

“Onkologie interdisziplinär II: HCC”

16. Kärntner & Steirisches Onkologiesymposium, Klagenfurt 080619

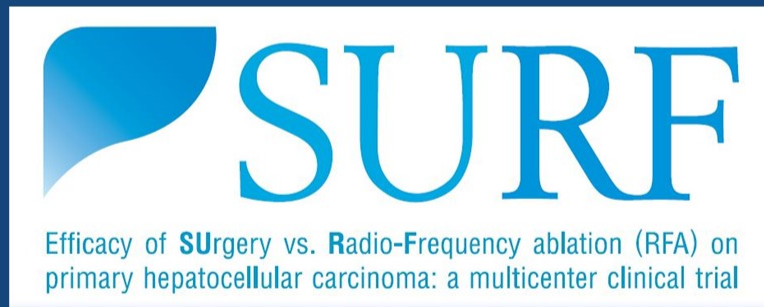


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Early Stage HCC – RFA *vs.* Resection

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



SURF Trial Group

Namiki izumi

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PRESENTED AT: **2019 ASCO**
ANNUAL MEETING

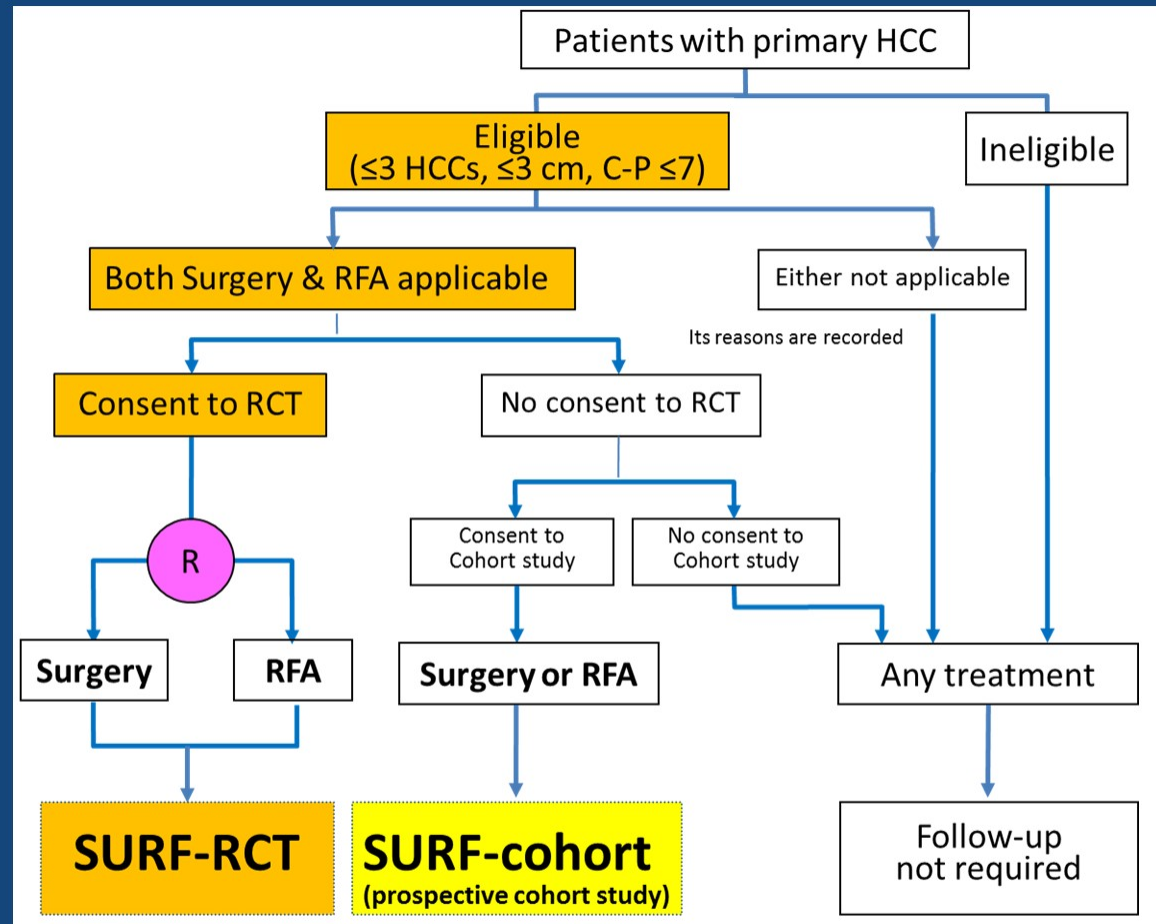
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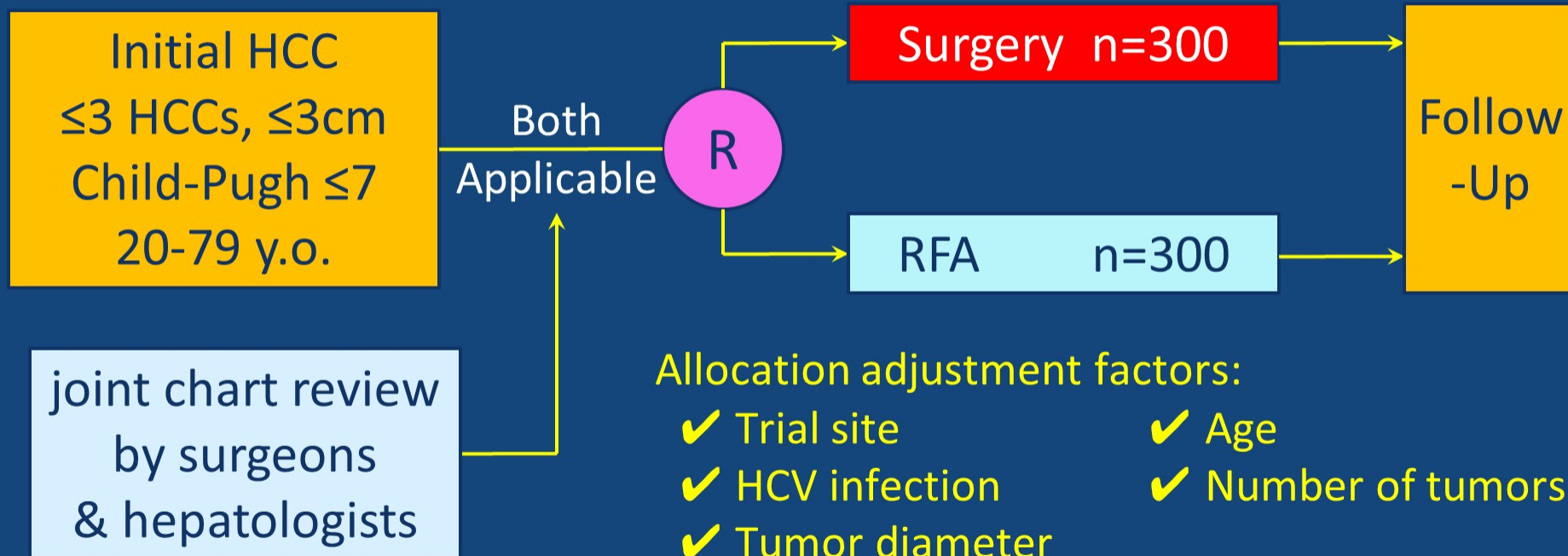
PRESENTED BY: Namiki Izumi

