Society for Immunotherapy of Cancer

SITC Webinar:
I-O Highlights from ASCO 2019

Wednesday, August 28, 2019

12:00 – 1:00 p.m. EDT

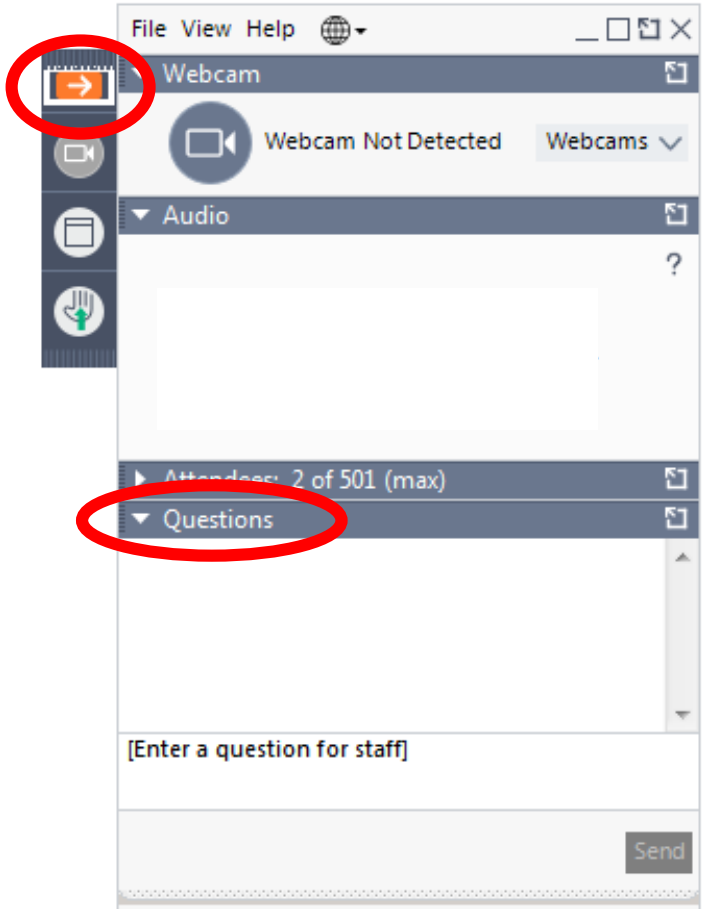
Society for Immunotherapy of Cancer

Webinar Agenda

12:00–12:05 p.m. EDT	Welcome, Introductions and Overview
12:05–12:40 p.m. EDT	Presentations: • First-Line and Neoadjuvant Studies • Cellular Therapies • Biomarkers and Checkpoint Inhibitors
12:40–12:55 p.m. EDT	Question and Answer Session
12:55–1:00 p.m. EDT	Closing Remarks

To Submit A Question

Computer



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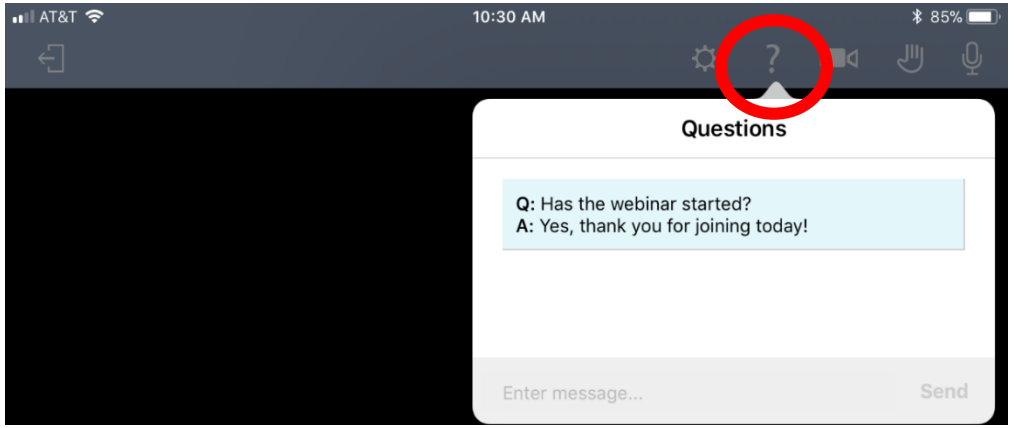


Webinar Faculty

James L. Gulley MD, PhD, FACP
National Cancer Institute

Kim A. Margolin, MD
City of Hope

Ahmad Tarhini, MD, PhD
Moffitt Comprehensive Cancer Center

First-Line and Neoadjuvant Studies

James L. Gulley, MD, PhD, FACP

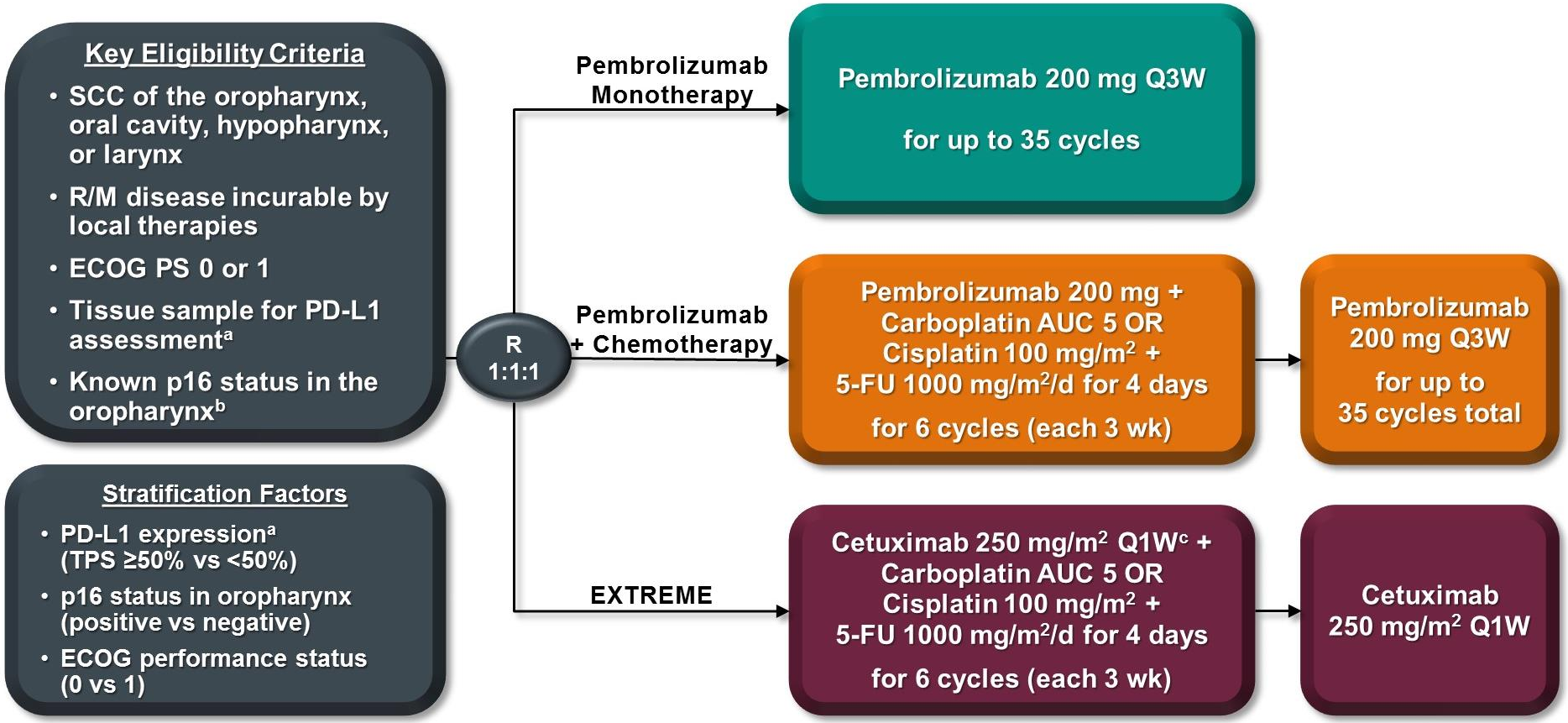
Checkpoint blockade as a first option

- Head and neck squamous cell carcinoma
  - KEYNOTE-048
- Renal cell carcinoma
  - KEYNOTE-426
- Triple negative breast cancer
  - IMpassion130

Protocol-specified final results of the KEYNOTE-048 trial of pembrolizumab as first-line therapy for recurrent/metastatic HNSCC

Danny Rischin, Kevin J. Harrington, Richard Greil, Denis Soulieres, Makoto Tahara, Gilberto de Castro, Amanda Psyrri, Neus Baste, Prakash C. Neupane, Ase Bratland, Thorsten Fuereder, Brett Gordon Maxwell Hughes, Ricard Mesia, Nuttapong Ngamphaiboon, Tamara Rordorf, Wan Zamaniah Wan Ishak, Yayan Zhang, Fan Jin, Burak Gumuscu, Barbara Burtness

KEYNOTE-048 study design

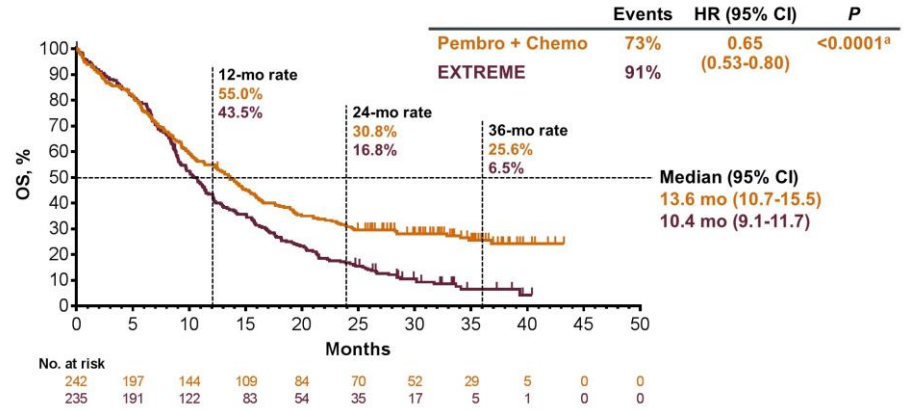


1° OS, PFS

[a]Assessed using the PD-L1 IHC 22C3 pharmDx assay (Agilent). TPS = tumor proportion score = % of tumor cells with membranous PD-L1 expression.
[b]Assessed using the CINtec p16 Histology assay (Ventana); cutpoint for positivity = 70%. [c]Following a loading dose of 400 mg/m^2.

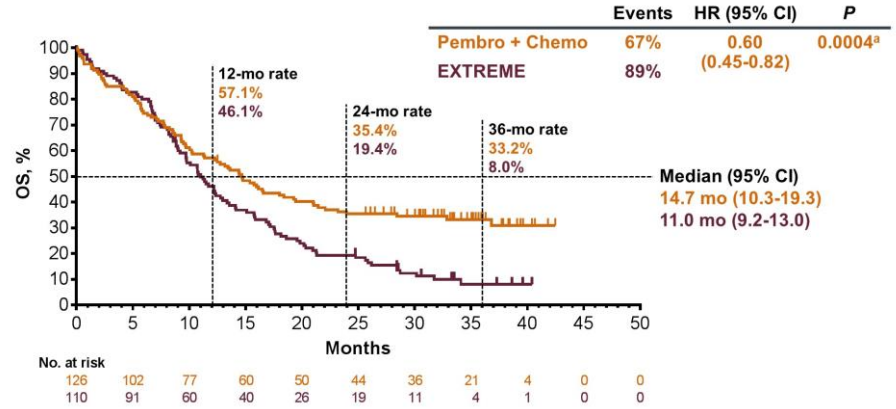
Rischin et al, ASCO 2019.

OS, P+C vs E, CPS ≥1 Population



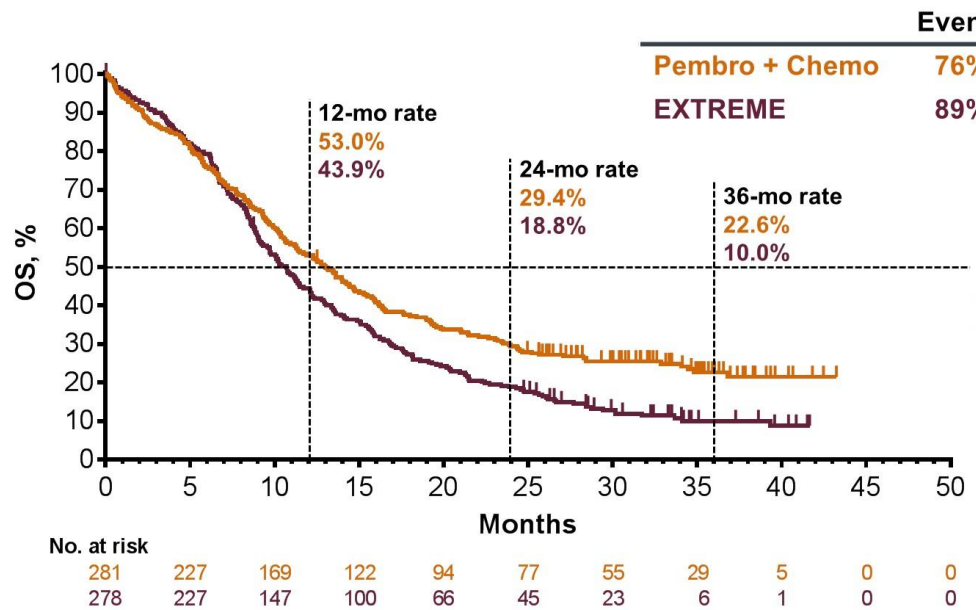
[a]Statistically significant at the superiority threshold of $P = 0.0026$.
FA (data cutoff date: Feb 25, 2019).

OS, P+C vs E, CPS ≥20 Population



[a]Statistically significant at the superiority threshold of $P = 0.0023$.
FA (data cutoff date: Feb 25, 2019).

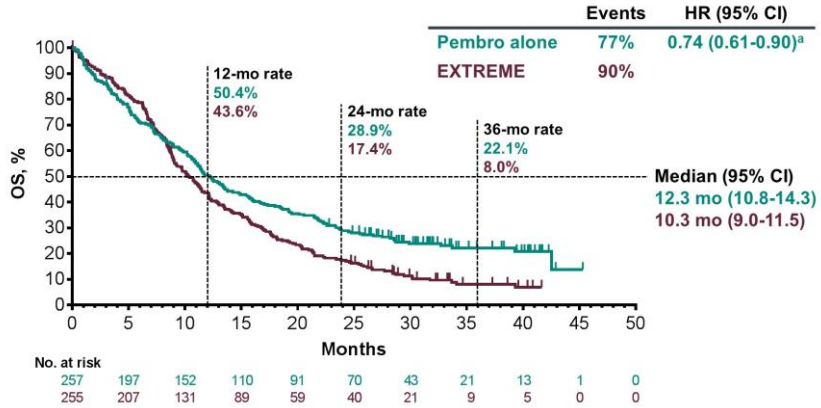
OS, P+C vs E, Total Population



[a]At IA2 (data cutoff date: Jun 13, 2018): HR 0.77 (95% CI 0.53–0.93).
FA (data cutoff date: Feb 25, 2019).

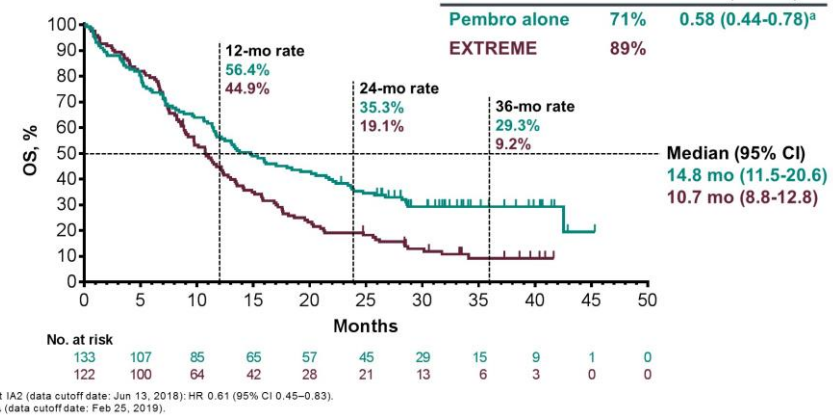
Rischin et al, ASCO 2019.

OS, P vs E, CPS ≥1 Population



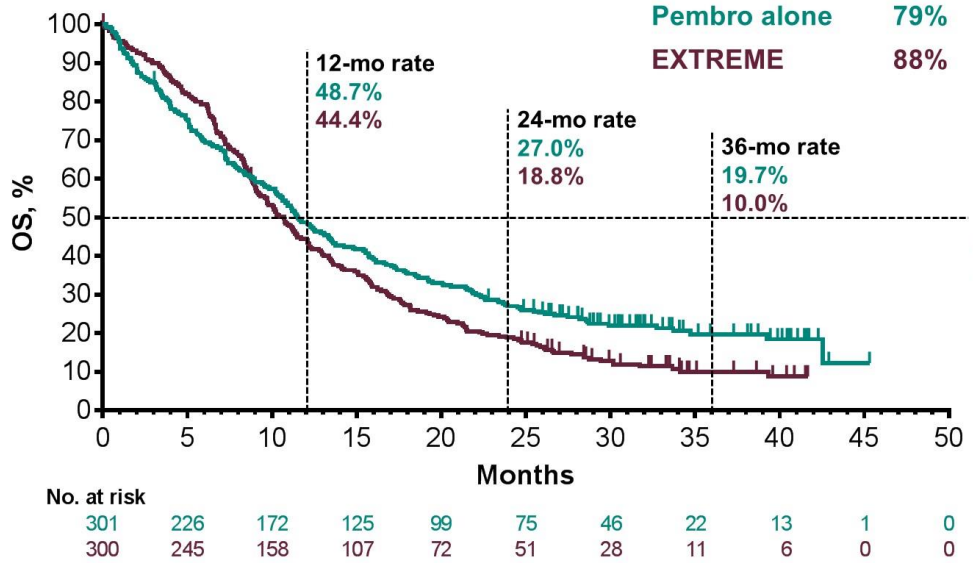
aAt IA2 (data cutoff date: Jun 13, 2018): HR 0.78 (95% CI 0.64–0.96).
FA (data cutoff date: Feb 25, 2019).

OS, P vs E, CPS ≥20 Population



aAt IA2 (data cutoff date: Jun 13, 2018): HR 0.61 (95% CI 0.45–0.83).
FA (data cutoff date: Feb 25, 2019).

OS, P vs E, Total Population



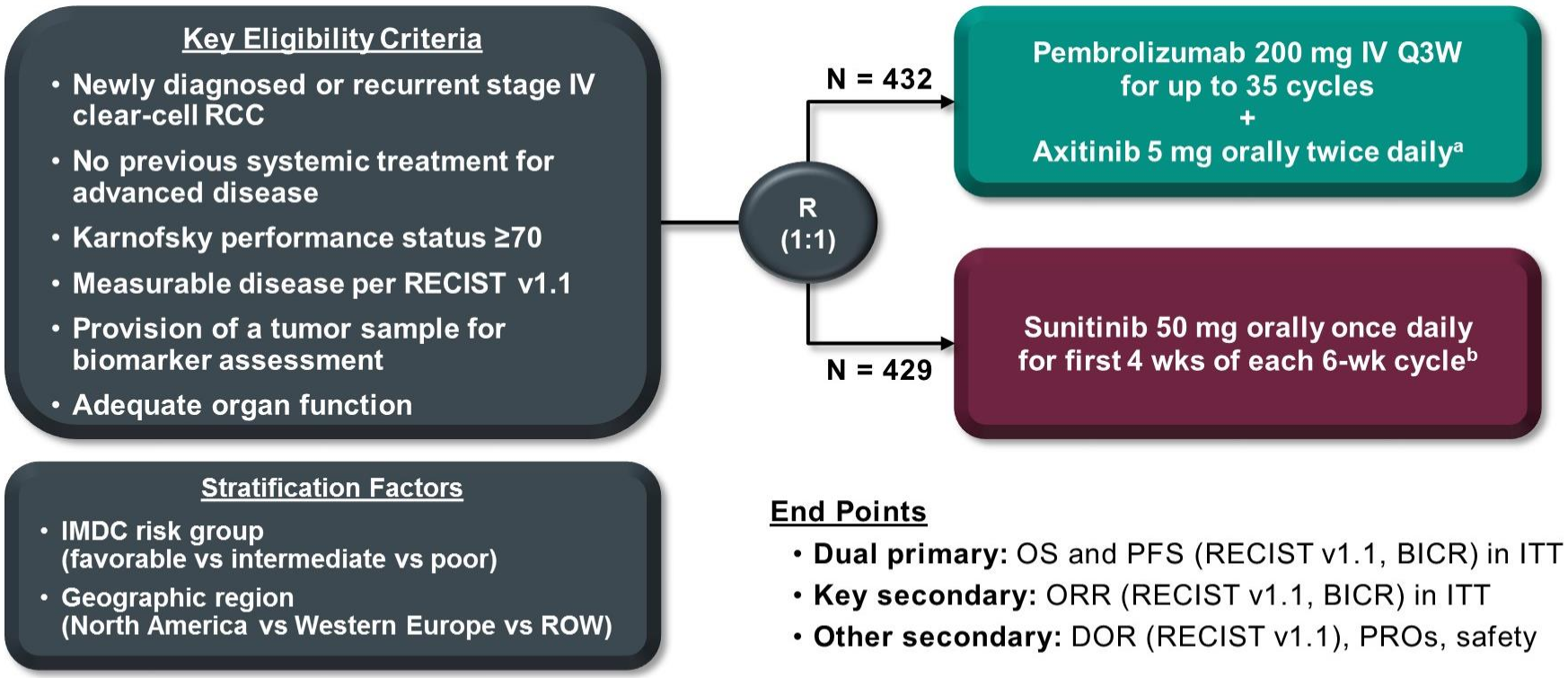
aNot statistically significant at the superiority threshold of $P = 0.0059$.
FA (data cutoff date: Feb 25, 2019).

Rischin et al, ASCO 2019.

Pembrolizumab plus axitinib as first-line therapy for mRCC: Outcomes in the combined IMDC intermediate/poor risk and sarcomatoid subgroups of KEYNOTE-426

Brian I. Rini, Elizabeth R. Plimack, Viktor Stus, Rustem Gafanov, Robert Hawkins, Dmitry Nosov, Frederic Pouliot, Denis Soulieres, Bohuslav Melichar, Ihor Vynnychenko, Sergio Jobim Azevedo, Delphine Borchiellini, Raymond S. McDermott, Jens Bedke, Satoshi Tamada, Shuyan Wan, Rodolfo F. Perini, Mei Chen, Michael B. Atkins, Thomas Powles

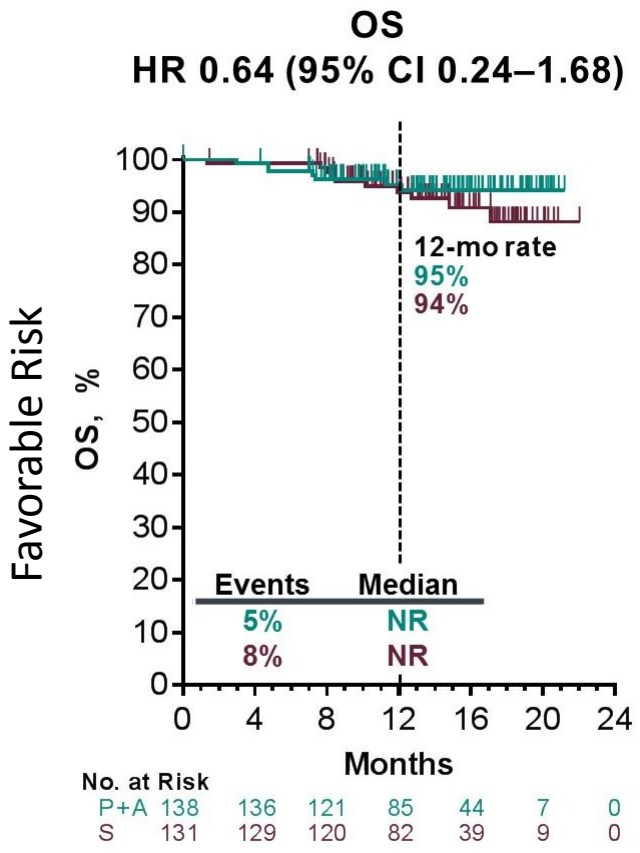
KEYNOTE-426 study design



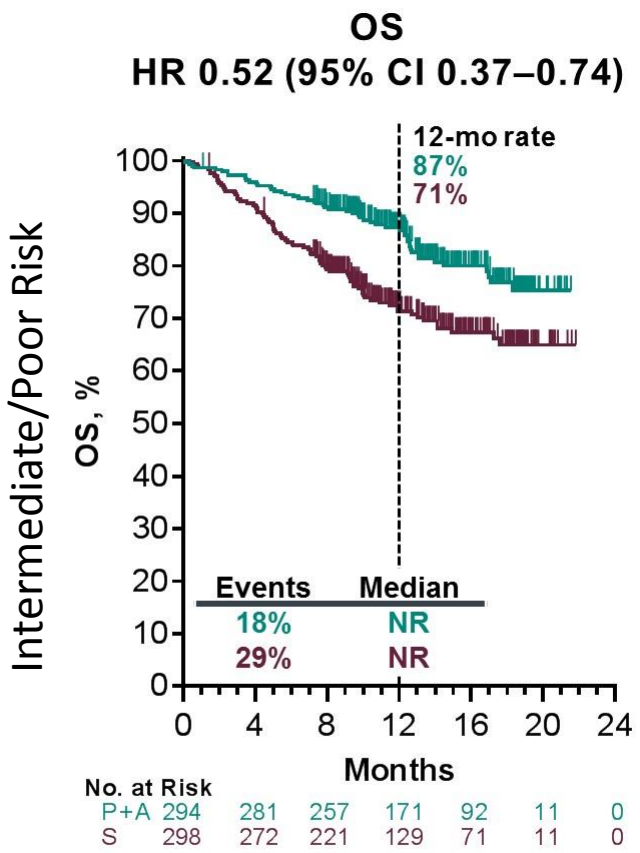
[a]Axitinib dose could be increased to 7 mg, then 10 mg, twice daily if safety criteria were met; dose could be reduced to 3 mg, then 2 mg, twice daily to manage toxicity.
[b]Sunitinib dose could be decreased to 37.5 mg, then 25 mg, once daily for the first 4 wks of each 6-wk cycle to manage toxicity.
BICR, blinded independent central radiologic review; DOR, duration of response; PROs, patient-reported outcomes; ROW, rest of world.
KEYNOTE-426 is a randomized, open-label, phase 3 study (ClinicalTrials.gov identifier NCT02853331).

