2019 AIOM REVIEW: FROM CHICAGO TO VERONA

JUNE 14-15 2019

Verona,
Palazzo della Gran Guardia
Piazza Bra, 1

Aiom
Associazione Italiana di Oncologia Medica

UNIVERSITÀ DEGLI STUDI DI BARI ALDO MORO

Istituto Tumori Bari

GASTROINTESTINAL (NO COLORECTAL)

Moderatori: *G. Aprile, R. Labianca*

Highlights

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DISCLOSURES

FINANCIAL SUPPORT	*Sponsor*
None	

Highlights

- **Esophageal and gastric cancer**
  - ARTIST 2
  - KEYNOTE-062
- **PDAC**
  - APACT
  - POLO
- **BTC**
  - ABC-06
- **HCC**
  - SURF
  - KEYNOTE-240

Highlights

- **Esophageal and gastric cancer**
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ARTIST 2: Interim results of a phase III trial involving adjuvant chemotherapy and/or chemoradiotherapy after D2-gastrectomy in stage II/III gastric cancer (GC)

Se Hoon Park,[1] Dae Young Zhang,[2] Boram Han,[2] Jun Ho Ji,[3] Tae Gyu Kim,[3] Sung Yong Oh,[4] In Gyu Hwang,[5] Jung Hoon Kim,[6] Dong Bok Shin,[7] Do Hoon Lim,[1] Kyoung Mee Kim,[1] Ji Yeong An,[1] Min-Gew Choi,[1] Jun-Ho Lee,[1] Tae Sung Sohn,[1] Jae-Moon Bae,[1] Sung Kim,[1] Seung Tae Kim,[1] Jeeyun Lee[1] and Won Ki Kang[1]

[1]Sungkyunkwan University, Samsung Medical Center, Seoul, Korea; [2]Hallym University Medical Center, Anyang, Korea; [3]Samsung Changwon Hospital, Changwon, Korea; [4]Dong-A University, Busan, Korea; [5]Chung-Ang University, Seoul, Korea; [6]Gyeongsang National University, Jinju, Korea; [7]Gachon University Gil Hospital, Incheon, Korea.

Adjuvant chemoRadioTherapy In Stomach Tumor 2

- 900 patients with D2 resected gastric adenocarcinoma
- pStage II to III, LN+
- Stratified by (1) stage, (2) type of surgery (STG *v* TG), (3) Lauren classification

RANDOMIZATION

- Adjuvant Chemotherapy with S-1 (S-1 for one year)
- Adjuvant Chemotherapy with SOX (S-1/oxaliplatin for 6 mo)
- Adjuvant Chemoradiotherapy (SOX x2 → S-1/RT → SOX x4)

- Primary endpoint: DFS
- S-1: 40-60 mg bid 4/2 wks q6wks
- SOX: S-1 40 mg/m^2 bid 2/1 wks q3wks + oxaliplatin 130 mg/m^2 D1
- S-1/RT: S-1 40 mg bid daily concurrently with RT 45 Gy for 5 wks

1 *ClinicalTrials.gov*, NCT0176146

ARTIST 2 Secondary Endpoints and Statistics

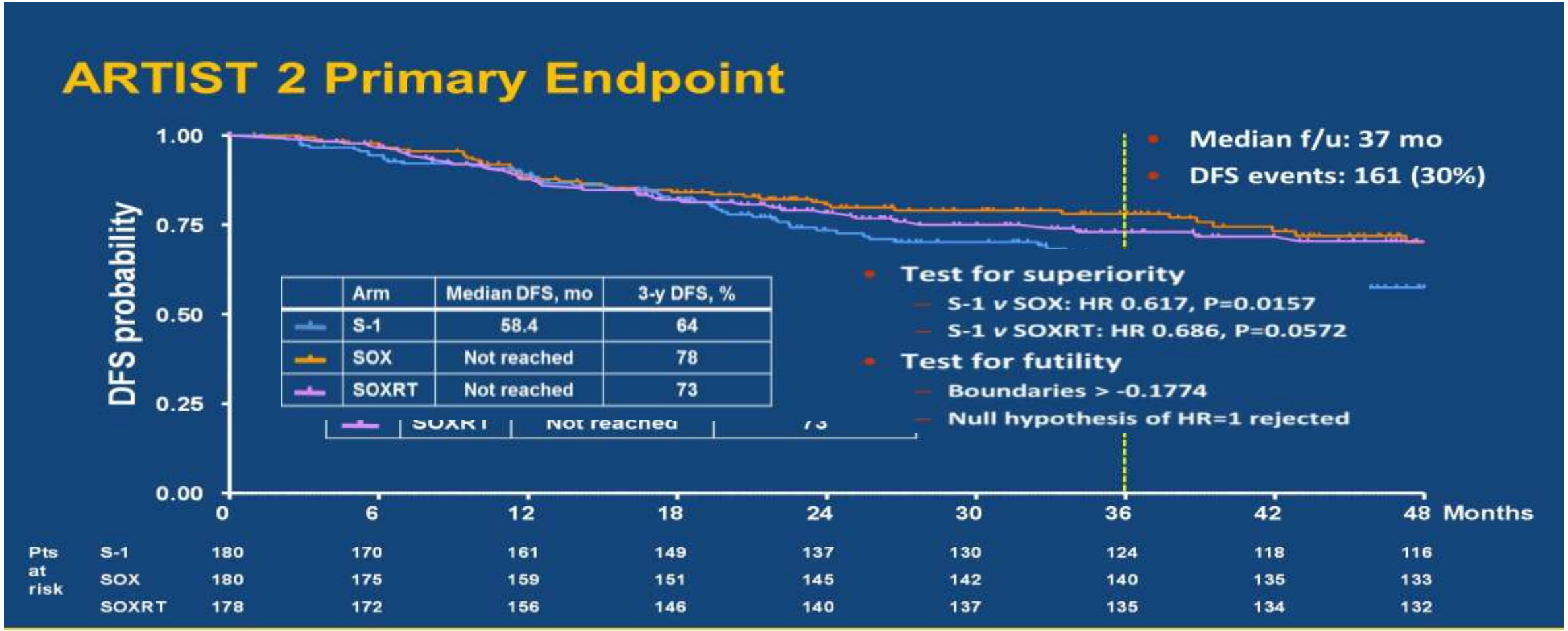
Secondary endpoints

- Safety
- Overall survival
- Patterns of recurrence
- Quality-of-life
- Biomarker studies

Statistical design

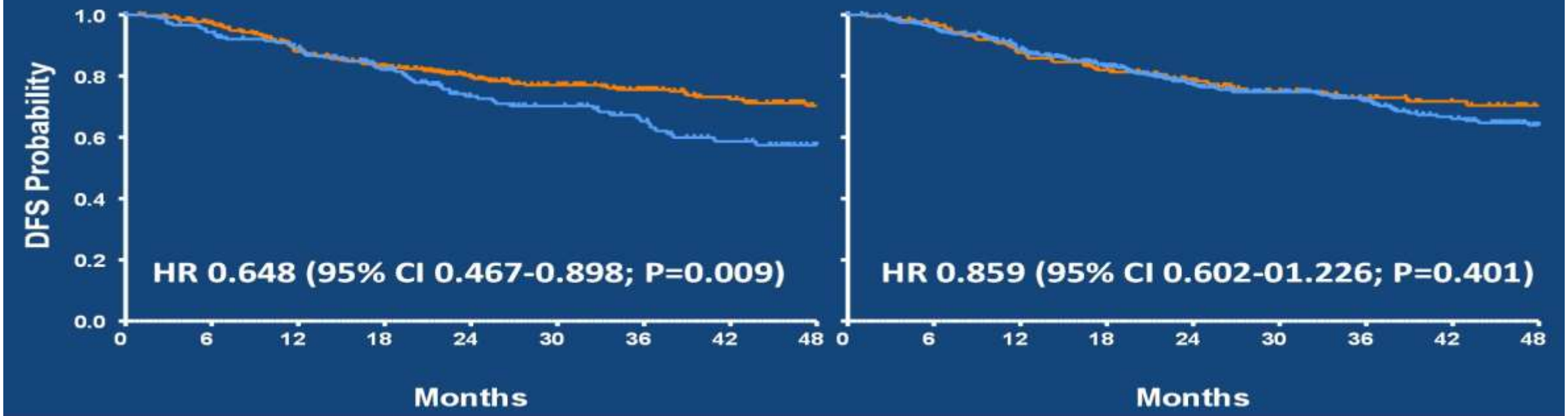
- Target of 226 DFS events (=855 eligible patients) provides 90% power to detect a HR of 0.67, assuming a 3-y DFS of,
  - 72.00% with S-1 arm
  - 80.33% with SOX or SOXRT arms
- Planned interim analyses
  - To test for both superiority and futility
  - By far, 5 interim analyses performed

ARTIST 2 Primary Endpoint



ARTIST 2 Subgroup Analysis of DFS

- S-1 *v* SOX/SOXRT
- S-1/SOX *v* SOXRT

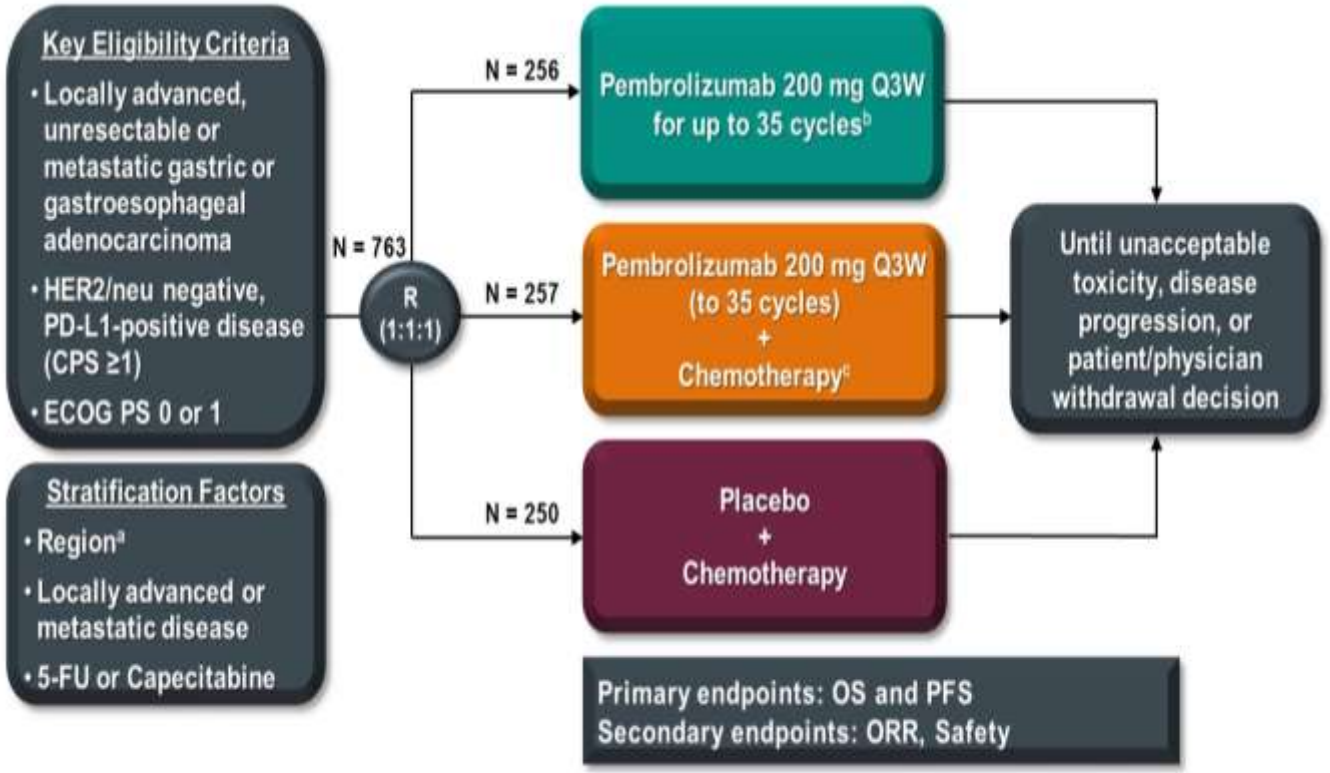


Conclusions

- In patients with curatively D2-resected, stage 2 or 3, node-positive GC, adjuvant SOX or SOXRT was effective in prolonging DFS, when compared to S-1 monotherapy.
  - Adjuvant S-1, SOX and SOXRT were well tolerated
  - No additional benefit with chemoradiotherapy
- Although the boundaries for stopping trial were not reached, the IDMC considered the results from this efficacy interim analysis sufficient to meet the endpoints of the ARTIST 2 trial.
  - As of Jan 2019, a total of 547 patients enrolled onto the ARTIST 2 trial
  - IDMC recommended stopping the trial
  - Prolonged follow-up data and secondary endpoints will be reported in the future.