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Overview of SURF Trial



RCT Design (from April 2009)



Two co-primary end-points

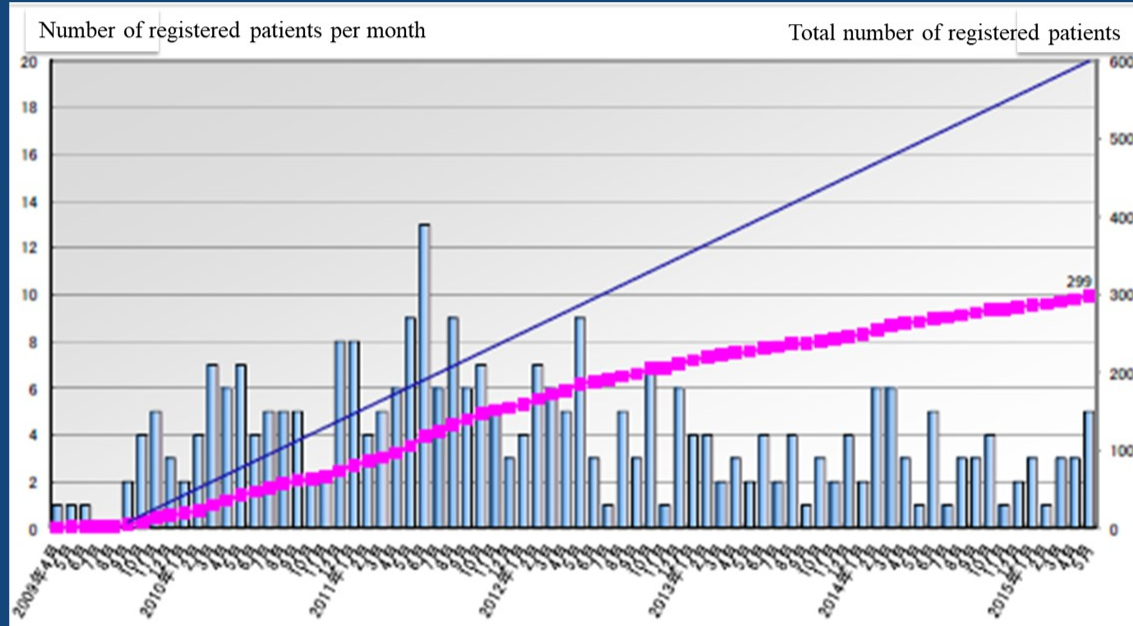
Primary Endpoints

- ✓ Recurrence-Free Survival
- ✓ Overall Survival

Secondary Endpoints

- ✓ Liver function 1, 3, 5 years after treatment
- ✓ Pattern of first recurrence
- ✓ Serious adverse events