Rini et al, ASCO 2019.

Overall survival in risk subgroups



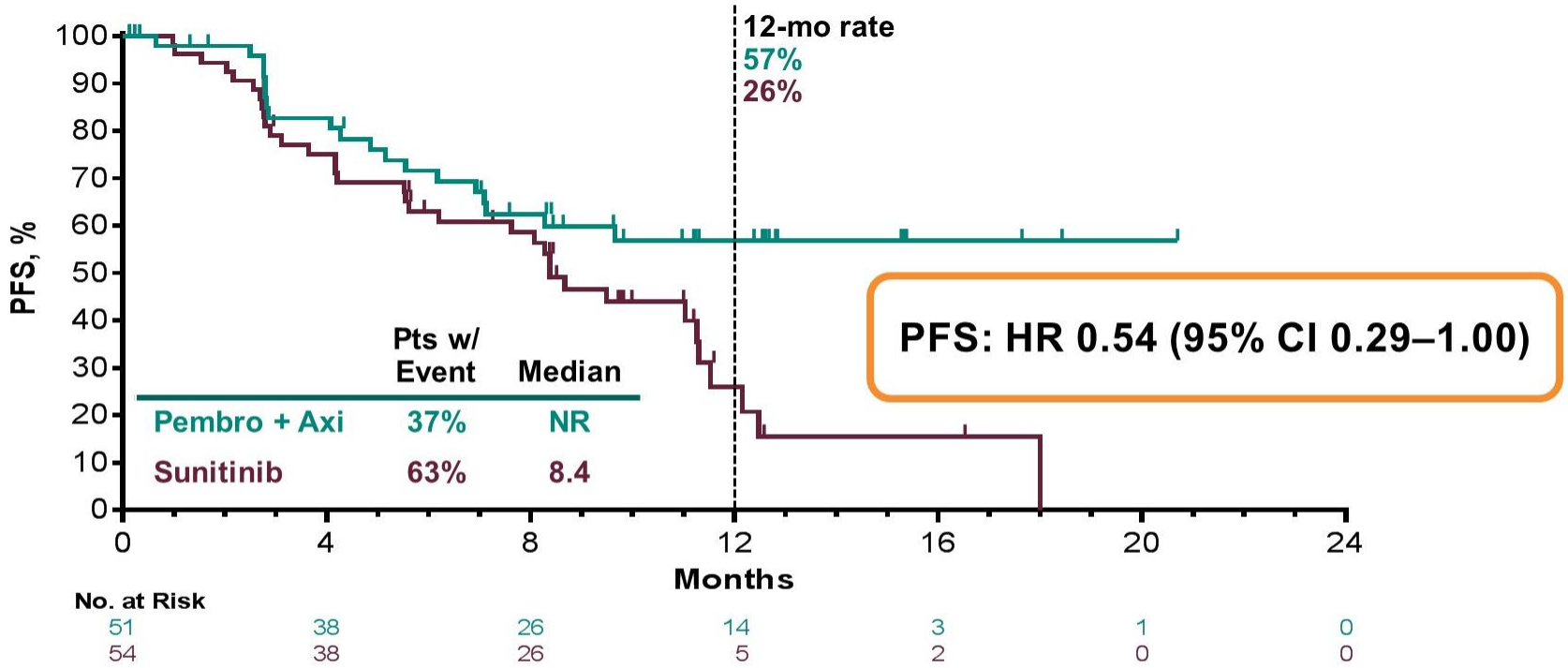
Data cutoff date: Aug 24, 2018.



Data cutoff date: Aug 24, 2018.

Rini et al, ASCO 2019.

PFS in presence of sarcomatoid features



PFS: HR 0.54 (95% CI 0.29–1.00)

OS: HR 0.58 (95% CI 0.21–1.59); median NR in either arm[b]

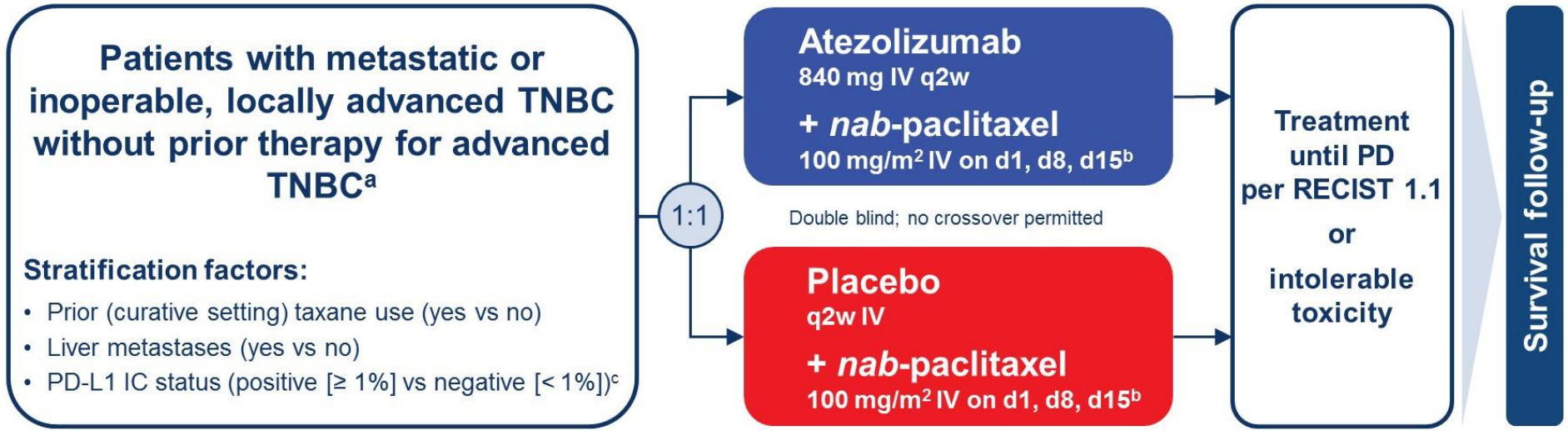
[a]Among the 578 participants with known status assessed by local pathology review and as indicated on the eCRF. [b]Pts who died: 16% in the pembro + axi arm, 20% in the sunitinib arm.
Data cutoff date: Aug 24, 2018.

Rini et al, ASCO 2019.

IMpassion130: Updated OS from a global, randomized, double-blind, placebo-controlled, Phase III study of atezolizumab + *nab*-paclitaxel in previously untreated locally advanced or metastatic TNBC

Peter Schmid, Sylvia Adams, Hope S. Rugo, Andreas Schneeweiss, Carlos H. Barrios, Hiroji Iwata, Veronique Dieras, Volkmar Henschel, Luciana Molinero, Stephen Y. Chui, Amreen Husain, Eric P. Winer, Sherene Loi, Leisha A. Emens

IMpassion130 study design

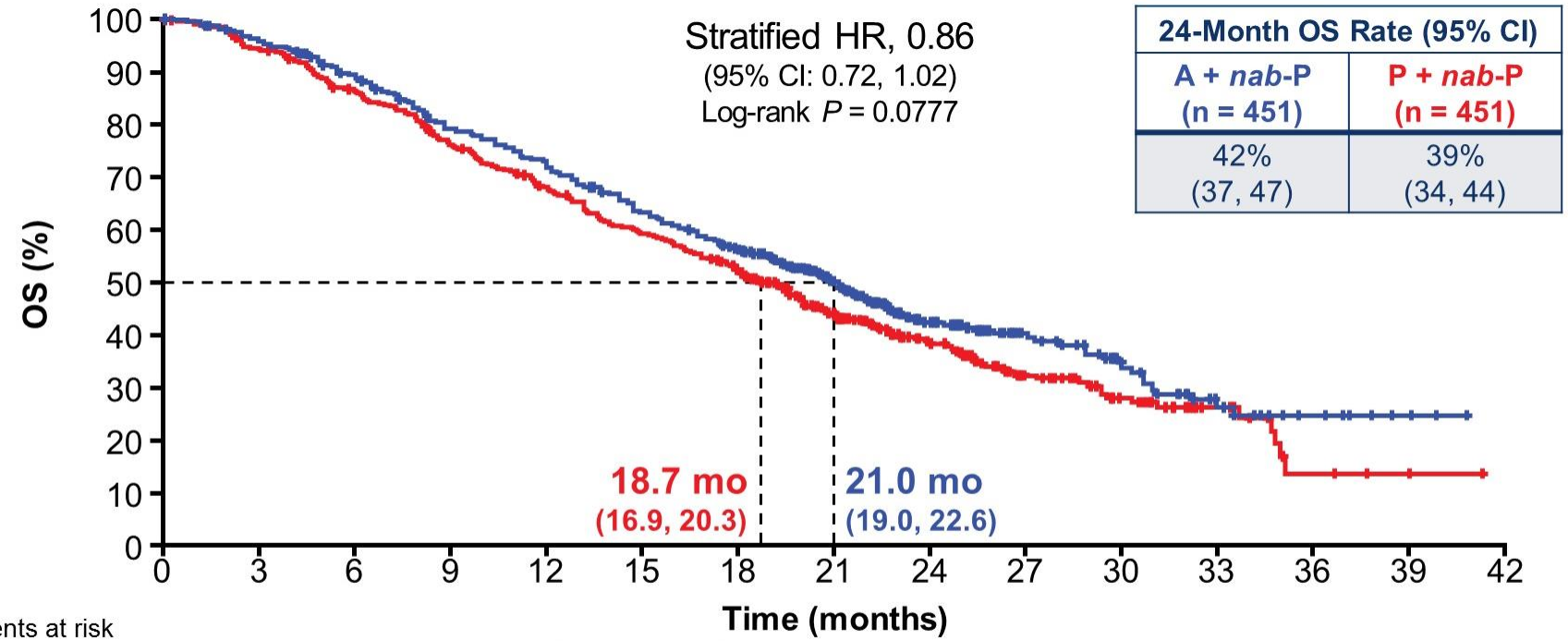


- Co-primary endpoints in ITT and PD-L1 IC+: PFS and OS[d]
- Pre-specified hierarchical testing of OS in ITT and, if significant, in PD-L1 IC+ patients
- In both treatment arms, 41% of patients were PD-L1 IC+

[a] Prior chemotherapy in the curative setting allowed if treatment-free interval ≥ 12 months. [b] 28-day cycle. [c] Centrally evaluated per VENTANA SP142 IHC assay.
[d] Efficacy endpoints assessed by investigators per RECIST 1.1. NCT02425891.

Schmid et al, ASCO 2019.

OS in ITT population



24-Month OS Rate (95% CI)	
A + *nab*-P (n = 451)	P + *nab*-P (n = 451)
42% (37, 47)	39% (34, 44)

Patients at risk

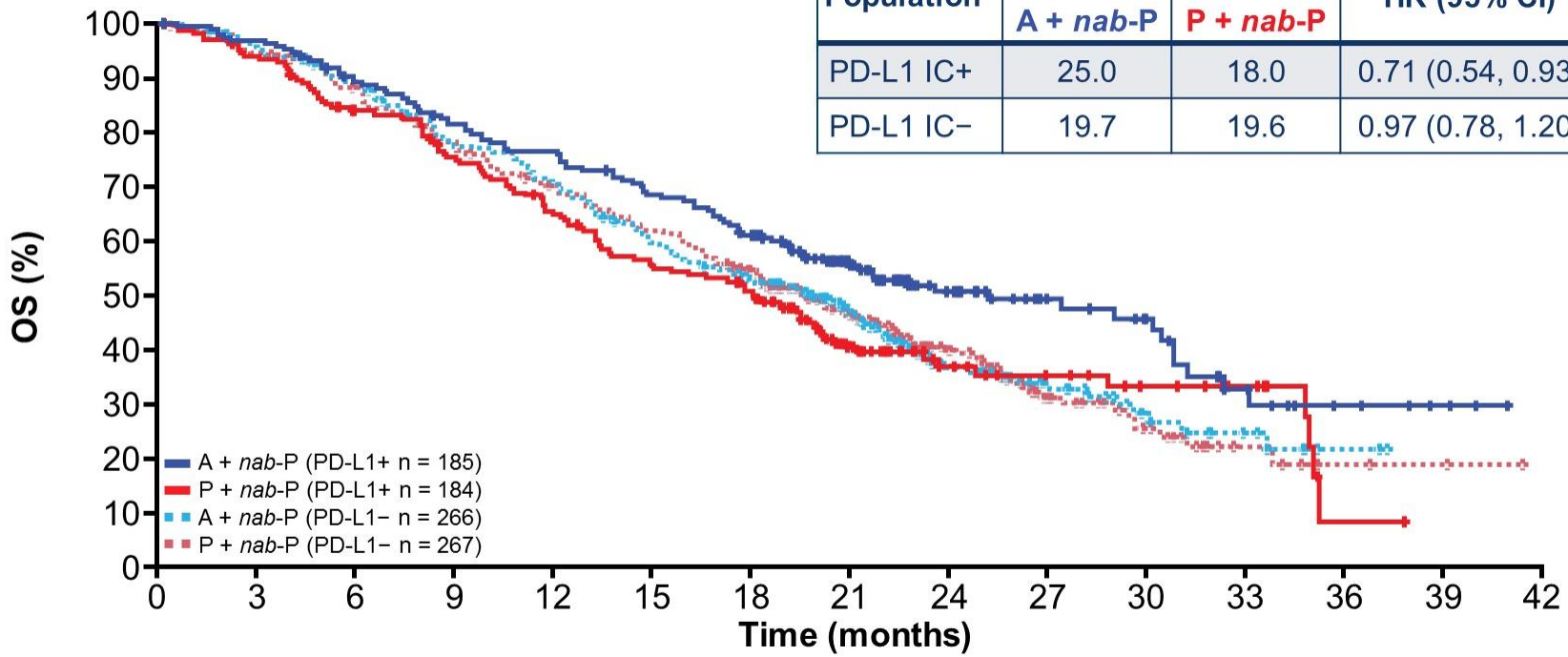
A + *nab*-P	451	426	389	342	312	270	235	162	88	56	35	19	8	3	NE
P + *nab*-P	451	420	376	329	291	252	216	145	87	51	33	17	4	1	NE

NE, not estimable. Clinical cutoff date: January 2, 2019. Median PFS (95% CI) is indicated on the plot. Median FU (ITT): 18.0 mo.

Schmid et al, ASCO 2019.

Comparison of OS in PD-L1+ and PD-L1- populations

Population	Median OS, mo		HR (95% CI)
	A + *nab*-P	P + *nab*-P	
PD-L1 IC+	25.0	18.0	0.71 (0.54, 0.93)
PD-L1 IC−	19.7	19.6	0.97 (0.78, 1.20)



Clinical cutoff date: January 2, 2019.

Schmid et al, ASCO 2019.

Neoadjuvant checkpoint blockade in NSCLC

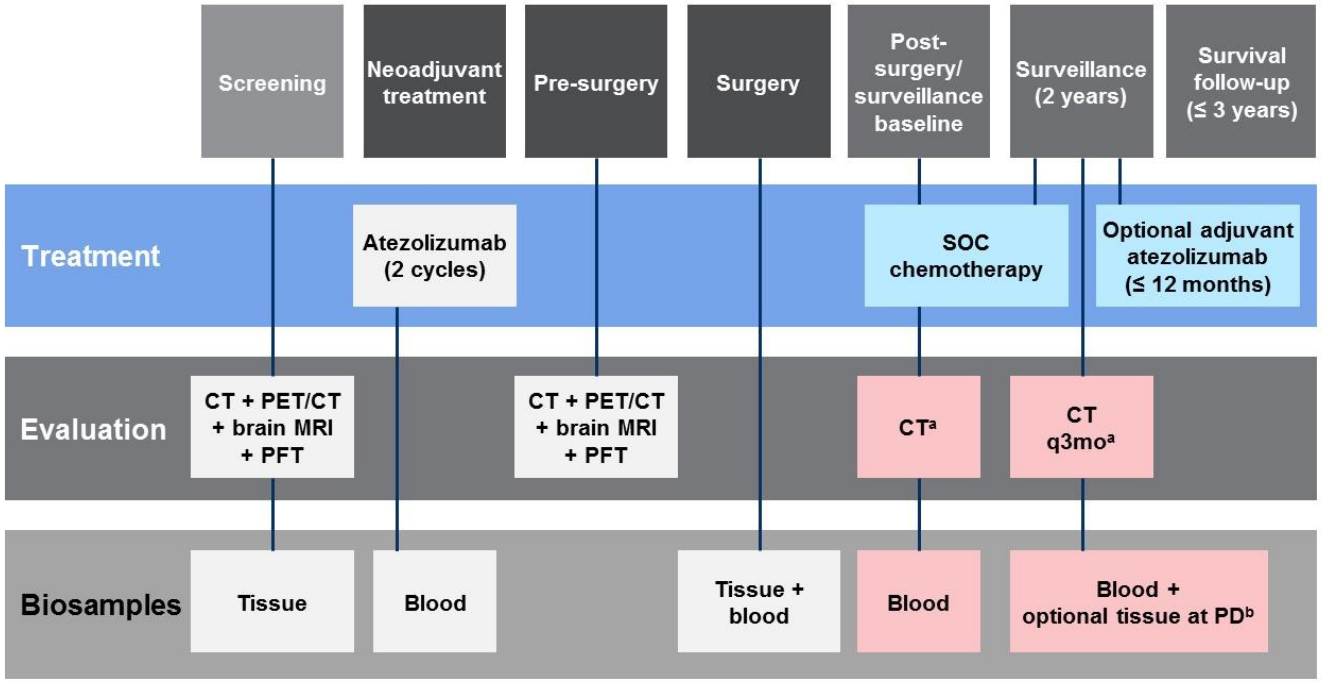
- Possibility of inducing major pathologic response prior to surgical intervention

- Atezolizumab
  - LCMC3
- Nivolumab or nivolumab + ipilimumab
  - NEOSTAR

Neoadjuvant atezolizumab in resectable non-small cell lung cancer: Interim analysis and biomarker data from a multicenter study (LCMC3)

David J. Kwiatkowski, Valerie W. Rusch, Jamie E. Chaft, Bruce E. Johnson, Alan Nicholas, Ignacio Ivan Wistuba, Robert Merritt, Jay M. Lee, Paul A. Bunn, Yan Tang, See-Chun Phan, Saiama Naheed Waqar, Alexander Patterson, Eric B. Haura, Eric M. Toloza, Karen L. Reckamp, Dan Raz, Katja Schulze, Ann Johnson, David Paul Carbone

LCMC3 study design



Primary endpoint:

- MPR at surgical resection, defined as ≤ 10% viable tumor cells

Secondary endpoints:

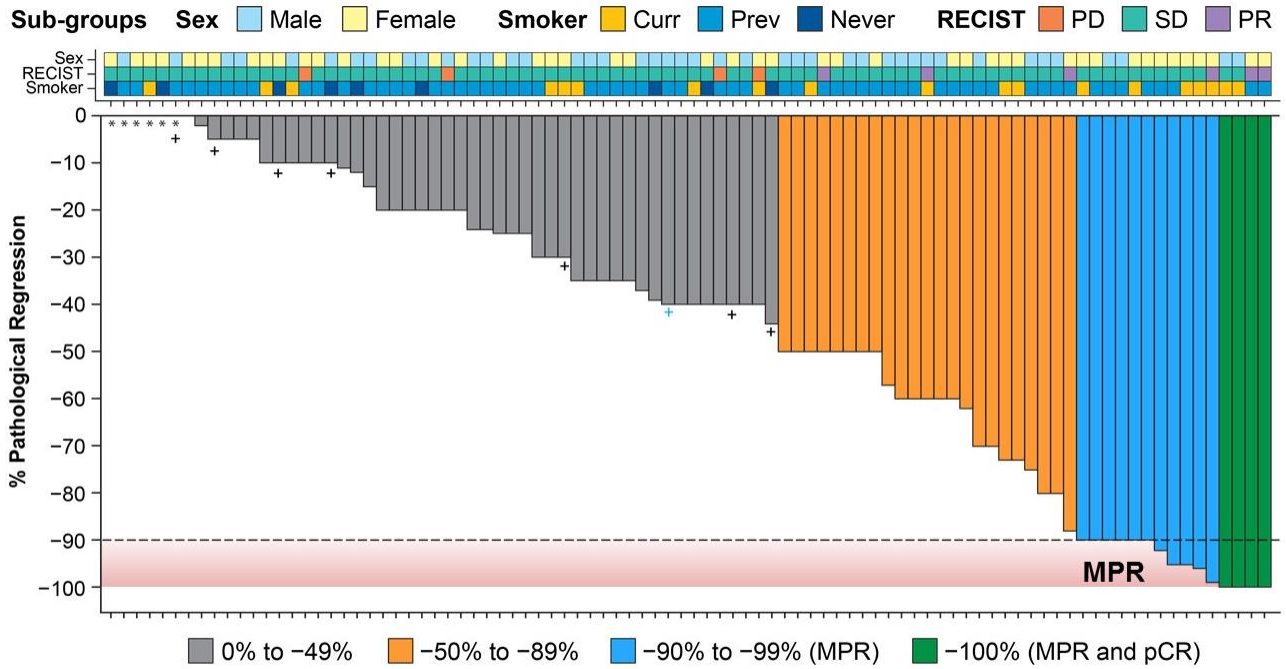
- Disease-free survival
- Response rate by RECIST 1.1
- OS
- Biomarkers
- Adverse events

MPR, major pathologic response, locally assessed; PFT, pulmonary function test; q3mo, every 3 months.
[a] Extended chest CT, including liver and adrenals. [b] At progression and/or recurrence. NCT02927301.

MPR (major pathologic response): residual viable tumor cells ≤10% of tumor bulk, Forde et al, *NEJM* 2018

Kwiatkowski et al, ASCO 2019.

Pathological regression in intended surgery population (n=90)



Patients in intended surgery population (n = 90)

- PR: 6 (7%); SD: 80 (89%); PD: 4 (4%)
- 3 of 8 EGFR/ALK+ had 40% to 50% pathological regression

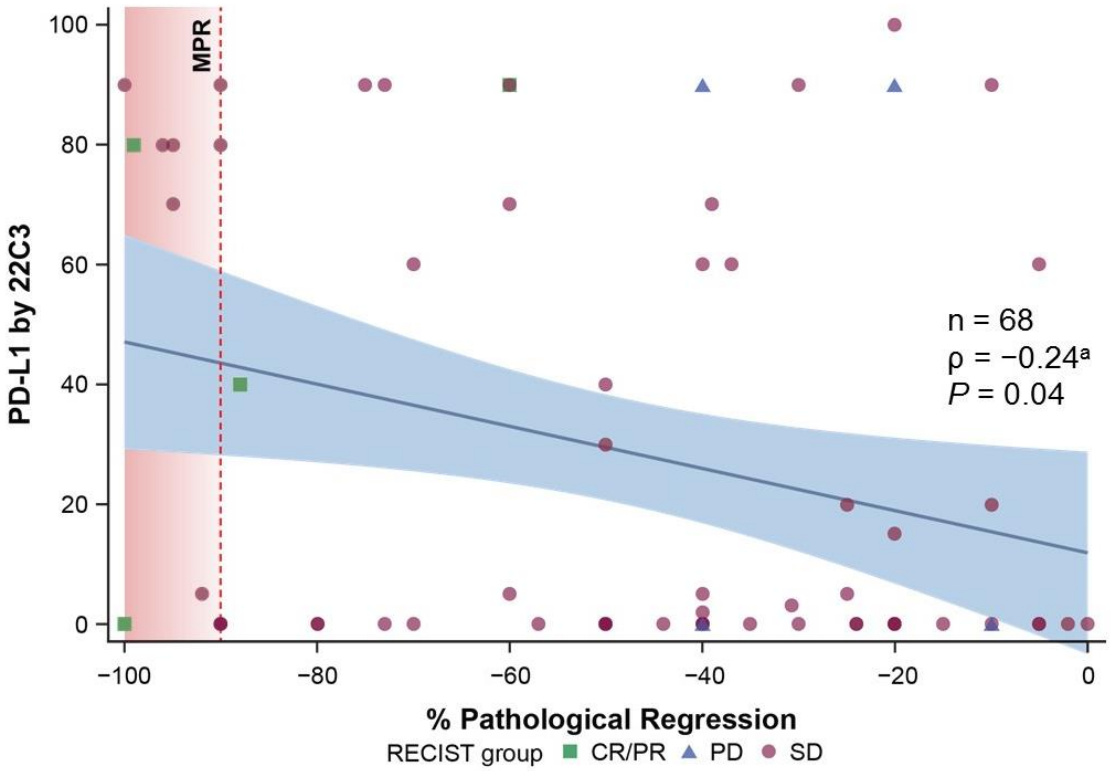
Primary efficacy population (n = 77)

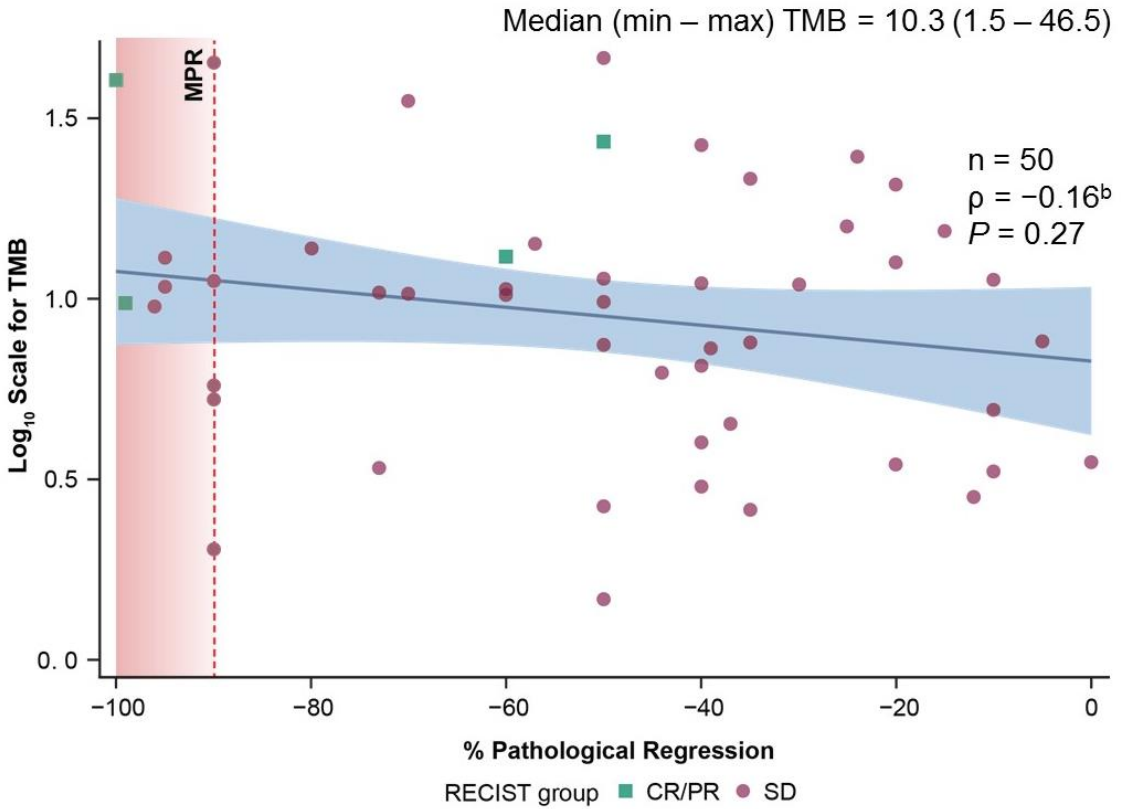
- MPR: 15 of 77 (19%; 95%CI: 11%, 30%)
- pCR: 4 of 77 (5%) patients
- 38 of 77 (49%) had ≥ 50% pathological regression

Pathologic regression defined as % viable tumor cells – 100%. pCR, pathologic complete response.
[a] 1 EGFR+ patient had aborted surgery. * Pathologic response could not be assessed. + EGFR+. + ALK+.