Pembrolizumab With or Without Chemotherapy Versus Chemotherapy in Advanced G/GEJ Adenocarcinoma: The Phase 3, KEYNOTE-062 Study

J.Tabernero,[1] E. Van Cutsem,[2] Y.J Bang,[3] C.S. Fuchs,[4] L. Wyrwicz,[5] K.-W. Lee,[6] I. Kudaba,[7] M. Garrido,[8] H.C. Chung,[9] H. Castro,[10] W. Mansoor,[11] M.I. Braghiroli,[12] E. Goekkurt,[13] J. Chao,[14] Z.A. Wainberg,[15] U. Kher,[16] S. Shah,[16] S.P. Kang,[16] K. Shitara[17]



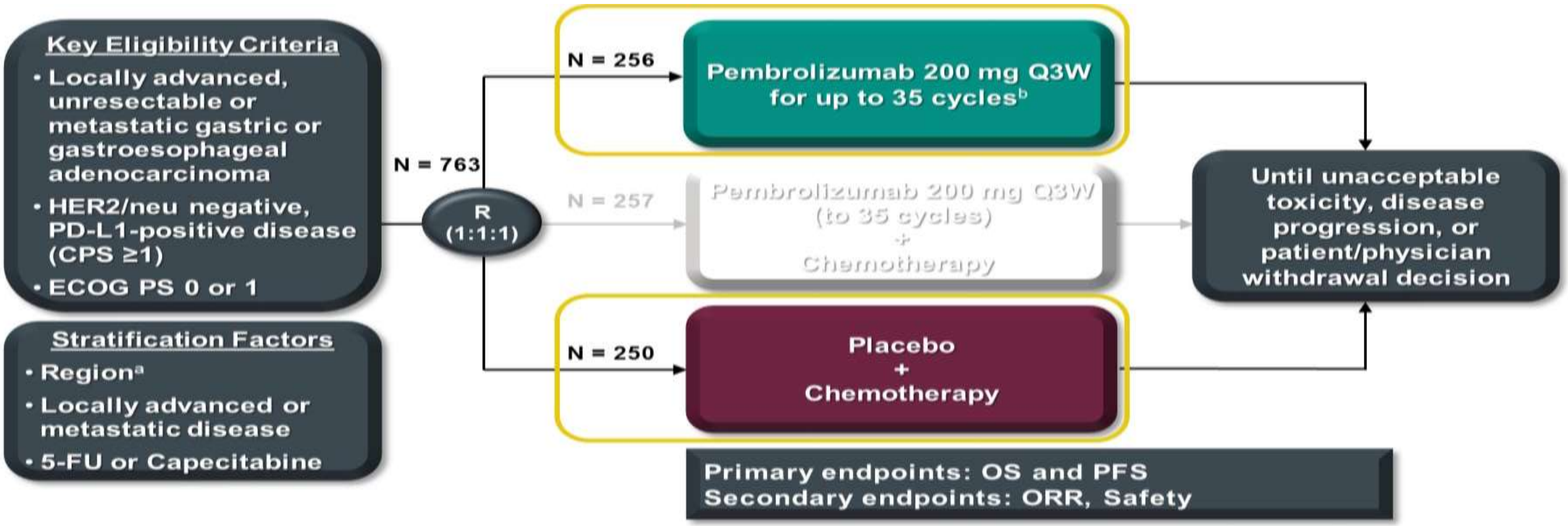
[a]EU/North America/Australia, Asia (South Korea, Hong Kong, Taiwan, Japan), Rest of World (including South America).
[b]Administration of pembrolizumab monotherapy was not blinded.
[c]Chemotherapy: Cisplatin 80 mg/m^2 Q3W + 5-FU 800 mg/m^2/d for 5 days Q3W or capecitabine BID d1-14 Q3W (Cisplatin may be capped at 6 cycles as per country guidelines).

Baseline Characteristics (CPS ≥1)

Characteristic, n (%)	Pembro N = 256	Pembro + Chemo N = 257	Chemo N = 250
Age, median (range), years	61.0 (20-83)	62.0 (22-83)	62.5 (23-87)
Male	180 (70)	195 (76)	179 (72)
ECOG PS 1	125 (49)	138 (54)	135 (54)
Metastatic disease	245 (96)	243 (95)	235 (94)
CPS ≥10	92 (36)	99 (39)	90 (36)
MSI-H	14 (5)	17 (7)	19 (8)
Region			
Europe/North America/Australia	148 (58)	148 (58)	147 (59)
Asia	62 (24)	64 (25)	61 (24)
Rest of World	46 (18)	45 (18)	42 (17)
Primary tumor location			
Stomach	176 (69)	170 (66)	181 (72)
GEJ	79 (31)	85 (33)	67 (27)
Backbone therapy[a]			
5-FU	-	98 (38)	95 (38)
Capecitabine	-	159 (62)	155 (62)

[a]Per stratification; Data cutoff: March 26, 2019.

KEYNOTE-062: P vs C



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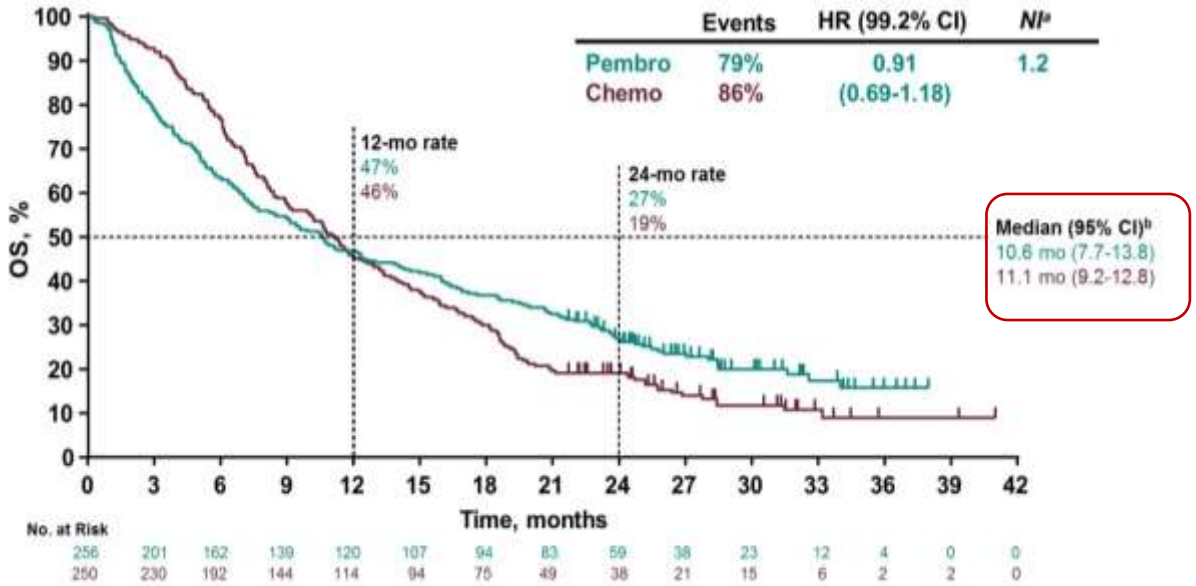
Overall Survival: P vs C

CPS ≥1



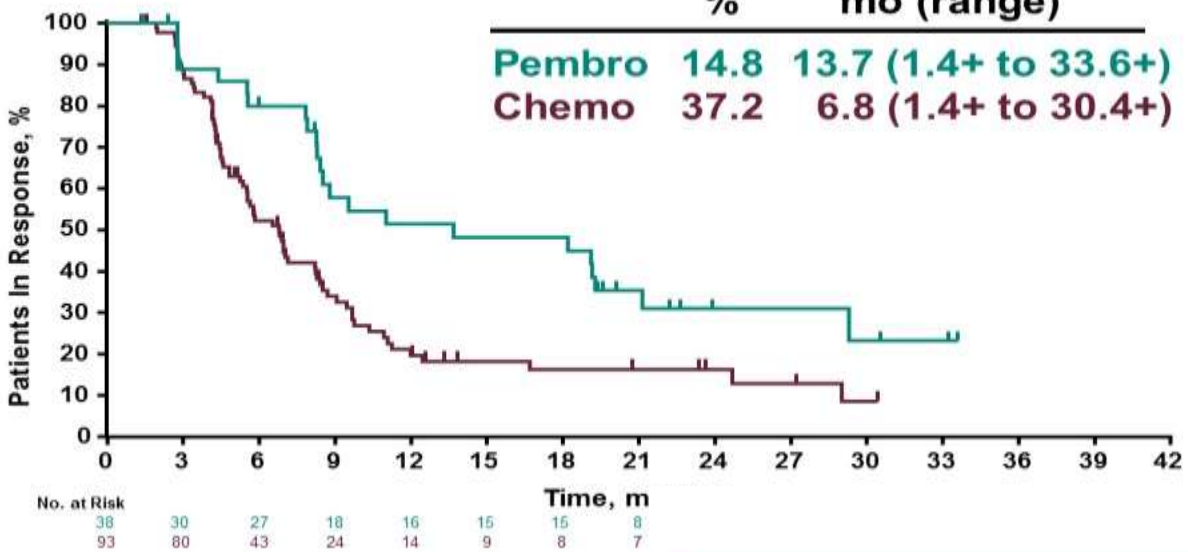
[a]NI, non-inferiority margin; [b]HR (95% CI) = 0.91 (0.74-1.10), $P = 0.162$ for superiority of P vs C; Data cutoff: March 26, 2019.

CPS ≥10

Response Summary: P vs C

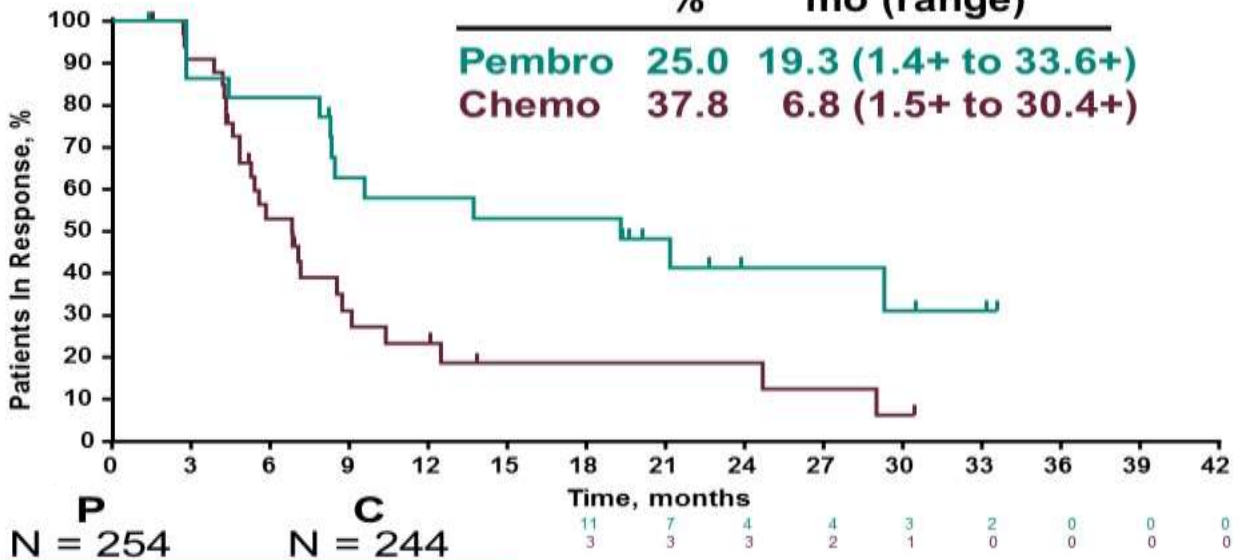
CPS ≥1

	ORR, %	Median DOR, mo (range)
Pembro	14.8	13.7 (1.4+ to 33.6+)
Chemo	37.2	6.8 (1.4+ to 30.4+)



CPS ≥10

	ORR, %	Median DOR, mo (range)
Pembro	25.0	19.3 (1.4+ to 33.6+)
Chemo	37.8	6.8 (1.5+ to 30.4+)



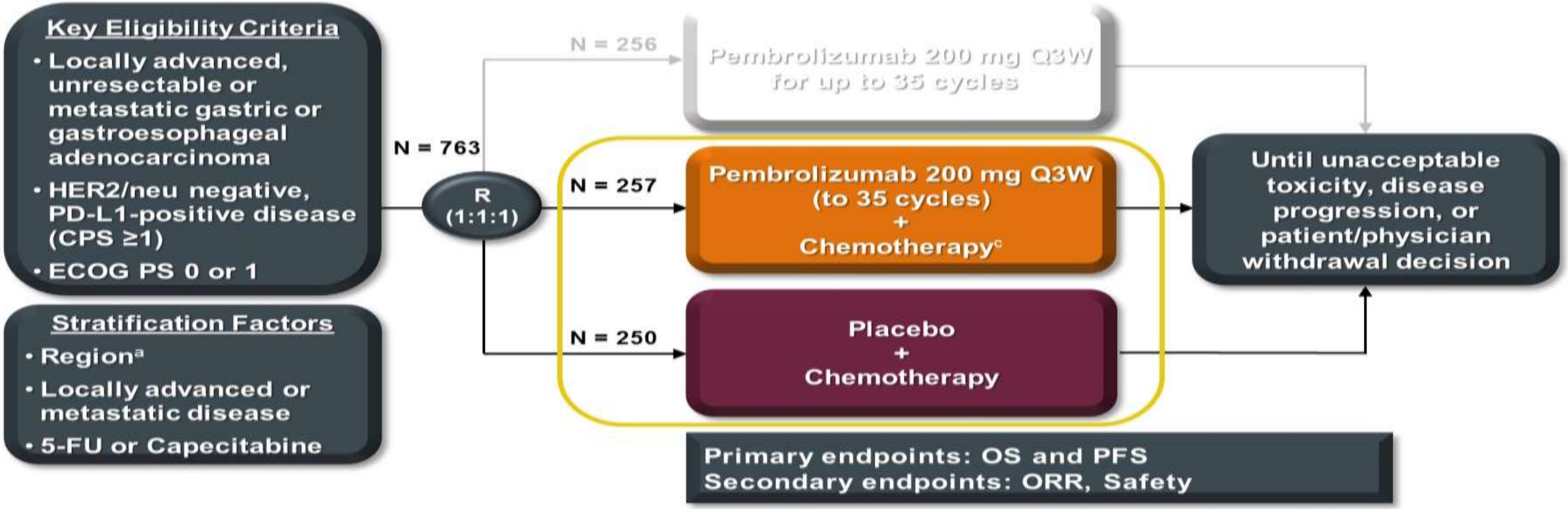
	P N = 254	C N = 244
Any	54%	92%
Grade 3-4	16%	68%

Response assessed per RECIST v1.1 by blinded independent central review. Data cutoff: March 26, 2019.