However... Too Late pace of registration



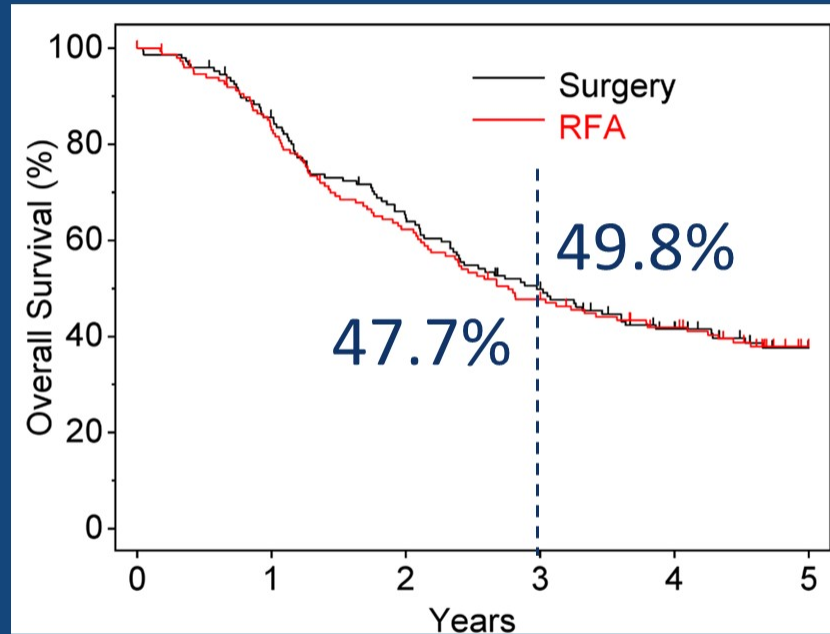
Demographic and Disease Characteristics at baseline (2)

	SUR (n=150)	RFA (n=151)	P-Value
Child-Pugh score			0.12*
A	117 (78.0%)	129 (85.4%)	
B	32 (21.3%)	22 (14.6%)	
PS			0.56*
0	147 (98.0%)	146 (96.7%)	
1-2	3 (2.0%)	5 (3.3%)	
Serum Bilirubin (mg/dL)			0.58†
median (range)	0.70 (0.3-1.9)	0.80 (0.3-1.8)	
Serum Albumin (g/dL)			0.48†
median (range)	4.0 (0.6-5.0)	4.1 (0.8-5.0)	
Liver Damage			0.10*
A	120 (80.0%)	118 (78.1%)	
B	17 (11.3%)	9 (6.0%)	
TAE before registration			0.59*
Performed	11 (7.3%)	12 (7.9%)	
Not Performed	139 (92.7%)	138 (91.4%)	

* Chi-square test

† Wilcoxon rank sum test

Kaplan-Meier estimate of RFS



Number at risk

150	123	92	69	50	33
151	121	90	68	55	37

median Follow-Up (years)

SUR 5.04 (0.36-9.49)

RFA 4.99 (0.00-8.70)

* median (95%CI)

RFS (years, median)

SUR 2.98 (2.33-3.86)

RFA 2.76 (2.17-3.80)

* median (95%CI)

p= 0.793 (0.72-1.28)

Adverse Events

	SUR	RFA	P-value
Length of Hospital Stay (day)			<0.01 [†]
median (range)	17.0 (12.0 , 23.0)	10.0 (7.0, 15.5)	
Operation or Procedure Time (min)			<0.01 [†]
median (range)	274.0 (203.0, 341.0)	40.0 (24.0, 70.0)	

[†] Wilcoxon rank sum test

There was no mortality in patients with both groups.

RCTs about small HCC therapy

Author	Year	Site	Size	Tumor No.	Child -Pugh	n	Conclusion
Chen DS Liang J-D	2005	Taiwan	≤3cm	≤2	A,B	76	NS
Chen M-S Lau WY	2005	Hongkong, Guangzhou	≤5cm	1	A	180	NS
Huang J Zeng Y	2010	Chengdu	≤3cm (Milan)	≤3	A,B	230	Favor (Surgery)
Feng K Dong J	2012	Chongqing	≤4cm	≤2	A,B	168	NS
SURF	2019	Japan	≤3cm	≤3	A,B	308	NS

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.

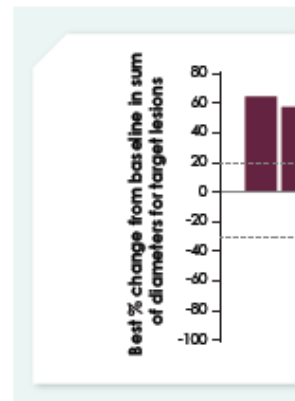
Advanced HCC - First Line Therapie des HCC

Avelumab + Axitinib: Advanced Stage HCC – P1b

Kudo *et al.*, ASCO 2019

- Avelumab: PD-L1 mAB; Axitinib: VEGFR-TKI; 22 Patients, Japan

Figure 3. Best change in target lesions from baseline, mRECIST (n=21)*



* Only includes patients with target lesions at baseline and ≥1 post-baseline assessment

Table 3. Patients with TRAEs (any grade in ≥20% of patients and all grade ≥3; N=22)

Preferred term	Any grade, n (%)	Grade ≥3, n (%)
Any TRAE	21 (95.5)	16 (72.7)
Hypertension	17 (77.3)	11 (50.0)
Appetite decreased	12 (54.5)	2 (9.1)
Dysphonia	11 (50.0)	0
Palmar-plantar erythrodysesthesia syndrome	10 (45.5)	5 (22.7)
Stomatitis	9 (40.9)	2 (9.1)
Hypothyroidism	7 (31.8)	0
Malaise	7 (31.8)	0
Weight decreased	7 (31.8)	0
Dysgeusia	6 (27.3)	0
Proteinuria	6 (27.3)	1 (4.5)
Rash	5 (22.7)	0
Diarrhea	5 (22.7)	0
Fatigue	3 (13.6)	2 (9.1)
Headache	2 (9.1)	1 (4.5)
Amylase increased	1 (4.5)	1 (4.5)
Mouth ulceration	1 (4.5)	1 (4.5)