Kwiatkowski et al, ASCO 2019.

MPR observed in all PD-L1 and TMB levels





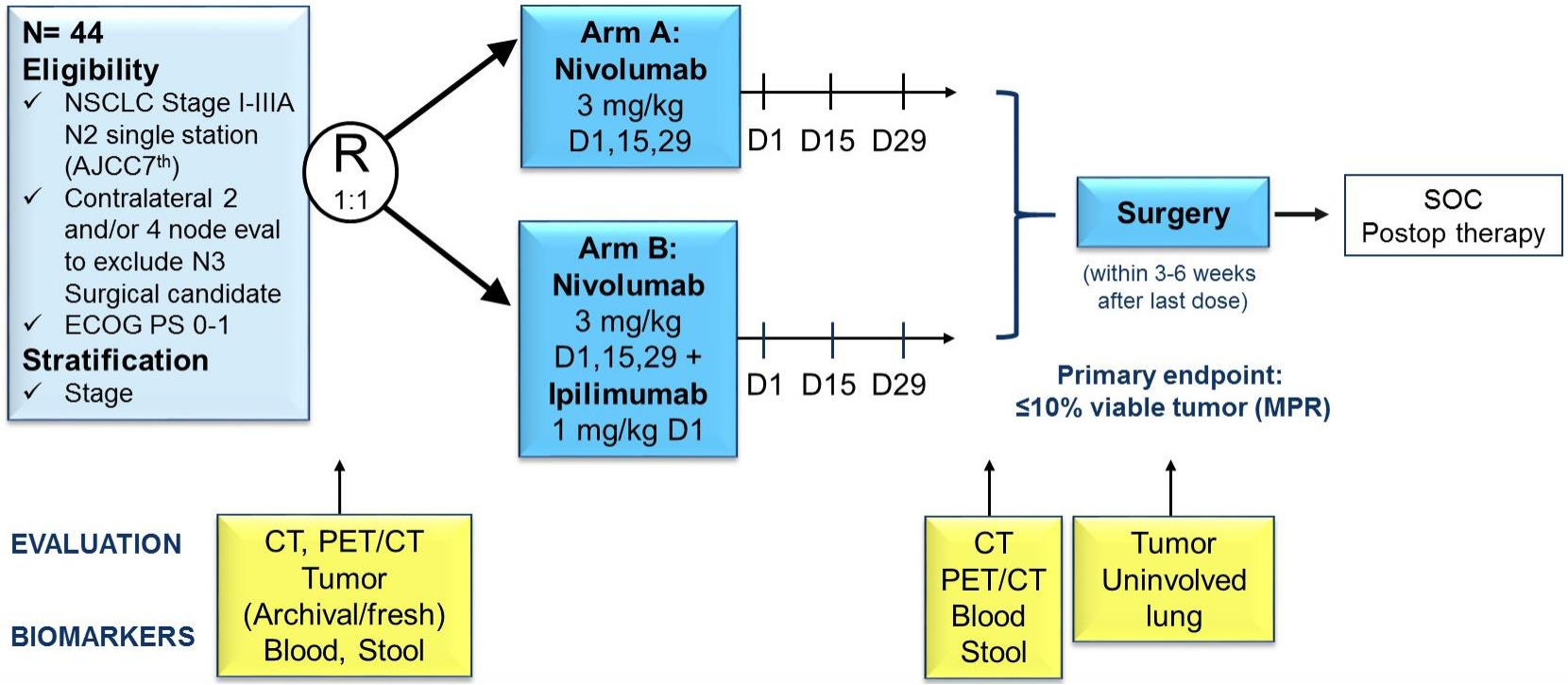
Kwiatkowski et al, ASCO 2019.

Neoadjuvant nivolumab (N) or nivolumab plus ipilimumab (NI) for resectable non-small cell lung cancer: Clinical and correlative results from the NEOSTAR study

Tina Cascone, William Nassib William, Annikka Weissferdt, Heather Y. Lin, Cheuk Hong Leung, Brett W. Carter, Frank V. Fossella, Frank Mott, Vassiliki Papadimitrakopoulou, George R. Blumenschein, Jr., Xiuning Le, Lorenzo Federico, Edwin Roger Parra Cuentas, Chantale Bernatchez, Ignacio Ivan Wistuba, Ara A. Vaporciyan, Don Lynn Gibbons, Stephen Swisher, John Heymach, Boris Sepesi, NEOSTAR Study Group

NEOSTAR study design

NEOSTAR: phase II study of induction checkpoint blockade for untreated stage I-IIIA NSCLC amenable for surgical resection

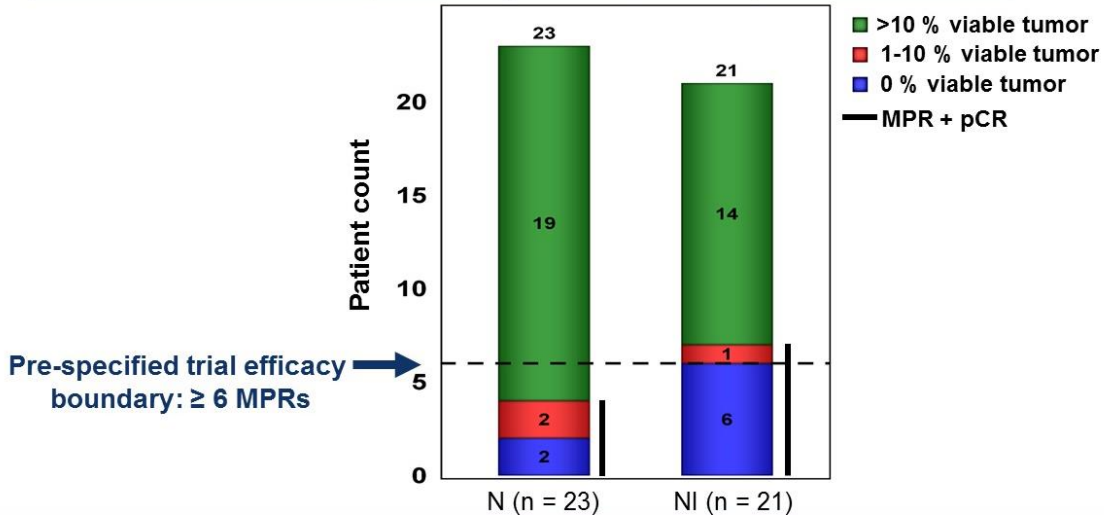


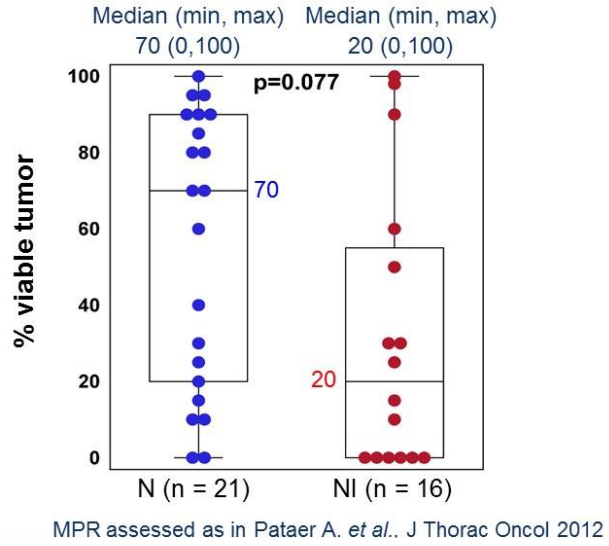
Cascone et al, ASCO 2019.

MPR rate: NI met pre-specified trial boundary

Overall ITT Resected + not resected*	Total n = 44	N n = 23	NI n = 21
MPR + pCR	**11 (25%)**	**4 (17%)** (95% CI:5%,39%)	**7 (33%)** (95% CI:15%,57%)
0% viable tumor (pCR)	8 (18%)	2 (9%)	6 (29%)
1-10% viable tumor	3 (7%)	2 (9%)	1 (5%)

Evaluable* Resected on trial	Total n = 37	N n = 21	NI n = 16
MPR + pCR	**11 (30%)**	**4 (19%)**	**7 (44%)**
0% viable tumor (pCR)	8 (22%)	2 (10%)	6 (38%)
1-10% viable tumor	3 (8%)	2 (10%)	1 (6%)

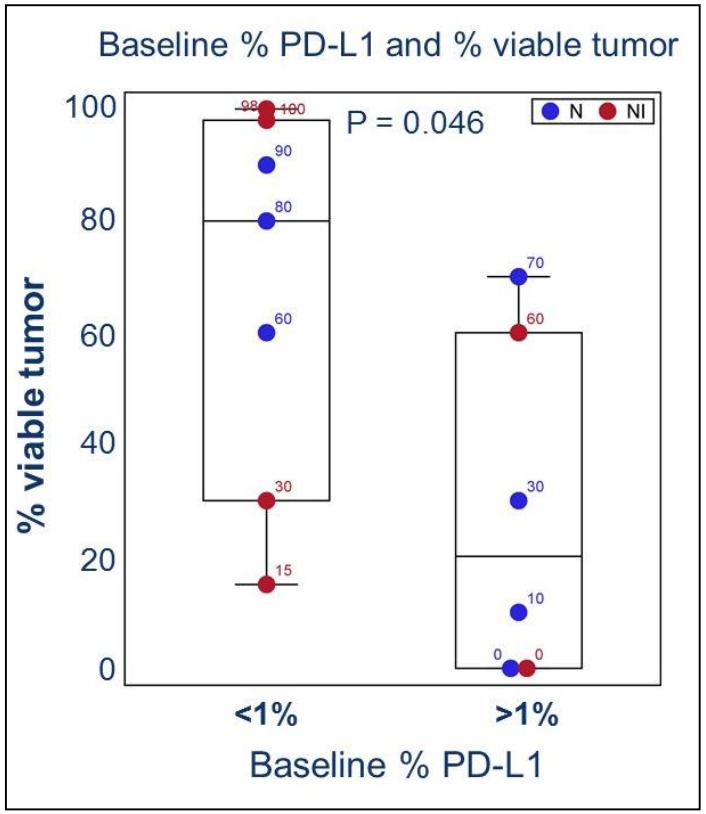


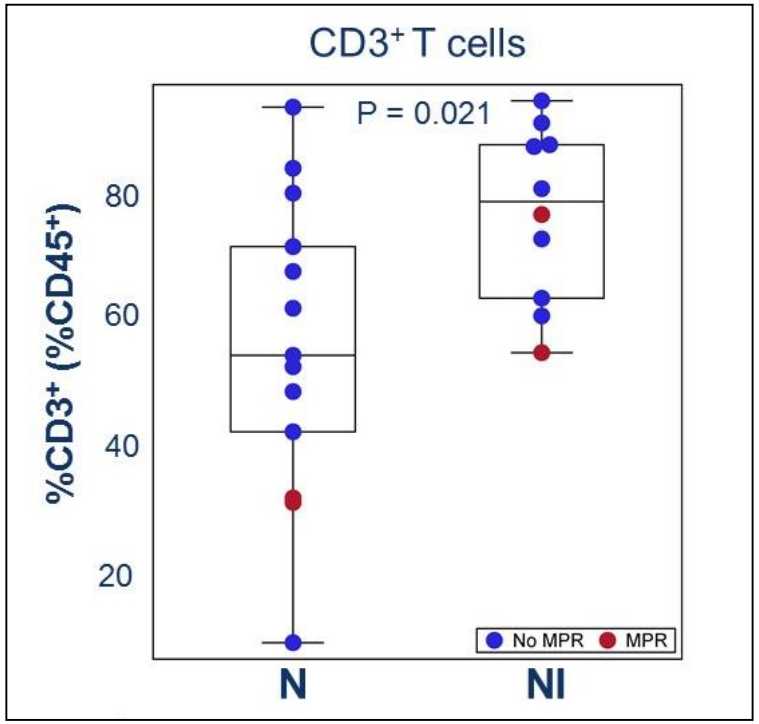


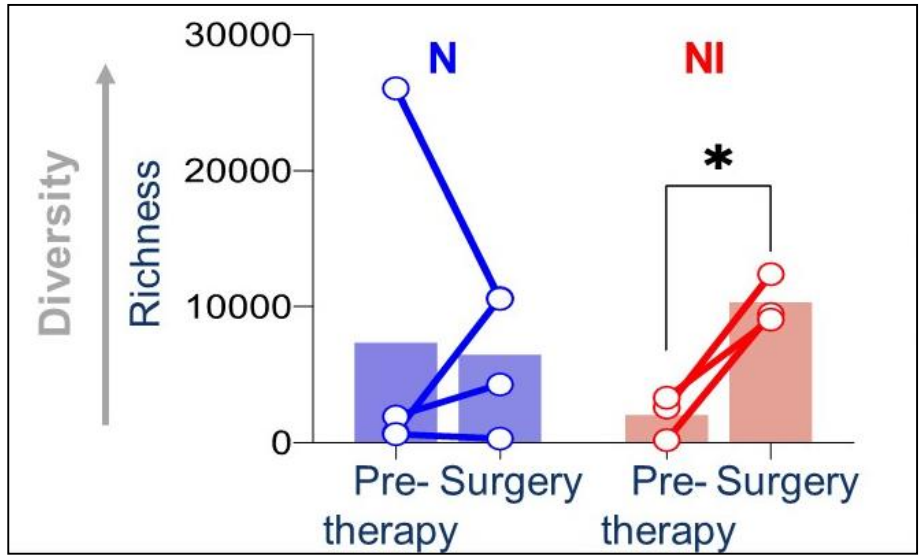
MPR assessed as in Pataer A. *et al.*, J Thorac Oncol 2012

Cascone et al, ASCO 2019.

Correlative results







Cascone et al, ASCO 2019.

Summary of studies

Study	Population	Arm(s)	Take-home results
KEYNOTE-048	R/M HNSCC – 1st line	• Pembrolizumab (P) • Pembrolizumab + chemo (P+C) • Chemo (EXTREME, E)	• OS improved for P+C over E in all groups • OS improved for P over E in PD-L1(+) • Longer DOR with P-containing regimens
KEYNOTE-426	Stage IV ccRCC – 1st line	• Pembrolizumab + axitinib • Sunitinib	• Tumor shrinkage increased with P+A over S • OS, PFS, ORR benefit seen with P+A across key subgroups
IMpassion130	mTNBC – 1st line	• Atezolizumab + *nab*-paclitaxel • Placebo + *nab*-paclitaxel	• PD-L1 IHC predicts benefit from atezolizumab • First evidence of IO benefit in 1st-line TNBC
LCMC3	Early-stage NSCLC - neoadjuvant	2 cycles of atezolizumab prior to resection	• Encouraging pCR and MPR rates • Atezolizumab well-tolerated
NEOSTAR	Early-stage NSCLC - neoadjuvant	• Nivolumab • Nivolumab + ipilumumab	• N+I met pre-specified MPR effectiveness boundary • N+I increased TILs, diversity, reactivity

Conclusions – First-line and Neoadjuvant Studies

- Benefits seen in both first-line and neoadjuvant settings for immune checkpoint inhibitors
- Often conflicting/unclear biomarker study results
- Moving into earlier lines of therapy warrants the question: what to do after checkpoint relapse/resistance?

Conclusions – First-line and Neoadjuvant Studies

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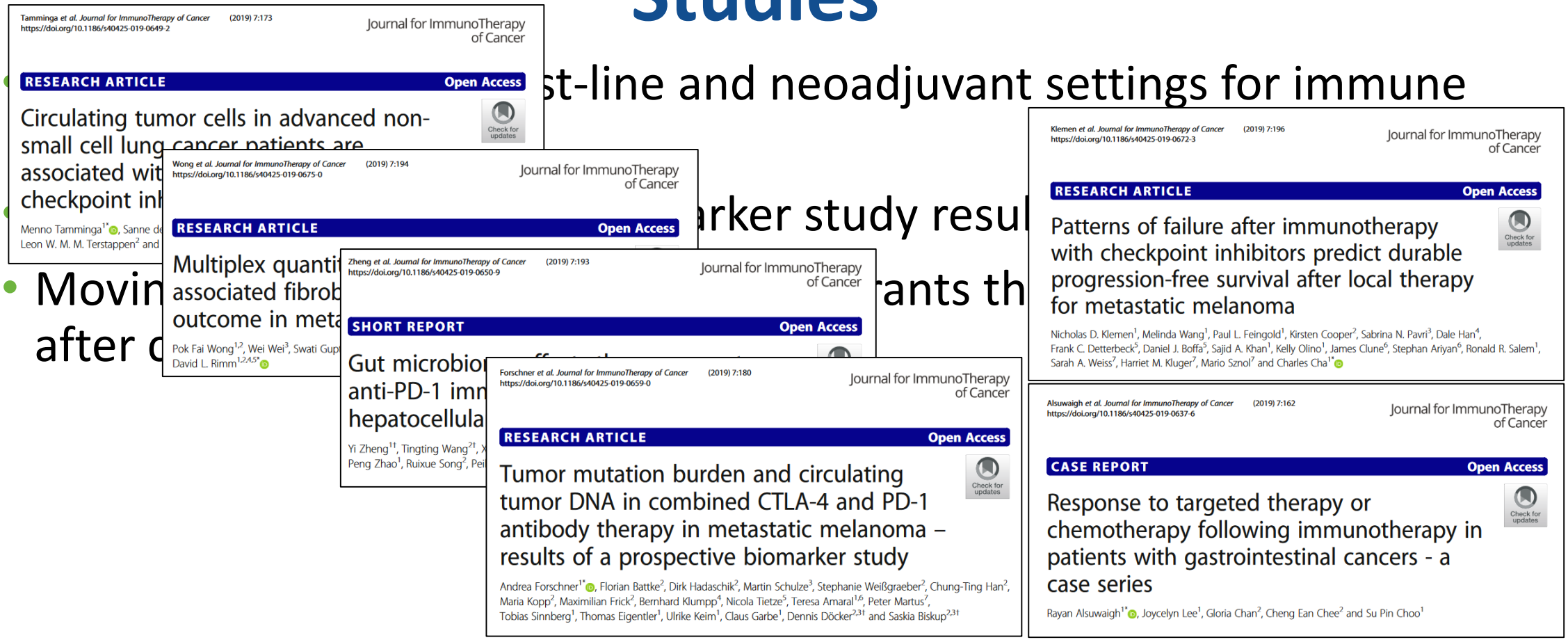
- arker study resul
- Movin ants th after c



Tamminga et al. Journal for ImmunoTherapy of Cancer (2019) 7:173
https://doi.org/10.1186/s40425-019-0649-2

Journal for ImmunoTherapy of Cancer

RESEARCH ARTICLE Open Access

Circulating tumor cells in advanced non-small cell lung cancer patients are associated wit checkpoint inh

Menno Tamminga[1*], Sanne de Leon W. M. M. Terstappen[2] and

Wong et al. Journal for ImmunoTherapy of Cancer (2019) 7:194
https://doi.org/10.1186/s40425-019-0675-0

Journal for ImmunoTherapy of Cancer

RESEARCH ARTICLE Open Access

Multiplex quanti associated fibrob outcome in meta

Pok Fai Wong[1,2], Wei Wei[3], Swati Gup David L. Rimm[1,2,4,5*]

Zheng et al. Journal for ImmunoTherapy of Cancer (2019) 7:193
https://doi.org/10.1186/s40425-019-0650-9

Journal for ImmunoTherapy of Cancer

SHORT REPORT Open Access

Gut microbio anti-PD-1 imm hepatocellula

Yi Zheng[1†], Tingting Wang[2†], X Peng Zhao[1], Ruixue Song[2], Pei

Forschner et al. Journal for ImmunoTherapy of Cancer (2019) 7:180
https://doi.org/10.1186/s40425-019-0659-0

Journal for ImmunoTherapy of Cancer

RESEARCH ARTICLE Open Access

Tumor mutation burden and circulating tumor DNA in combined CTLA-4 and PD-1 antibody therapy in metastatic melanoma – results of a prospective biomarker study

Andrea Forschner[1*], Florian Battke[2], Dirk Hadaschik[2], Martin Schulze[3], Stephanie Weißgraeber[2], Chung-Ting Han[2], Maria Kopp[2], Maximilian Frick[2], Bernhard Klumpp[4], Nicola Tietze[5], Teresa Amaral[1,6], Peter Martus[7], Tobias Sinnberg[1], Thomas Eigentler[1], Ulrike Keim[1], Claus Garbe[1], Dennis Döcker[2,3†] and Saskia Biskup[2,3†]

Klemen et al. Journal for ImmunoTherapy of Cancer (2019) 7:196
https://doi.org/10.1186/s40425-019-0672-3

Journal for ImmunoTherapy of Cancer

RESEARCH ARTICLE Open Access

Patterns of failure after immunotherapy with checkpoint inhibitors predict durable progression-free survival after local therapy for metastatic melanoma

Nicholas D. Klemen[1], Melinda Wang[1], Paul L. Feingold[1], Kirsten Cooper[2], Sabrina N. Pavri[3], Dale Han[4], Frank C. Detterbeck[5], Daniel J. Boffa[5], Sajid A. Khan[1], Kelly Olino[1], James Clune[6], Stephan Ariyan[6], Ronald R. Salem[1], Sarah A. Weiss[7], Harriet M. Kluger[7], Mario Sznol[7] and Charles Cha[1*]

Alsuwaigh et al. Journal for ImmunoTherapy of Cancer (2019) 7:162
https://doi.org/10.1186/s40425-019-0637-6

Journal for ImmunoTherapy of Cancer

CASE REPORT Open Access

Response to targeted therapy or chemotherapy following immunotherapy in patients with gastrointestinal cancers - a case series

Rayan Alsuwaigh[1*], Joycelyn Lee[1], Gloria Chan[2], Cheng Ean Chee[2] and Su Pin Choo[1]

Society for Immunotherapy of Cancer

SITC Cancer Immunotherapy Guidelines

- Published:
  - Non-small cell lung cancer
  - Cutaneous melanoma
  - Bladder cancer
  - Hematologic malignancies
  - Renal cell carcinoma
  - Prostate carcinoma
  - Head and neck cancers
- Upcoming:
  - Acute leukemia
  - Lymphoma
  - Multiple myeloma
  - Toxicity – Checkpoints and ACT

