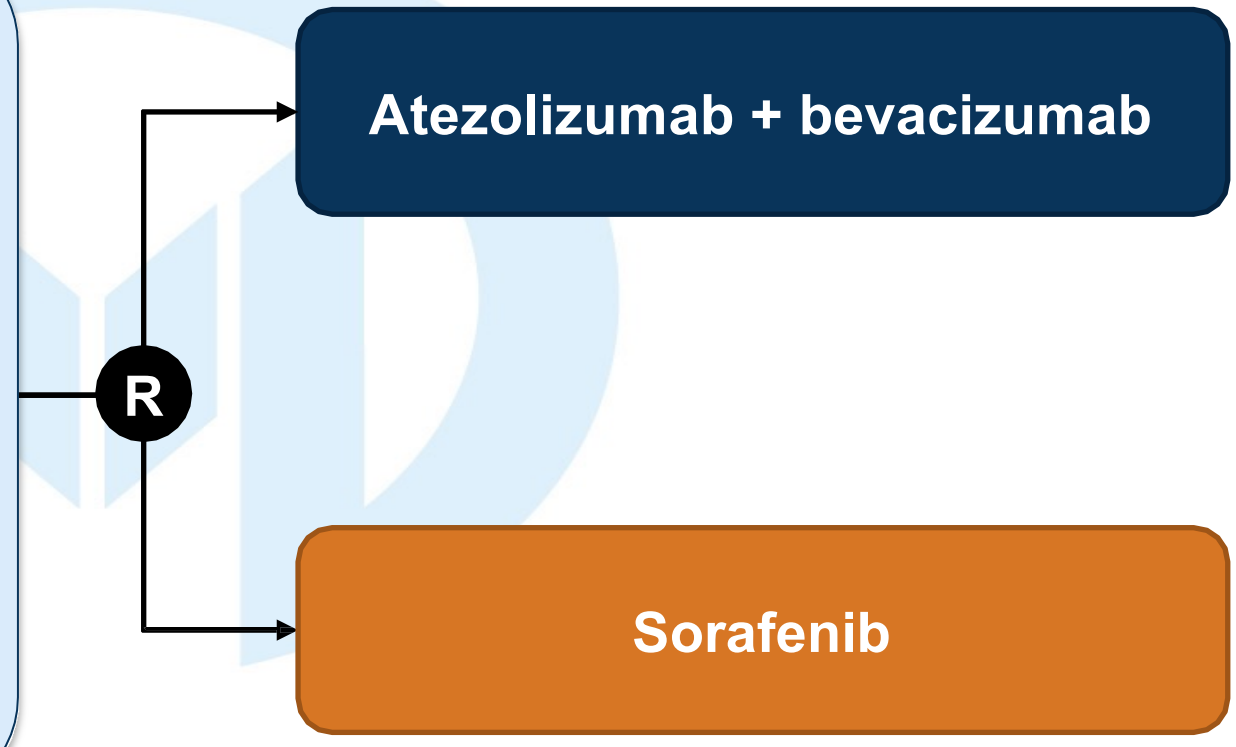


1. Reig M et al. *J Hepatol*. 2022;76:681-693.

Phase 3 IMbrave150 Trial: Atezolizumab Plus Bevacizumab Versus Sorafenib in Untreated Patients[1]