Table 4. Summary

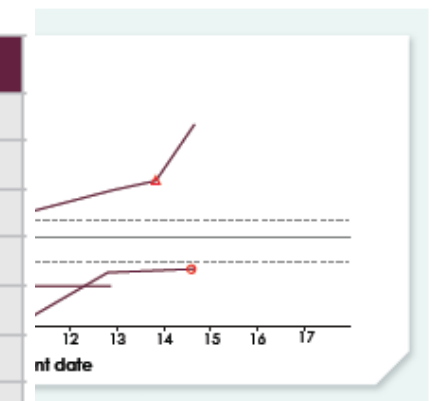
N=22
ORR, % (95% CI)
DCR, % (95% CI)
Best overall response
Complete response
Partial response
Stable disease
Progressive disease
Not evaluable
Median, mo (95% CI)
PFS*
DOR†
TTP
TTR†
OS*
Event-free rate
PFS*
Event-free rate
OS*

54.5 (32.1-72.4)

NA

0 (0/1)

Figure 4. Change in target lesions from baseline over time, mRECIST (n=21)*



baseline and ≥1 post-baseline assessment

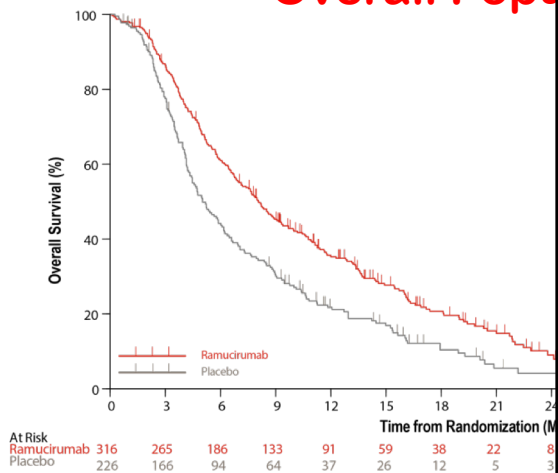
TRAE, % (n)
13)
9)
6)
16)
11)
11)
19)
3)
8)
14)
8)
5)
9)
17)
20 (11/4)
0 (0/1)

Advanced HCC - Second Line Therapie des HCC

RAM in So

■ Pooled anal

Overall Popu

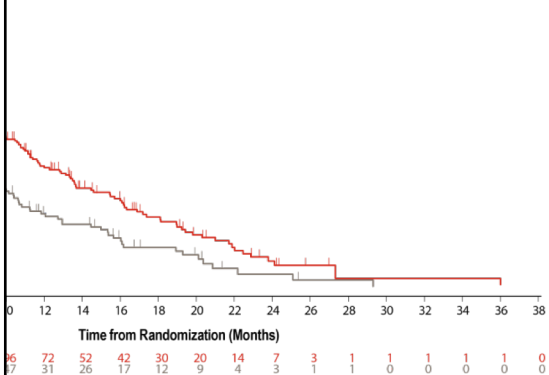


N (%)
ORR
DCR

- Acknowledging limitations of sample size, the ramucirumab treatment benefit in sorafenib intolerant patients was consistent with the pooled population
- Ramucirumab was well tolerated in sorafenib intolerant patients with low rates of discontinuation due to related-AEs and no deleterious effects on patient-reported disease symptoms
- Ramucirumab is a treatment option for sorafenib-intolerant patients with advanced HCC and AFP ≥ 400 ng/mL

EACH 1+2)