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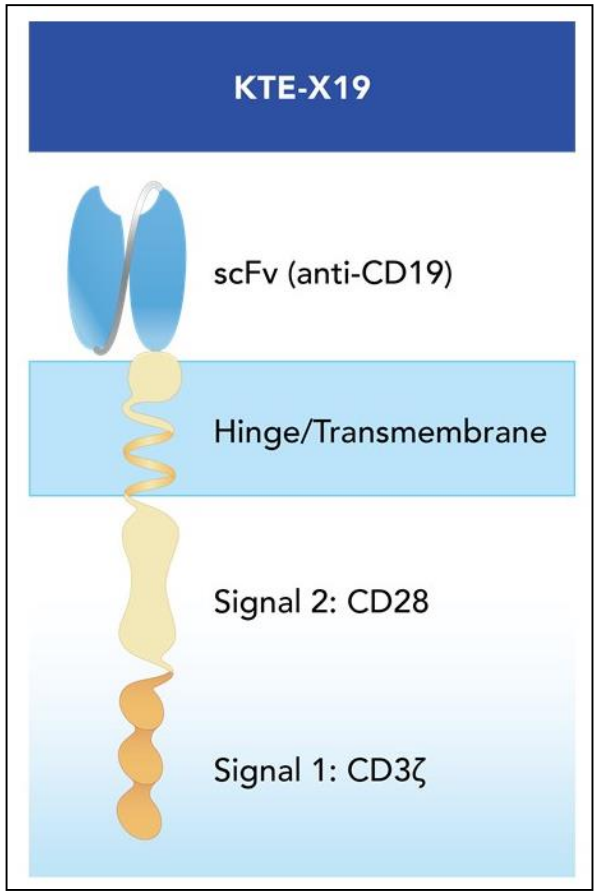
Cellular Therapies

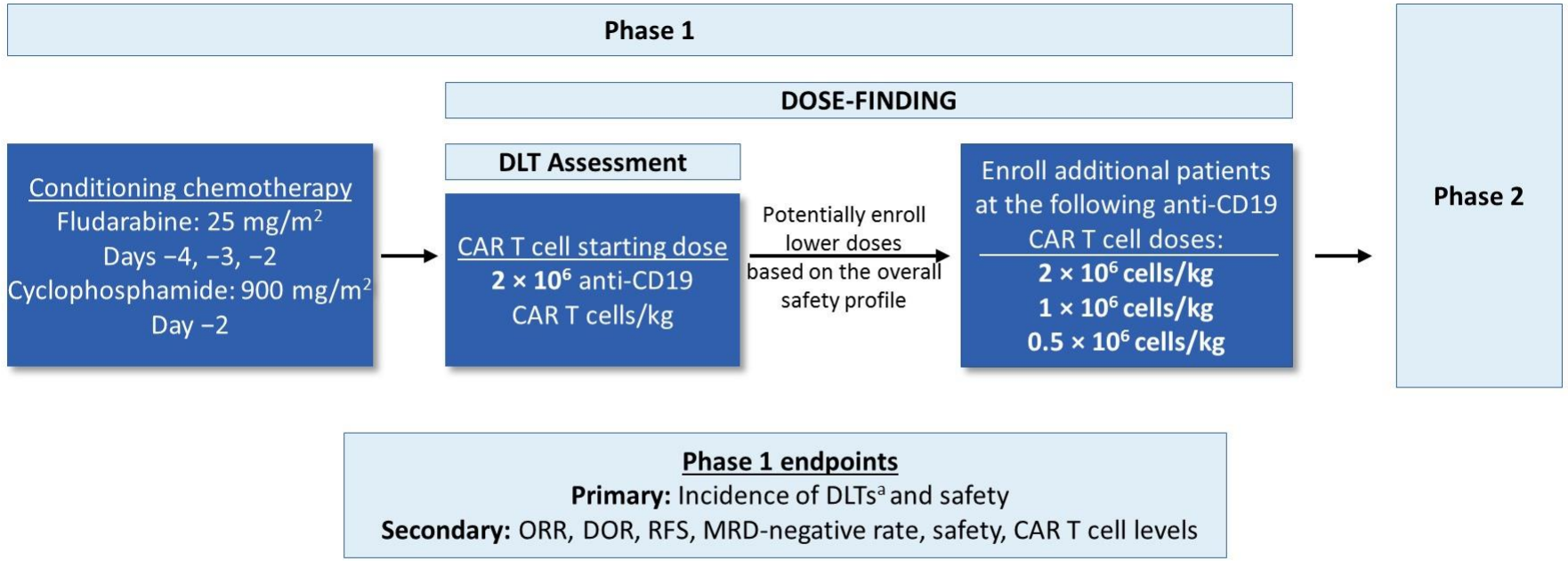
Kim A. Margolin, MD

End of phase 1 results of ZUMA-3, a phase 1/2 study of KTE-X19, an anti-CD19 chimeric antigen receptor T cell therapy, in adults with relapsed/refractory acute lymphoblastic leukemia

Bijal D. Shah, Michael Russell Bishop, Olalekan O. Oluwole, Aaron Logan, Maria R. Baer, William Bruce Donnellan, Kristen Marie Carr-O'Dwyer, Houston Holmes, Martha Lucia Arellano, Armin Ghobadi, John M. Pagel, Yi Lin, Ryan Daniel Cassaday, Jae Hong Park, Armen Mardiros, Tong Shen, Lovely Goyal, Remus Vezan, Rajul K. Jain, William G. Wierda

ZUMA-3 study design





[a]DLT defined as Grade 3 nonhematologic AEs lasting > 7 days and all Grade 4 nonhematologic AEs regardless of duration, with the exception of prespecified expected events (eg, tumor lysis syndrome) or Grade 4 hematologic AEs lasting > 30 days, except lymphopenia; within 28 days of initial infusion.
CAR, chimeric antigen receptor; DLT, dose-limiting toxicity; DOR, duration of response; MRD, minimal residual disease; ORR, objective response rate; RFS, relapse-free survival.

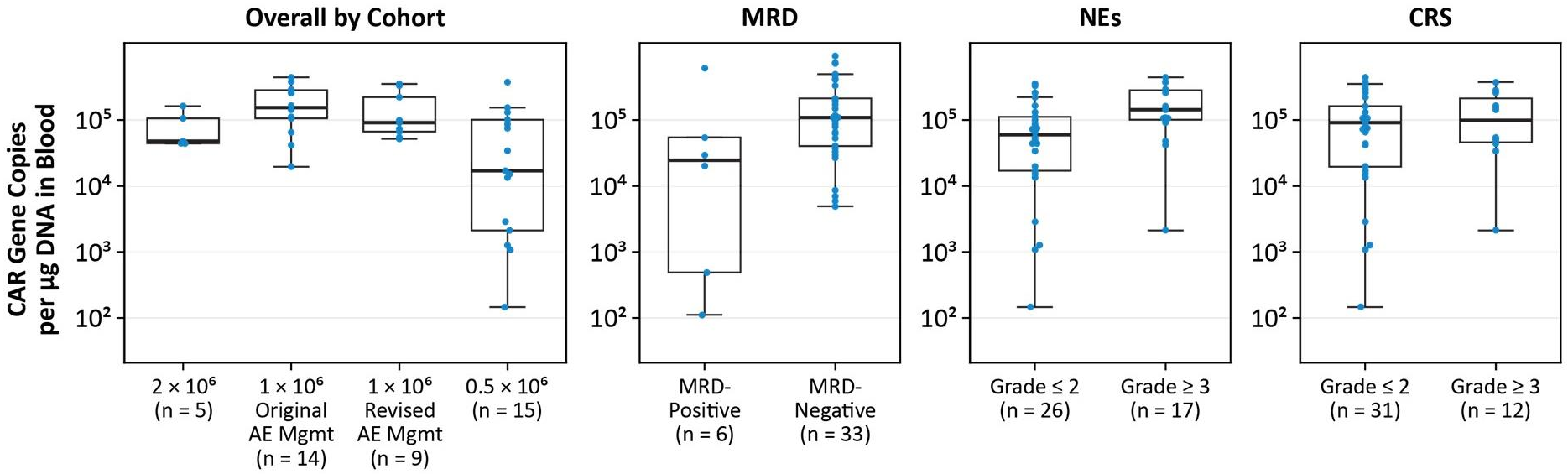
KTE-K19 (axicabtagene ciloleucel, Yescarta, is approved
adults with relapsed or refractory large B-cell lymphoma after ≥ 2 lines of systemic therapy

Shah et al, ASCO 2019.

Trial design and results

- Primary endpoint=DLT rate
- Additional endpoints
  - KTE-X19 levels
  - Incidence of Aes
  - MRD
  - CR/Cri
- Results
  - 45 pts treated, median f/u 16 mo
  - 66% had ≥3 prior Rxs
  - Median pre-Rx blasts 70%
  - Cell doses per kg
    - 6 at 2 x 10^6
    - 23 at 10^6
    - 16 at .5 x 10^6
- Toxicities
  - Management included early steroid, higher threshold tocilizumab
  - No DLT
  - 1/3 of pts had hypotension, fever, thrombocytopenia
  - 2 deaths from CRS
  - 1/3 of pts had neurotoxicity
  - 1/3 of pts had CRS
- Responses
  - Across dose levels, CR/Cri, MRD-neg in 70-80% range

Peak CAR T cell expansion in blood

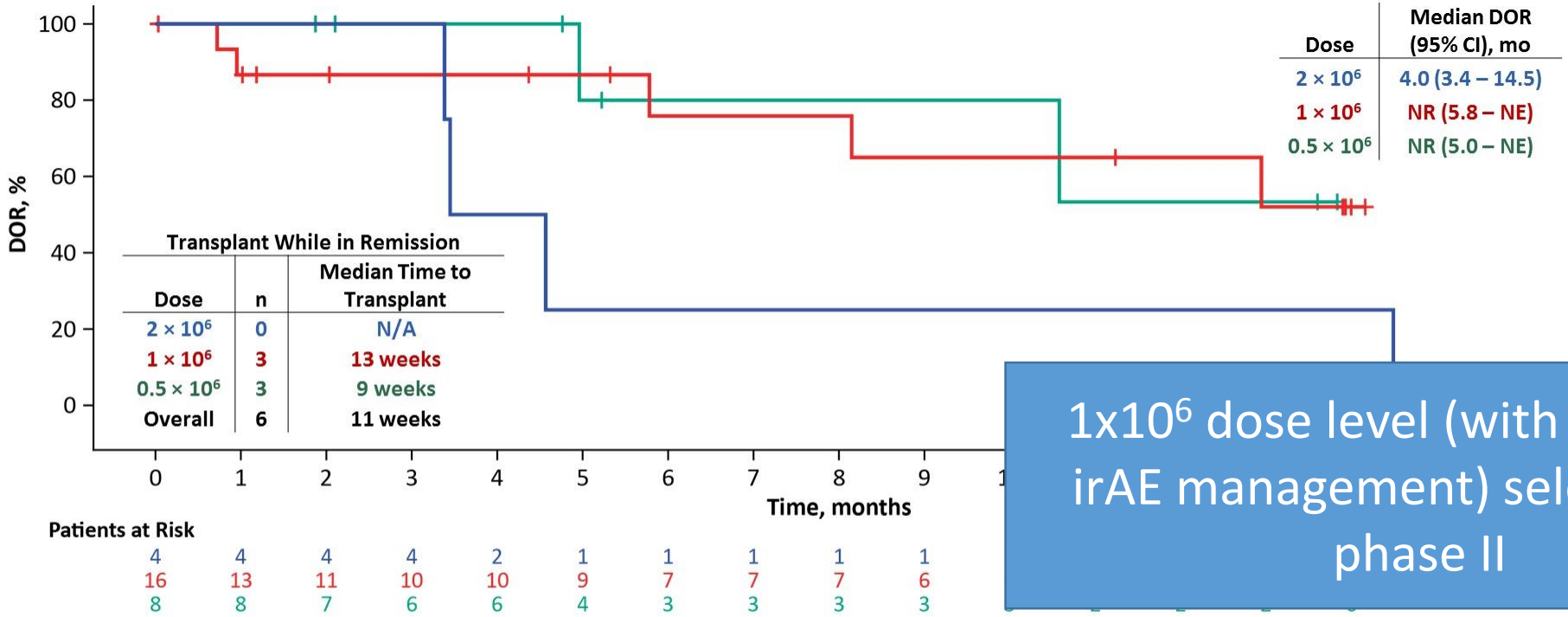


- Although sample size was limited, the median CAR T cell expansion was similar between the 1×10^6 dose groups with the revised and original AE management

AE, adverse event; CAR, chimeric antigen receptor; CRS, cytokine release syndrome; mgmt, management; MRD, minimal residual disease; NE, neurologic event; TEAE, treatment-emergent adverse event.

Shah et al, ASCO 2019.

Duration of remission (not censored at transplant)



1x10^6 dose level (with modified irAE management) selected for phase II

- Of the 6 patients who received transplant, 3 have ongoing remission as of the data cutoff

Figure includes all patients who achieved a CR + CRi with at least 2 months of follow up (n = 28) without censoring at transplant. Ticks indicate censored events.
DOR, duration of remission; N/A, not applicable; NE, not evaluable; NR, not reached.

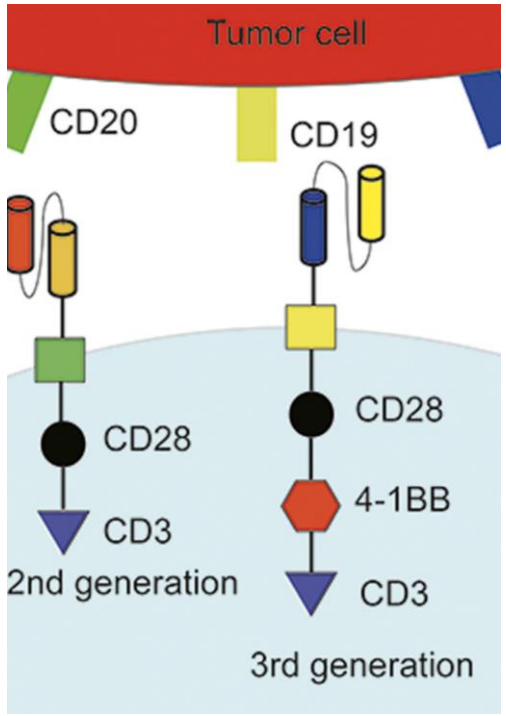
Shah et al, ASCO 2019.

Results of a phase I study of bispecific anti-CD19, anti-CD20 chimeric antigen receptor (CAR) modified T cells for relapsed, refractory, non-Hodgkin lymphoma

Nirav Niranjan Shah, Fenlu Zhu, Dina Schneider, Carolyn Taylor, Winfried Krueger, Andrew Worden, Walter L. Longo, Mehdi Hamadani, Timothy Fenske, Bryon Johnson, Boro Dropulic, Rimas Orentas, Parameswaran Hari

CD19/CD20 CAR T study design

Construct:
Lentiviral
4-IBB/CD3z



Cohort 1: Dose-escalation *CAR-T infusion split 30%/70% over 2 days* *3+3 design* DL0 = $2.5x10^5$ cells/kg DL1 = $7.5x10^5$ cells/kg DL2 = $2.5x10^6$ cells/kg **Completed**	**Cohort 3: Single infusion** *Single infusion of CAR-T cells* 6 patient cohort at selected dose from Cohort 1 **Actively enrolling**
Cohort 2: Dose-expansion *CAR-T infusion split 30%/70% over 2 days* 6 patient expansion at selected dose from Cohort 1 **Completed**	**Cohort 4: Exploratory Dose** *Single infusion of CAR-T cells* 3+3 cohort at $5x10^6$ cells/kg **Pending**

Shah NN et al, ASCO 2019.

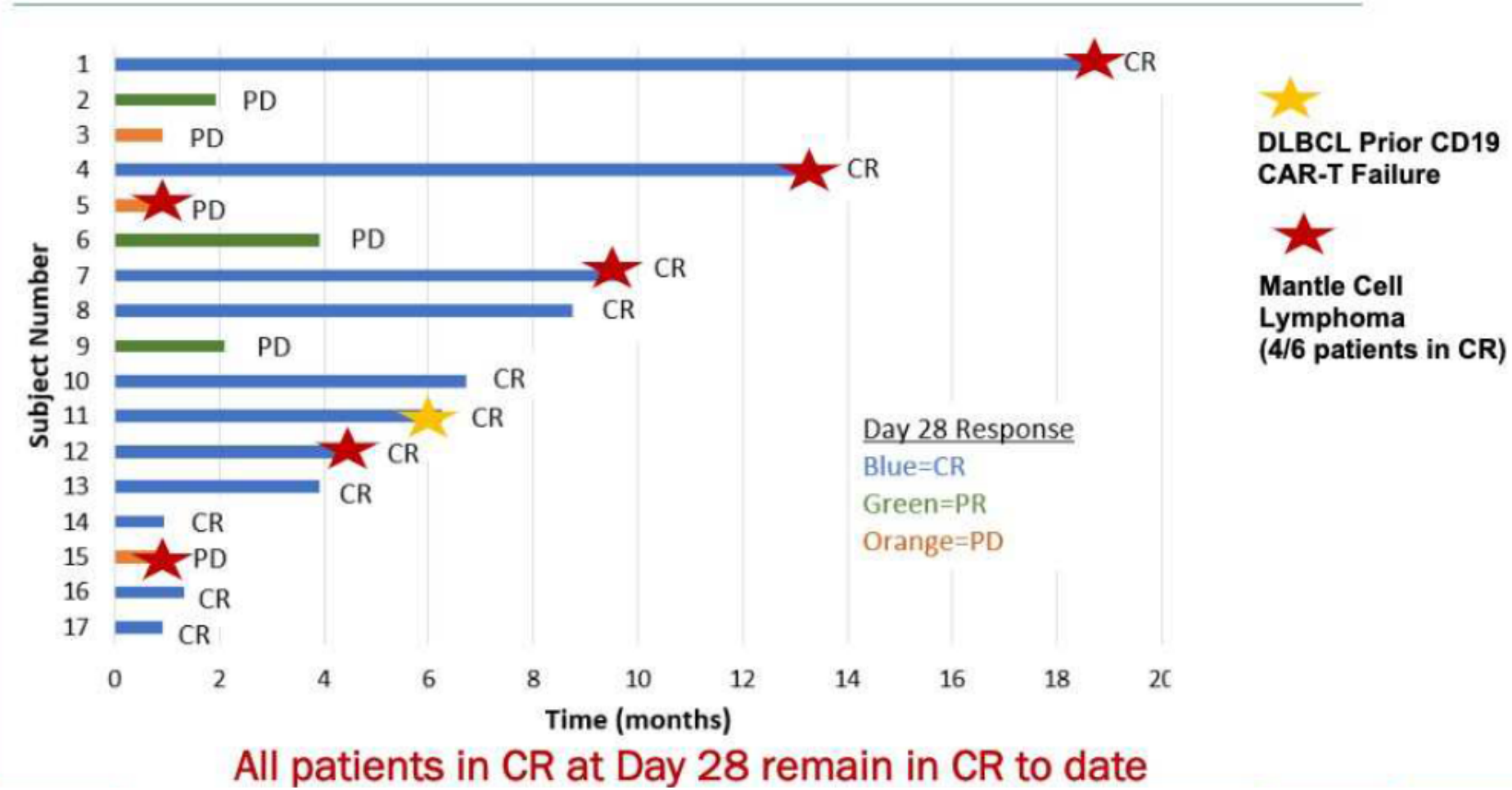
Primary outcome: Safety/Feasibility

- Feasibility (N=17) 100% CAR-T production, goal dose met in all pts
- Safety (N=17) No dose limiting toxicities to date, no ICU, no pressors
- RP2D (cells) 2.5 x 10^6/kg

Cytokine release syndrome (CRS)	Neurotoxicity (NTX)
• No grade 3-4 CRS • Grade 1 CRS = 7 patients (41%) • Grade 2 CRS = 4 patients (24%) • Tocilizumab = 5 patients (max 2 doses) • Corticosteroids = 5 patients (for CRS or NTX) • Median time to CRS = 7 days (0-13)	• Grade 1 NTX = 2 patients (12%) • Grade 2 NTX = 1 patient (6%) • Grade 3 = 2 pts • (no Grade 4) • Median time to NTX = 9 d (0-13)

Shah NN et al, ASCO 2019.

2º outcome: Response 82%—6/11 CR, 3/11 PR



All patients in CR at Day 28 remain in CR to date

Shah NN et al, ASCO 2019.

TRANSCEND CLL 004: Minimal residual disease (MRD) negative responses after lisocabtagene maraleucel (liso-cel; JCAR017), a CD19-directed CAR T cell product, in patients with relapsed/refractory chronic lymphocytic lymphoma (CLL/SLL)

Tanya Siddiqi, Kathleen Anne Dorritie, Jacob Drobnyk Soumerai, Deborah Marie Stephens, Jason A Dubovsky, Heidi H. Gillenwater, Lucy Gong, Jerill Thorpe, Lin Yang, William G. Wierda

TRANSCEND CLL 004 phase I study design

Key Eligibility

- Relapsed/refractory CLL/SLL
- Failed or ineligible for BTKi[a]
- High-risk disease[b]: failed ≥2 prior therapies
- Standard-risk disease: failed ≥3 prior therapies
- ECOG PS 0-1

Dose-Escalation: mTPI-2 Design[c]

28-day DLT period

Primary Objectives

Determine recommended dose

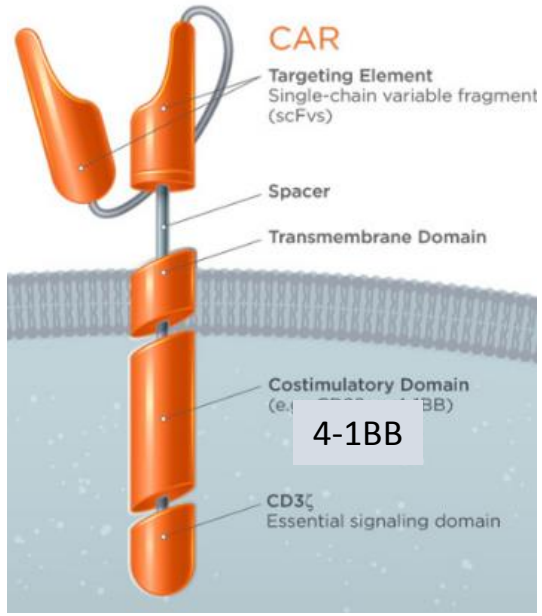
Safety

Exploratory Objectives

Antitumor activity

Pharmacokinetic profile

Dose Level	Dose	Evaluable (N=23)
1	50×10^6 CAR+ T cells	9
2	100×10^6 CAR+ T cells	14



[a]Failure defined as SD or PD as best response, or PD after previous response, or discontinuation due to intolerance (unmanageable toxicity). Ineligibility defined as requirement for full-dose anticoagulation or history of arrhythmia. [b]Complex cytogenetics abnormalities, del(17p), TP53 mutation, or unmutated IGHV. [c]Guo W et al. *Contemp Clin Trials*. 2017;58:23-33.
BTKi, Bruton tyrosine kinase inhibitor; CAR, chimeric antigen receptor; CLL, chronic lymphocytic leukemia; DLT, dose-limiting toxicity; ECOG PS, Eastern Cooperative Oncology Group Performance Status; IGHV, immunoglobulin heavy chain variable region; mTPI, modified toxicity probability interval for dose escalation; PD, progressive disease; SD, stable disease; SLL, small lymphocytic lymphoma.

Siddiqi et al, ASCO 2019.

Treatment-related adverse events

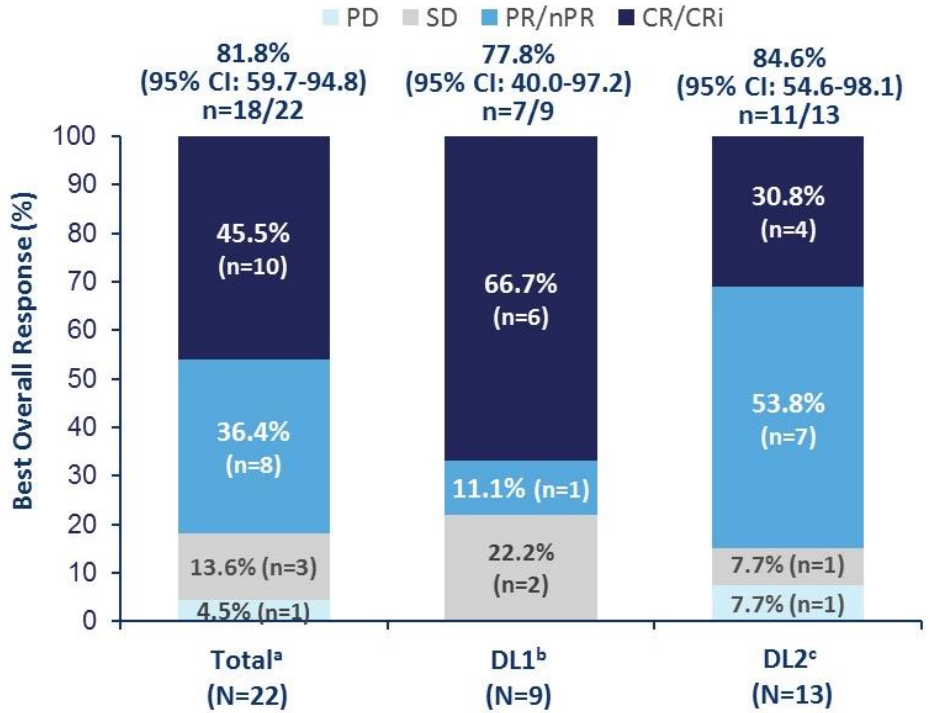
	All Grades (N=23)	Grade ≥3 (N=23)	DL1 Grade ≥3 (n=9)	DL2 Grade ≥3 (n=14)
Any TEAE, n (%)	**23 (100)**	**22 (95.7)**	8 (88.9)	14 (100)
Anemia	19 (82.6)	18 (78.3)	7 (77.8)	11 (78.6)
Cytokine release syndrome	17 (73.9)	2 (8.7)	0	2 (14.3)
Thrombocytopenia	17 (73.9)	16 (69.6)	4 (44.4)	12 (85.7)
Neutropenia	13 (56.5)	13 (56.5)	4 (44.4)	9 (64.3)
Leukopenia	11 (47.8)	10 (43.5)	4 (44.4)	6 (42.9)
Hypokalemia	9 (39.1)	0	0	0
Pyrexia	9 (39.1)	0	0	0
Nausea	8 (34.8)	0	0	0
Diarrhea	7 (30.4)	0	0	0
Hypophosphatemia	7 (30.4)	4 (17.4)	0	4 (28.6)
Tremor	7 (30.4)	0	0	0
Febrile neutropenia	6 (26.1)	5 (21.7)	0	5 (35.7)
Hypomagnesemia	6 (26.1)	0	0	0
Lymphopenia	6 (26.1)	6 (26.1)	2 (22.2)	4 (28.6)

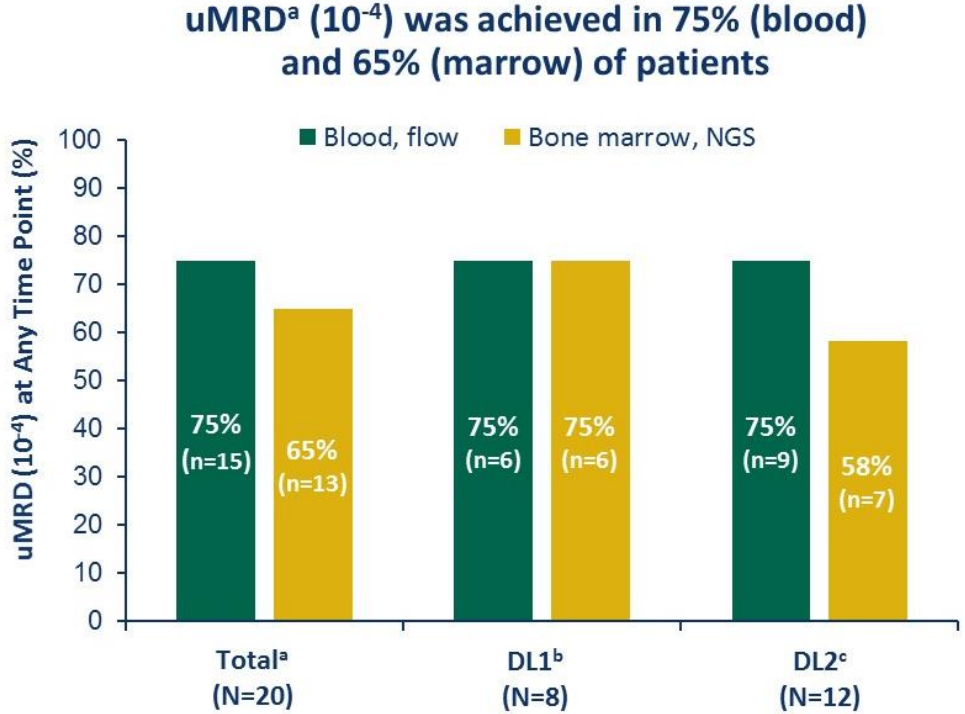
- **DLTs occurred in 2 patients receiving DL2:**
  - **Patient 1: G4 hypertension**
  - **Patient 2: G3 encephalopathy, G3 muscle weakness, G4 TLS**

DL, dose level; DLT, dose-limiting toxicity; G, grade; TEAE, treatment-emergent adverse event; TLS, tumor lysis syndrome.

