# **Melanoma** & Skin Cancers

**Sanjiv S. Agarwala, MD**
Professor, Temple University
Philadelphia, USA
CMO, Cancer Expert Now

# Disclosure of Conflict(s) of Interest

- Sanjiv S. Agarwala, MD reported no relevant financial relationships or relationships with ineligible companies of any amount during the past 24 months.

# Overview

- Current Status of Melanoma Therapy
- Learnings from ASCO 2021

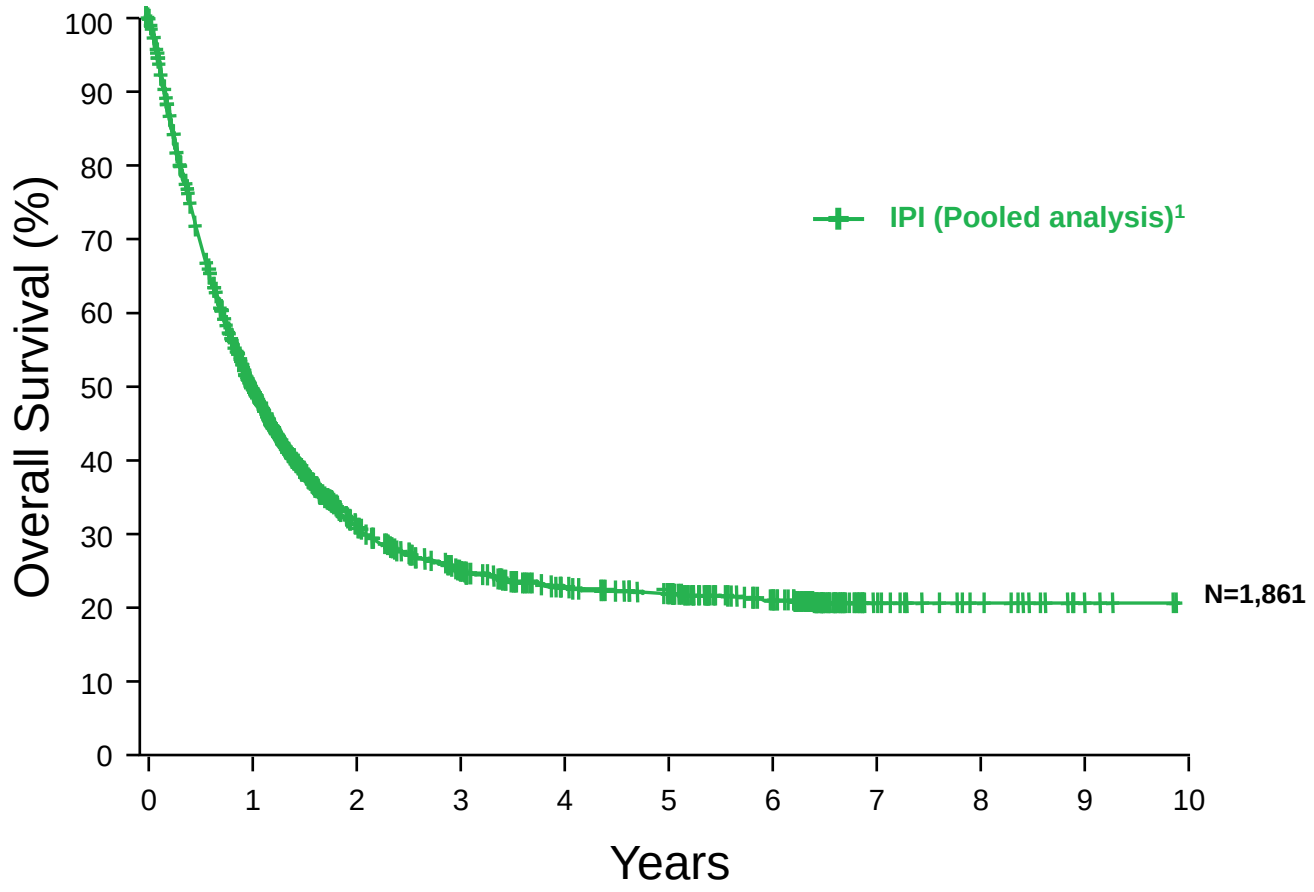
# Overview

- Current Status of Melanoma Therapy
- Learnings from ASCO 2021

# Metastatic Melanoma

- Immunotherapy
  - Anti-PD1 (nivolumab, pembrolizumab)
  - Anti-PD1+Anti-CTLA4 (ipilimumab + nivolumab)
- Targeted Therapy
  - BRAF/MEK combinations
- Triple Therapy
  - BRAF/MEK/Anti-PD1