sion on Sorafenib



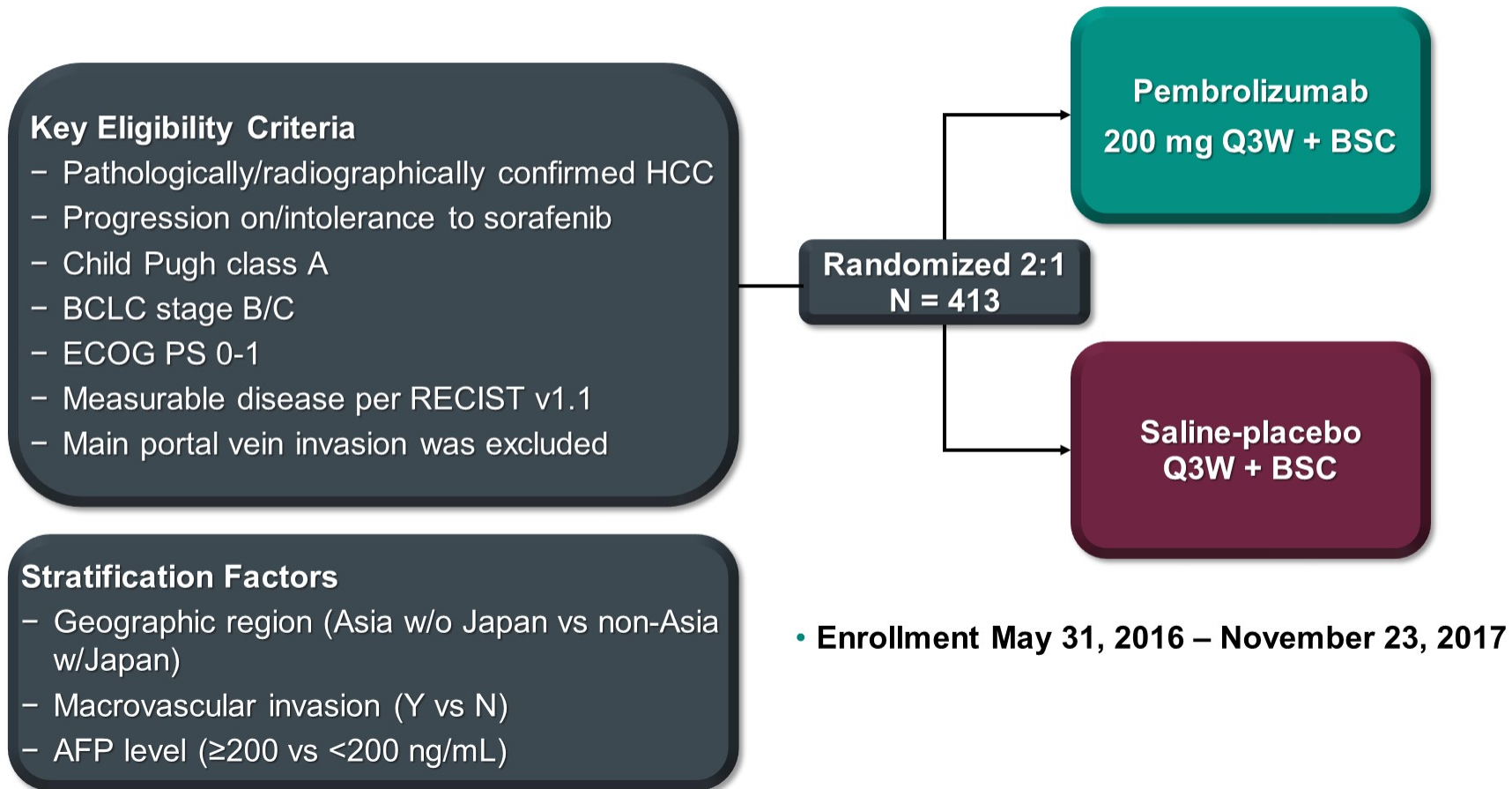
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3)
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4)

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

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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

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¹⁰Chiba University Graduate School of Medicine, Chiba, Japan; ¹¹The University at Hong Kong, Hong Kong, China; ¹²Pontificia Universidad Católica de Chile, Santiago, Chile; ¹³State Key Laboratory of Translation Oncology, Sir YK Pao Centre for Cancer, The Chinese University of Hong Kong, Shatin, Hong Kong, China; ¹⁴Princess Margaret Cancer Centre and University of Toronto, Toronto, Canada; ¹⁵Ospedale del Mare, Napoli, Italy; ¹⁶Merck & Co., Inc., Kenilworth, NJ, USA; ¹⁷Massachusetts General Hospital Cancer Center and Harvard Medical School, Boston, MA, USA; ¹⁸National Taiwan University Hospital and National Taiwan University Cancer Center, Taipei, Taiwan

KEYNOTE-240 Study Design



Study Endpoints

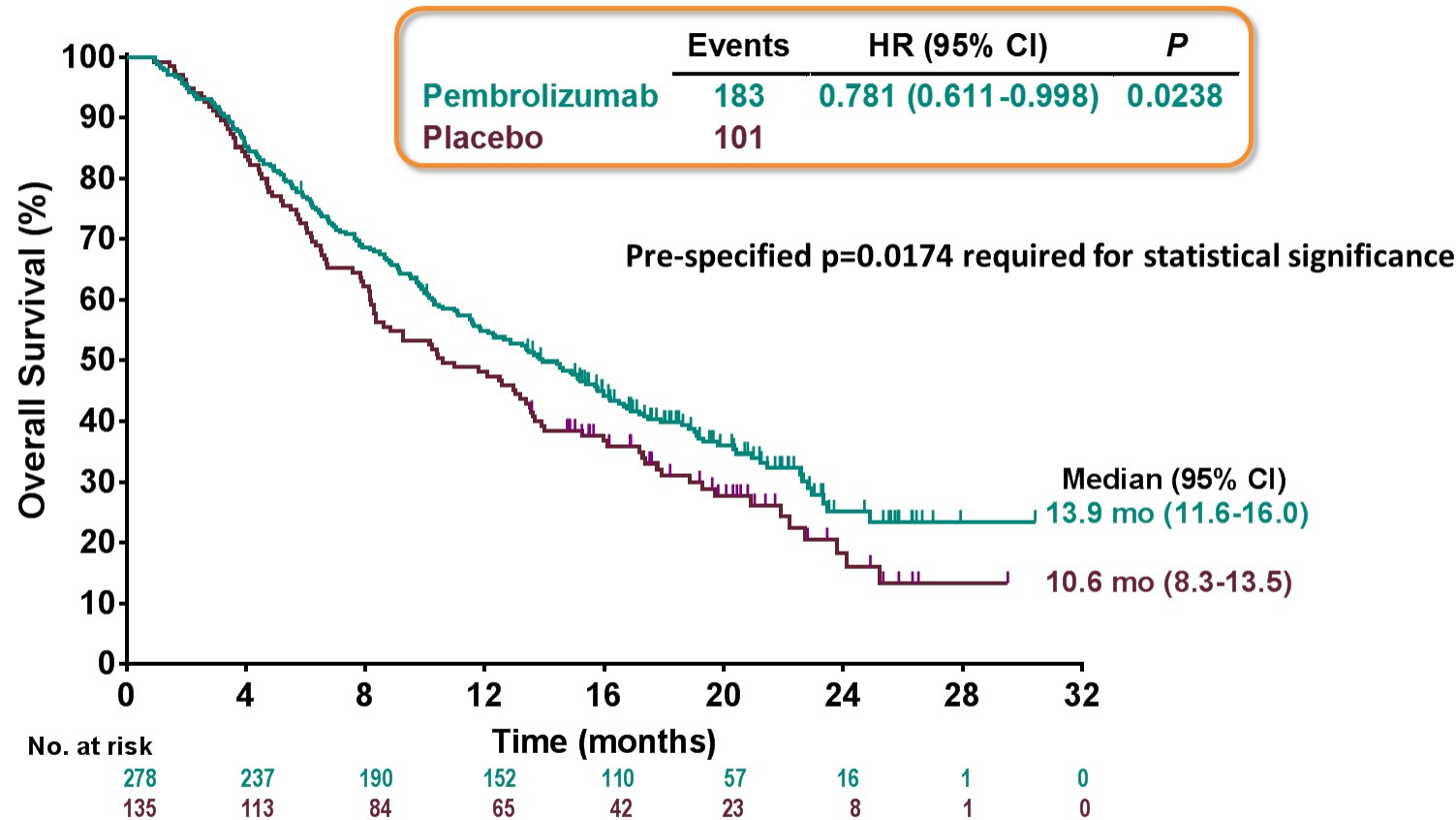
- **Primary**
 - OS
 - PFS (RECIST v1.1, central review)
- **Secondary**
 - ORR, DOR, DCR and TTP (all RECIST v1.1, central review)
 - Safety and tolerability
- **Response was assessed Q6W**