Siddiqi et al, ASCO 2019.

Best overall response and undetectable MRD





Median study follow-up, 9 months | Minimum follow-up, 1 month

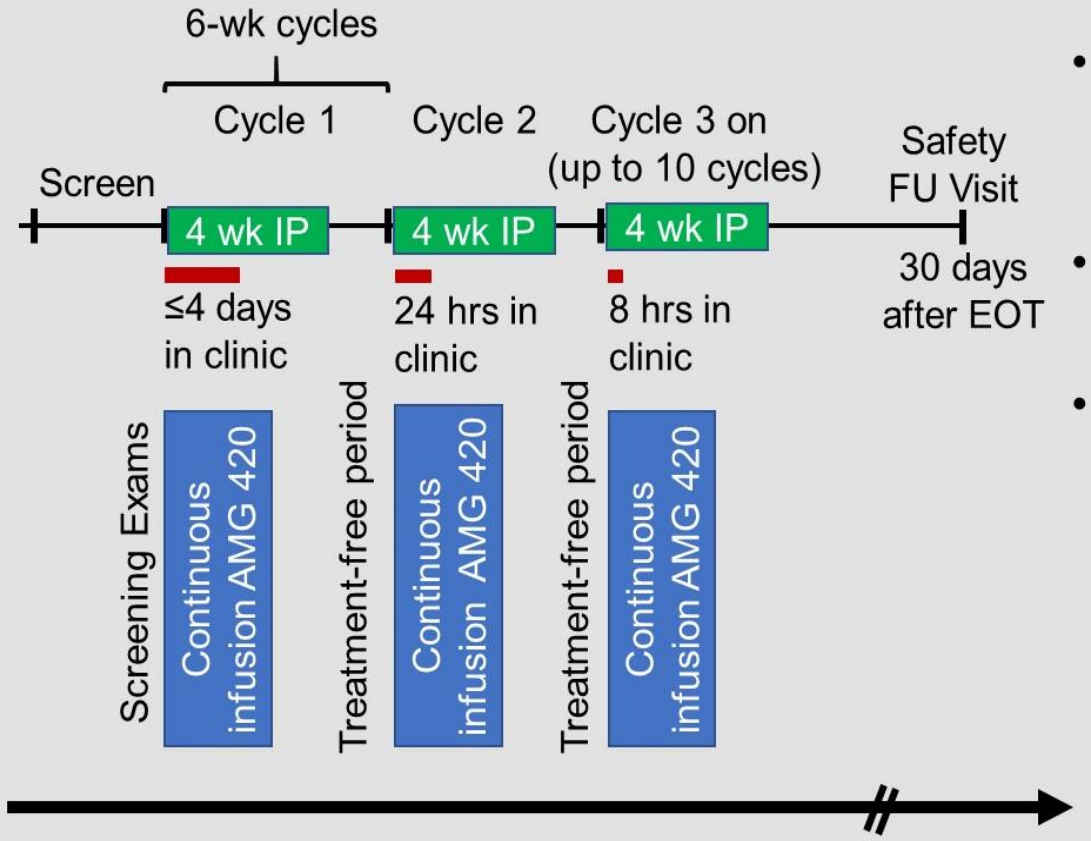
[a]Evaluable for response defined as having a pretreatment assessment and at least one postbaseline assessment; evaluable for MRD was defined as patients with detectable MRD at baseline. One patient was not evaluable for response. [b]50×10^6 CAR T+ cells. [c]100×10^6 CAR T+ cells.
CAR, chimeric antigen receptor; CI, confidence interval; CR, complete response; CRi, complete response with incomplete blood count recovery; DL, dose level; MRD, minimal residual disease; NGS, next-generation sequencing; nPR, nodular partial response; PD, progressive disease; PR, partial response; SD, stable disease; uMRD, undetectable minimal residual disease.

Siddiqi et al, ASCO 2019.

AMG 420, an anti-BCMA bispecific T-cell engager (BiTE®) molecule, in patients with R/R multiple myeloma: Updated results of a first-in-human phase 1 dose escalation study

Max S. Topp, Johannes Duell, Gerhard Zugmaier, Michel Attal, Philippe Moreau, Christian Langer, Jan Kroenke, Thierry Facon, Alexey Salnikov, Robin Lesley, Karl Beutner, James Kalabus, Erik Rasmussen, Kathrin Riemann, Alex C. Minella, Gerd Michael Munzert, Hermann Einsele

Study schematic & objectives



- First-in-human (FIH) phase 1 dose escalation study* of AMG 420 for up to 10 cycles, depending on response.
- Single-patient cohorts [0.2-1.6 µg/day (d)] were followed by cohorts of 3-6 patients (3.2-800 µg/d).
- Objectives of this phase 1 study of AMG 420 in patients with relapsed and/or refractory (R/R) MM included:
  - Assessing safety and tolerability per CTCAE 4.03
  - Determining the maximum tolerated dose (MTD)
  - Assessing anti-tumor activity

* NCT02514239. EOT, end of treatment; FU, follow-up; IP, investigational product.

Topp et al, ASCO 2019.

CRS and other serious adverse events

		N=42	# Gr 1	# Gr 2	# Gr 3	# Gr 4	# Gr 5
CRS	All treatment-related, max grade	16 (38%)	13	2	1	-	-
SAEs in ≥2 patients	Infections	13 (31%)	-	3	8	-	2*
	Peripheral polyneuropathy	2 (5%)	-	-	2	-	-
Treatment-related SAEs	Peripheral polyneuropathy	2 (5%)	-	-	2	-	-
	Edema	1 (2%)	-	-	1	-	-

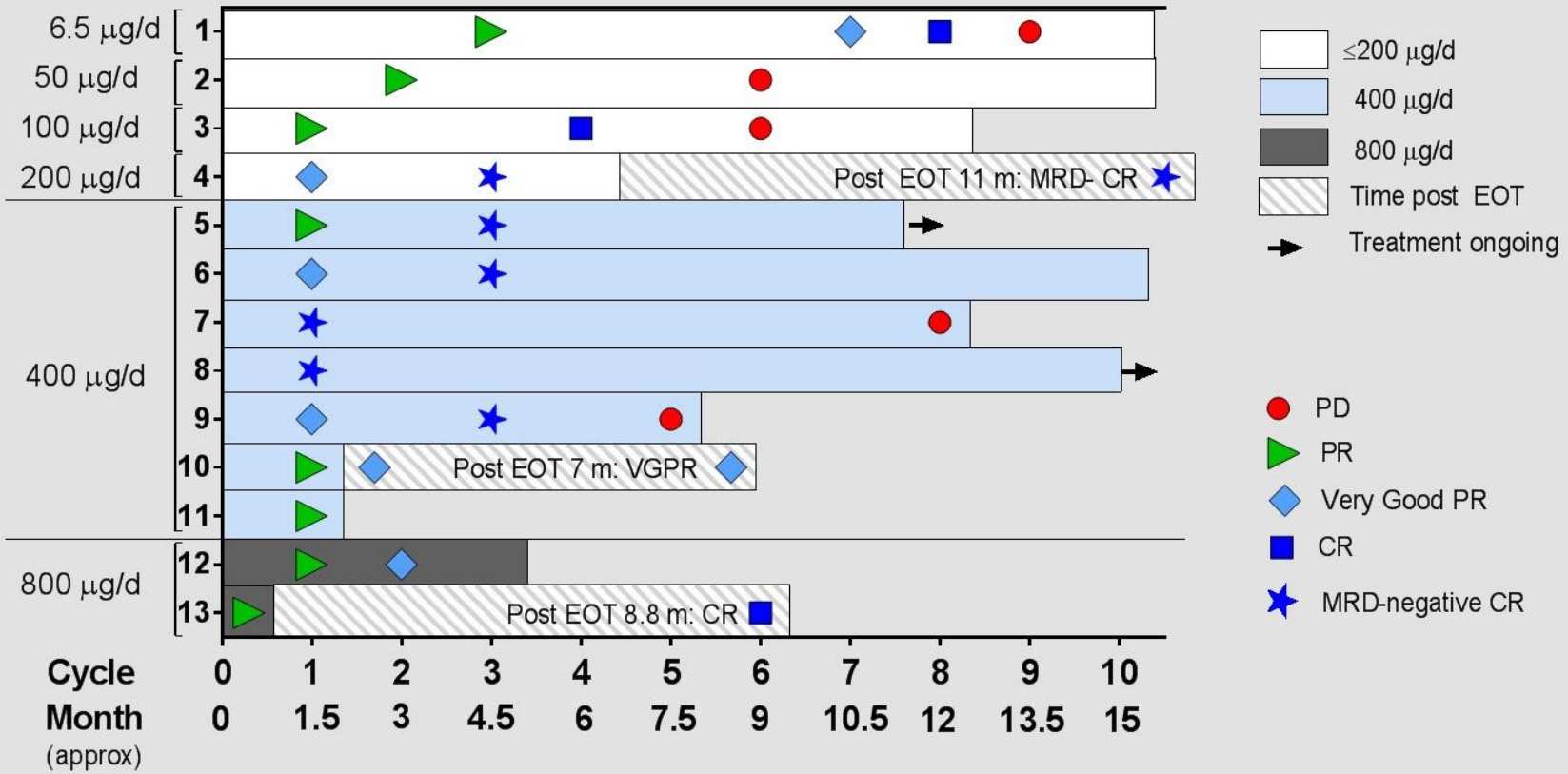
* One patient died of aspergillosis / flu and one of fulminant hepatitis related to adenovirus infection, neither treatment-related.

- Of those with serious AEs (n=19, 45%), 16 patients were hospitalized and 4 had prolonged hospitalization (one patient had both on separate occasions).
- No grade 3 or 4 central nervous system toxicities were observed.

As of Feb 27, 2019

Topp et al, ASCO 2019.

Responding patients



Unless PD was the last response indicated, patients were responding at last evaluation.

As of Apr 8, 2019. CR, complete response; EOT, end of treatment; PD, progressive disease; PR, partial response.

Topp et al, ASCO 2019.

Summary of studies

Study	Population	Arm(s)	Take-home results
ZUMA-3	Previously treated R/R ALL	Dose-finding: $2x10^6$, $1x10^6$, $0.5x10^6$ cells/kg	• Promising CR and MRD rates • Revised irAE management improved safety profile • $1x10^6$ cells/kg recommended for phase II
CD19/CD20 CAR T	R/R non-Hodgkin lymphoma	Dose-finding: $2.5x10^5$ to $2.5x10^6$ cells/kg	• No dose limiting toxicities • 83% ORR • $2.5x10^6$ cells/kg recommended moving forward
TRANSCEND CLL 004	Previously treated R/R CLL	Dose-finding: $50x10^6$ or $100x10^6$ cells	• Manageable toxicities • Rapid clinical responses observed • $100x10^6$ cells recommended for phase II
AMG 420 BiTE	Previously treated R/R multiple myeloma	Dose escalation: from 0.2 µg/day to 800 µg/day	• 70% response rate • DLTs observed at 800 µg/day and 400 µg/day • 400 µg/day recommended for phase 1b/2

Conclusions – Cellular therapies

- Chimeric T cell receptor and bispecific T-cell engager therapies show promise in hematologic malignancies
- High response rates observed – but what about duration of response?
- Moving cellular therapies into solid tumors and addressing scalability are ongoing challenges

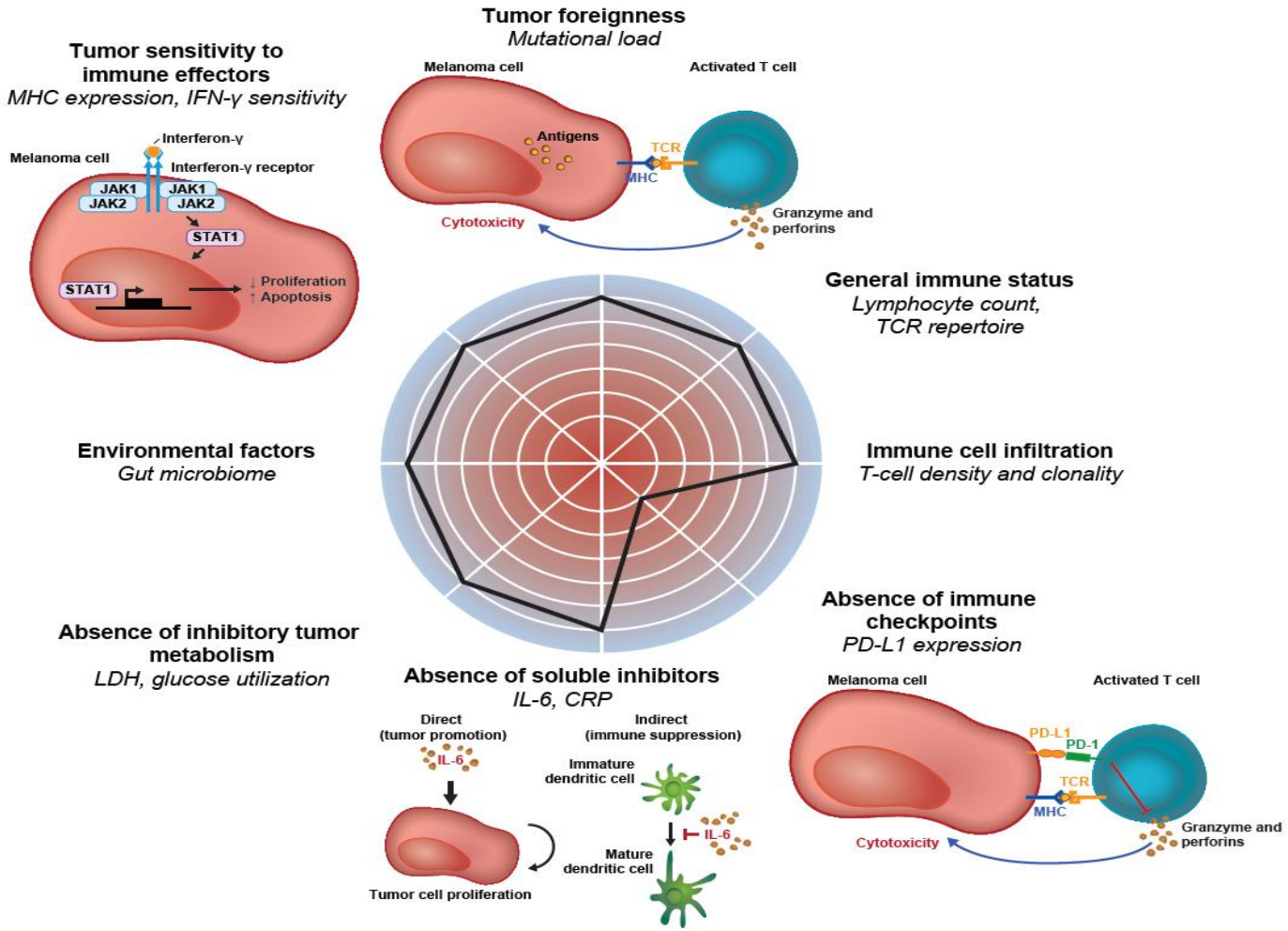
SITC Resources

- Adoptive Cellular Therapies workshop – September 5-6, 2019
- Journal for ImmunoTherapy of Cancer
- SITC Annual Meeting – November 7-10, 2019
  - SITC-ASH session: Lessons and challenges from the immunotherapy of hematologic malignancies: Informing the next generation of cancer immunotherapies
  - Harnessing antigen-presenting cells to boost anti-tumor immunity
  - NK cells: From basic science to clinical application
  - Innovations in cellular therapy for therapeutically targeting advanced malignancies

Biomarkers and checkpoint inhibitors

Ahmad Tarhini, MD, PhD

Modified Immunogram: Cancer-Immune Interaction

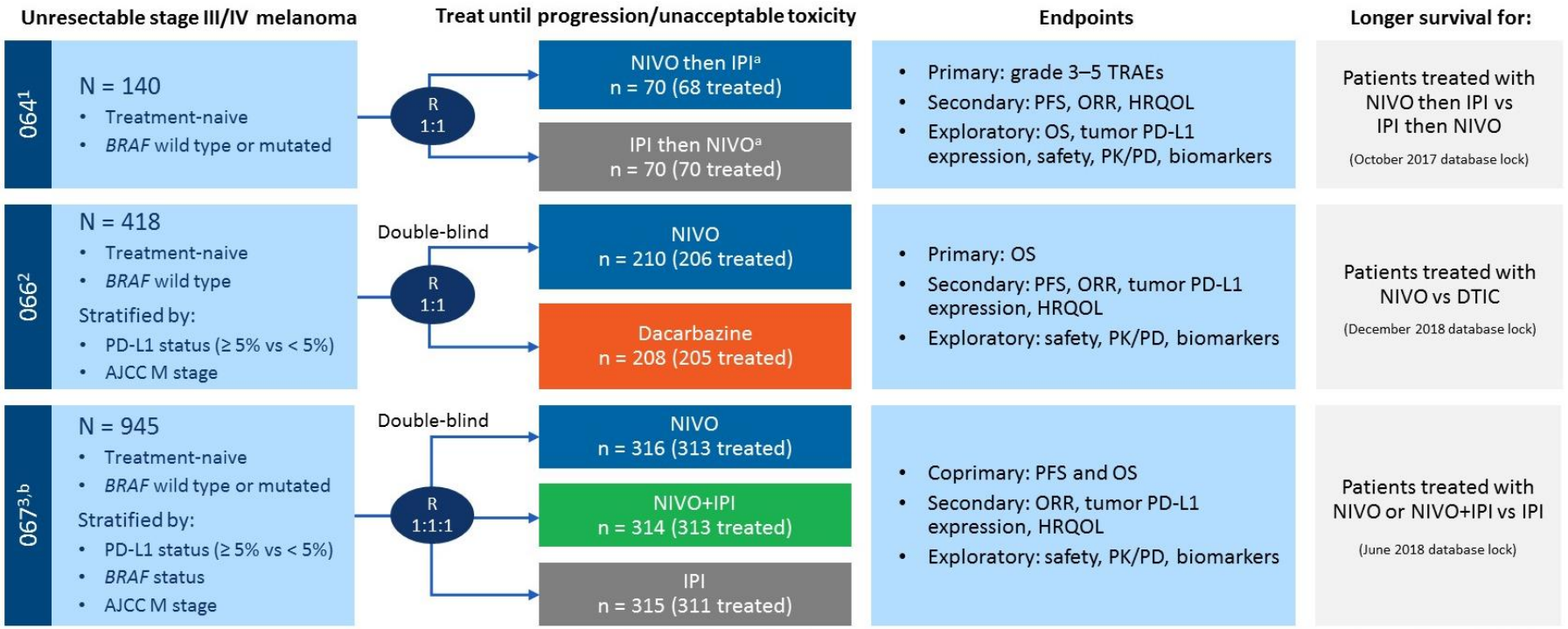


Tarhini et al. Cancer Treat Rev. 20182018 Dec;71:8-18

Serum IL-6 and CRP as prognostic factors in melanoma patients receiving single agent and combination checkpoint inhibition

Jeffrey S. Weber, Hao Tang, Lauren Hippeli, Max Qian, Megan Wind-Rotolo, James M.G. Larkin, Jedd D. Wolchok, Mario Sznol, Caroline Robert, David Michael Woods, Andressa Sodre Laino, F. Stephen Hodi

Exploratory, post-hoc analysis of samples

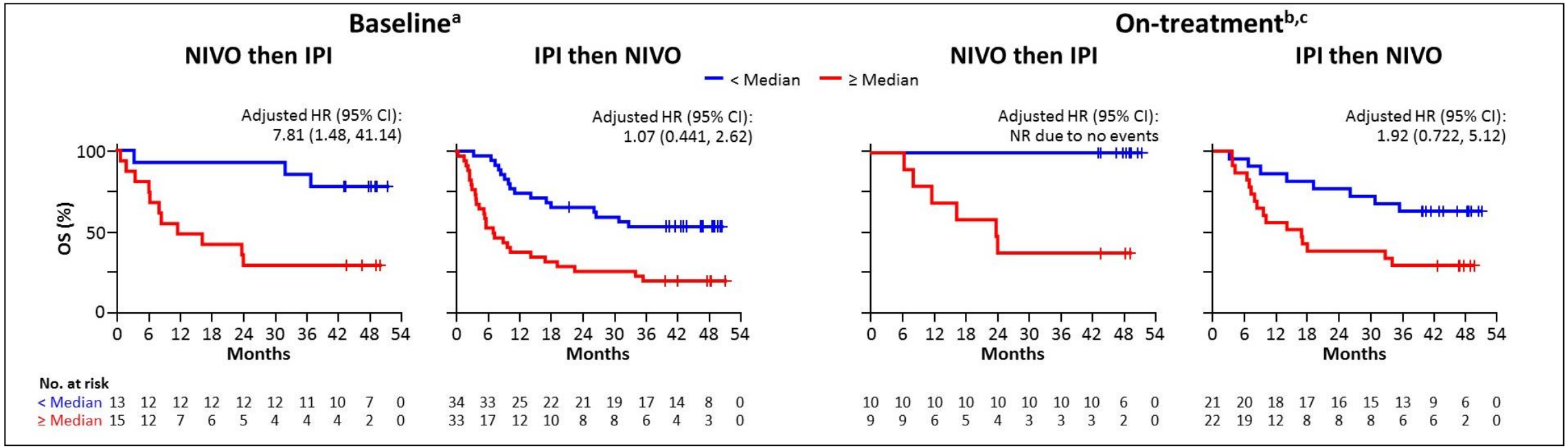


[a]Switch in treatment at week 13; [b]CheckMate 067 was not designed for a formal statistical comparison between NIVO+IPI and NIVO monotherapy. AJCC, American Joint Committee on Cancer; HRQOL, health-related quality of life; ORR, objective response rate; OS, overall survival; PD, pharmacodynamics; PFS, progression-free survival; PK, pharmacokinetics; R, randomized; TRAE, treatment-related adverse event. 1. Weber JS, et al. *Lancet Oncol* 2016;17:943–955; 2. Robert C, et al. *N Engl J Med* 2015;372:320–330; 3. Larkin J, et al. *N Engl J Med* 2015;373:23–34.

Weber et al, ASCO 2019.