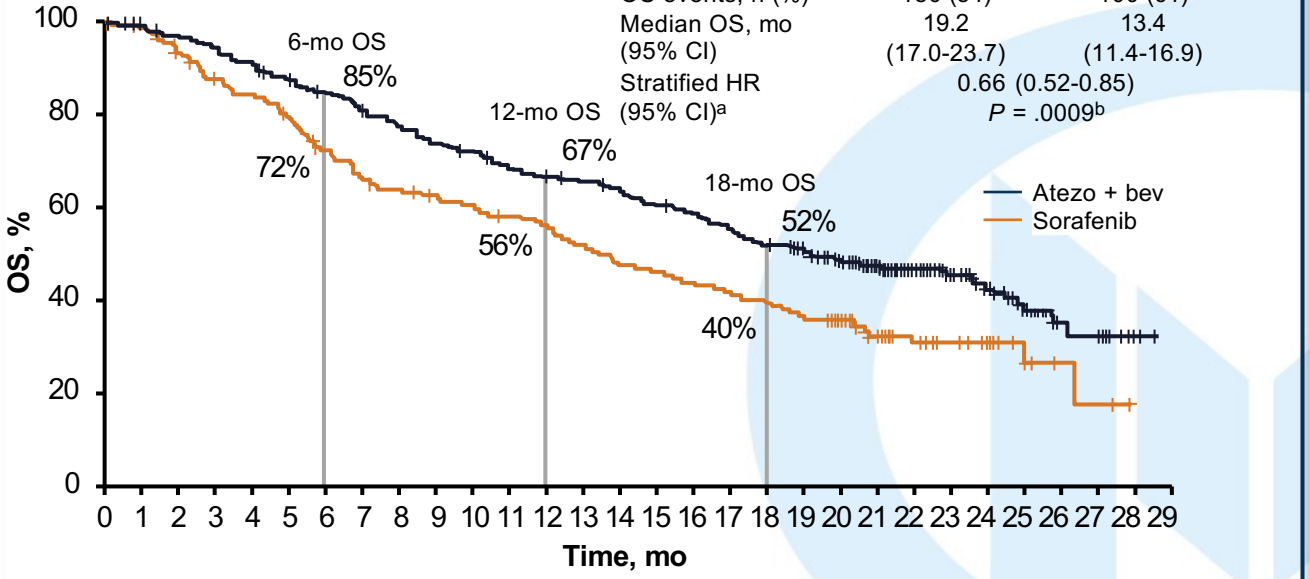
- Locally advanced or metastatic and/or unresectable HCC
- No prior systemic therapy for HCC
- ≥1 measurable untreated lesion
- ECOG PS 0-1
- Esophagogastroduodenoscopy (EGD) within 6 months
- Adequate hematologic and end-organ function
- Child–Pugh A

N = ~480

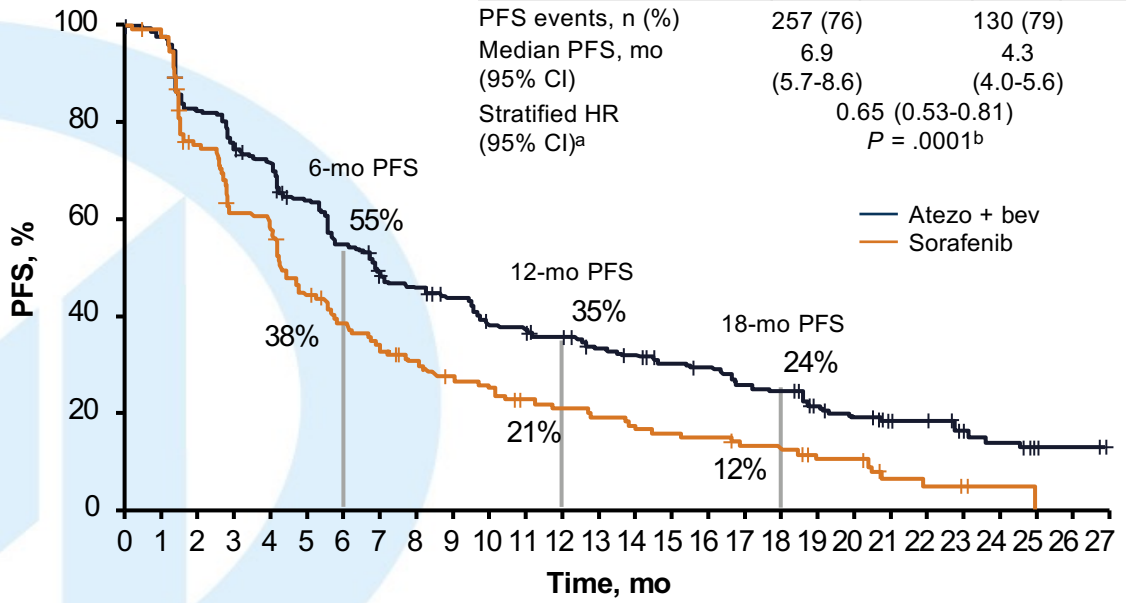


1. https://clinicaltrials.gov/ct2/show/NCT03434379.