Baseline Characteristics

Characteristic n (%)	Pembrolizumab (N=278)	Placebo (N=135)
ECOG PS 1	116 (41.7)	64 (47.4)
Child Pugh Score		
A	277 (99.6)	133 (98.5)
B	1 (0.4)	2 (1.5)
Overall BCLC stage		
B	56 (20.1)	29 (21.5)
C	222 (79.9)	106 (78.5)
HBV-positive ^a	72 (25.9)	29 (21.5)
HCV-positive ^a	43 (15.5)	21 (15.6)
Discontinuation of prior sorafenib		
Intolerance	36 (12.9)	18 (13.3)
PD	242 (87.1)	117 (86.7)
Extrahepatic disease	195 (70.1)	93 (68.9)
Macrovascular invasion	36 (12.9)	16 (11.9)
Baseline AFP ≥200 ng/mL	129 (46.4)	58 (43.0)

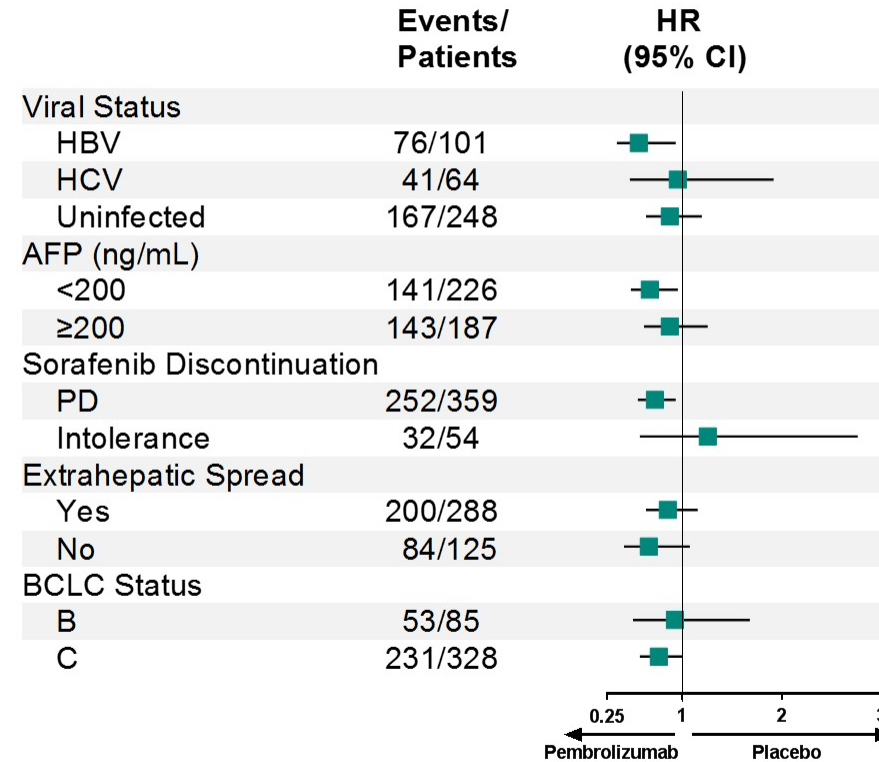
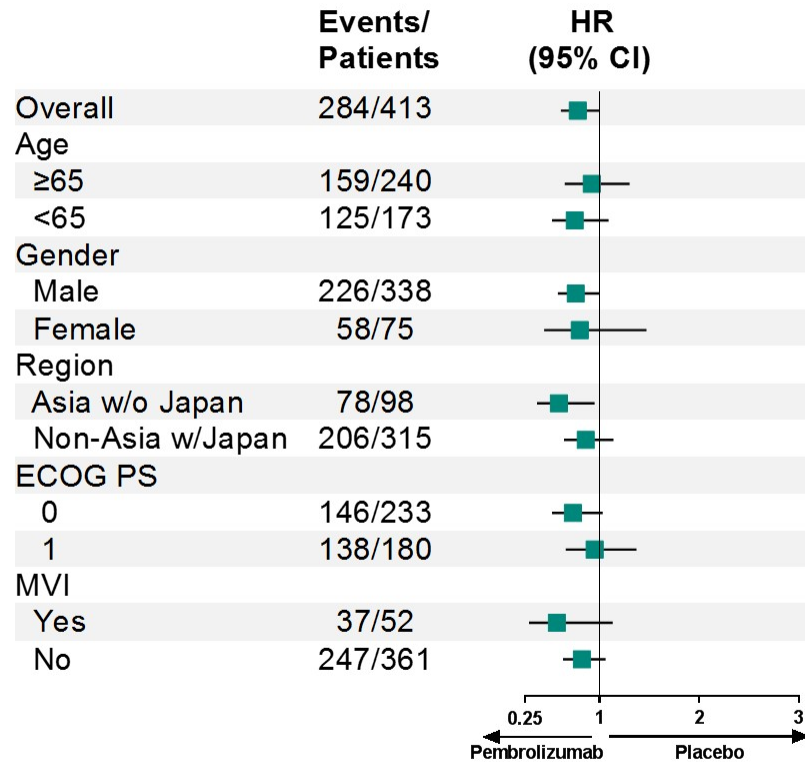
^a163 (58.6%) and 85 (63.0%) uninfected patients in pembrolizumab and placebo groups respectively.
Data cut-off: Jan 2, 2019.