# Fare clic per modificare lo stile del titolo



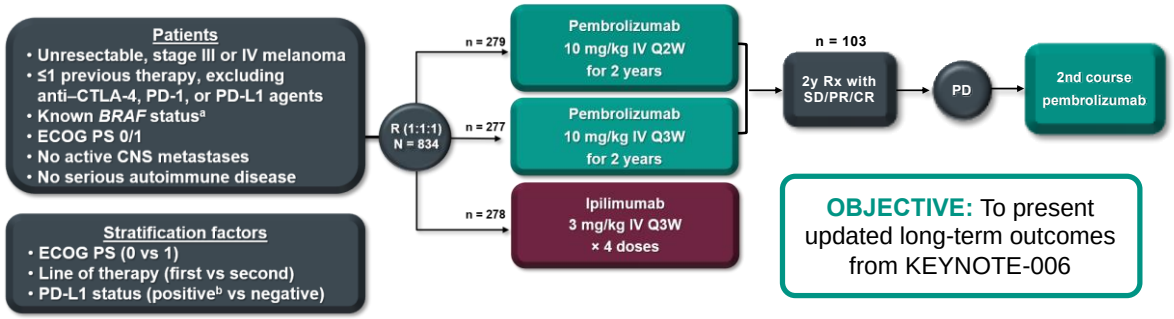

1. Schadendorf et al. *J Clin Oncol* 2015;33:1889-1894; 2. Current analysis; 3. Poster presentation by Dr. Victoria Atkinson at SMR 2015 International Congress.

# Long-Term Survival From Pembrolizumab Completion and Pembrolizumab Retreatment: Phase 3 KEYNOTE-006 in Advanced Melanoma

G. V. Long[1-4], J. Schachter[5], A. Arance[6], J.-J. Grob[7], L. Mortier[8], A. Daud[9], M. S. Carlino[1,2,10,11], A. Ribas[12], C. M. McNeil[2,13], M. Lotem[14], J. Larkin[15], P. Lorigan[16], B. Neyns[17], C. U. Blank[18], T. M. Petrella[19], O. Hamid[20], E. Jensen[21], C. Krepler[21], S. J. Diede[21], C. Robert[22]

## ASCO 2020

[1]Melanoma Institute Australia, Sydney, NSW, Australia; [2]University of Sydney, Sydney, NSW, Australia; [3]Royal North Shore Hospital, Sydney, NSW, Australia; [4]Mater Hospital, North Sydney, NSW, Australia; [5]Sheba Medical Center, Tel HaShomer Hospital, Tel Aviv, Israel, [6]Hospital Clinic de Barcelona, Barcelona, Spain; [7]Aix Marseille University, Hôpital de la Timone, Marseille, France; [8]Université Lille, Centre Hospitalier Regional Universitaire de Lille, Lille, France; [9]UCSF, San Francisco, CA, USA; [10]Blacktown Hospital, Blacktown, NSW, Australia; [11]Crown Princess Mary Cancer Centre, Westmead Hospital, Sydney, NSW, Australia; [12]David Geffen School of Medicine at UCLA, Los Angeles, CA, USA; [13]Chris O'Brien Lifehouse, Camperdown, NSW, Australia; [14]Sharett Institute of Oncology, Hadassah Hebrew Medical Center, Jerusalem, Israel; [15]Royal Marsden Hospital, London, England; [16]University of Manchester and the Christie NHS Foundation Trust, Manchester, England; [17]Universitair Ziekenhuis Brussel, Brussels, Belgium; [18]Netherlands Cancer Institute, Amsterdam, Netherlands; [19]Sunnybrook Health Sciences Centre, Toronto, ON, Canada; [20]The Angeles Clinic and Research Institute, Los Angeles, CA, USA; [21]Merck & Co., Inc., Kenilworth, NJ, USA; [22]Gustave Roussy and Paris-Sud University, Villejuif, France



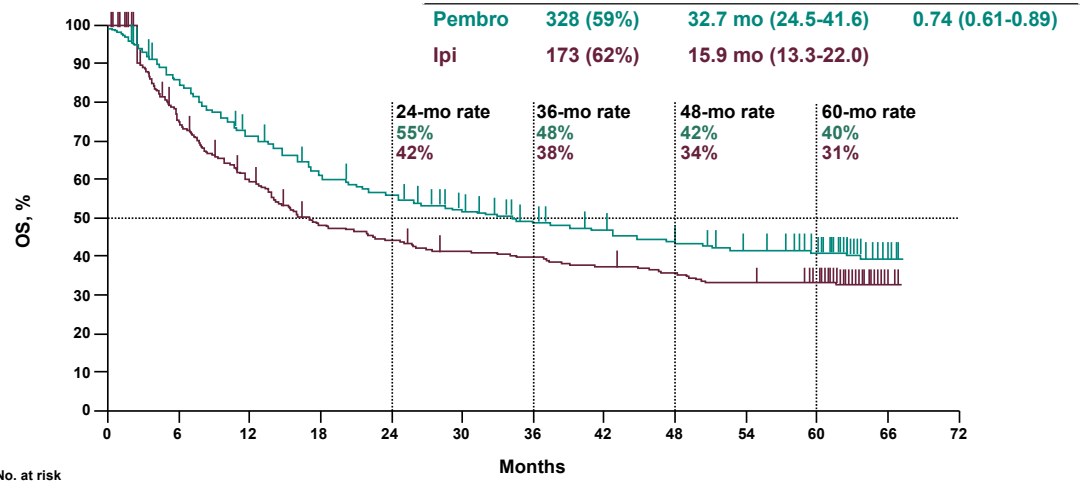

**OBJECTIVE:** To present updated long-term outcomes from KEYNOTE-006

- Two pembrolizumab arms pooled as similar efficacy[2]
- Patients completing ≥94 weeks of pembrolizumab with SD/PR/CR were considered to have completed 2 years of treatment
- Patients could receive a 2nd course of 1 year of pembrolizumab if progressed after SD/PR/CR
- Data cut-off: July 31, 2019; median follow-up: 66.8 months (range, 65.0-70.4); time from last patient enrolled to data cutoff, 65.0 months

[a]Prior anti-BRAF therapy was not required for patients with normal LDH levels and no clinically significant tumor-related symptoms or evidence of rapidly progressing disease.
[b]Defined as ≥1% staining in tumor and adjacent immune cells as assessed by IHC using 22C3 antibody.