Updated Results



Updated OS	Atezo + Bev (n = 336)	Sorafenib (n = 165)
OS events, n (%)	180 (54)	100 (61)
Median OS, mo (95% CI)	19.2 (17.0-23.7)	13.4 (11.4-16.9)
Stratified HR (95% CI)[a]	0.66 (0.52-0.85)	
	P = .0009[b]	



Updated PFS	Atezo + Bev (n = 336)	Sorafenib (n = 165)
PFS events, n (%)	257 (76)	130 (79)
Median PFS, mo (95% CI)	6.9 (5.7-8.6)	4.3 (4.0-5.6)
Stratified HR (95% CI)[a]	0.65 (0.53-0.81)	
	P = .0001[b]	

- **With an additional 12 months of follow-up**
  - ORR and CR per RECIST v1.1: 30% and 8% vs 11% and <1%
  - Safety and tolerability remains consistent with known safety profiles

Clinical cutoff: August 31, 2020; median follow-up: 15.6 mo.

[a] Stratification factors included in the Cox model are geographic region (Asia excluding Japan vs rest of the world), AFP level (<400 ng/mL vs ≥400 ng/mL) at baseline and MVI and/or EHS (Yes vs No) per interactive voice/web response system (IxRS). [b] *P* value for descriptive purposes only.

1. Finn RS et al. ASCO GI 2021. Abstract 267. 2. Finn RS et al. *N Engl J Med.* 2020;382:1894-1905. 3. Cheng AL et al. *J Hepatol*. 2022;76:862-873.

Phase 3 IMbrave150: Response Rate and Duration of Response[1,2]

Parameter	RECIST 1.1		HCC mRECIST	
	Atezo + Bev (n = 326)	Sorafenib (n = 159)	Atezo + Bev (n = 325)[a]	Sorafenib (n = 158)
Confirmed ORR, % (95% CI)	30 (25-35)	11 (7-17)	35 (30-41)	14 (9-20)
CR, n (%)	25 (8)	1 (<1)	39 (12)	4 (3)
PR, n (%)	72 (22)	17 (11)	76 (23)	18 (11)
SD, n (%)	144 (44)	69 (43)	121 (37)	65 (41)
PD, n (%)	63 (19)	40 (25)	65 (20)	40 (25)
DCR, n (%)	241 (74)	87 (55)	236 (72)	87 (55)
Ongoing response, n (%)	54 (56)	5 (28)	58 (50)	6 (27)
Median DOR, mo (95% CI)[b]	18.1 (14.6-NE)	14.9 (4.9-17.0)	16.3 (13.1-21.4)	12.6 (6.1-17.7)

Phase 3 IMbrave150: Response Rate and Duration of Response[1,2]

[a] Only patients with measurable disease at baseline were included in the analysis of ORR. [b] Only confirmed responders were included in the analysis of ORR and DOR. Data cutoff: August 31, 2020; median survival follow-up: 15.6 mo.