Summary: P vs C

- Pembrolizumab was noninferior to chemotherapy for OS in patients with advanced G/GEJ cancer with CPS ≥1
  - HR = 0.91; 99.2% CI, 0.69-1.18 (prespecified non-inferiority margin = 1.2)
- There was clinically meaningful improvement in OS with pembrolizumab vs chemotherapy in CPS ≥10
  - Median OS = 17.4 vs 10.8 mo (HR = 0.69; 95% CI, 0.49-0.97)
- Improved safety profile with pembrolizumab vs chemotherapy
  - Lower incidence of any-grade (54% vs 92%), grade 3-4 (16% vs 68%) treatment-related adverse events
  - No new toxicities observed with pembrolizumab vs chemotherapy

KEYNOTE-062: P+C vs C



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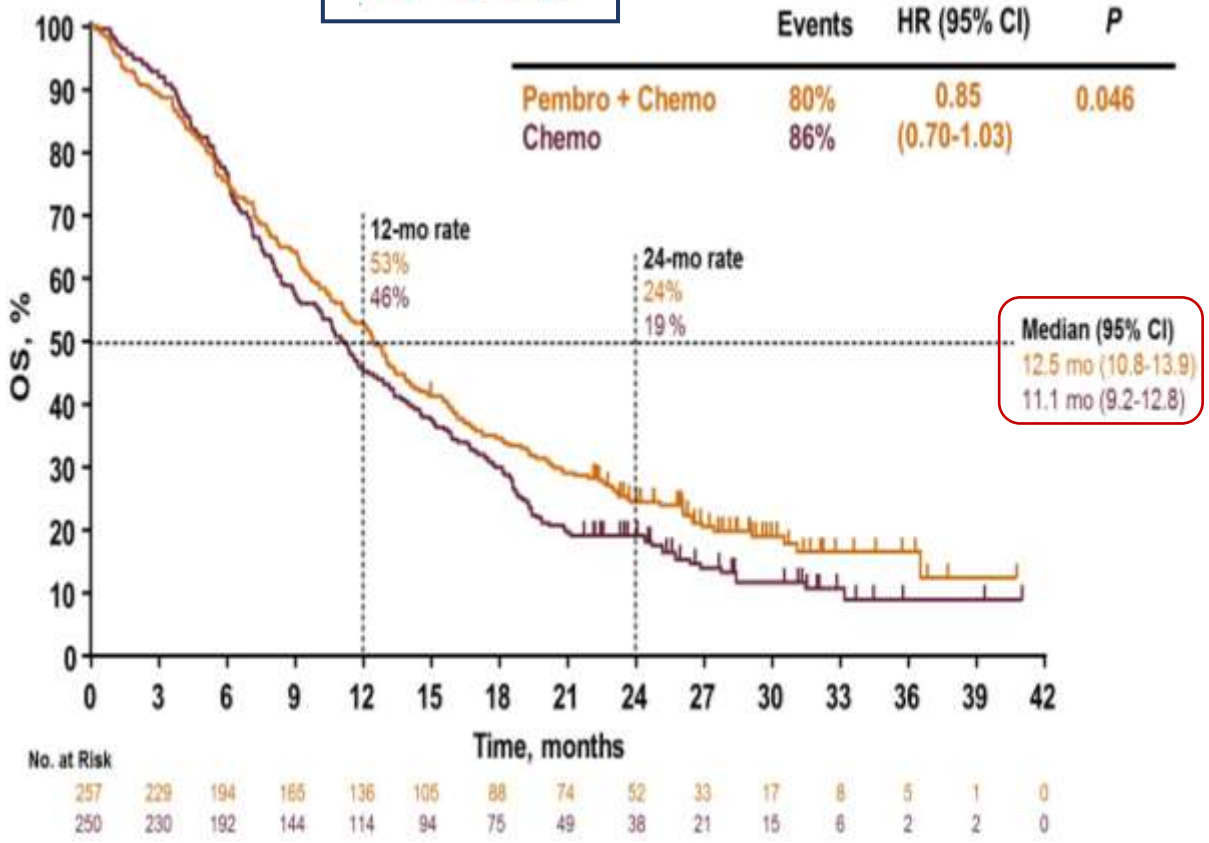
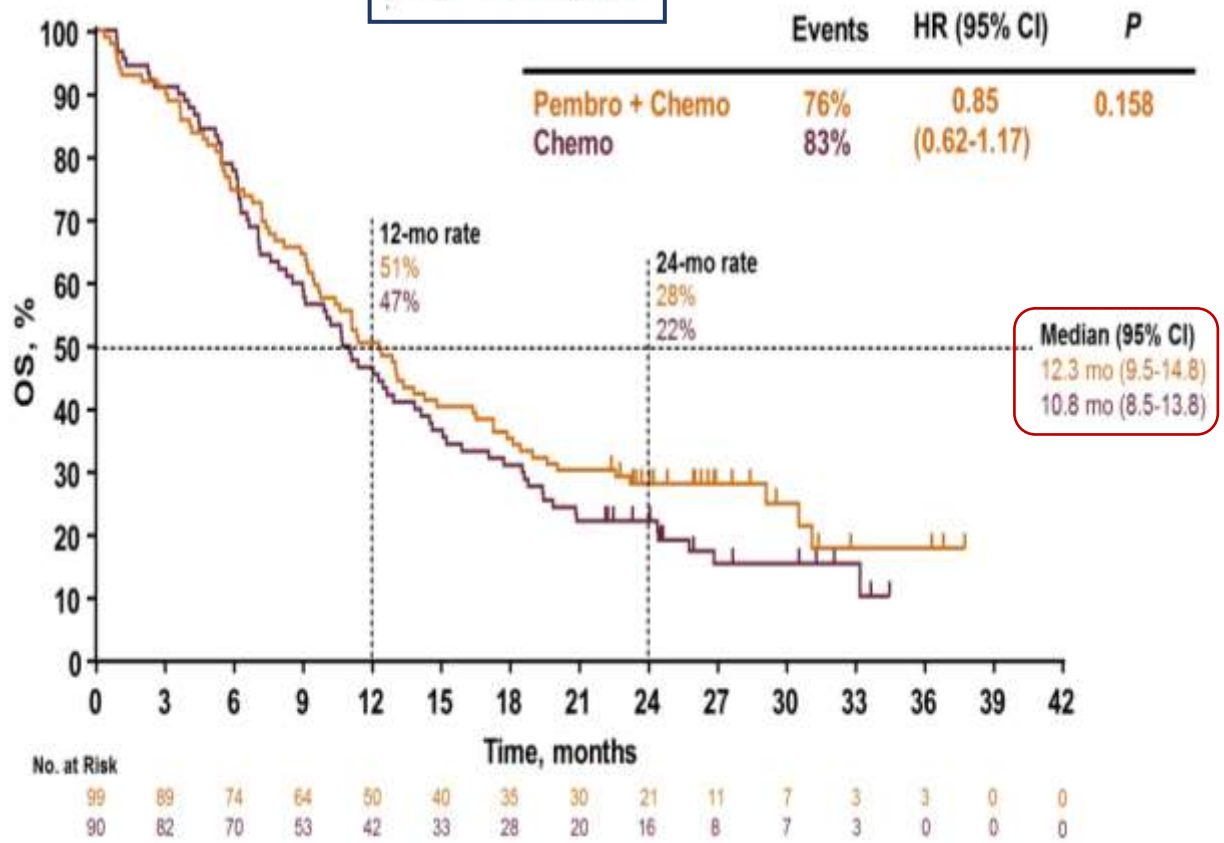
Overall Survival: P+C vs C

CPS ≥1

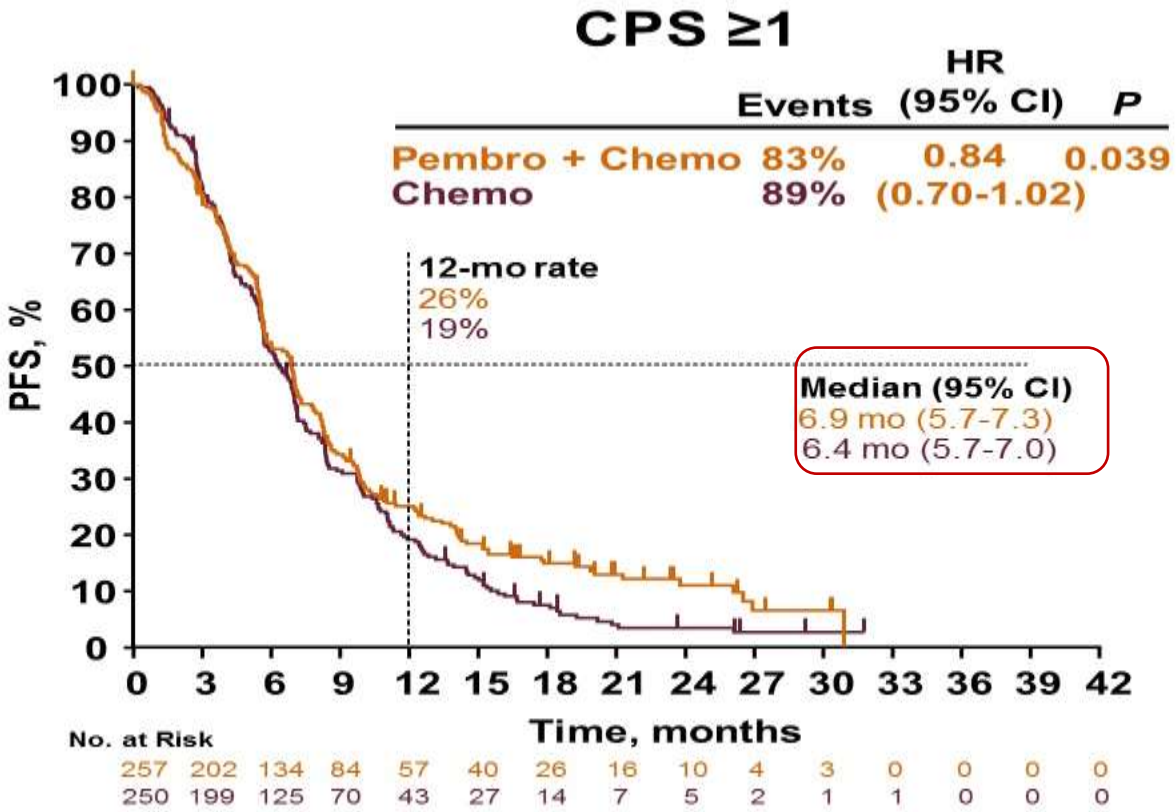


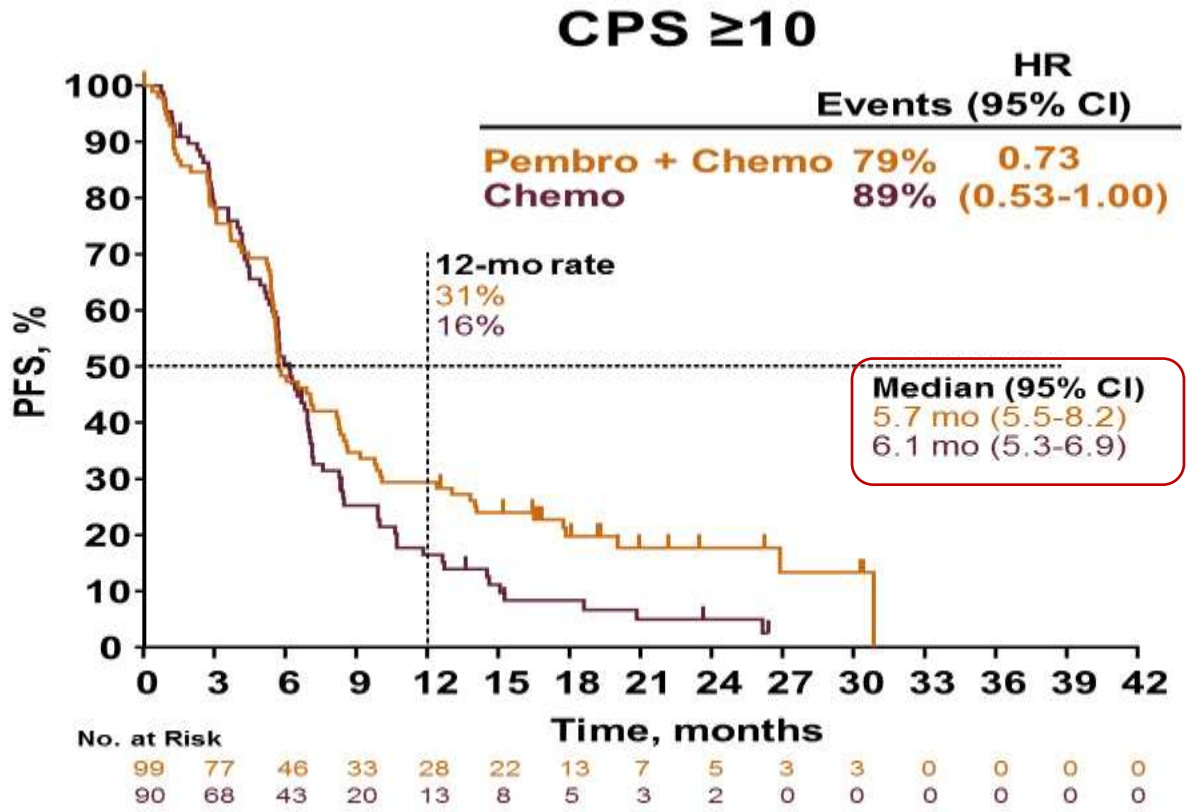
CPS ≥10



Data cutoff: March 26, 2019.