## Overall Survival: Total Population

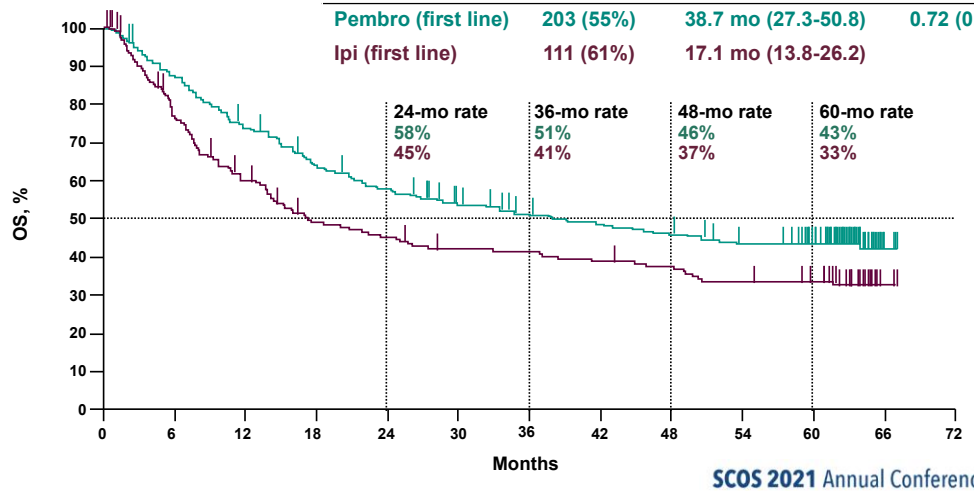
| | Events, n (%) | Median OS (95% CI) | HR[a] (95% CI) |
|---|---|---|---|
| Pembro | 328 (59%) | 32.7 mo (24.5-41.6) | 0.74 (0.61-0.89) |
| Ipi | 173 (62%) | 15.9 mo (13.3-22.0) | |




Data cut-off: July 31, 2019. [a]Based on Cox regression model with treatment as a covariate stratified by line of therapy (1st vs 2nd), PD-L1 status (positive vs negative) and ECOG (0 vs 1); in instances where there were no patients in one of the treatment groups involved in a comparison for a particular stratum, that stratum was excluded from the treatment comparison.

## Overall Survival: First Line Patients

| | Events, n (%) | Median OS (95% CI) | HR[a] (95% CI) |
|---|---|---|---|
| Pembro (first line) | 203 (55%) | 38.7 mo (27.3-50.8) | 0.72 (0.57-0.91) |
| Ipi (first line) | 111 (61%) | 17.1 mo (13.8-26.2) | |

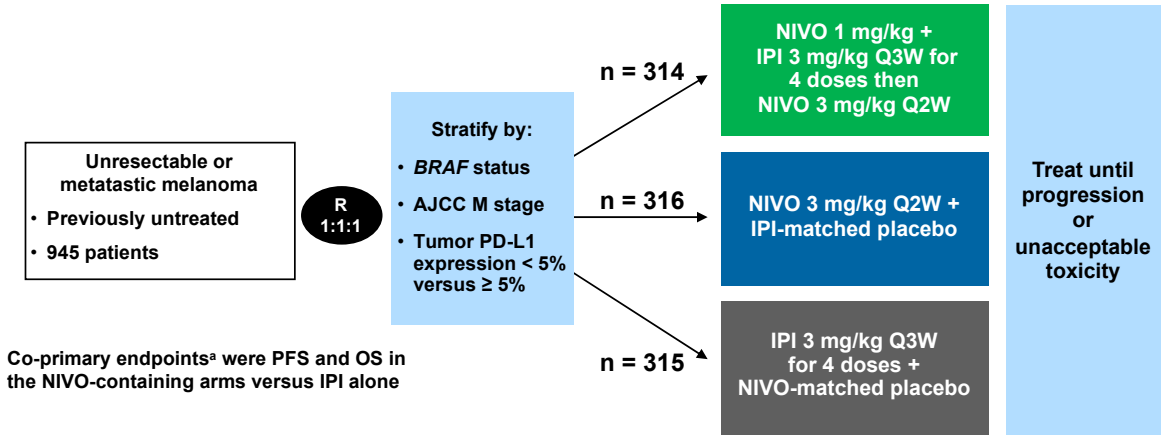



Data cut-off: July 31, 2019. [a]Based on Cox regression model with treatment as a covariate stratified by line of therapy (1st vs 2nd), PD-L1 status (positive vs negative) and ECOG (0 vs 1); in instances where there were no patients in one of the treatment groups involved in a comparison for a particular stratum, that stratum was excluded from the treatment comparison.