1. Finn RS et al. ASCO GI 2021. Abstract 267. 2. Finn RS et al. *N Engl J Med.* 2020;382:1894-1905.

Phase 3 HIMALAYA Trial: First-Line Durvalumab Plus Tremelimumab Versus Sorafenib[1]

- Unresectable HCC not eligible for LRTs
- BCLC stage B or C
- Child–Pugh A
- No prior systemic therapy

N ≈ 1,200

R

- Durvalumab 1,500 mg Q4W
- ~~Durvalumab 1,500 mg Q4W + Tremelimumab 75 mg x 4 dose~~
- Durvalumab 1,500 mg Q4W + Tremelimumab 300 mg x 1 dose (STRIDE)
- Sorafenib

- **Primary endpoint:** OS
- **Other endpoints:** TTP, PFS, ORR, DCR, DOR, and QOL

1. https://clinicaltrials.gov/ct2/show/NCT03298451.

MOFFITT MEDICAL GROUP

Phase 3 HIMALAYA Trial: Survival Benefits of First-Line Durvalumab Plus Tre… Sorafenib[1]

October 21, 2022: Tremelimumab + durvalumab FDA approved for adult patients with unresectable HCC

1. Abou-Alfa G et al. *NEJM Evid.* 2022;1(8).

Phase 3 HIMALAYA Trial: Response Rate and Duration of Response[1]

Parameter	STRIDE (n = 393)	Durvalumab (n = 389)	Sorafenib (n = 389)
Response, n (%)			
Objective[a]	79 (20.1)	66 (17.0)	20 (5.1)
CR	12 (3.1)	6 (1.5)	0
PR	67 (17.0)	60 (15.4)	20 (5.1)
SD, n (%)	157 (39.9)	147 (37.8)	216 (55.5)
DCR, n (%)	236 (60.1)	213 (54.8)	236 (60.7)
DOR, mo[b]			
Median	22.34	16.82	18.43
IQR	8.54-NR	7.43-NR	6.51-25.99
Time to response, mo			
Median	2.17	2.09	3.78
95% CI	1.84-3.98	1.87-3.98	1.89-8.44

[a] Best objective response by investigator assessment using RECIST v1.1. Responses were confirmed. [b] Time from the first documentation of a response until the date of progression, death, or the last evaluable RECIST assessment.

1. Abou-Alfa G et al. *NEJM Evid.* 2022;1(8).

AE Summary

Event, n (%)	STRIDE (n = 388)		Durvalumab (n = 388)		Sorafenib (n = 374)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
Diarrhea	103 (26.5)	17 (4.4)	58 (14.9)	6 (1.5)	167 (44.7)	16 (4.3)
Constipation	36 (9.3)	0	42 (10.8)	0	35 (9.4)	0
Abdominal pain	46 (11.9)	5 (1.3)	37 (9.5)	4 (1.0)	63 (16.8)	12 (3.2)
Nausea	47 (12.1)	0	37 (9.5)	0	53 (14.2)	0
Pruritus	89 (22.9)	0	56 (14.4)	0	24 (6.4)	1 (0.3)
Rash	87 (22.4)	6 (1.5)	40 (10.3)	1 (0.3)	51 (13.6)	4 (1.1)
Alopecia	2 (0.5)	0	5 (1.3)	0	53 (14.2)	0

1. Abou-Alfa G et al. *NEJM Evid.* 2022;1(8).

MOFFITT MEDICAL GROUP

Adjuvant Trials with Immunothe

- Multiple phase III studies ongoi
  - EMERALD-2: durvalu
    (NCT0384742
  - KEYN 867084)
  - (NCT03383458)
  - umab + bevacizumab
    8)

1/18/2023 Press release
Phase III study met its primary endpoint of
recurrence-free survival (RFS) at the
prespecified interim analysis.

1/18/2023 Phase III study met its primary endpoint of recurrence-free survival (RFS) at the prespecified interim analysis.

Conclusions

- Atezolizumab and bevacizumab or durvalumab Plus tremelimumab is the new SOC for advanced HCC, Child-Pugh class A cirrhosis.
- Sequential therapy is an evolving field, and maximizing options is our obligation.
- Combined therapy evaluation is still underway
- Integration of systemic therapy into early-stage disease/adjuvant setting may evolve based on ongoing clinical studies.

Thank You for Your Attention

Richard.kim@moffitt.org