IL-6 and overall survival

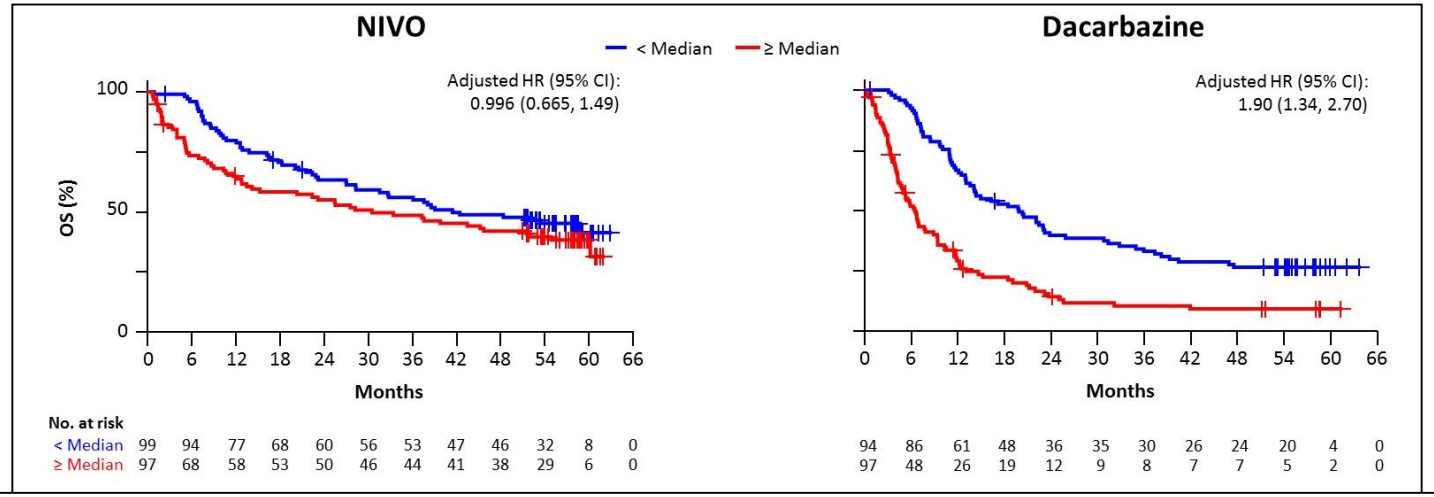
CheckMate 064



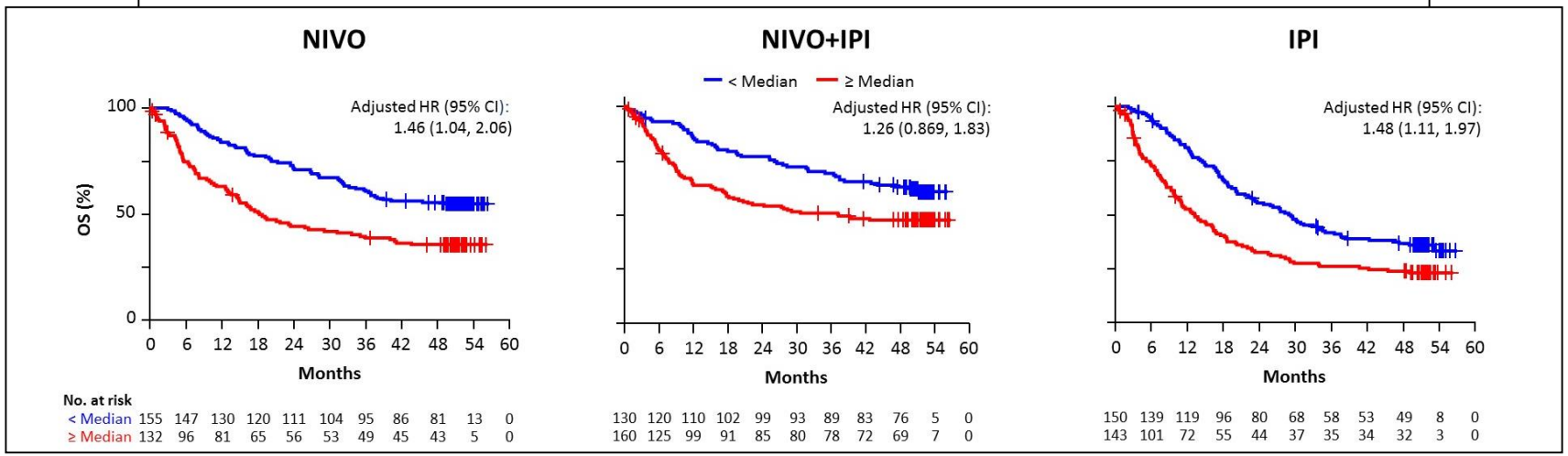
Weber et al, ASCO 2019.

Baseline CRP and overall survival

CheckMate 066



CheckMate 067



Weber et al, ASCO 2019.

Biomarker analysis from JAVELIN Renal 101: Avelumab + axitinib (A+Ax) versus sunitinib (S) in advanced renal cell carcinoma

Toni K. Choueiri, Laurence Albiges, John B. A. G. Haanen, James M.G. Larkin, Motohide Uemura, Sumanta K. Pal, Gwenaelle Gravis, Matthew T Campbell, Konstantin Penkov, Jae-Lyun Lee, Keith A. Ching, Xinmeng Jasmine Mu, Xiao Wang, Weidong Zhang, Jing Wang, Aleksander Chudnovsky, Alessandra di Pietro, Paul B. Robbins, Robert J. Motzer

Biomarker assessments and methodology

Analysis	Assay	Threshold
PD-L1 expression n=804	• IHC: Ventana SP263	• ≥1% PD-L1+ IC for IHC (+ vs −)
CD8 expression n=795	• IHC: clone C8/144B	• Median value (≥ vs <)
Gene expression profiling n=720	• RNA-seq: Illumina NovaSeq	• Median value (≥ vs <)
Mutations and polymorphisms n=733	• Whole-exome sequencing: Illumina NovaSeq	• Presence of protein-altering somatic mutations • Polymorphisms in Fcγ receptor genes that alter the affinity for IgG1

All analyses were performed on baseline tumor biopsies collected within 1 year of screening and prior to systemic therapy.

IC, immune cell; **IHC**, immunohistochemistry; **RNA-seq**, RNA sequencing.

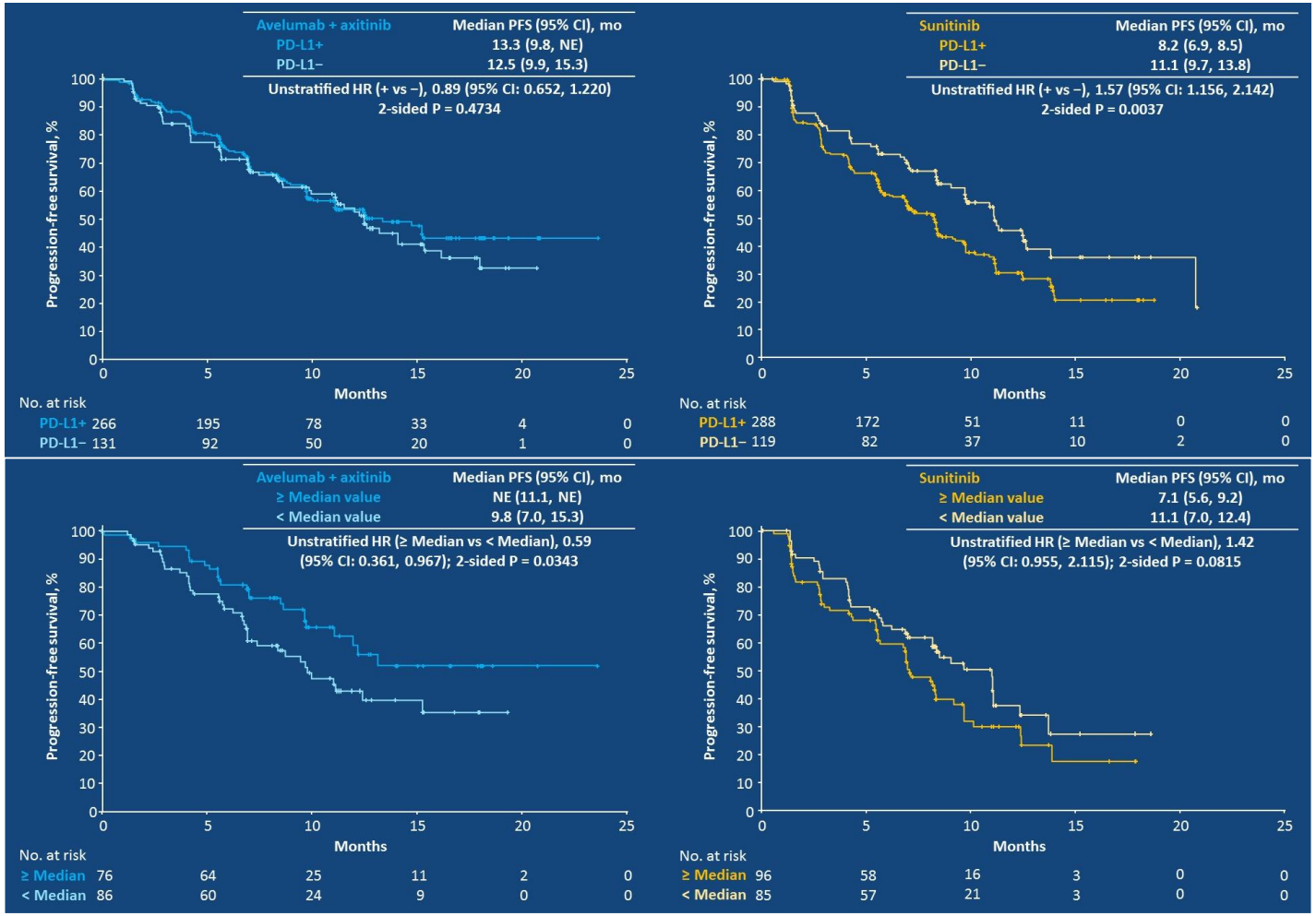
Choueiri et al, ASCO 2019.

Society for Immunotherapy of Cancer

PD-L1 and CD8 IHC

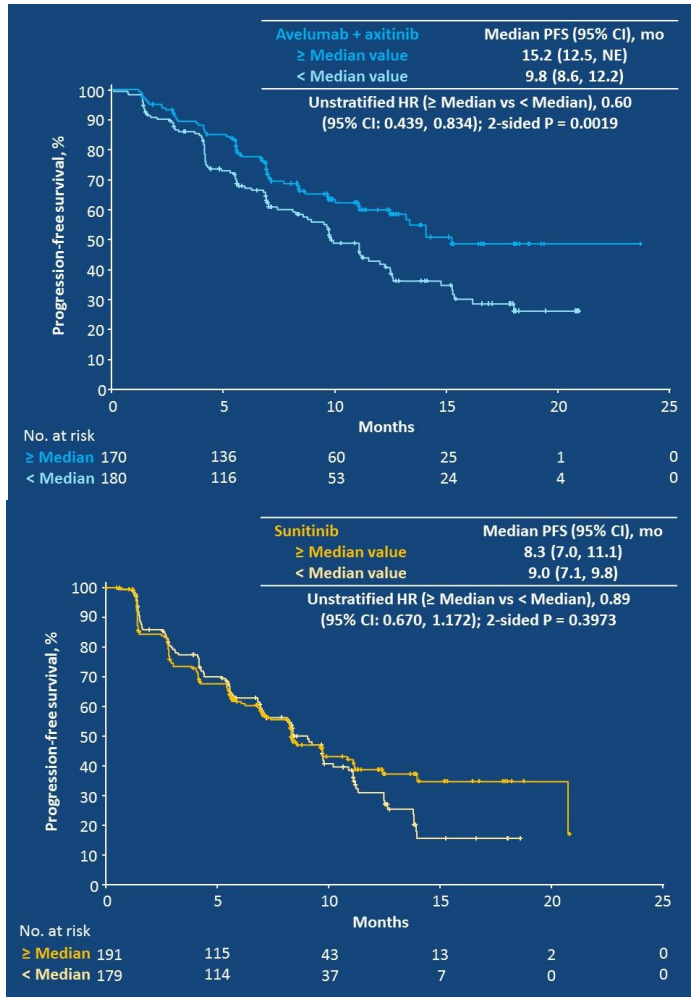
PD-L1

CD8 cells at invasive margin

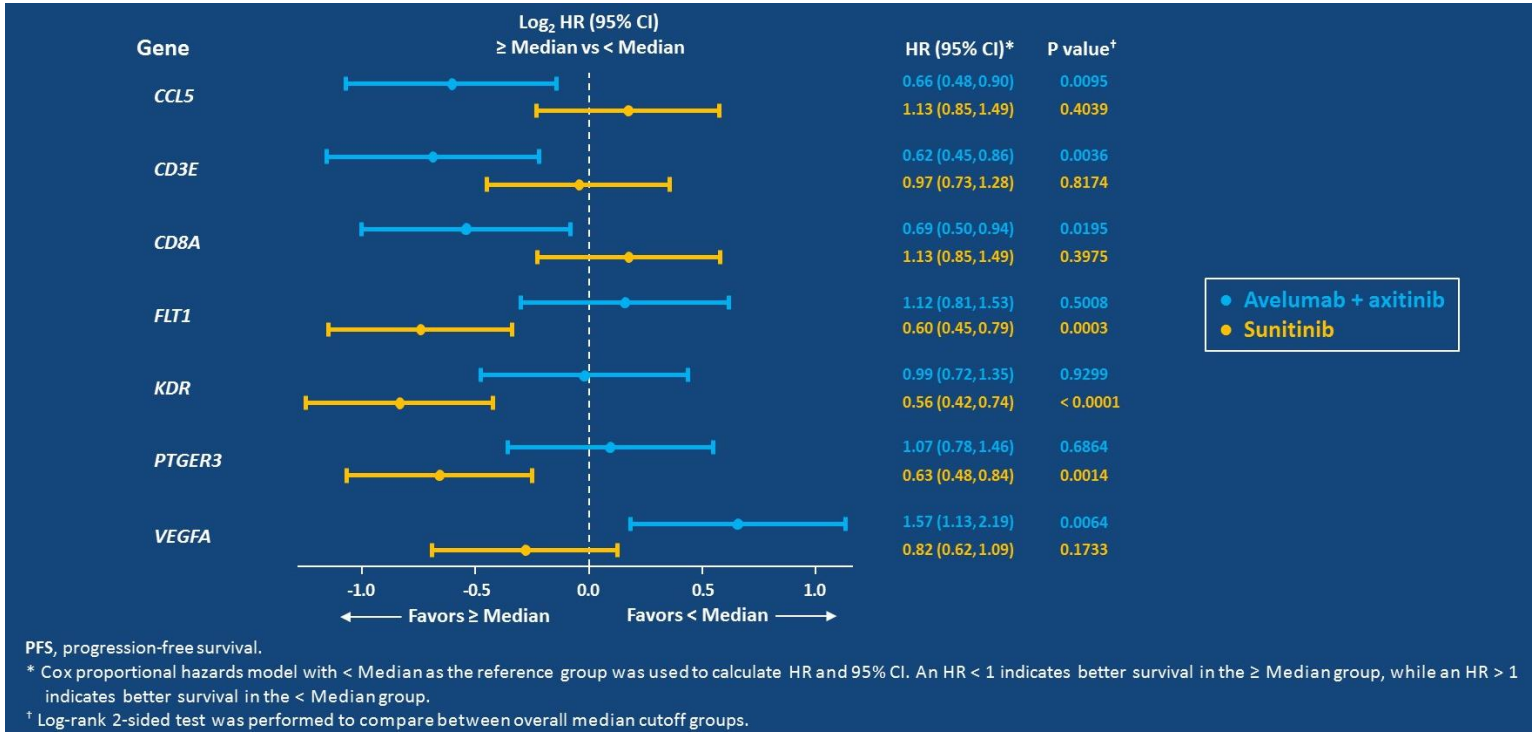


Choueiri et al, ASCO 2019.

PFS according to 26-gene JAVELIN Renal 101 signature



Gene expression



PFS, progression-free survival.
* Cox proportional hazards model with < Median as the reference group was used to calculate HR and 95% CI. An HR < 1 indicates better survival in the ≥ Median group, while an HR > 1 indicates better survival in the < Median group.
† Log-rank 2-sided test was performed to compare between overall median cutoff groups.

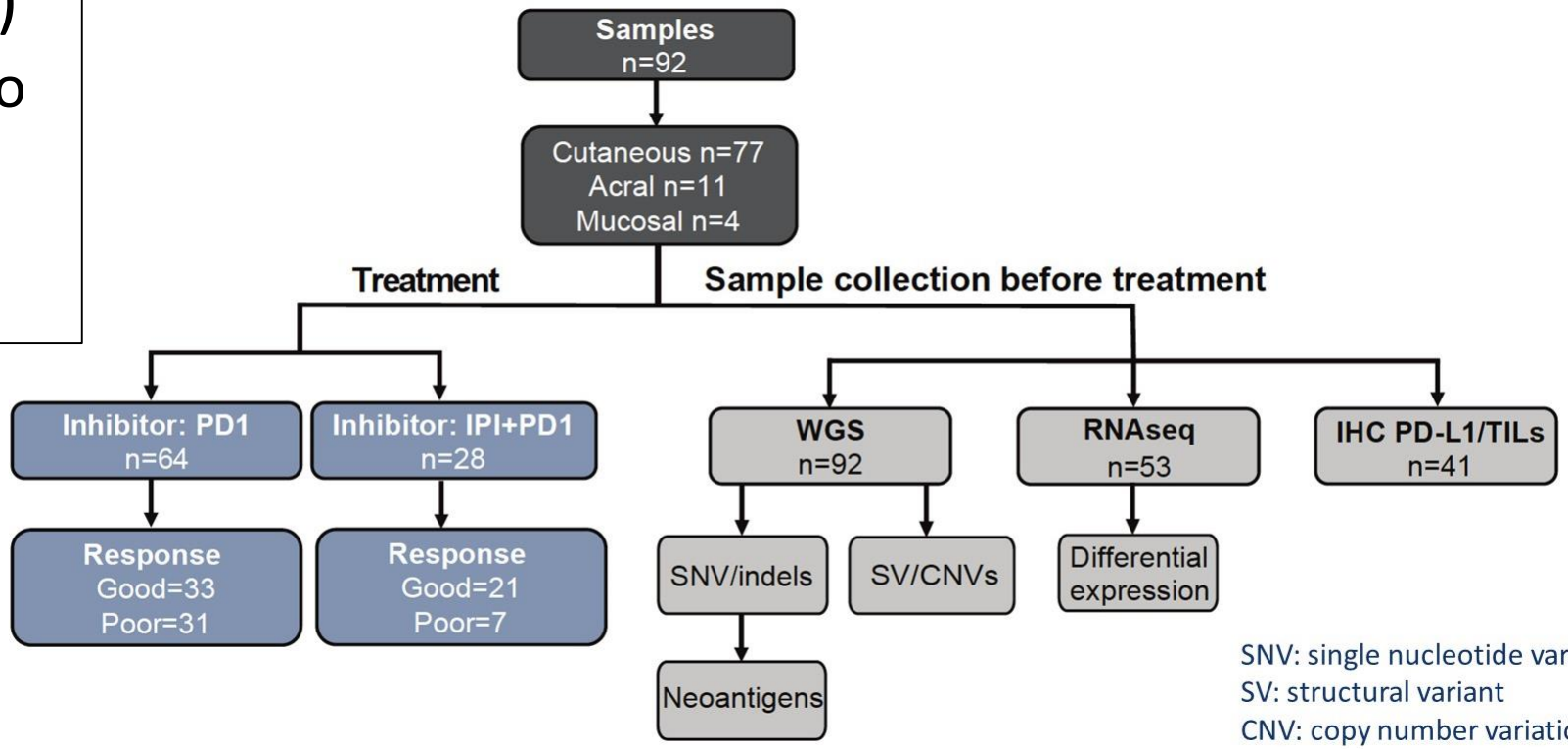
Choueiri et al, ASCO 2019.

Comprehensive molecular profiling of metastatic melanoma to predict response to monotherapy and combination immunotherapy

Ines Esteves Domingues Pires Da Silva, Alexander M. Menzies, Felicity Newell, James S. Wilmott, Matteo S. Carlino, Peter M. Ferguson, Jarem Edwards, Andrew Spillane, Kerwin Shannon, Robyn Saw, John F. Thompson, Helen Rizos, Graham J. Mann, Peter Johansson, Nicholas Hayward, Richard A. Scolyer, Nic Waddell, Georgina V. Long

Methodology

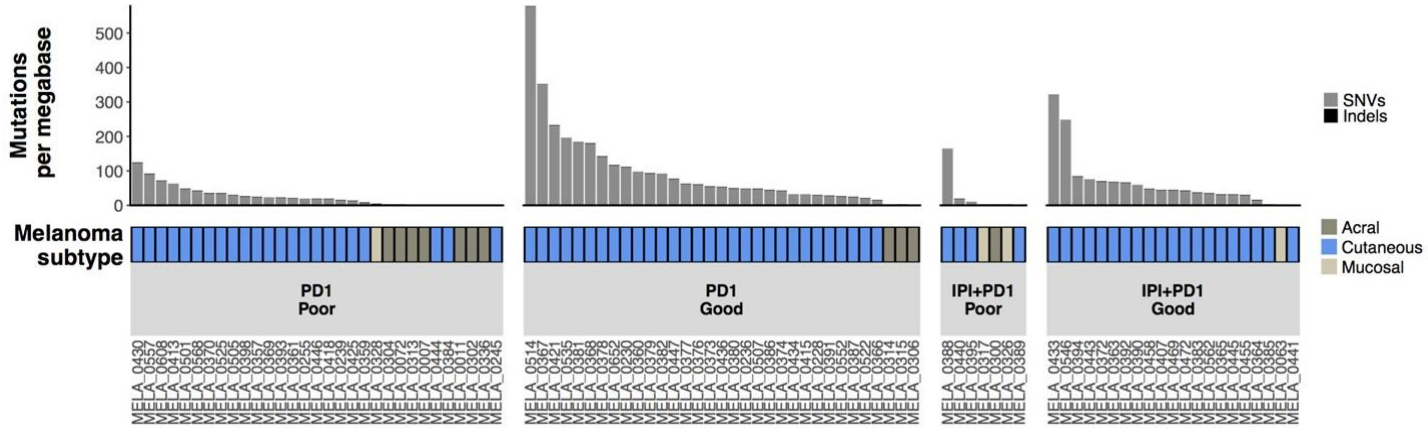
- Good responders (n=54)
  - RECIST CR, PR, SD > 6 mo
- Poor responders (n=38)
  - RECIST PD or SD ≤ 6 mo



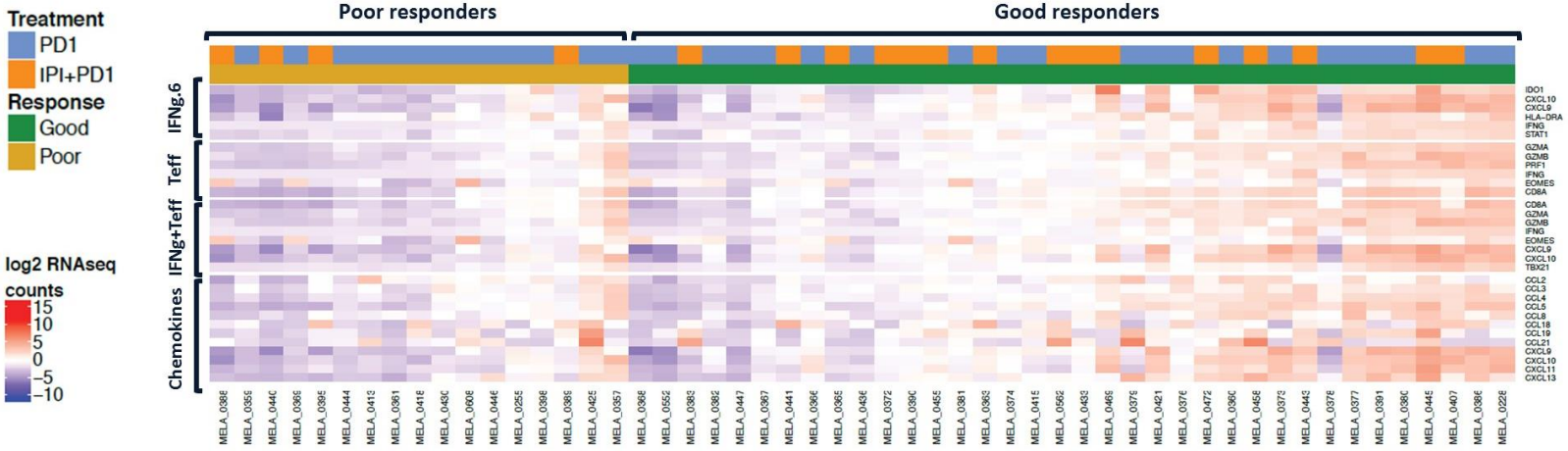
SNV: single nucleotide variant
SV: structural variant
CNV: copy number variation

Ines Pires Da Silva et al, ASCO 2019.