# Five-Year Survival Outcomes of the CheckMate 067 Phase 3 Trial of Nivolumab Plus Ipilimumab Combination Therapy in Advanced Melanoma

James Larkin,[1] Vanna Chiarion-Sileni,[2] Rene Gonzalez,[3] Jean-Jacques Grob,[4] Piotr Rutkowski,[5] Christopher D. Lao,[6] C. Lance Cowey,[7] Dirk Schadendorf,[8] John Wagstaff,[9] Reinhard Dummer,[10] Pier F. Ferrucci,[11] Michael Smylie,[12] David Hogg,[13] Andrew Hill,[14] Ivan Márquez-Rodas,[15] John Haanen,[16] Jasmine I. Rizzo,[17] Agnes Balogh,[17] Andriy Moshyk,[17] F. Stephen Hodi,[18*] Jedd Wolchok[19*]

[1]The Royal Marsden NHS Foundation Trust, London, UK; [2]Oncology Institute of Veneto IRCCS, Padua, Italy; [3]University of Colorado Cancer Center, Aurora, CO, USA; [4]Aix-Marseille University, APHM Hospital, Marseille, France; [5]Maria Sklodowska-Curie Institute - Oncology Center, Warsaw, Poland; [6]University of Michigan, Ann Arbor, MI, USA; [7]Texas Oncology-Baylor Charles A. Sammons Cancer Center, Dallas, TX, USA; [8]Department of Dermatology, University of Essen, Essen, Germany; & German Cancer Consortium, Heidelberg, Germany; [9]The College of Medicine, Swansea University, Swansea, UK; [10]Universitäts Spital, Zurich, Switzerland; [11]European Institute of Oncology, Milan, Italy; [12]Cross Cancer Institute, Alberta, Canada; [13]Princess Margaret Cancer Centre, Toronto, ON, Canada; [14]Tasman Oncology Research, QLD, Australia; [15]General University Hospital Gregorio Marañon, Madrid, Spain; [16]The Netherlands Cancer Institute, Amsterdam, The Netherlands; [17]Bristol-Myers Squibb, Princeton, NJ; USA, [18]Dana-Farber Cancer Institute, Boston, MA; USA, [19]Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, New York, NY, USA
*Contributed equally.

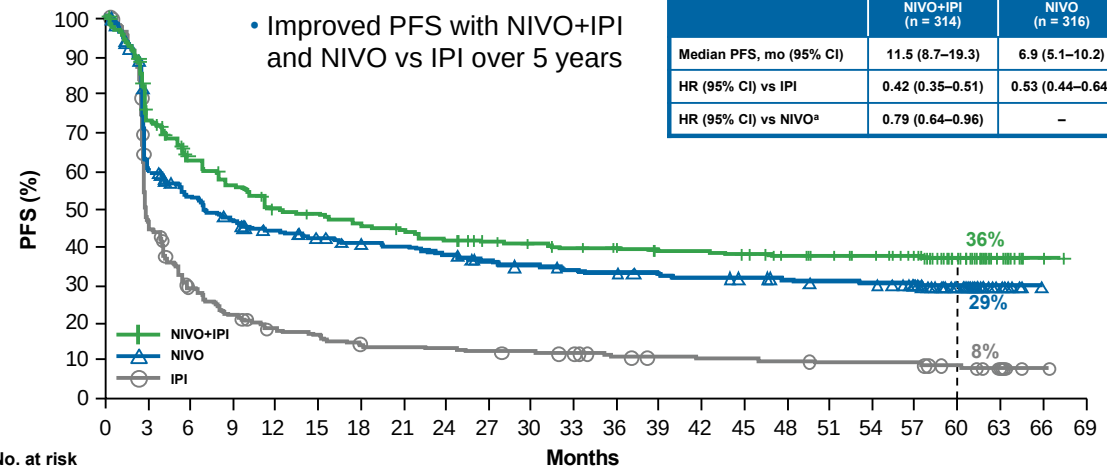



**Co-primary endpoints[a] were PFS and OS in the NIVO-containing arms versus IPI alone**

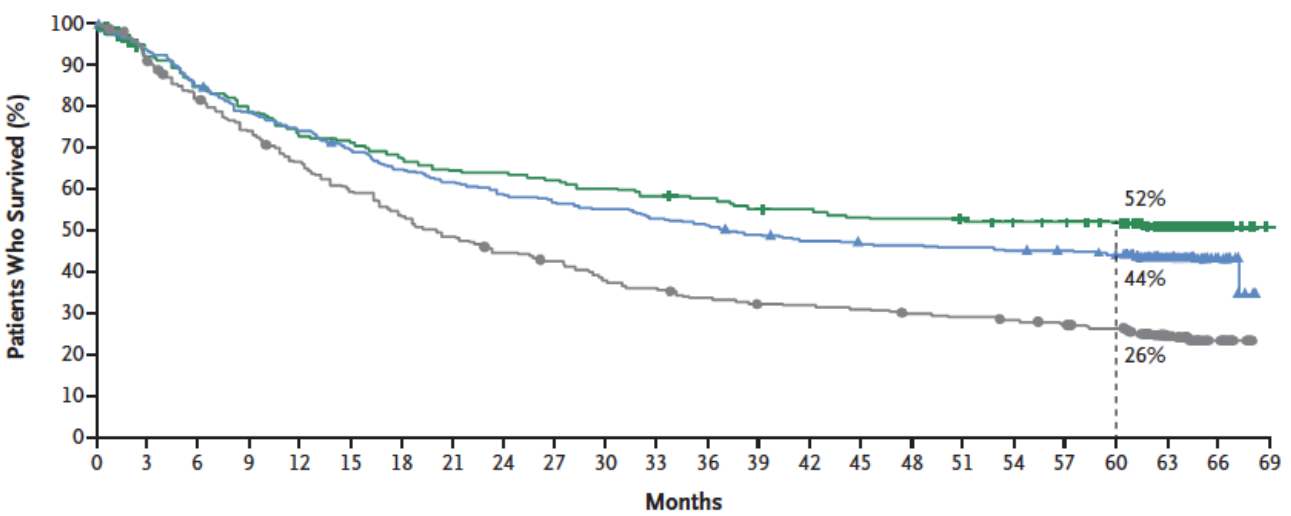
**Database lock: July 2, 2019; minimum follow-up of 60 months for all patients**