Progression-Free Survival: P+C vs C



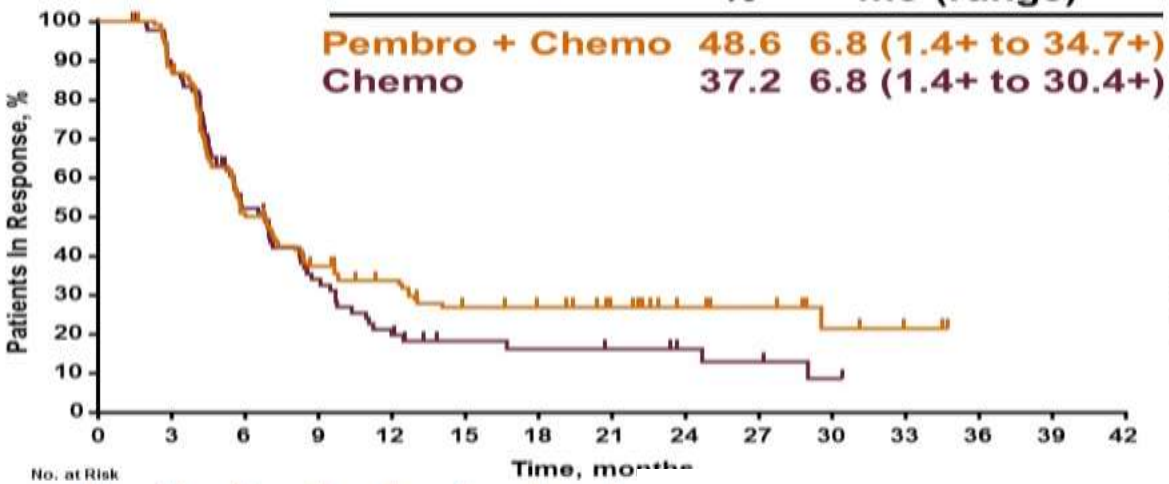


PFS assessed per RECIST v1.1 by blinded independent central review (final analysis of PFS occurred at IA2); Data cutoff: Sept 28, 2018.

Response Summary: P+C vs C

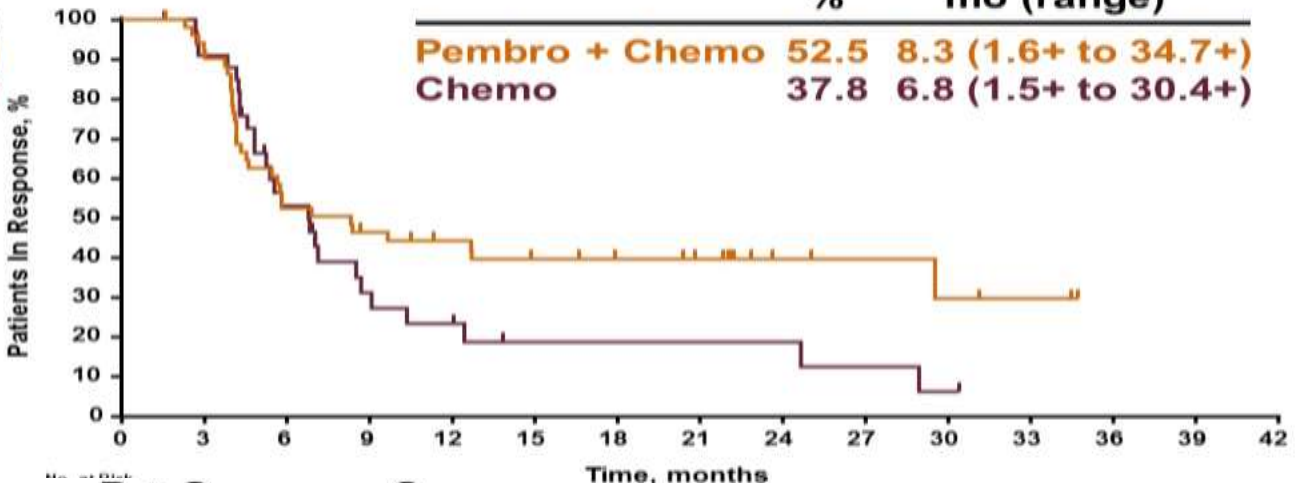
CPS ≥1

	ORR, %	Median DOR, mo (range)
Pembro + Chemo	48.6	6.8 (1.4+ to 34.7+)
Chemo	37.2	6.8 (1.4+ to 30.4+)



CPS ≥10

	ORR, %	Median DOR, mo (range)
Pembro + Chemo	52.5	8.3 (1.6+ to 34.7+)
Chemo	37.8	6.8 (1.5+ to 30.4+)



	P + C N = 250	C N = 244
Any	94%	92%
Grade 3-4	71%	68%

Response assessed per RECIST v1.1 by blinded independent central review; DOR, duration of response; Data cutoff: March 26, 2019.

Summary: P+C vs C

- Pembrolizumab + chemotherapy was not superior to chemotherapy for OS in patients with advanced G/GEJ cancer with CPS ≥1 (HR = 0.85; *P* = 0.046) or CPS ≥10 (HR = 0.85; *P* = 0.158) per pre-specified boundaries
  - Modest PFS and ORR benefit with pembrolizumab plus chemotherapy vs chemotherapy
- Comparable safety profile with pembrolizumab plus chemotherapy vs chemotherapy
  - Similar incidence of any-grade (94% vs 92%), grade 3-4 (71% vs 68%) treatment-related adverse events
  - No new toxicities observed with pembrolizumab plus chemotherapy

Highlights

- **Esophageal and gastric cancer**
  - ARTIST 2
  - KEYNOTE-062

  ✓*Adjuvant SOX or SOXRT vs S-1: ↑DFS;* ***no additional benefit with CTRT vs S-1/SOX***

  ✓*First-line P vs CT: similar benefit in OS for CPS≥1 and* ***favorable effect for CPS ≥10****; better tolerability profile for P; modest additional benefit of P+CT vs CT*
- **PDAC**
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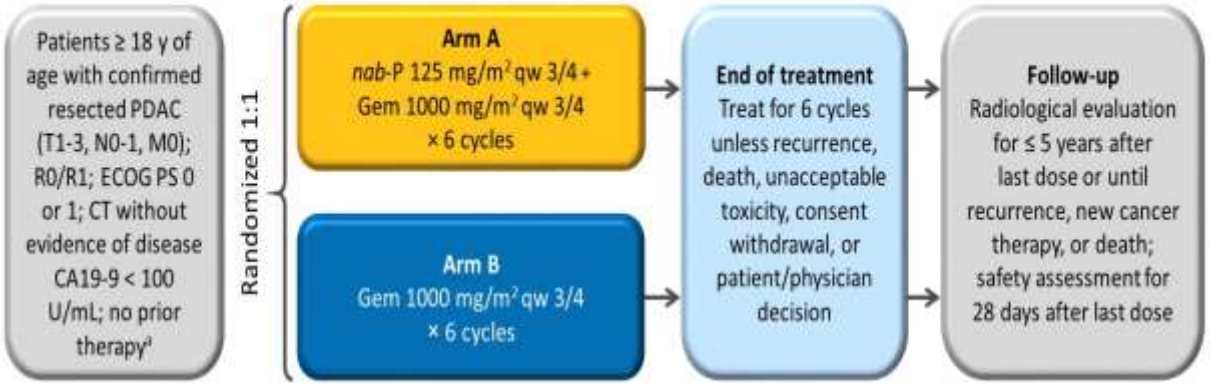
Abstract 4000

APACT: Phase III, Multicenter, International, Open-Label, Randomized Trial of Adjuvant *nab*®-Paclitaxel Plus Gemcitabine vs Gemcitabine for Surgically Resected Pancreatic Adenocarcinoma

Margaret A. Tempero,[1] Michele Reni,[2] Hanno Riess,[3] Uwe Pelzer,[3] Eileen M. O'Reilly,[4] Jordan Winter,[5] Do-Youn Oh,[6] Chung-Pin Li,[7] Giampaolo Tortora,[8,9] Heung-Moon Chang,[10] Charles D. Lopez,[11] Josep Tabernero,[12] Eric Van Cutsem,[13] Philip Philip,[14] David Goldstein,[15] Jordan D. Berlin,[16] Stefano Ferrara,[17] Mingyu Li,[17] Brian Lu,[17] Andrew Biankin[18]



- Patients were randomized as early as possible after adequate recovery from surgery but no later than 12 weeks after surgery
- Stratification factors: resection status (R0 vs R1); lymph node status (LN+ vs LN–); geographic region (North America, Europe and Australia vs Asia Pacific)

CA19-9, carbohydrate antigen 19-9; ECOG PS, Eastern Cooperative Oncology Group performance status; LN, lymph node; PDAC, pancreatic ductal adenocarcinoma; qw 3/4, the first 3 of 4 weeks; R0/R1, macroscopic complete resection with tumor-free/microscopically positive margin.
[a] Neoadjuvant, radiation, or systemic therapy.

- **Primary endopint**: *independently assessed DFS*
- **Secondary endpoints:** *OS, safety*
- **Exploratory endpoints**: *tumor and blood analysis, QoL*
- **Prespecified sensitivity analyses**: *investigator-assessed DFS*

PRESENTED AT: 2019 ASCO ANNUAL MEETING #ASCO19

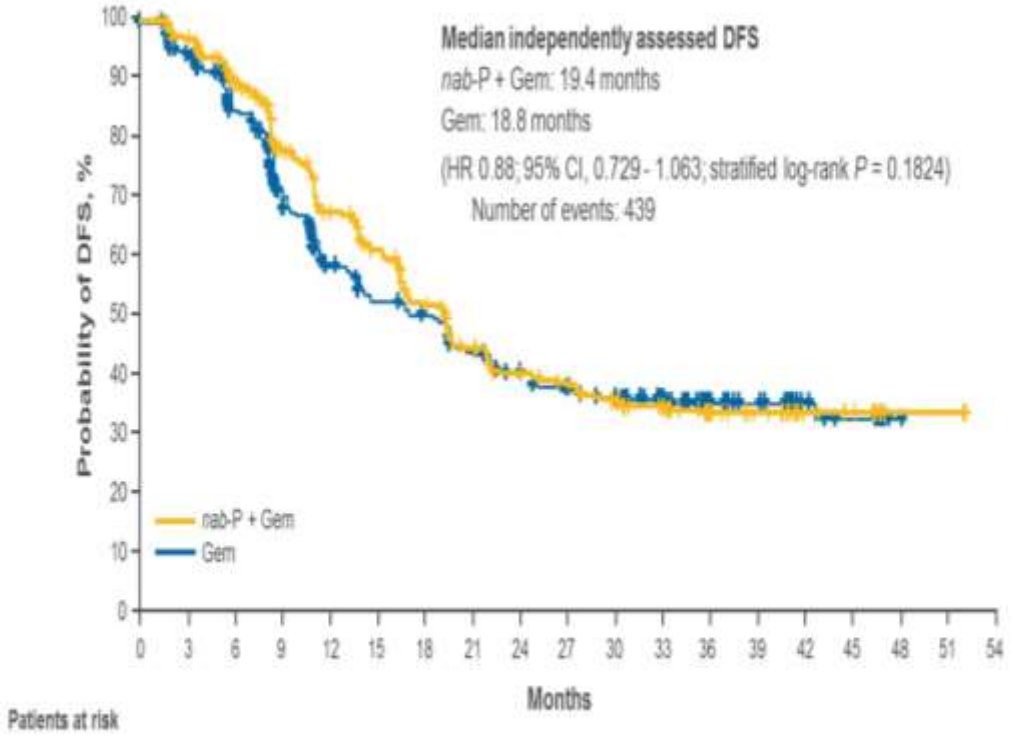
PRESENTED BY: Margaret Tempero

SELECTED BASELINE CHARACTERISTICS (ITT POPULATION)

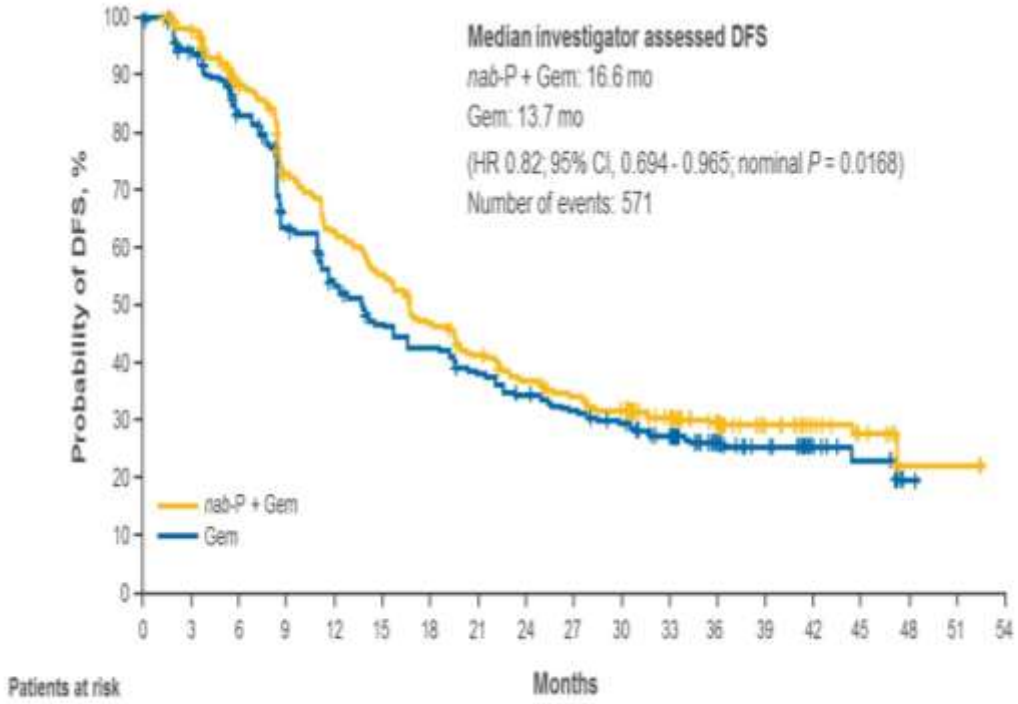
apact

Characteristic	*nab*-P + Gem (n = 432)	Gem (n = 434)	Total (N = 866)
Age, median (range), years	64.0 (34 - 83)	64.0 (38 - 86)	64.0 (34 - 86)
Sex, male, n (%)	228 (53)	253 (58)	481 (56)
ECOG PS, n (%)			
0	252 (58)	268 (62)	520 (60)
1	180 (42)	166 (38)	346 (40)
Resection status, n (%)			
R0 (tumor-free margin)	327 (76)	334 (77)	661 (76)
R1 (microscopically positive margin)	105 (24)	100 (23)	205 (24)
Nodal status, n (%)			
Lymph node negative	121 (28)	122 (28)	243 (28)
Lymph node positive	311 (72)	312 (72)	623 (72)
Baseline CA19-9			
n	423	429	852
Median, U/mL	14.31	12.90	13.65
Tumor grade, n (%)			
Well differentiated	49 (11)	55 (13)	104 (12)
Moderately differentiated	264 (61)	241 (56)	505 (58)
Poorly differentiated	101 (23)	115 (26)	216 (25)
Undifferentiated	1 (< 1)	2 (< 1)	3 (< 1)
Other/unknown	17 (4)	21 (5)	38 (4)