Overall Survival



Data Cutoff: Jan 2, 2019.

Overall Survival in Subgroups



Data cutoff: Jan 2, 2019.

Post-study Anticancer Therapy

Type, n (%)	Pembrolizumab N=278	Placebo N=135
Any		
Yes	116 (41.7)	64 (47.4)
No	162 (58.3)	71 (52.6)
Approved Anticancer Therapy		
Yes	88 (31.7)	43 (31.9)
Anti-PD1/PD-L1 Agents ^a	19 (6.8)	14 (10.4)
Others ^b	69 (24.8)	29 (21.5)
No	190 (68.3)	92 (68.1)

^aIncluded both with/without prior exposure to other post-treatment anticancer medications. ^bIncluded regorafenib, lenvatinib, cabozantinib, and ramucirumab.
Data cut-off: Jan 2, 2019.

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)

CHECKMATE 040: Nivolumab + Ipilimumab Advanced HCC-second line, P1/2

Yau *et al.*, ASCO 2019, A4019

■ Combination part of Checkmate 040 Study

Figure 1. CheckMate 040 nivolumab plus ipilimumab combination cohort study design

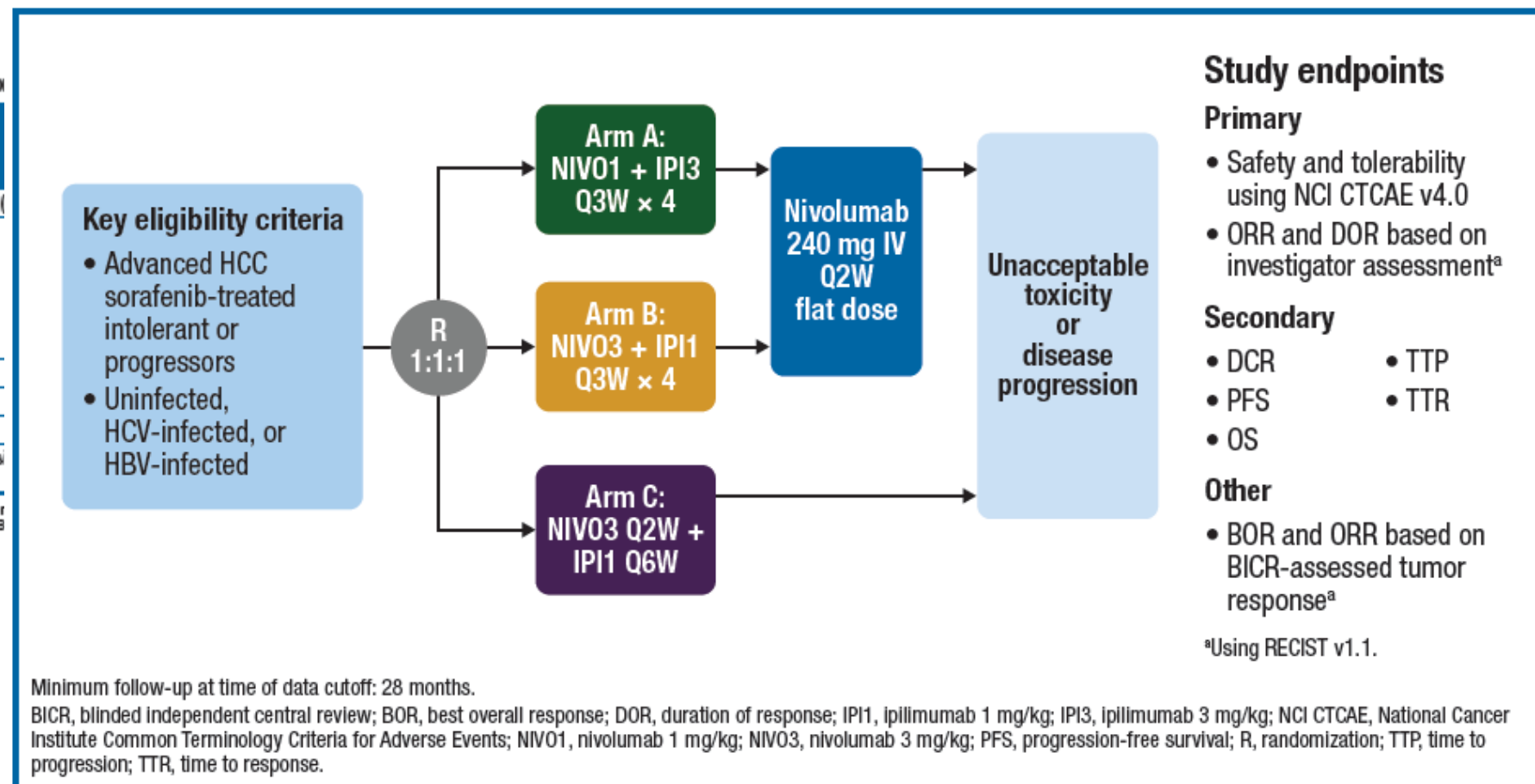
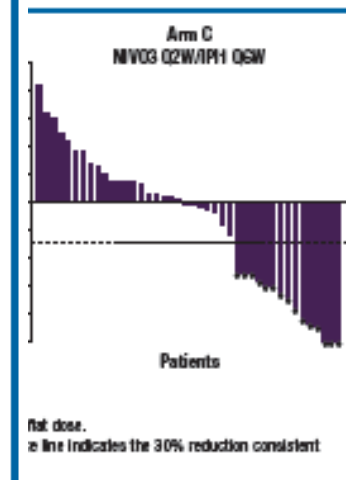