- Improved PFS with NIVO+IPI and NIVO vs IPI over 5 years

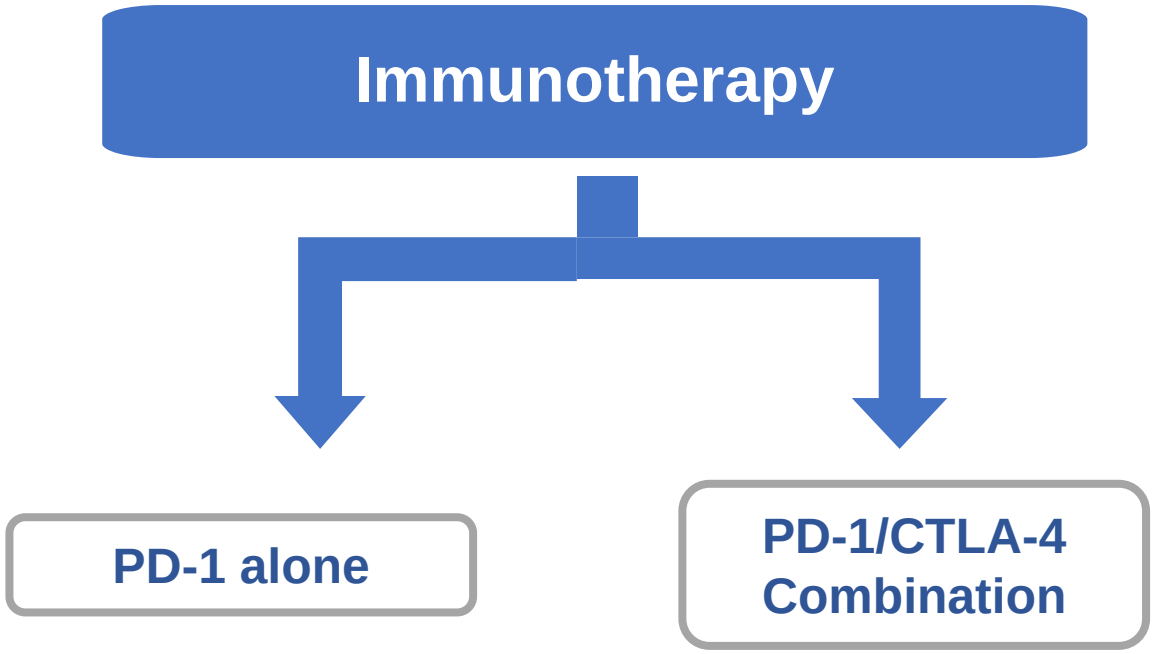
| | NIVO+IPI (n = 314) | NIVO (n = 316) | IPI (n = 315 |
|---|---|---|---|
| Median PFS, mo (95% CI) | 11.5 (8.7–19.3) | 6.9 (5.1–10.2) | 2.9 (2.8–3. |
| HR (95% CI) vs IPI | 0.42 (0.35–0.51) | 0.53 (0.44–0.64) | – |
| HR (95% CI) vs NIVO[a] | 0.79 (0.64–0.96) | – | – |