PRIMARY ENDPOINT:
INDEPENDENTLY ASSESSED DFS (ITT POPULATION)

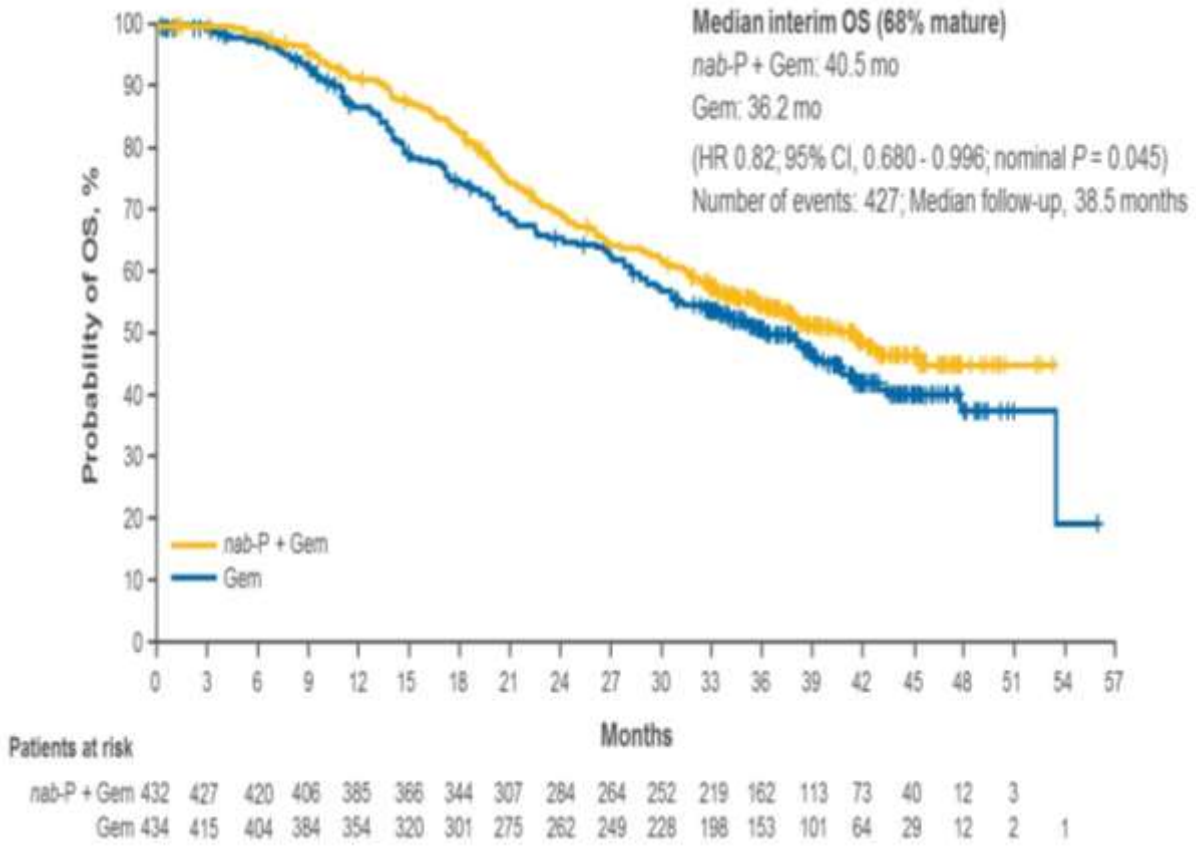


PRESPECIFIED SENSITIVITY ANALYSIS:
INVESTIGATOR ASSESSED DFS



- The concordance rate between disease recurrence by independent radiological review and by investigator review was 77%

SECONDARY ENDPOINTS: INTERIM OS, SAFETY



Event, n (%)	*nab*-P + Gem	Gem
Safety summary	**(n = 429)**	**(n = 423)**
Patients with ≥ 1 grade ≥ 3 TEAE	371 (86)	286 (68)
Patients with ≥ 1 serious TEAE	176 (41)	96 (23)
Grade ≥ 3 hematologic TEAEs (occurring in ≥ 5% of patients in either treatment arm)		
Any hematologic TEAEs	250 (58)	204 (48)
Neutropenia	212 (49)	184 (43)
Anemia	63 (15)	33 (8)
Leukopenia	36 (8)	20 (5)
Febrile neutropenia	21 (5)	4 (1)
Grade ≥ 3 nonhematologic TEAEs (occurring in ≥ 5% of patients in either treatment arm)		
Peripheral neuropathy (SMQ)[a]	64 (15)	0
Fatigue	43 (10)	13 (3)
Diarrhea	22 (5)	4 (1)
Asthenia	21 (5)	8 (2)
Hypertension	17 (4)	27 (6)

- TEAEs led to death in 2 patients in each arm
- Ten patients (16%) with grade ≥ 3 peripheral neuropathy improved to grade ≤ 1
- The incidence of TEAEs of special interest—gastrointestinal events, hepatic toxicity, and sepsis—was generally low in both arms

PRESENTED BY: Margaret Tempero

CONCLUSIONS (APACT)

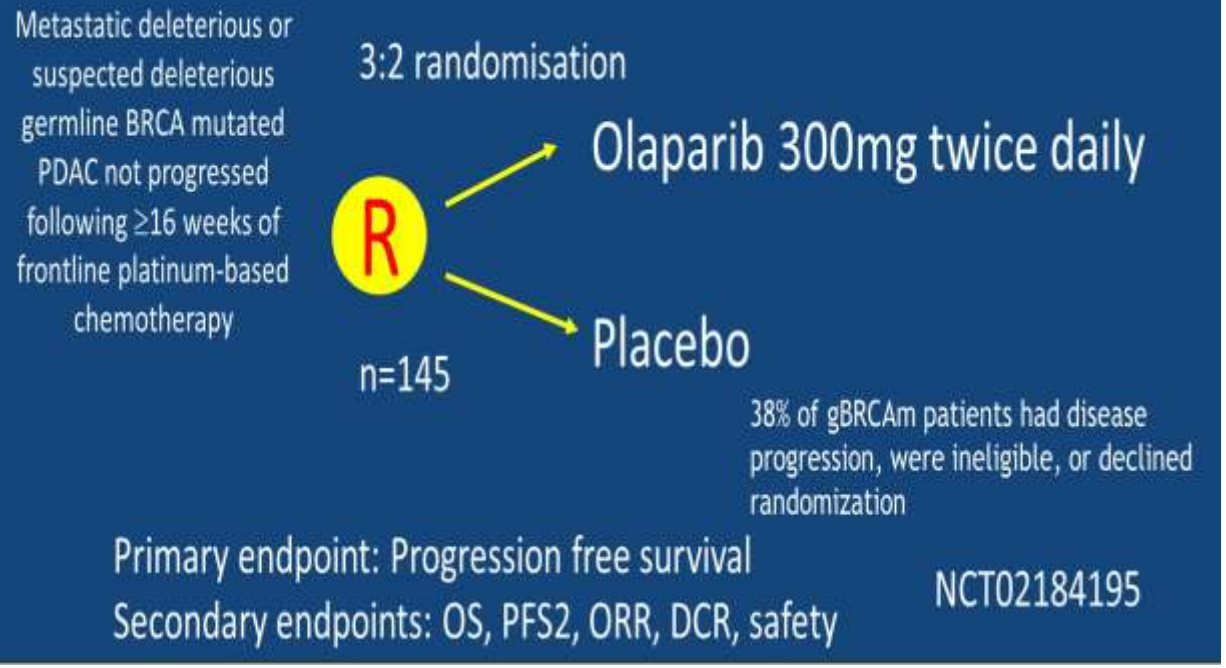
- The primary endpoint of independently assessed DFS was not met
  - APACT is the first trial of adjuvant therapy in PC to use independently assessed DFS
  - Investigator-assessed DFS aligned more closely with OS results than independently assessed DFS
- Consistent with other trials, the survival with Gem monotherapy was markedly improved, suggesting better patient selection and benefit from treatment with contemporary therapies upon recurrence of disease
- The *nab*-P + Gem safety profile was consistent with what was observed in the MPACT trial[1]
- Results of ongoing biomarker and QoL analyses will be presented at future meetings
- Final OS data will clarify the role for adjuvant *nab*-P + Gem in resected PC
  - Continued investigation of the regimen (eg, in patients with positive lymph nodes or R1 resection as well as those who are not candidates for FOLFIRINOX) is warranted

1. Von Hoff DD, et al. *N Engl J Med.* 2013; 369:1691-1703.

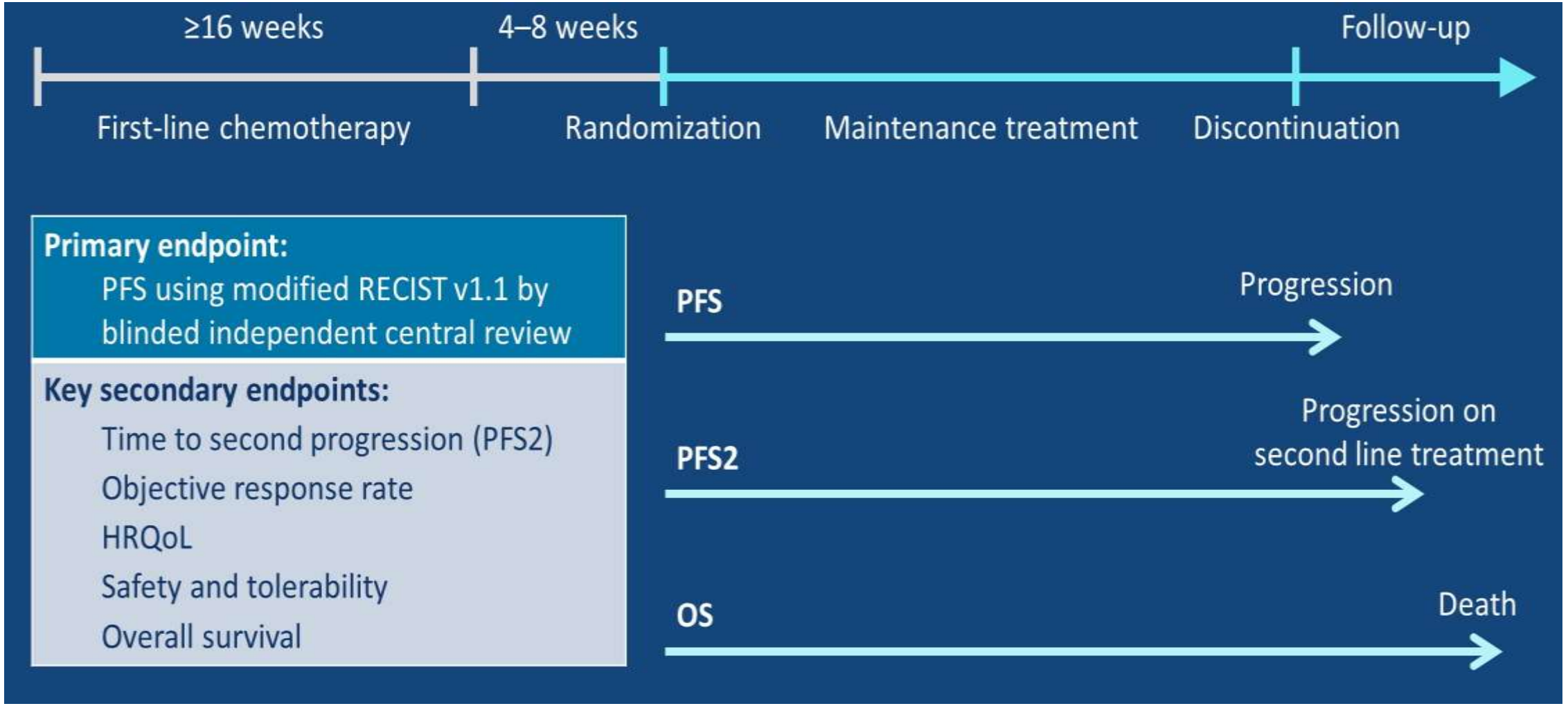
Olaparib as maintenance treatment following first-line platinum-based chemotherapy in patients with a germline BRCA mutation and metastatic pancreatic cancer: Phase III POLO trial

Hedy L Kindler,[1] Pascal Hammel,[2] Michele Reni,[3] Eric Van Cutsem,[4] Teresa Macarulla,[5] Michael J Hall,[6] Joon Oh Park,[7] Daniel Hochhauser,[8] Dirk Arnold,[9] Do-Youn Oh,[10] Anke Reinacher-Schick,[11] Giampaolo Tortora,[12] Hana Algül,[13] Eileen M O'Reilly,[14] David McGuinness,[15] Karen Y Cui,[16] Katia Schlienger,[17] Gershon Y Locker,[16] Talia Golan[18]