Table 4. Response, disease control

ORR by BICR using RECIST v1.1, n (%)
BOR, n (%)
CR
PR
SD ^a
PD
Unable to determine
DCR, n (%)
Median TTR (range), months
Median DOR (range), months
ORR by investigator assessment using RECIST v1.1, n (%)

^aNIVO1/IPI3 Q3W × 4 followed by nivolumab 240 mg IV Q2W flat dose. n = 2 patients in Arm A and 1 patient in Arm B. PR, partial response; SD, stable disease.



CHECKMATE 040: Nivolumab + Ipilimumab Advanced HCC-second line, P1/2

Yau *et al.*, ASCO 2019, A4019

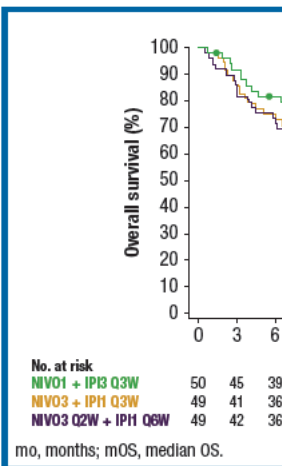
Table 7. Summary of IMAEs

n (%)	Arm A NIVO1/IP13 Q3W ^a n = 49		Arm B NIVO3/IP11 Q3W ^b n = 49		Arm C NIVO3 Q2W/IP11 Q6W n = 48	
	Any grade	Grade 3–4	Any grade	Grade 3–4	Any grade	Grade 3–4
Rash	17 (35)	3 (6)	14 (29)	2 (4)	8 (17)	0
Hepatitis	10 (20)	10 (20)	6 (12)	5 (10)	3 (6)	3 (6)
Adrenal insufficiency	9 (18)	2 (4)	3 (6)	0	3 (6)	0
Diarrhea/colitis	5 (10)	3 (6)	1 (2)	1 (2)	1 (2)	1 (2)
Pneumonitis ^c	5 (10)	3 (6)	0	0	0	0
Nephritis/renal dysfunction	0	0	1 (2)	0	1 (2)	1 (2)
Hypersensitivity	0	0	1 (2)	1 (2)	1 (2)	0
Hypophysitis	1 (2)	0	0	0	1 (2)	1 (2)
Hyperthyroidism	0	0	1 (2)	0	1 (2)	0
Hypothyroidism/thyroiditis	0	0	0	0	1 (2)	0
Diabetes mellitus	0	0	0	0	0	0

^aNIVO1/IP13 Q3W × 4 followed by nivolumab 240 mg IV Q2W flat dose; ^bNIVO3/IP11 Q3W × 4 followed by nivolumab 240 mg IV Q2W flat dose; ^cWithin 100 days after the final dose of study drug, 1 patient from Arm A died of a serious TRAE (grade 5 pneumonitis).

IMAEs are specific events considered as potential immune-mediated events by investigator occurring within 100 days of last dose, regardless of causality, treated with immune-modulating medication.

Figure 3. Overall survival



	All patients N = 148
RECIST v1.1, ^a n (%)	46 (31)
ne	7 (5) 39 (26) 23 (16) 65 (44) 11 (7) 72 (49)

SD does not include 2 patients in Arm A and were reported as non-CR/non-PD; ^aDefined as CR/non-PD.

at lesions at baseline and so do not meet the