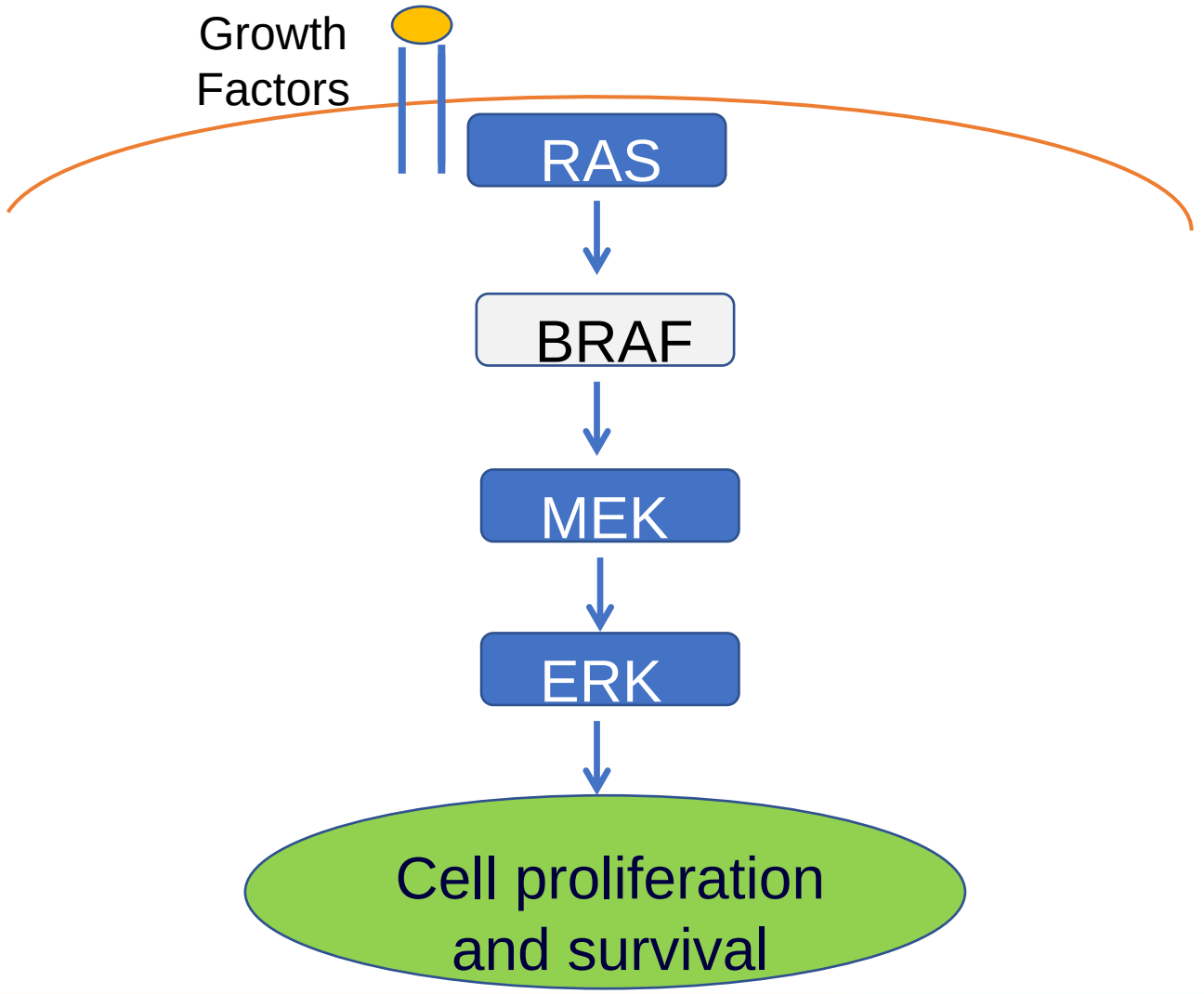

| No. at risk | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| NIVO+IPI | 314 | 218 | 174 | 155 | 136 | 131 | 124 | 117 | 110 | 104 | 101 | 97 | 95 | 91 | 90 | 88 | 82 | 79 | 76 | 69 | 45 | 19 | 2 | 0 |
| NIVO | 316 | 177 | 151 | 132 | 120 | 112 | 106 | 103 | 97 | 88 | 84 | 80 | 78 | 76 | 73 | 71 | 68 | 66 | 65 | 60 | 40 | 13 | 1 | 0 |
| IPI | 315 | 136 | 78 | 58 | 46 | 42 | 34 | 32 | 31 | 29 | 28 | 26 | 21 | 19 | 18 | 18 | 17 | 15 | 15 | 15 | 11 | 8 | 1 | 0 |



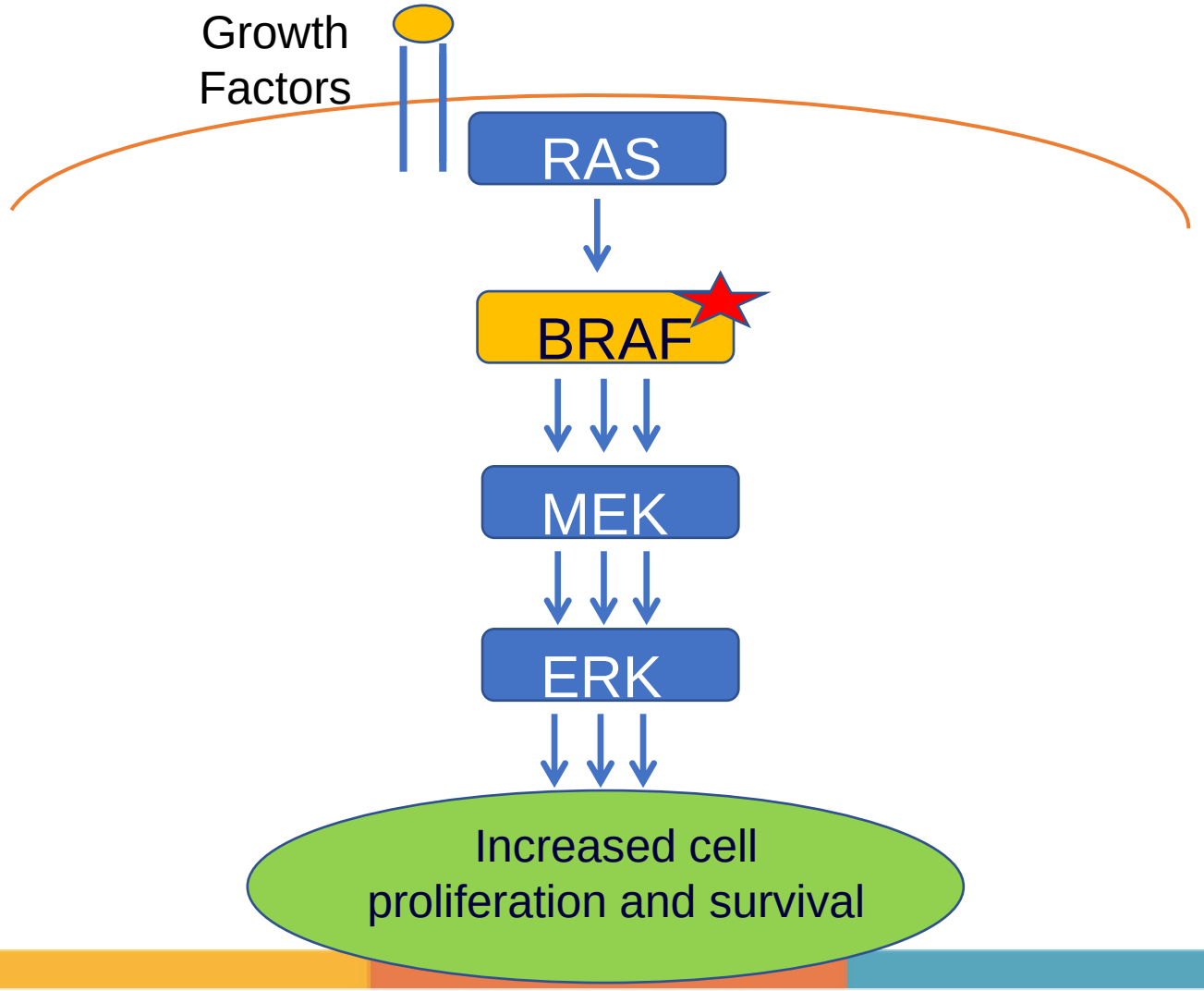
# Combination or monotherapy?