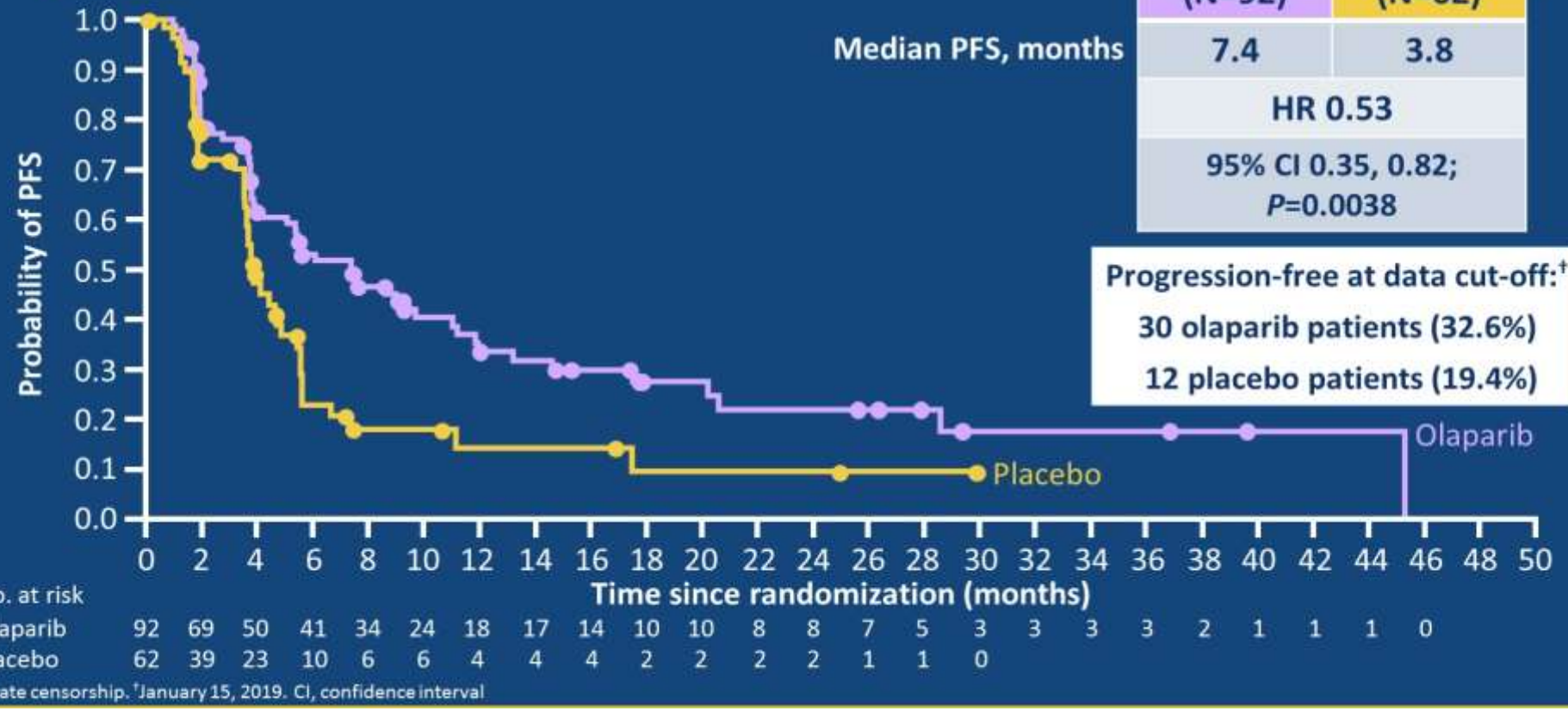
POLO: Phase III maintenance RCT for olaparib in BCRA mutated metastatic PDAC after platinum-based chemotherapy



STUDY ENDPOINTS



Primary endpoint: PFS by blinded independent central review*

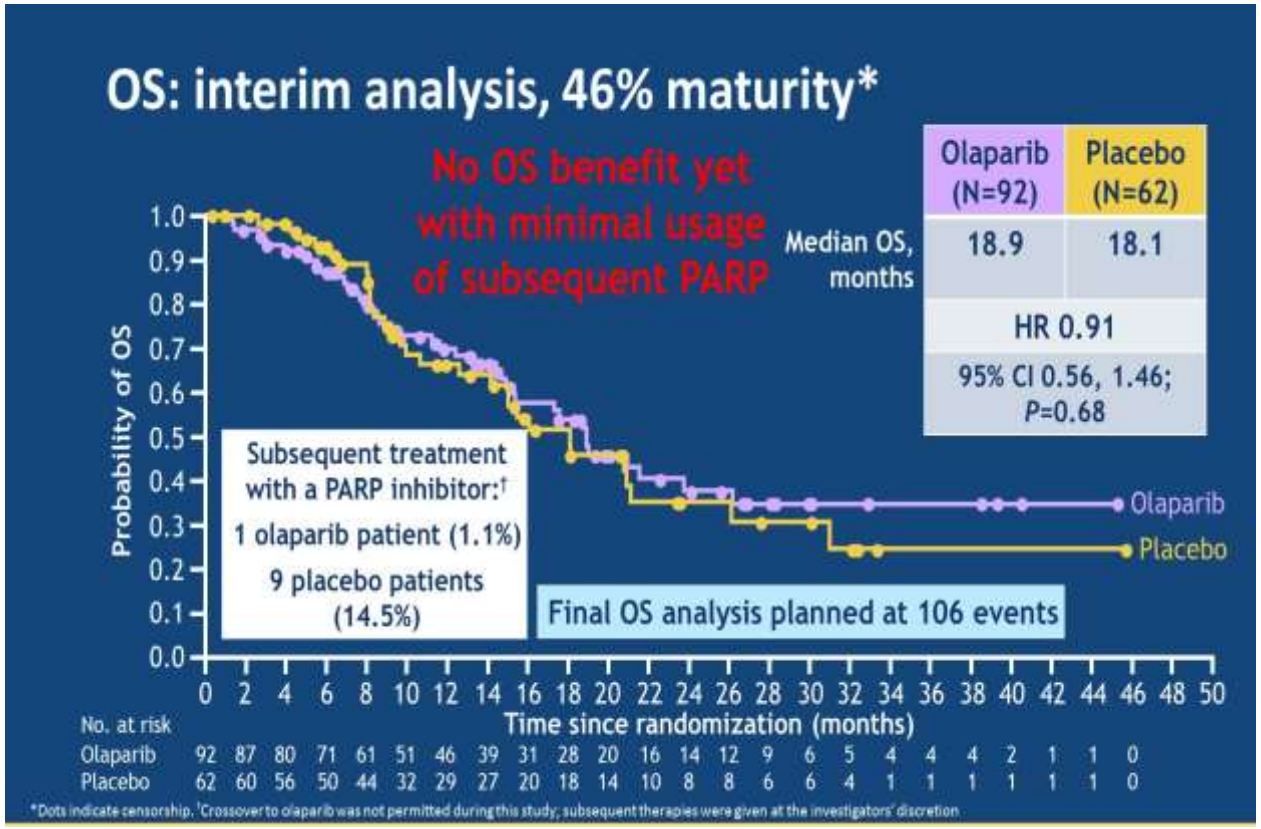


	Olaparib (N=92)	Placebo (N=62)
Median PFS, months	7.4	3.8
HR 0.53		
95% CI 0.35, 0.82; *P*=0.0038		

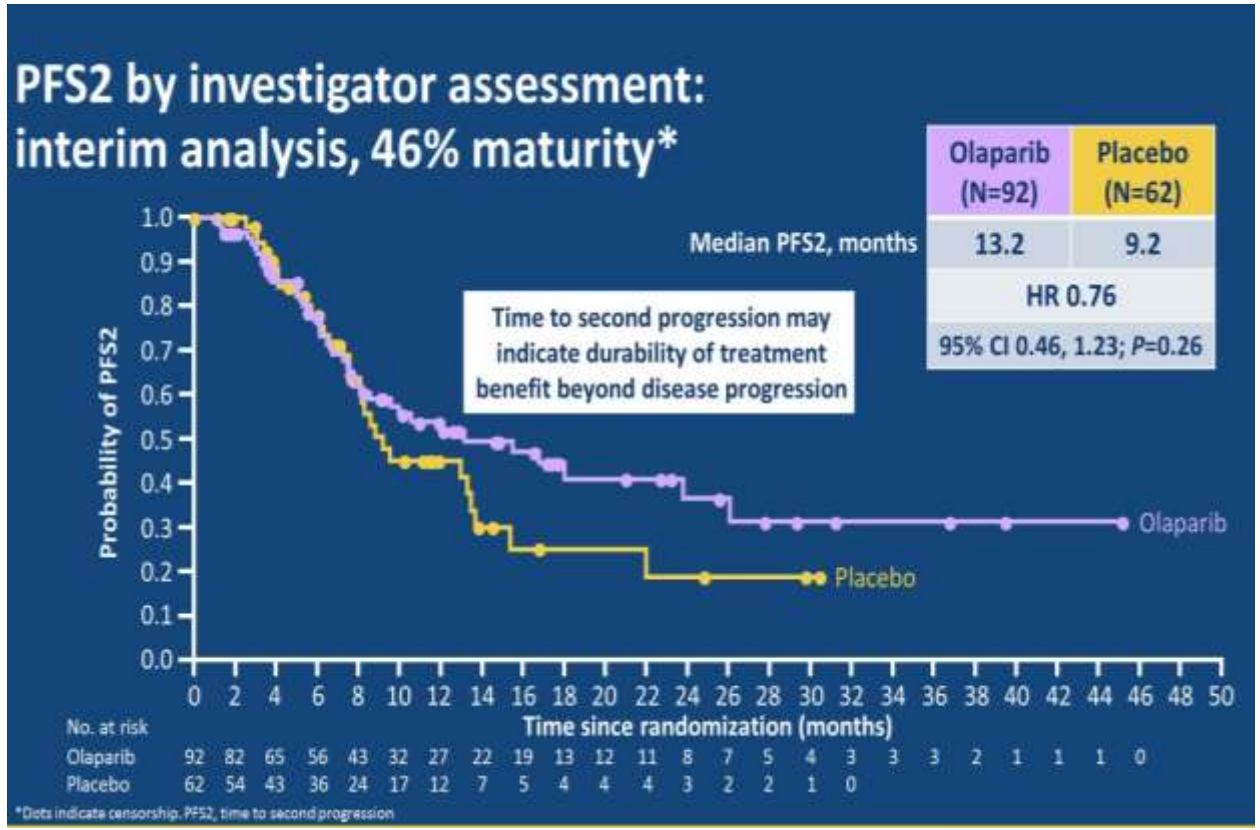
Progression-free at data cut-off:†
30 olaparib patients (32.6%)
12 placebo patients (19.4%)

*Dots indicate censorship. †January 15, 2019. CI, confidence interval

OS: interim analysis, 46% maturity*



PFS2 by investigator assessment: interim analysis, 46% maturity*



Conclusions

This article was published on June 2, 2019, at NEJM.org.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Maintenance Olaparib for Germline *BRCA*-Mutated Metastatic Pancreatic Cancer

Talia Golan, M.D., Pascal Hammel, M.D., Ph.D., Michele Reni, M.D., Eric Van Cutsem, M.D., Ph.D., Teresa Macarulla, M.D., Ph.D., Michael J. Hall, M.D., Joon-Oh Park, M.D., Ph.D., Daniel Hochhauser, M.D., Ph.D., Dirk Arnold, M.D., Ph.D., Do-Youn Oh, M.D., Ph.D., Anke Reinacher-Schick, M.D., Ph.D., Giampaolo Tortora, M.D., Ph.D., Hana Algül, M.D., Ph.D., M.P.H., Eileen M. O'Reilly, M.D., David McGuinness, M.Sc., Karen Y. Cui, M.D., Ph.D., Katia Schlienger, M.D., Ph.D., Gershon Y. Locker, M.D., and Hedy L. Kindler, M.D.

Highlights

❖ **Esophageal and gastric cancer**

- ARTIST 2
- KEYNOTE-062

✓*Adjuvant SOX or SOXRT vs S-1:* ↑*DFS;* ***no additional benefit with CTRT vs S-1/SOX***

✓*First-line P vs CT: similar benefit in OS for CPS≥1 and* ***favorable effect for CPS ≥10****; better tolerability profile for P; modest additional benefit of P+CT vs CT*

❖ **PDAC**

- APACT
- POLO

✓*Adjuvant Gem+Abraxane vs Gem:* ***indipendently assessed DFS was not met****; modest additional benefit in interim OS for Gem+Abraxane*

✓***Maintance olaparib improved PFS in BRCAm metastatic PDAC*** *whose disease had not progressed durimg platinum-based CT*

❖ **BTC**

- ABC-06

❖ **HCC**

- SURF
- KEYNOTE-240

Highlights

- **Esophageal and gastric cancer**
  - ARTIST 2
  - KEYNOTE-062

  ✓***Adjuvant SOX or SOXRT vs S-1:*** *DFS; no additional benefit with CTRT vs S-1/SOX*

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- **BTC**
  - ABC-06

- **HCC**
  - SURF
  - KEYNOTE-240

ABC-06 | A randomised phase III, multi-centre, open-label study of Active Symptom Control (ASC) alone or ASC with oxaliplatin / 5-FU chemotherapy (ASC + mFOLFOX) for patients with locally advanced / metastatic biliary tract cancers (ABC) previously-treated with cisplatin/gemcitabine (CisGem) chemotherapy

Angela Lamarca, Daniel H Palmer, Harpreet S Wasan, Paul J Ross, Yuk Ting Ma, Arvind Arora, Stephen Falk, Roopinder Gillmore, Jonathan Wadsley, Kinnari Patel, Alan Anthoney, Anthony Maraveyas, Justin S Waters, Claire Hobbs, Safia Barber, David Ryder, John Ramage, Linda M Davies, John A Bridgewater, Juan W Valle

ABC-06 study design

Phase III, randomised, open-label

Inclusion criteria

- Histo/cytologically verified advanced BTC
- ECOG performance score 0-1
- Progression after 1st-line CisGem
- Max 6 weeks progression to randomisation
- Adequate haematological, renal & hepatic function

R

1:1

Arm A

Active Symptom Control (ASC)

- May include: biliary drainage, antibiotics, analgesia, steroids, anti-emetics etc
- 4-weekly clinical review

Arm B

Active Symptom Control + mFOLFOX

- Chemotherapy every 14 days for up to 12 cycles
- Day 1: Oxaliplatin 85mg/m^2, L-folinic acid 175 mg (or folinic acid 350 mg), 5 FU 400 mg/m^2 (bolus), 5 FU 2400 mg/m^2 46 hours continuous infusion
- 4-weekly clinical review after chemotherapy
- 3-monthly radiological assessment