TMB and IFN signatures correlate with response

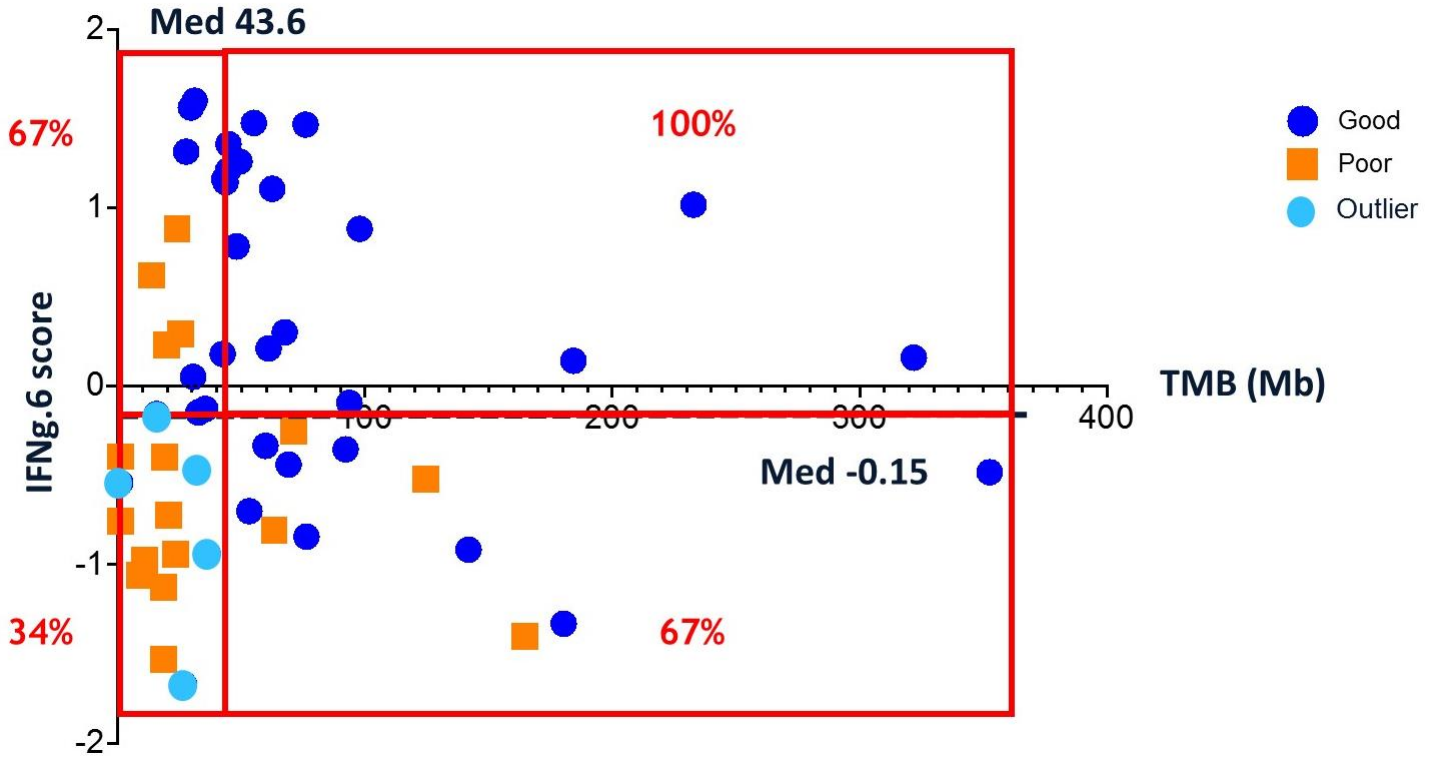


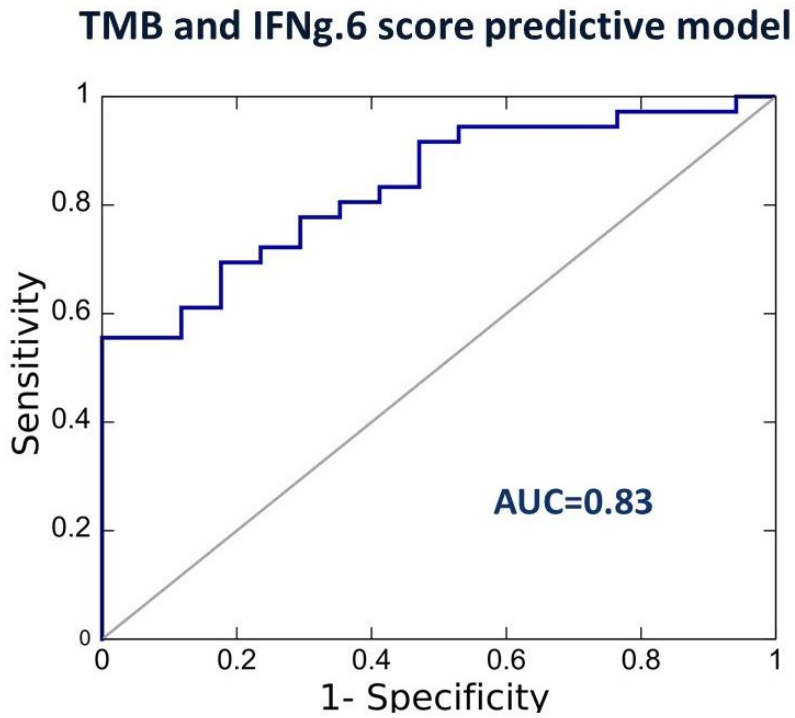
TMB (mutations per megabase): SNVs + indels count; SV: structural variant



Ines Pires Da Silva et al, ASCO 2019.

Multivariate predictive model for PFS





Ines Pires Da Silva et al, ASCO 2019.

Predictive Biomarkers for Anti-PD1 Efficacy in Melanoma / Discussion by Thomas Gajewski, MD

Conclusions and implications

- Features of the tumor microenvironment have a major impact on clinical efficacy of anti-PD-1-based immunotherapy
  - T cell infiltration with local reactivation➔immune gene expression signature
  - Mutation load➔increased likelihood of neoantigens
  - Integration of both gives strongest predictive value
- When everything comes together properly, therapeutic efficacy follows a predictable process (Happy Family)
- Mechanisms of non-response will likely be multiple and derived from distinct categories of etiology (Unhappy Families)
  - Tumor cell-intrinsic oncogenic pathways, host genetics, composition of microbiota
  - Seeking patterns in subsets of patients may nonetheless identify druggable strategies for expanding efficacy

Phase 2 trial of durvalumab in advanced endometrial cancer (PHAEDRA)

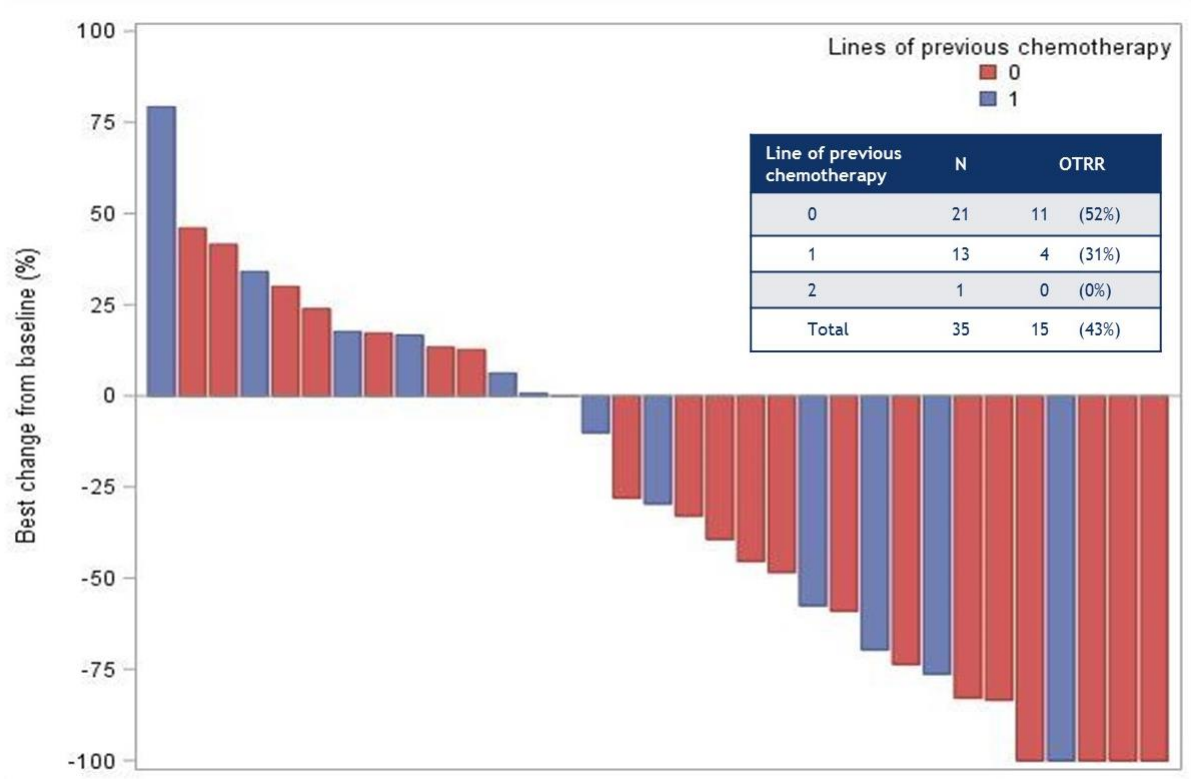
Yoland Catherine Antill, Peey Sei Kok, Kristy Robledo, Elizabeth Barnes, Michael Friedlander, Sally E. Baron-Hay, Catherine M. Shannon, Jermaine Coward, Philip James Beale, Geraldine Goss, Tarek Meniawy, Sonia Yip, Deborah Smith, Amanda B. Spurdle, Michelle Parry, John Andrews, Marzena Kelly, Martin R. Stockler, Linda R. Mileshkin, Australia New Zealand Gynaecological Oncology Group (ANZGOG)

Phase 2 study of avelumab in patients with microsatellite stable, microsatellite instable, and polymerase epsilon mutated recurrent/persistent endometrial cancer (NCT02912572)

Panagiotis A. Konstantinopoulos, Joyce F. Liu, Weixiu Luo, Carolyn N. Krasner, Jeffrey Joseph Ishizuka, Allison Ann Gockley, Mary K. Buss, Susana M. Campos, Elizabeth Stover, Alexi A. Wright, Whitfield Board Growdon, Jennifer Curtis, Ariana Peralta, Patrice Basada, Roxanne Quinn, Kathryn P. Gray, Richard T. Penson, Stephen A. Cannistra, Gini F. Fleming, Ursula A. Matulonis

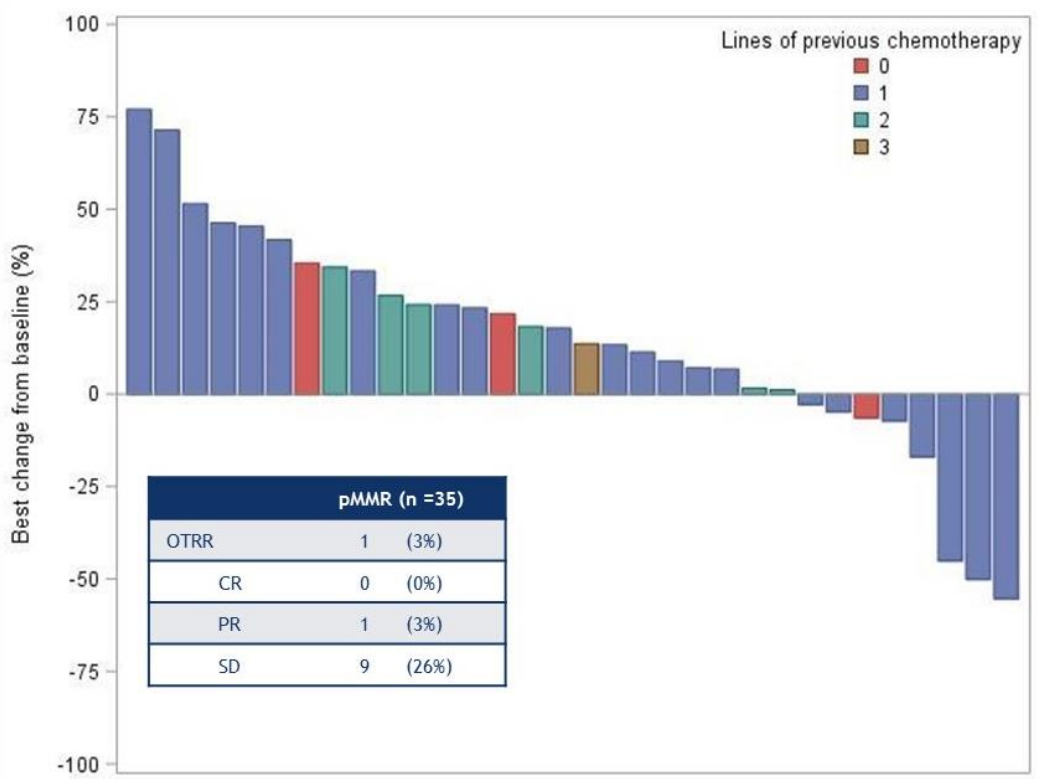
PHAEDRA: dMMR vs pMMR

dMMR (n=35)



Line of previous chemotherapy	N	OTRR	
0	21	11	(52%)
1	13	4	(31%)
2	1	0	(0%)
Total	35	15	(43%)

pMMR (n=35)

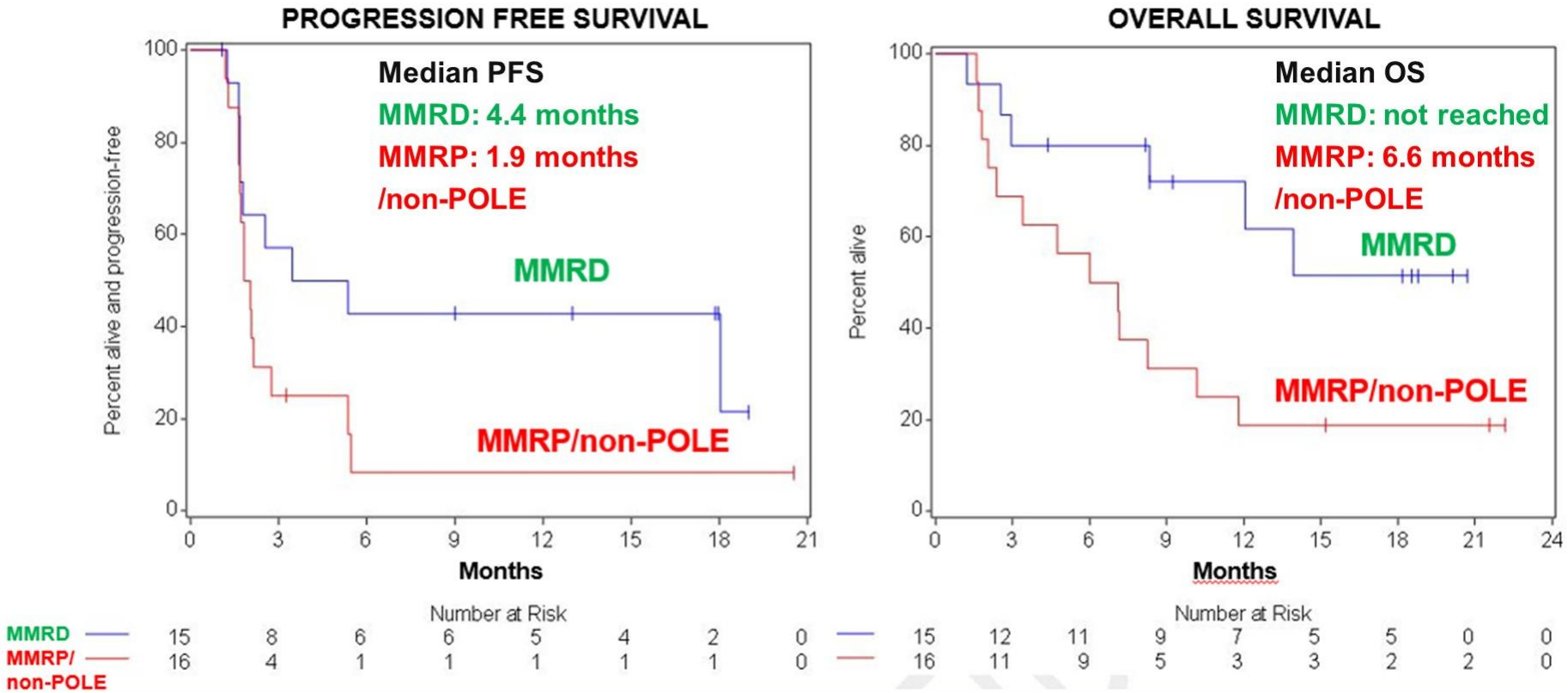


pMMR (n =35)		
OTRR	1	(3%)
CR	0	(0%)
PR	1	(3%)
SD	9	(26%)

Durvalumab 1500 mg Q4W

Antill et al, ASCO 2019.

NCT02912572: MMRD and MMRP



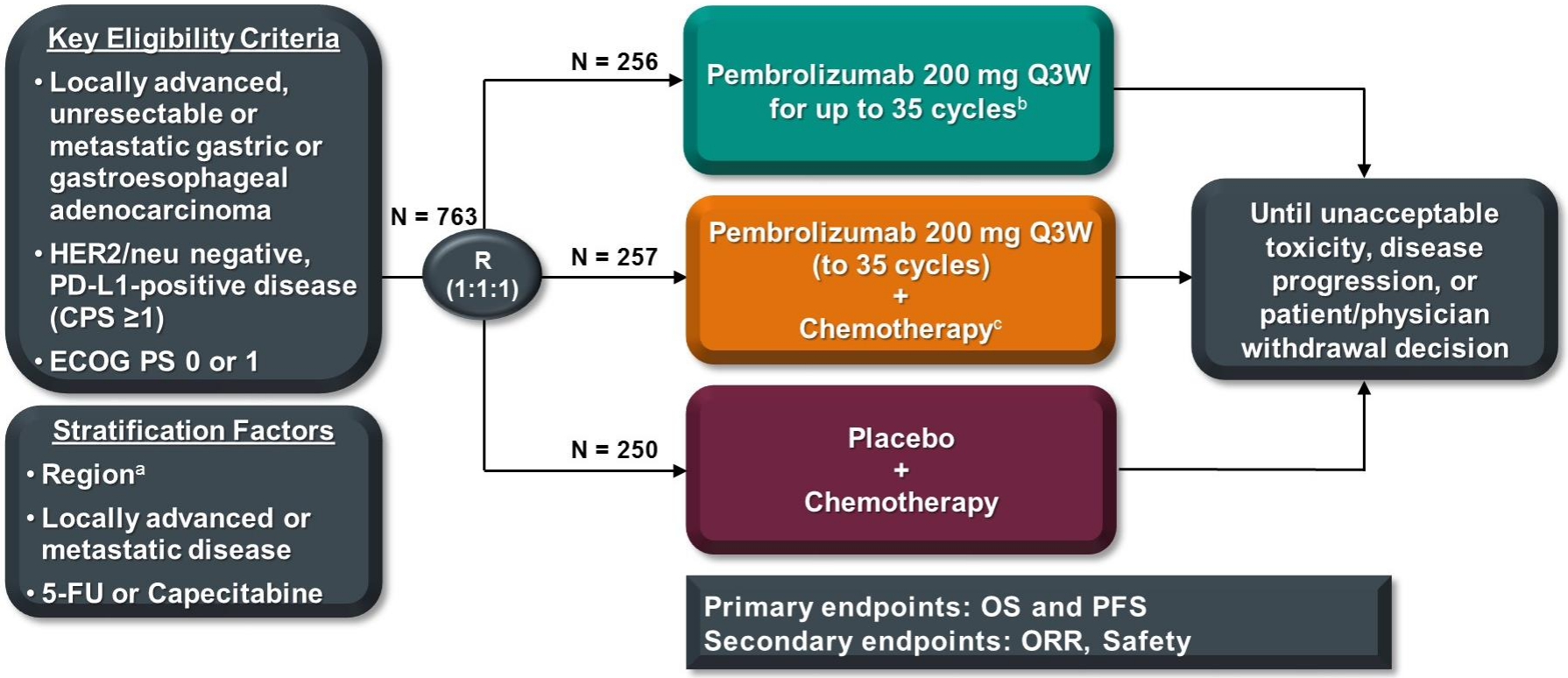
Avelumab Q2W

Konstantinopoulos et al, ASCO 2019.

Pembrolizumab with or without chemotherapy versus chemotherapy for advanced gastric or gastroesophageal junction (G/GEJ) adenocarcinoma: The phase III KEYNOTE-062 study

Josep Tabernero, Eric Van Cutsem, Yung-Jue Bang, Charles S. Fuchs, Lucjan Wyrwicz, Keun Wook Lee, Iveta Kudaba, Marcelo Garrido, Hyun Cheol Chung, Hugo Raul Castro Salguero, Wasat Mansoor, Maria Ignez Freitas Melro Braghiroli, Eray Goekkurt, Joseph Chao, Zev A. Wainberg, Uma Kher, Sukrut Shah, SoonMo Peter Kang, Kohei Shitara

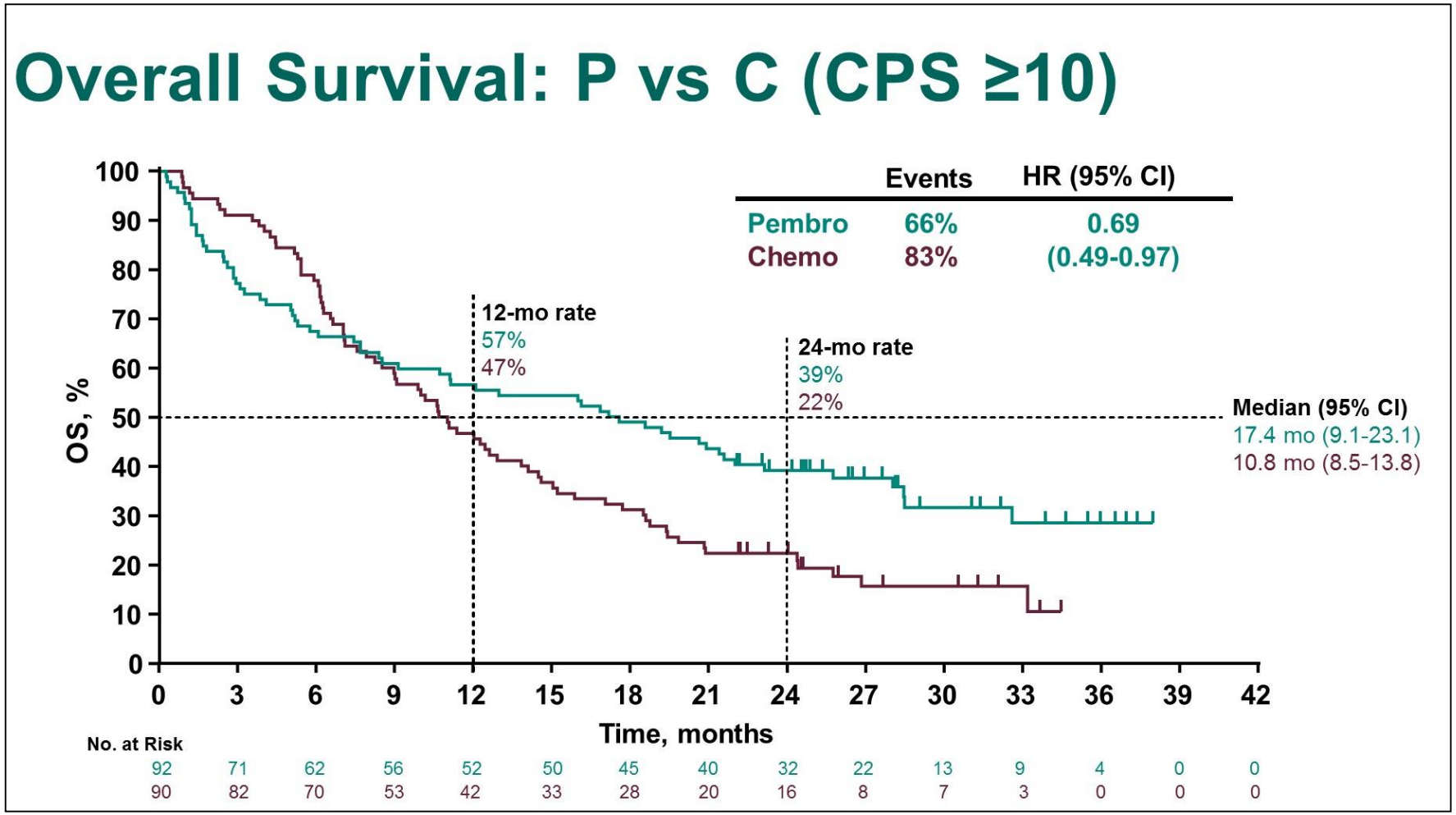
KEYNOTE-062 study design



[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).

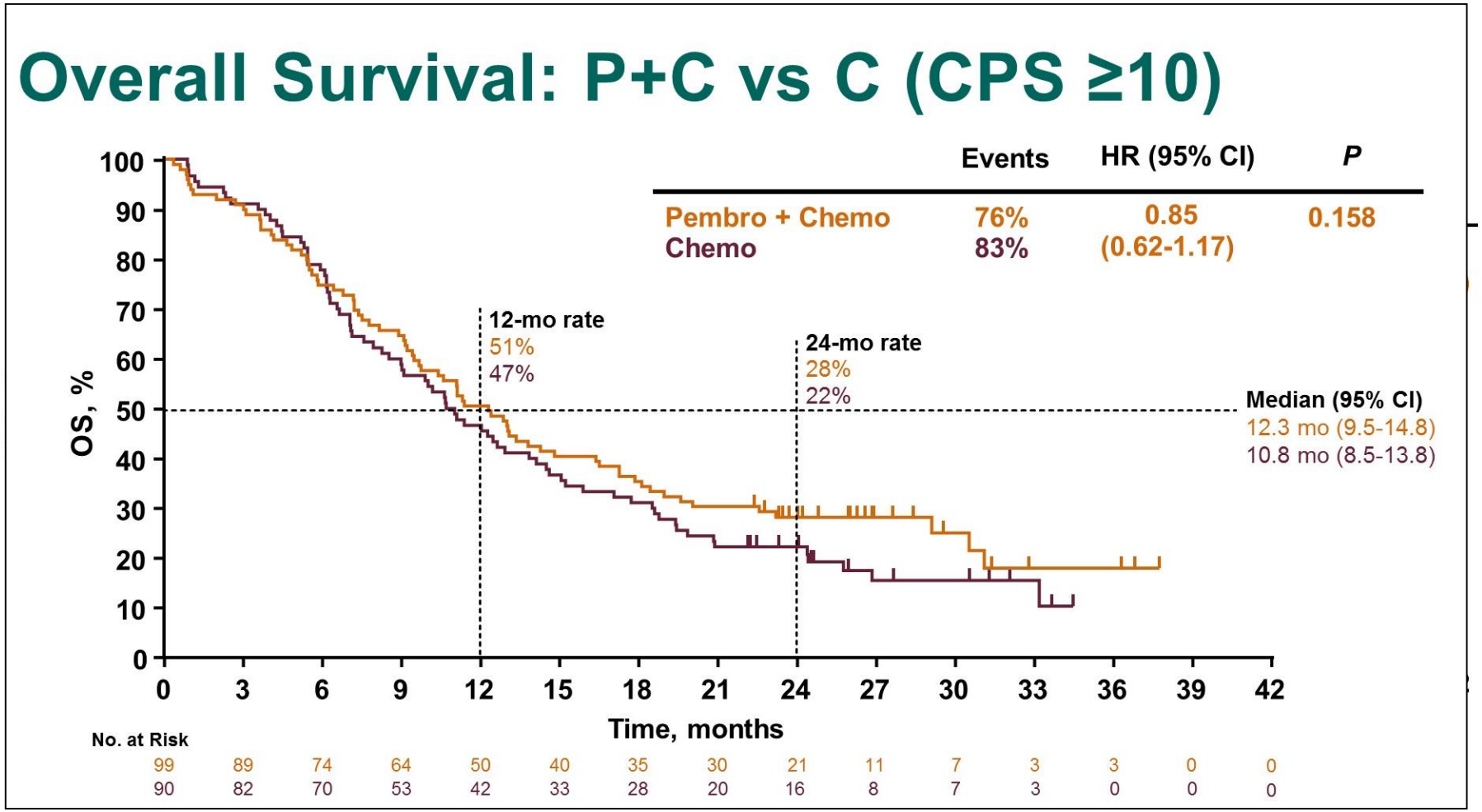
Tabernero et al, ASCO 2019.