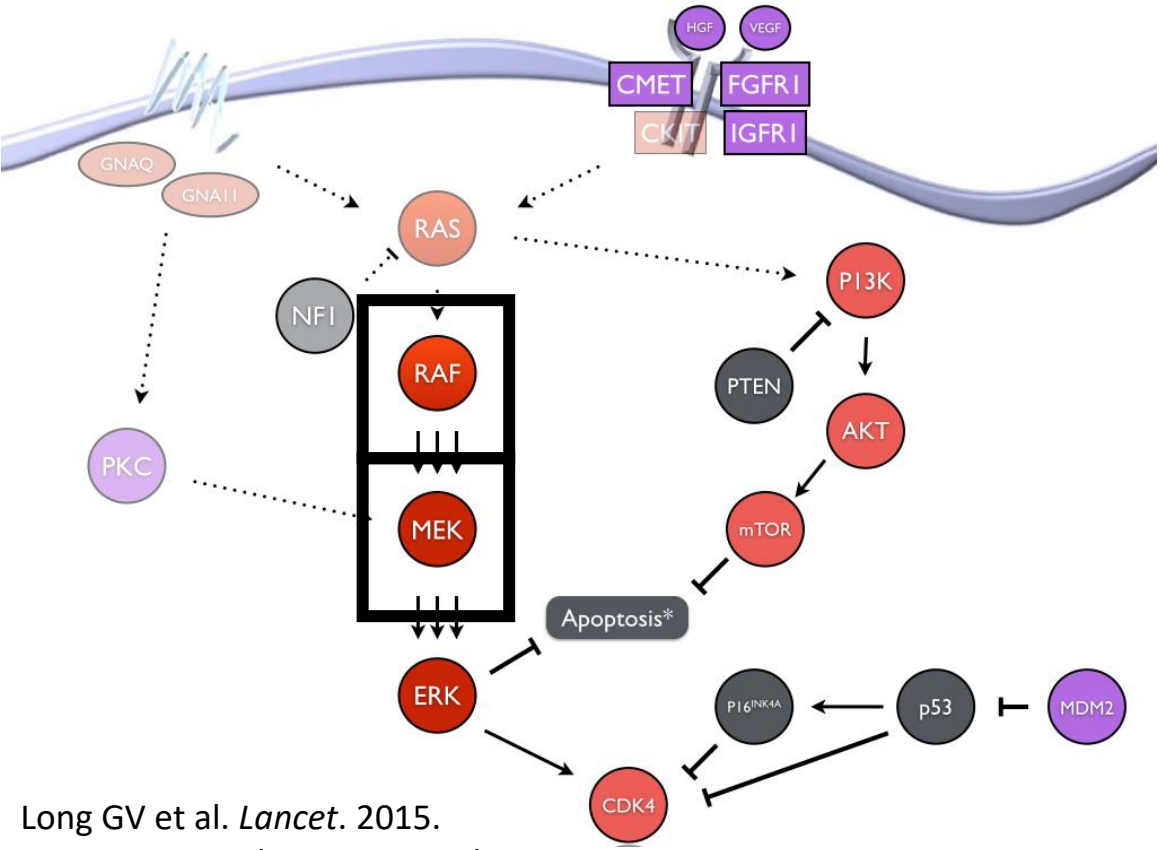
# Targeted Therapy: MAPK Pathway

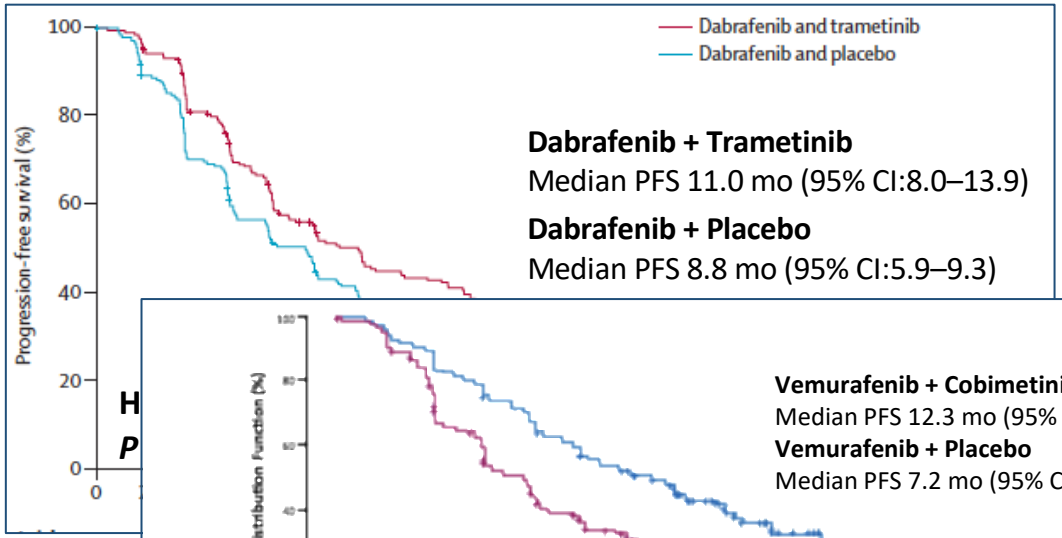


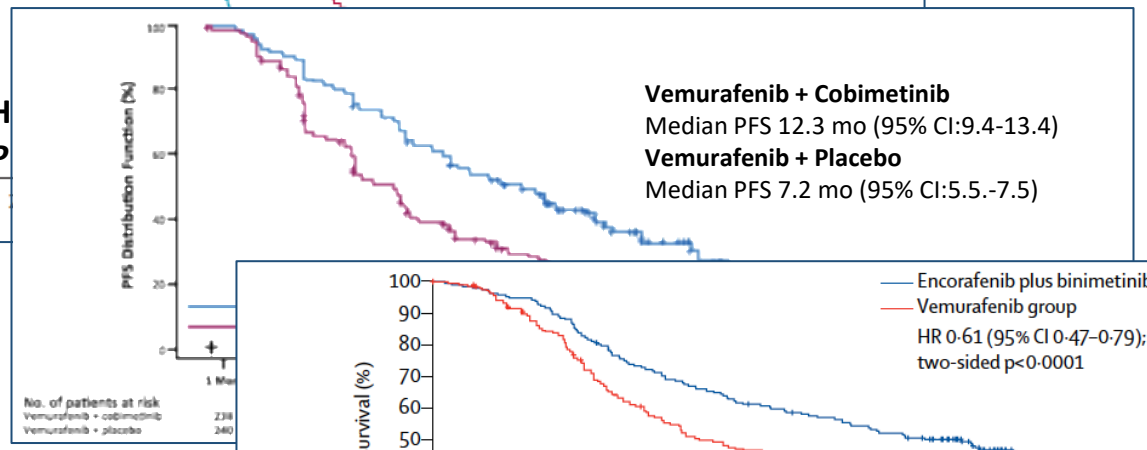