Follow up

- **Overall survival** = primary end-point
- Until death or until completion of 12 months after enrolment of the final patient (whichever happened first)

Stratification factors

- **Platinum sensitivity** (yes vs. no; determined from first-line CisGem*)
- **Serum albumin** (<35 vs. ≥35 g/L)
- **Stage** (locally advanced vs. metastatic disease)

*determined from first-line CisGem: sensitive (progression after three months (90 days) of day 1 of the last cycle of 1st-line CisGem), refractory (progression during 1st line CisGem), resistant (progression within the first three months (90 days) after completion of day 1 of the last cycle of 1st line CisGem). CisGem: cisplatin and gemcitabine; BTC: biliary tract cancer; ECOG: Eastern Cooperative Oncology Group

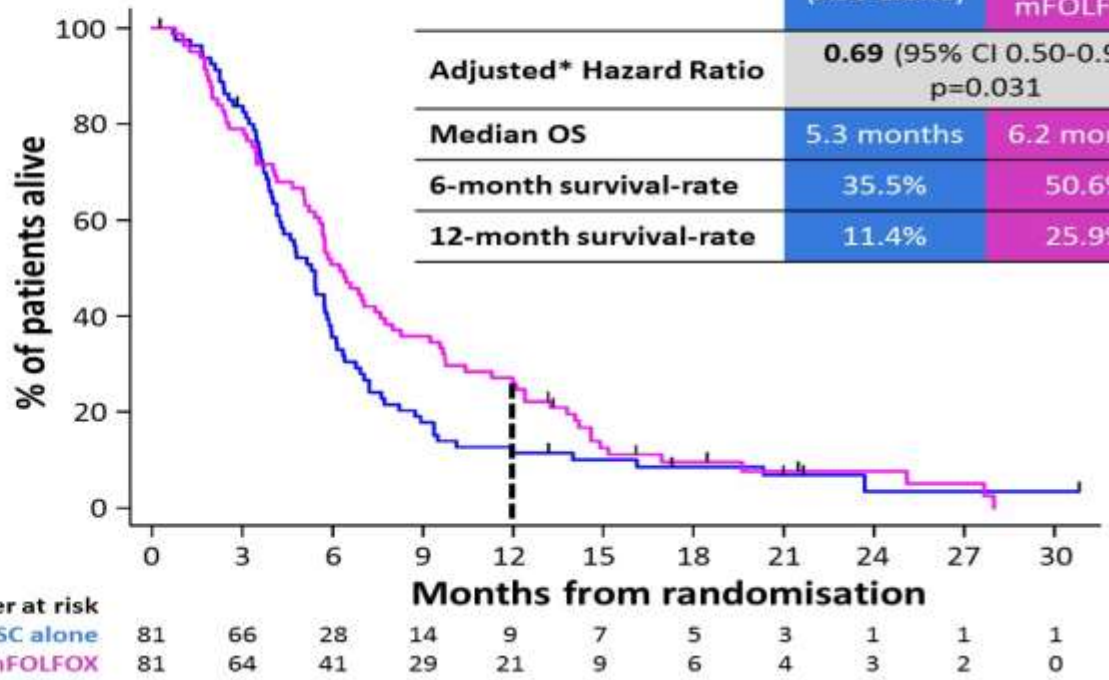
Primary end-point: Overall Survival (ITT)

- The **primary end-point was met**: adjusted* HR was 0.69 (95% CI 0.50-0.97; p=0.031) for OS in favour of ASC + mFOLFOX arm (vs ASC)

- No marked evidence was identified against the key proportional hazards assumption**; which confirmed the validity of using the Cox Regression analysis

*adjusted for platinum sensitivity, albumin and stage
**proportional hazards assumption test p-value 0.6521
ITT: intention-to-treat analysis; ASC: active symptom control

Overall survival by trial arm

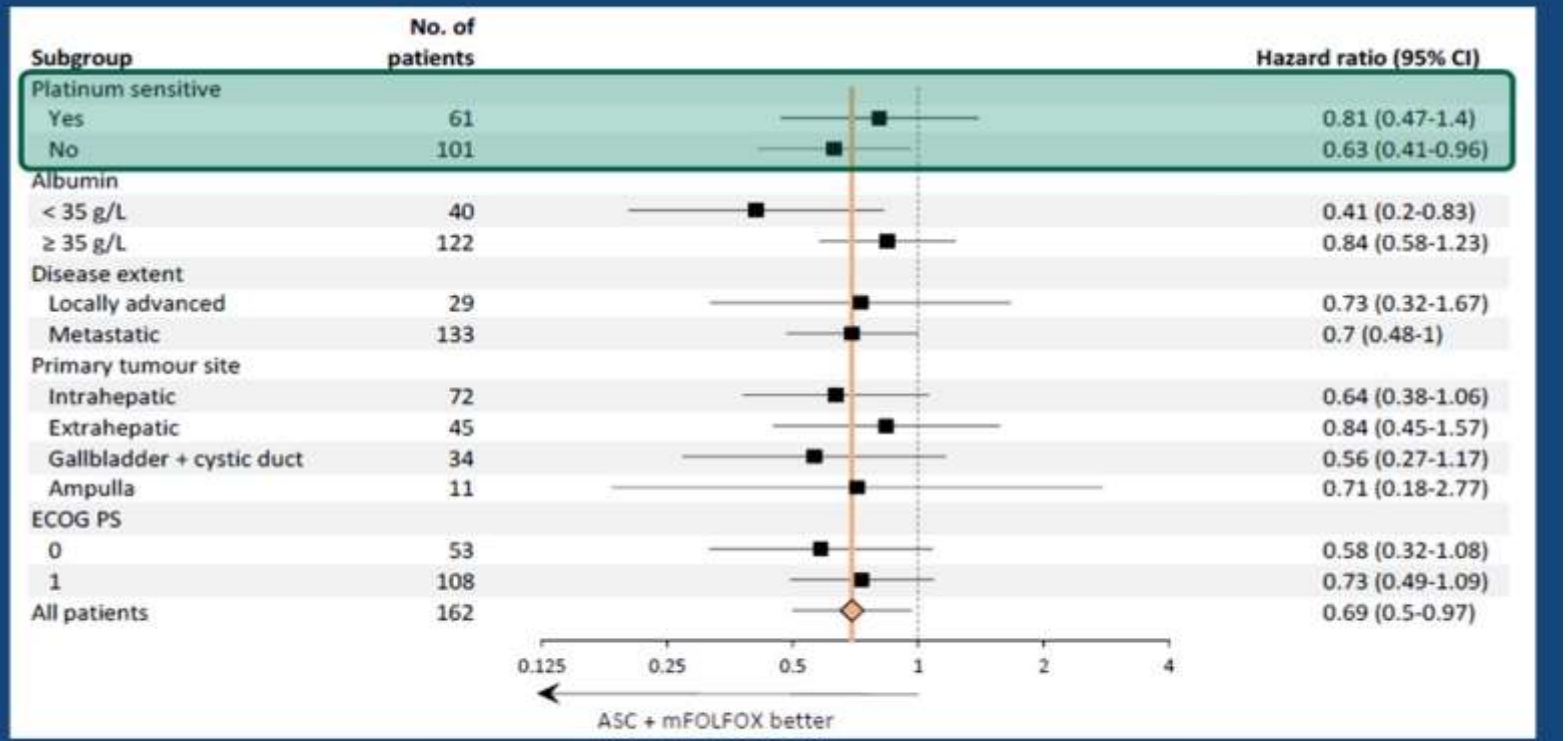


	Arm A (ASC alone)	Arm B (ASC + mFOLFOX)
Adjusted* Hazard Ratio	**0.69** (95% CI 0.50-0.97) p=0.031	
Median OS	5.3 months	6.2 months
6-month survival-rate	35.5%	50.6%
12-month survival-rate	11.4%	25.9%

Primary end-point: Overall Survival (ITT)

Exploratory subgroup analysis

- The **benefit of chemotherapy** was **consistent** across the exploratory subgroups
- Subgroups with poorer prognosis seemed to benefit the most from mFOLFOX
  - Platinum resistant/refractory
  - Low albumin
  - Metastatic disease



*adjusted for platinum sensitivity, albumin and stage, ITT: intention-to-treat analysis; ASC: active symptom control

Conclusions

- This is the first prospective phase III study evaluating the **benefit of chemotherapy after CisGem in patients with advanced BTC**
- **Survival** with **active symptom control** [4-weekly clinical assessment for symptom control, early detection and treatment of biliary-related complications] was **greater than anticipated** (5.3 vs 4 mo)
- Chemotherapy (**mFOLFOX**) combined with active symptom control improved OS after progression to CisGem with:
  - A clinically meaningful **reduction in risk of death** (HR* 0.69)
  - A clinically meaningful **increase in 6 month** (+15%) and **12 month** (+15%) **OS rate**
- **mFOLFOX chemotherapy combined with active symptom control should become standard of care in the second-line setting for patients with advanced BTC**
- Quality of life, health economic evaluation and translational research are ongoing

*adjusted for platinum sensitivity, albumin and stage

CisGem: cisplatin + gemcitabine; BTC: biliary tract cancer; OS: overall survival; HR: hazard ratio; +: increase; mFOLFOX: 5-FU + oxaliplatin

Highlights

❖ Esophageal and gastric cancer

- ARTIST 2
- KEYNOTE-062

✓***Adjuvant SOX or SOXRT vs S-1:*** *DFS; no additional benefit with CTRT vs S-1/SOX*

✓***First-line P vs CT:*** *similar benefit in OS for CPS≥1 and favorable effect for CPS ≥10; better tolerability profile for P; modest additional benefit of P+CT vs CT*

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❖ BTC

- ABC-06

✓***mFOLFOX + ASC:*** *standard of care in second-line*

❖ HCC

- SURF
- KEYNOTE-240

Highlights

❖ **Esophageal and gastric cancer**

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❖ **BTC**

- ABC-06

✓***mFOLFOX + ASC:*** *standard of care in second-line*

❖ **HCC**

- SURF
- KEYNOTE-240

A multicenter randomized controlled trial to evaluate the efficacy of SUrgery vs. RadioFrequency ablation for small hepatocellular carcinoma

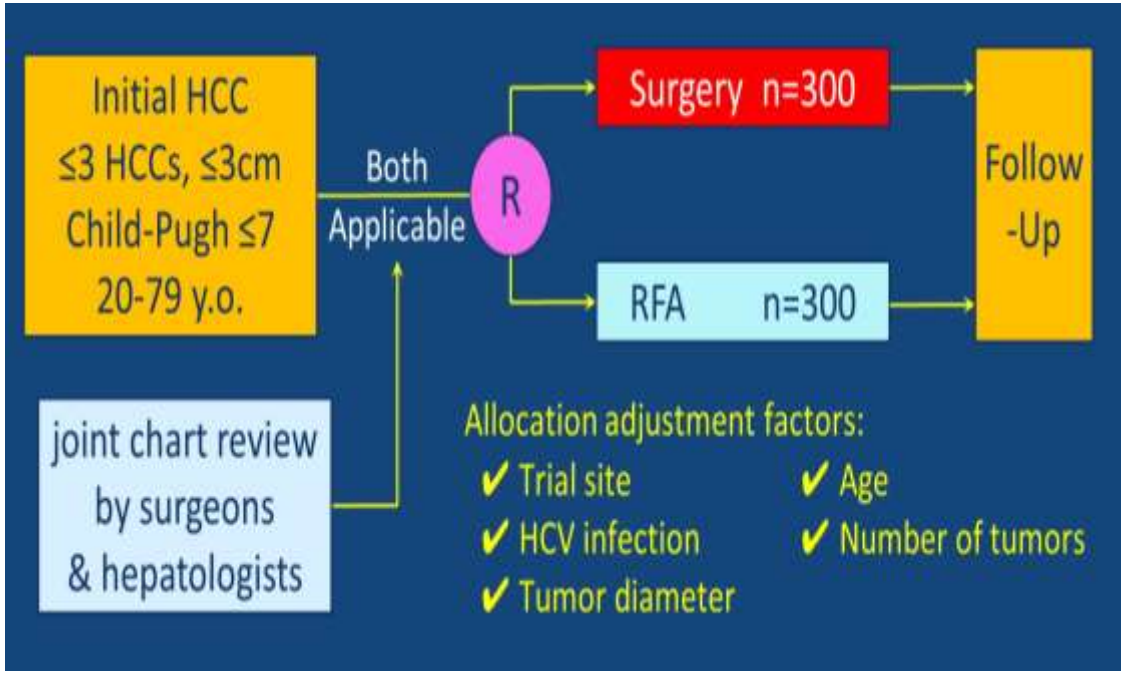
SURF

Efficacy of SUrgery vs. Radio-Frequency ablation (RFA) on primary hepatocellular carcinoma: a multicenter clinical trial

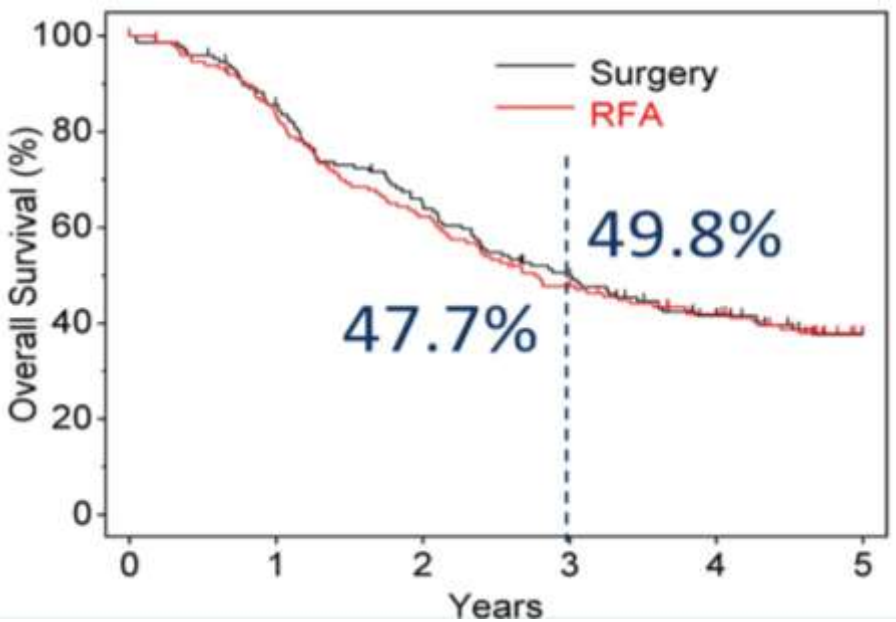
SURF Trial Group

Namiki izumi

Kiyoshi Hasegawa, Yujiro Nishioka, Tadatoshi Takayama
Naoki Yamanaka, Masatoshi Kudo, Mitsuo Shimada
Masahumi Inomata, Shuichi Kaneko, Hideo Baba
Kazuhiko Koike, Masao Omata, Masatoshi Makuuchi
Yutaka Matsuyama, Norihiro Kokudo