Pembrolizumab versus chemotherapy



Tabernero et al, ASCO 2019.

Pembrolizumab + chemotherapy versus chemotherapy



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

Tabernero et al, ASCO 2019.

North American Intergroup E1609 – A phase III study of adjuvant ipilimumab (3 or 10 mg/kg) versus high-dose interferon-α2b for resected high-risk melanoma

Ahmad A. Tarhini, Sandra J. Lee, F. Stephen Hodi, Uma N. M. Rao, Gary Irvin Cohen, Omid Hamid, Laura Fulper Hutchins, Jeffrey Alan Sosman, Harriet M. Kluger, Vernon K. Sondak, Henry B. Koon, Donald P. Lawrence, Kari Lynn Kendra, David R. Minor, Carrie B. Lee, Mark R. Albertini, Lawrence E. Flaherty, Teresa M. Petrella, John M. Kirkwood

Intergroup E1609: Study Design and Accrual

Society for Immunotherapy of Cancer

Patients with resected IIIB, IIIC M1a, M1b melanoma

RANDOMIZED

Ipi3

Ipi10

Ipi3

Ipi10

FOLLOW UP

Stratified by: IIIB, IIIC, M1a, M1b

N = 1673

Arm	Activation	Termination	Final
Ipi10	5/25/11	4/4/14	511
HD-IFN	5/25/11	8/15/14	636
Ipi3	2/7/12	8/15/14	523

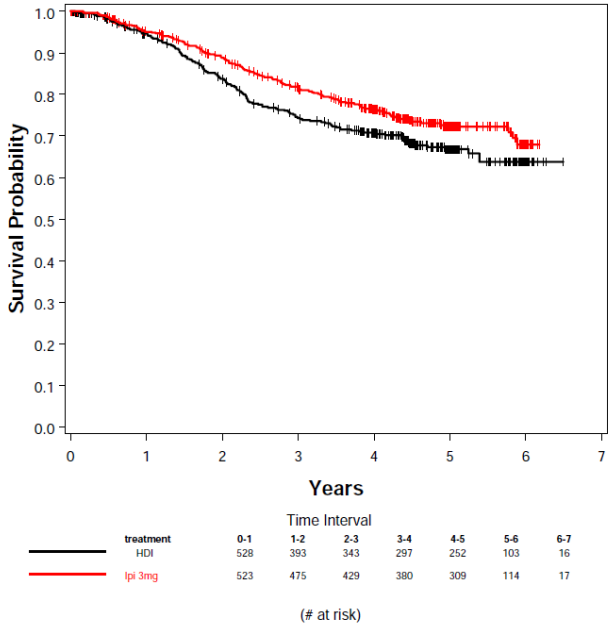
ECOG-ACRIN cancer research group

Reshaping the future of patient care

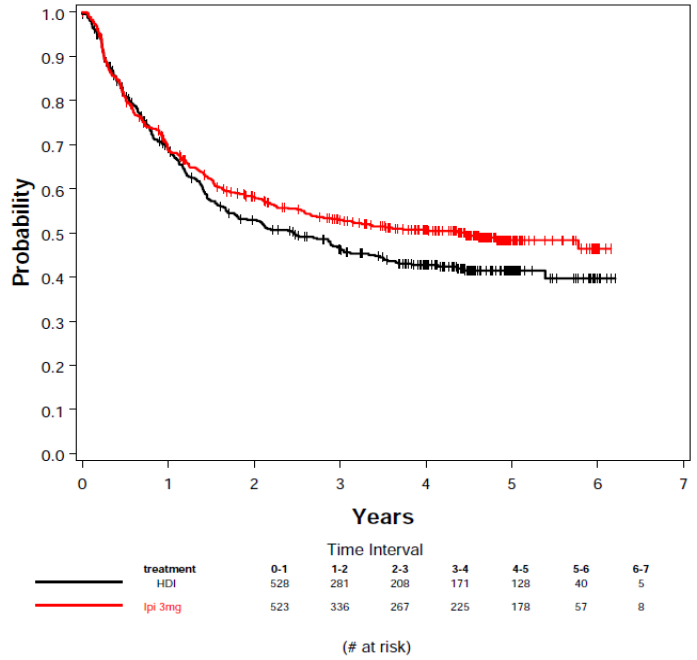
First-step comparison of Ipi3 versus HDI: OS & RFS

ITT concurrently randomized cases (N=1051)

	Ipi3	HDI
Events/patients	130/523	134/528
HR (95.6% RCI)	0.78 (0.61, 0.99)	
Log-rank P value	0.044	
5-yr OS (95% CI)	0.72 (0.68, 0.76)	0.67 (0.62, 0.72)



	Ipi3	HDI
Events/patients	248/523	238/528
HR (99.4% CI)	0.85 (0.66, 1.09)	
Log-rank P value	0.065	
Median (95% CI)	4.5 years (2.6, -)	2.5 years (1.7, 3.3)

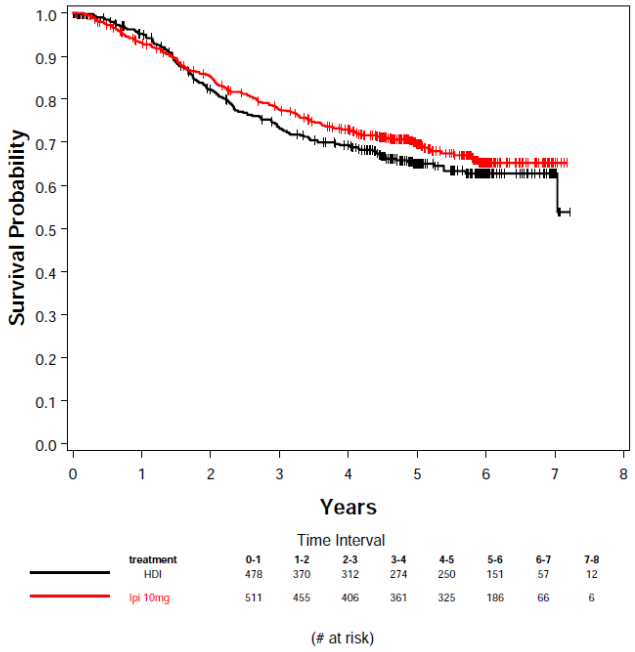


Second-step comparison of Ipi10 versus HDI: OS & RFS

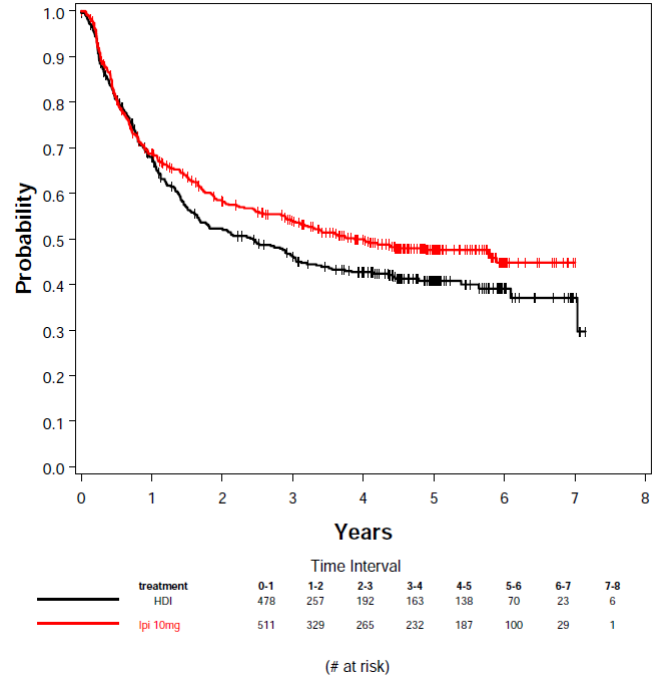
Society for Immunotherapy of Cancer

ITT concurrently randomized cases (N=989)

	Ipi10	HDI
Events/patients	151/511	136/478
HR (95.6% RCI)	0.88 (0.69, 1.12)	
Log-rank P value	NS	
5-yr OS (95% CI)	0.70 (0.65, 0.74)	0.65 (0.60, 0.70)



	Ipi10	HDI
Events/patients	249/511	228/478
HR (99.4% CI)	0.84 (0.65, 1.09)	
Log-rank P value	NS	
Median (95% CI)	3.9 years (2.9, -)	2.4 years (1.6, 3.0)



ECOG-ACRIN cancer research group
Reshaping the future of patient care

Exploratory Analysis of OS and RFS with Ipi3 vs. Ipi10

ITT concurrently randomized patients (N=773)

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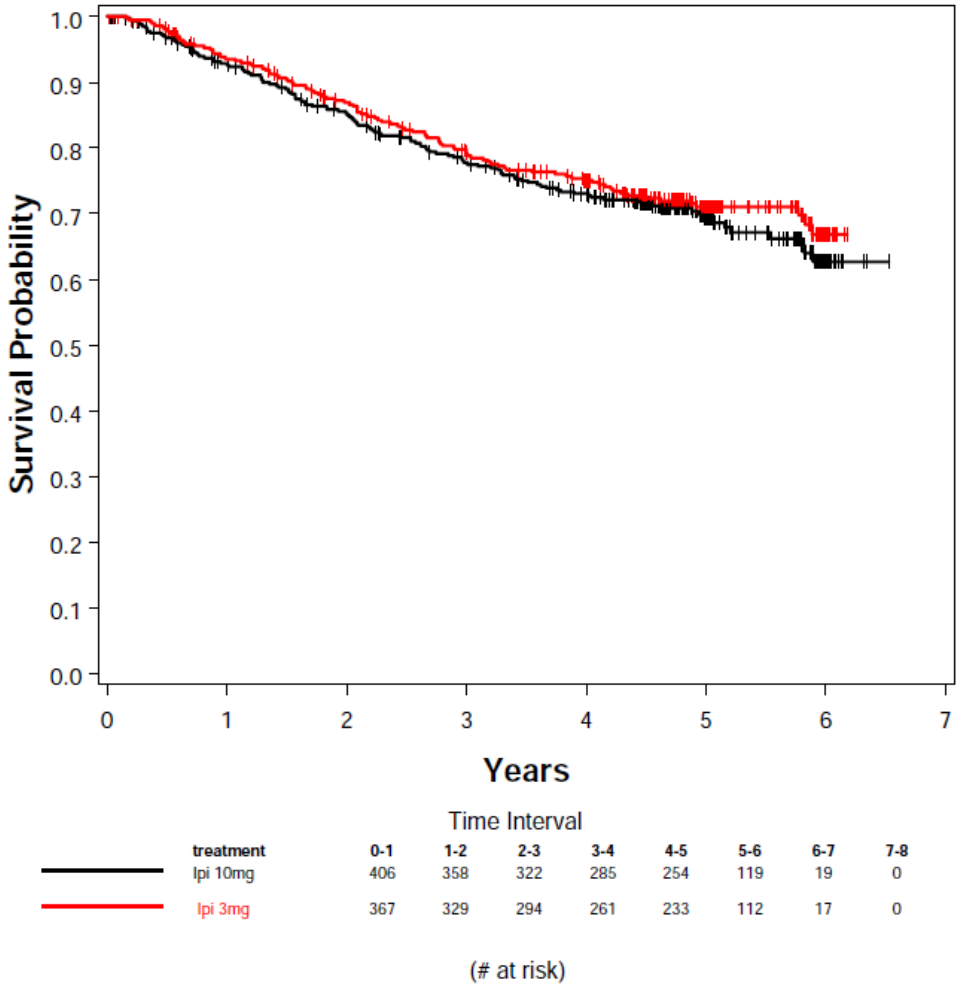
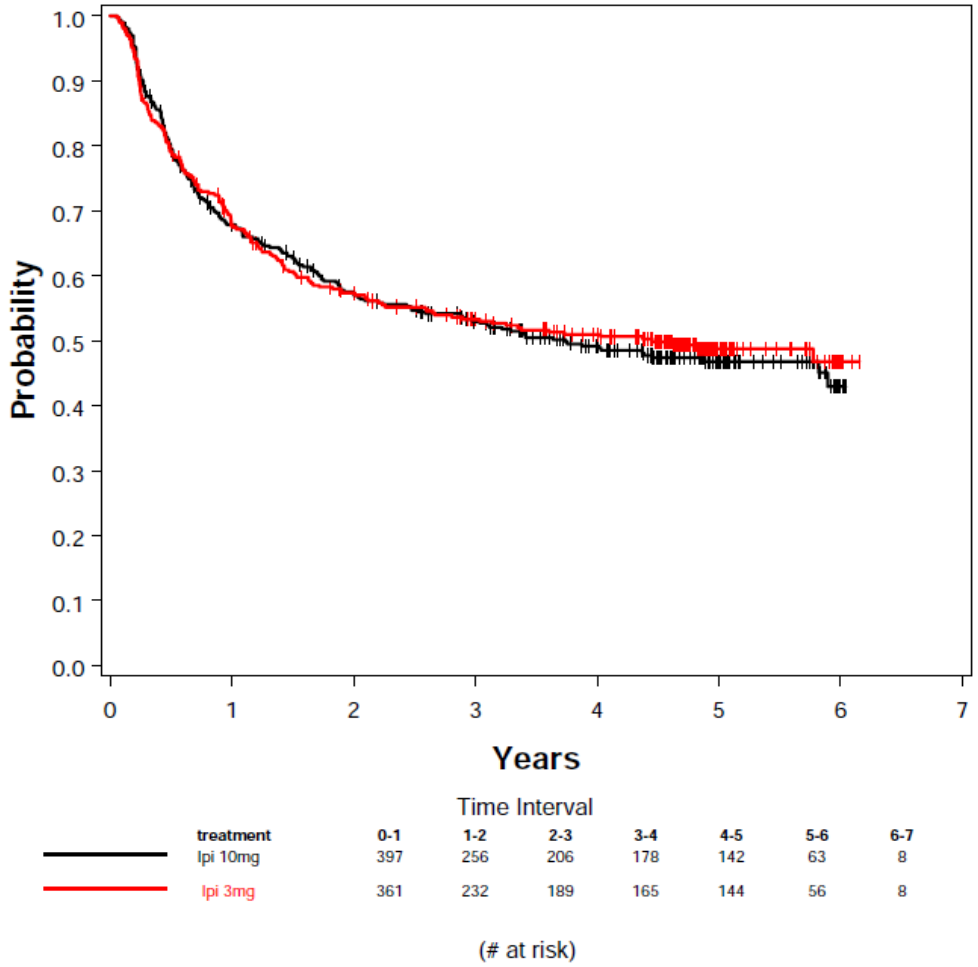




Ahmad Tarhini, MD, PhD

ECOG-ACRIN cancer research group

Reshaping the future of patient care

Summary of studies

Biomarker Study	Population	Take-home results
Serum IL-6 and CRP	Melanoma treated with nivolumab +/- ipilimumab	• High levels of IL-6 and/or CRP associated with shorter OS in all groups • Blockade of IL-6 and/or CRP synthesis/activity may boost immune checkpoint therapies
JAVELIN Renal 101	1st line advanced RCC treated with avelumab + axitinib vs sunitinib	On checkpoint treatment: • PD-L1 doesn't distinguish PFS • Higher CD8+ cells → longer PFS • Novel gene signature predicted responders
Molecular profiling of melanoma	Cutaneous metastatic melanoma treated with anti-PD-1 and/or anti-CTLA-4	• TMB, neoantigen load, IFNγ expression, PD-L1, and T cell expression in TME associated with IO response • Multivariate predictive model included TMB and IFNγ.6 score

Summary of studies

Checkpoint Study	Population	Arm(s)	Take-home results
PHAEDRA	MMR proficient or deficient adv/rec endometrial cancer	Durvalumab	• 43% response rate in dMMR • 3% response rate in pMMR • Reasonable safety profile
NCT02912572	MMR proficient or deficient rec/pers endometrial cancer	Avelumab	• Closed pMMR cohort due to poor activity • 22-30% ORR in dMMR • MMR assays varied in their results
KEYNOTE-062	Advanced, unresectable/metastatic G/GEJ adenocarcinoma	• Pembrolizumab • Pembrolizumab + chemo • Chemotherapy	• Pembrolizumab monotherapy had favorable OS effect in PD-L1 CPS ≥ 10 • P+C not superior to chemotherapy for OS with any PD-L1 expression • Reasonable tolerability profiles of both regimens
E1609	Resected IIIB, IIIC, M1a, M1b melanoma	• Ipilimumab 3 or 10 mg/kg • HD-IFN	• Adjuvant ipilimumab 3 mg/kg demonstrated survival benefits • Reasonable safety with ipilimumab 3 mg/kg

Conclusions – Biomarkers and checkpoint inhibitors

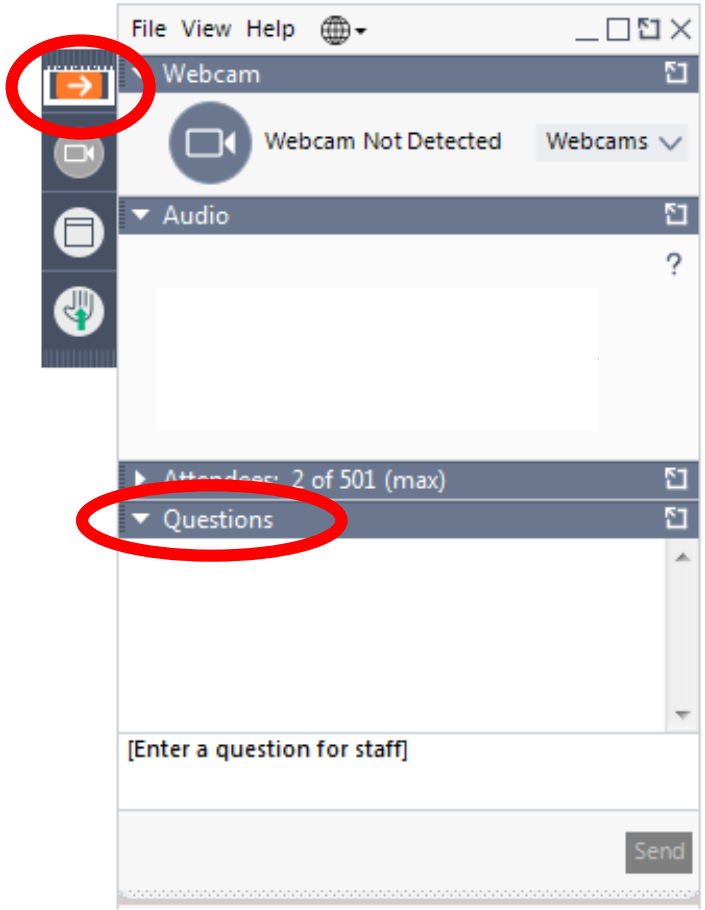
- Biomarkers are being identified for individual cancers in certain treatment settings
- No universal markers discovered
- Checkpoint inhibitors are demonstrating promise in difficult-to-treat cancers

SITC Resources

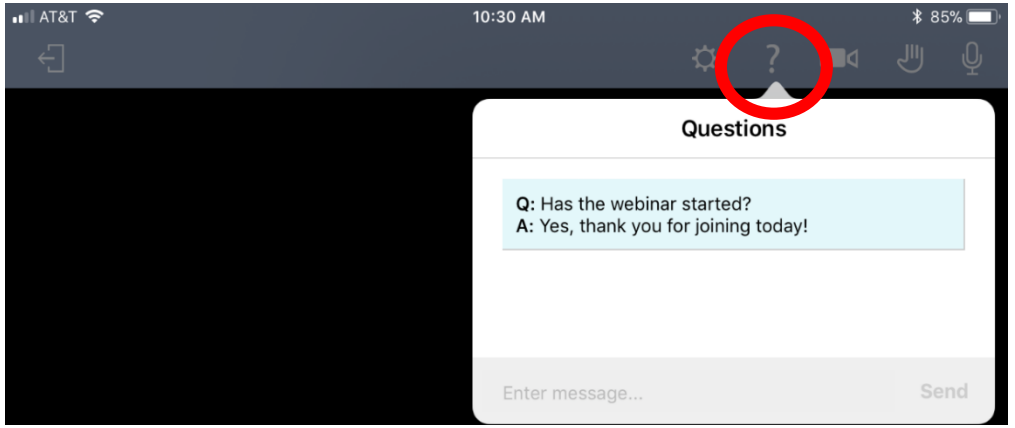
- Biomarker Task Force – several white papers published
- Cancer Immune Responsiveness Workshop – September 4-5, 2019
- SITC Annual Meeting – November 7-10, 2019
  - Immune Checkpoints: Newer targets and update on combinations
  - Imaging technologies
  - High impact clinical trials

Question & Answer Session

Computer

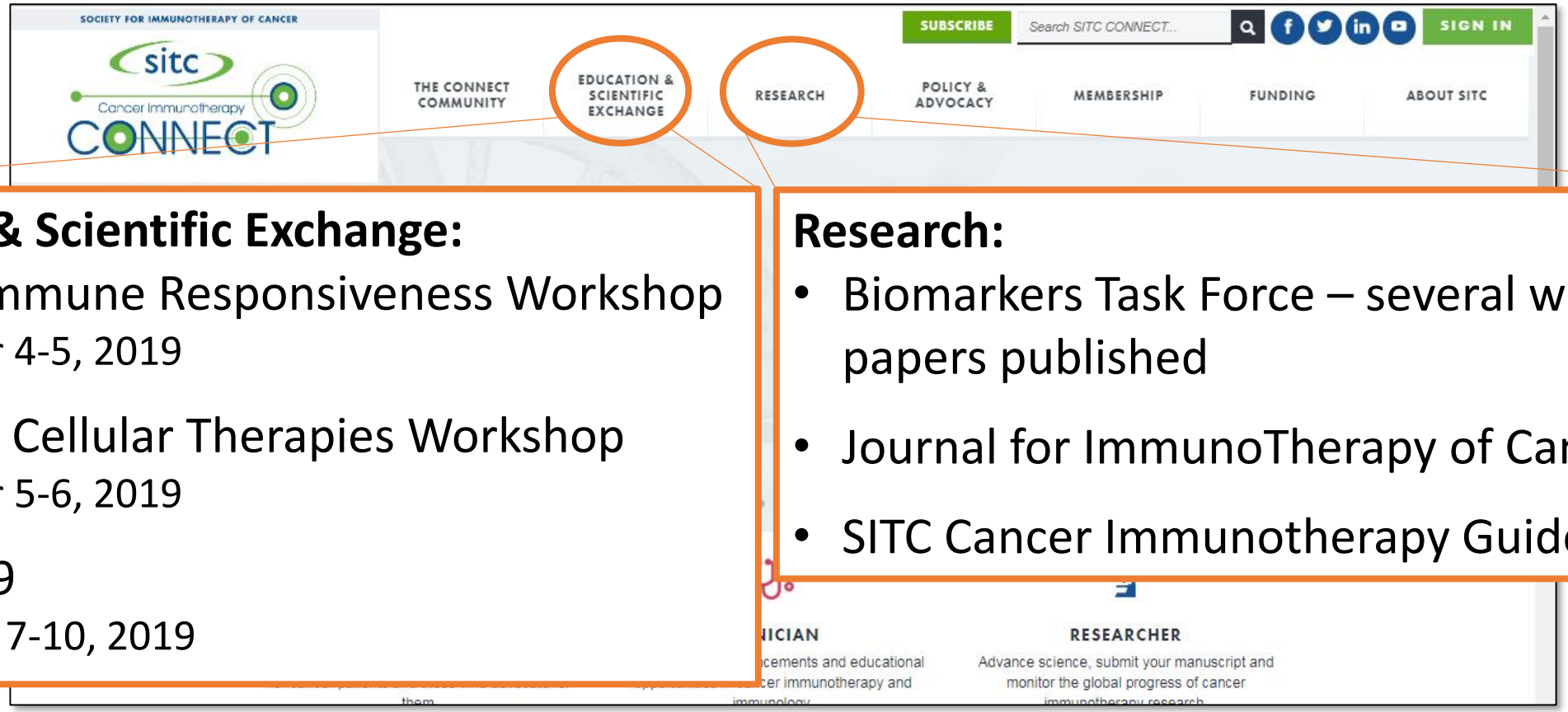


Mobile Phone



Resources and Education from SITC

www.sitcancer.org



Education & Scientific Exchange:

- Cancer Immune Responsiveness Workshop
  September 4-5, 2019
- Adoptive Cellular Therapies Workshop
  September 5-6, 2019
- SITC 2019
  November 7-10, 2019

Research:

- Biomarkers Task Force – several white papers published
- Journal for ImmunoTherapy of Cancer (JITC)
- SITC Cancer Immunotherapy Guidelines

Society for Immunotherapy of Cancer

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Thank you for attending the SITC Webinar: I-O Highlights from ASCO 2019!

Questions or comments: connectED@sitcancer.org