- **PRIMARY ENDPOINTS:**
  - RFS; OS
- **SECONDARY ENDPOINTS:**
  - Liver function 1, 3, 5 years after
  - Pattern of first recurrence; SAE



RFS (years, median)
- Surgery 2.98 (2.33-3.86)
- RFA 2.76 (2.17-3.80)

p=0.793 (0.72-1.28)

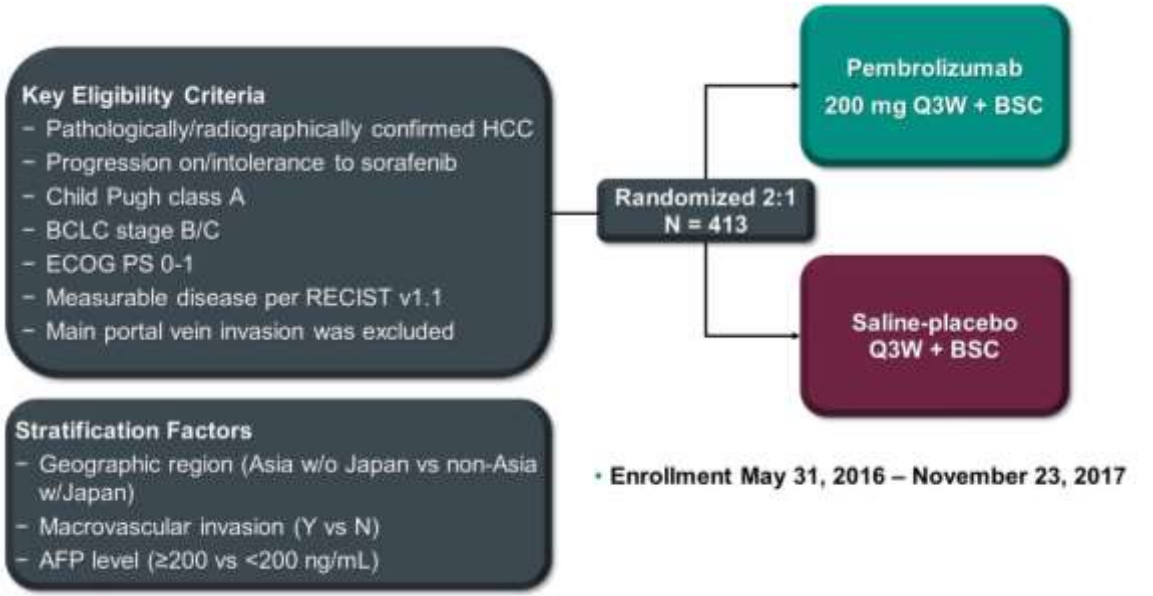
	SUR (n=150)	RFA (n=151)	P-Value
Number of Tumors			0.98
Solitary	135 (90.0%)	136 (90.1%)	
Multiple	15 (10.0%)	15 (9.9%)	

Conclusion

- ✓ Surgical resection (SUR) and radiofrequency ablation (RFA) were both safe therapeutic approaches.
- ✓ Both of them provided similar recurrence-free survival (RFS) for early stage HCC smaller than 3 cm.
- ✓ OS will be analyzed two years later.

Results of KEYNOTE-240: Phase 3 Study of Pembrolizumab vs Best Supportive Care for Second-Line Therapy in Advanced Hepatocellular Carcinoma

Richard S. Finn,[1] Baek-Yeol Ryoo,[2] Philippe Merle,[3] Masatoshi Kudo,[4] Mohamed Bouattour,[5] Ho-Yeong Lim,[6] Valeriy Breder,[7] Julien Edeline,[8] Yee Chao,[9] Sadahisa Ogasawara,[10] Thomas Yau,[11] Marcelo Garrido,[12] Stephen L. Chan,[13] Jennifer Knox,[14] Bruno Daniele,[15] Scot W. Ebbinghaus,[16] Erluo Chen,[16] Abby B. Siegel,[16] Andrew X. Zhu,[17] Ann-Lii Cheng,[18] for the KEYNOTE-240 Investigators



- **Primary endopoints**:
  - OS; PFS
- **Seconday endopoints** :
  - ORR, DOR, DCR and TTP
  - safety

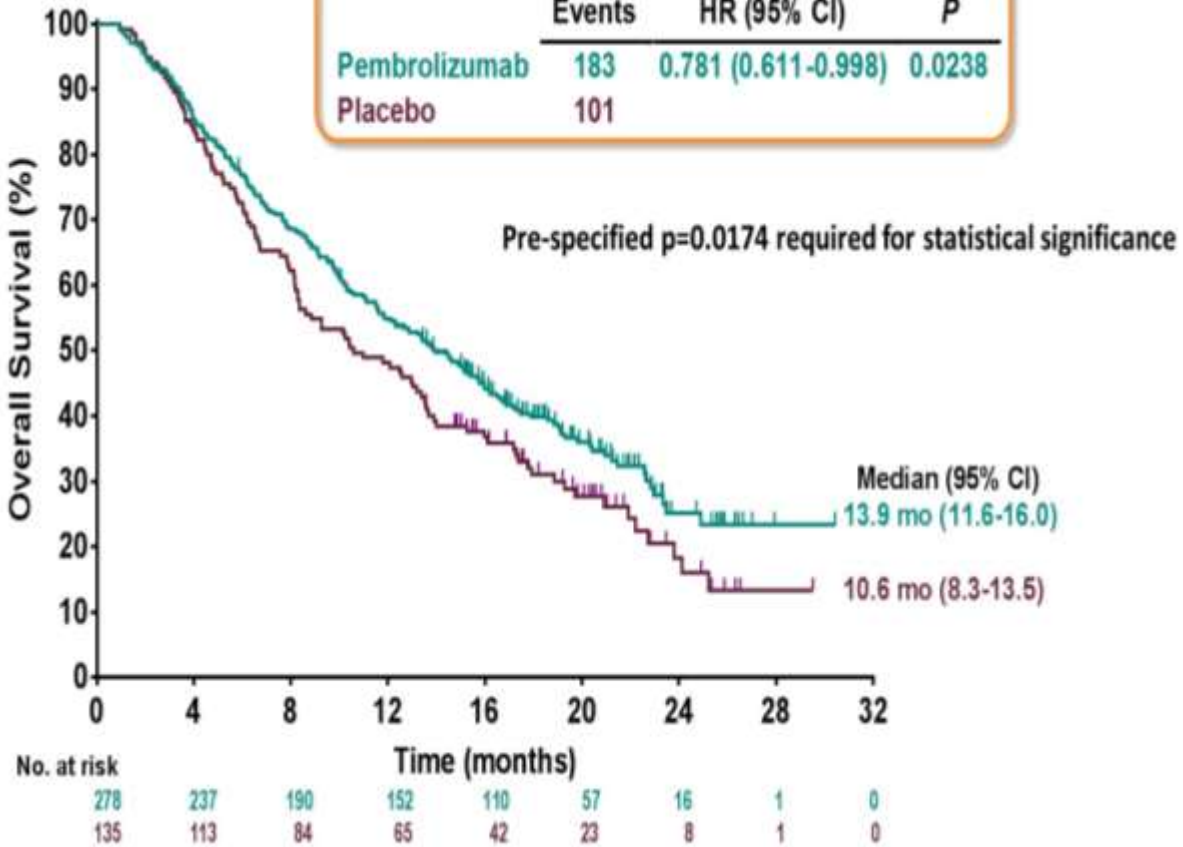
Statistical Considerations

- Overall Type I error (α)=0.025 controlled across testing of PFS, OS and ORR[1]
  - Initial α allocation
    - PFS α=0.002; OS α=0.023
    - ORR α=0.0 (tested only if OS or PFS criteria met)
  - α re-allocated per multiplicity strategy specified in the protocol
- OS testing by group sequential design
  - α controlled over 2 interim and final efficacy analyses (O'Brien-Fleming spending function[2])
  - Primary analysis of PFS and ORR at 1st interim cut-off
- Efficacy boundaries
  - p=0.0174 for OS (final analysis cutoff, Jan 2, 2019, based on 284 observed events)
  - p=0.0020 for PFS (at 1st interim cutoff, Mar 26, 2018)
- Study power
  - 92% for OS with 273 deaths at α=2.3%, HR=0.65
  - 94% for PFS with 331 PFS events at α=0.2%, HR=0.60

1. Maurer W, Bretz F. *Stat Biopharm Res* 2013; 5(4): 311-20. 2. Lan KKG, Demets DL. *Biometrika* 1983; 70(3): 659-63.

Overall Survival

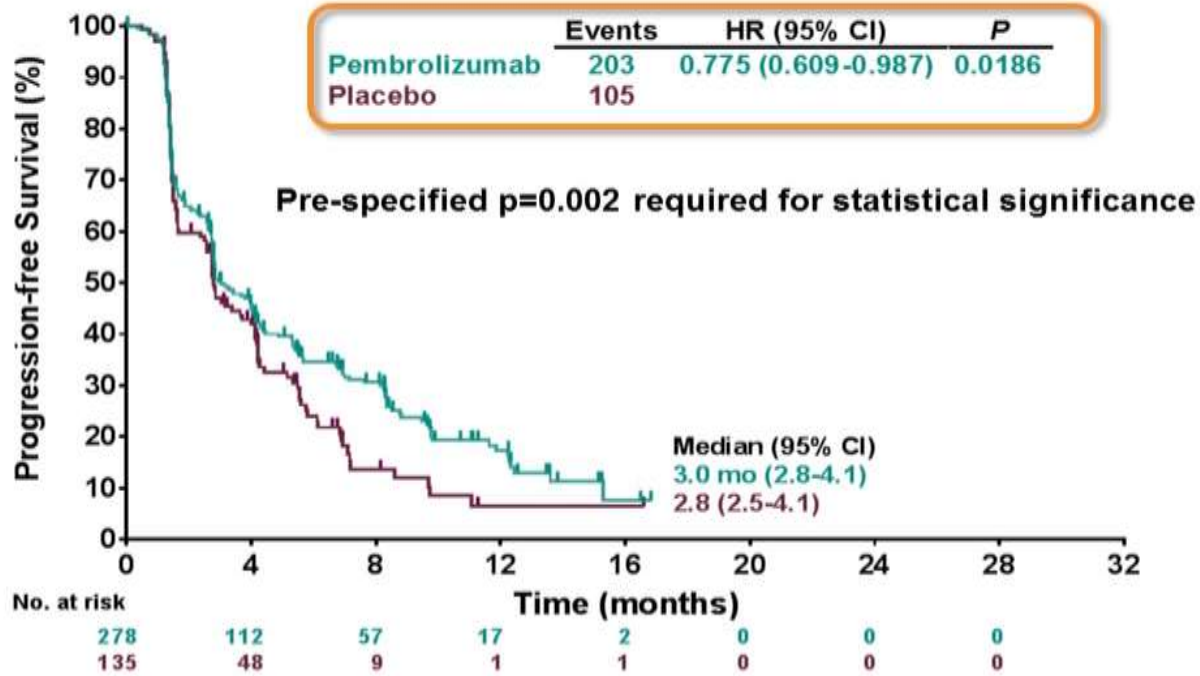
	Events	HR (95% CI)	P
Pembrolizumab	183	0.781 (0.611-0.998)	0.0238
Placebo	101		



Progression-Free Survival

Primary Analysis

	Events	HR (95% CI)	P
Pembrolizumab	203	0.775 (0.609-0.987)	0.0186
Placebo	105		



These differences did not meet significance per the prespecified statistical plan

Summary

- Pembrolizumab reduced the risk of death by 22% and improved PFS over placebo in patients with advanced HCC
  - HR=0.781 (*P*=0.0238) for OS; HR=0.718 (*P*=0.0022) for PFS
  - Prespecified efficacy boundaries were not reached
- ORR was higher for pembrolizumab (18.3%) than placebo (4.4%)
  - Responses to pembrolizumab were durable (13.8 months)
- The safety profile, including incidence of immune-mediated events and hepatitis, was similar to that of pembrolizumab in other tumor types; no HBV or HCV viral flares were identified

Conclusions

- KEYNOTE-240 did not meet the statistical criteria for either of the dual endpoints
- The magnitude of benefit as captured by the HR for OS and PFS, the ORR and response duration are consistent with the findings of KEYNOTE-224
- Taken together, these data support that the risk-benefit balance for pembrolizumab is favorable in the second-line setting for HCC
- An additional phase 3 study evaluating pembrolizumab as second-line therapy in previously treated patients with advanced HCC is ongoing in the Asia-Pacific region (KEYNOTE-394; NCT03062358)

Highlights

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  - ARTIST 2
  - KEYNOTE-062

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  - ABC-06

  ✓***mFOLFOX + ASC:*** *standard of care in second-line*

- **HCC**
  - SURF
  - KEYNOTE-240

  ✓***Surgery vs RFA:*** *no differences in RFS for HCC <3 cm*

  ✓***Pembro vs PLB:*** *statistical criteria for OS and PFS were not meet*

Thanks!

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