# BRAF Mutation

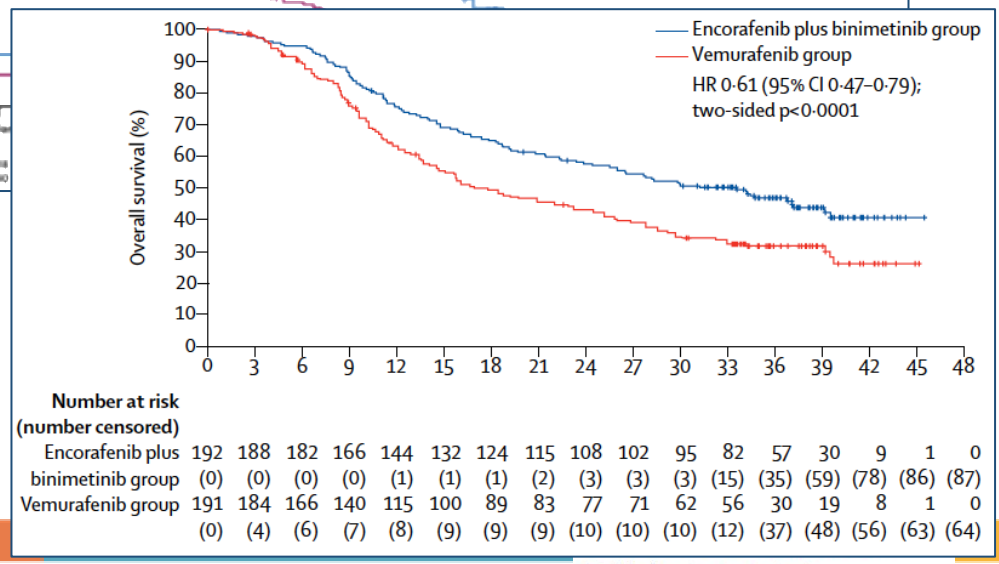


# Dual BRAF and MEK Inhibition Is Associated With High Response Rates and Improved PFS and OS



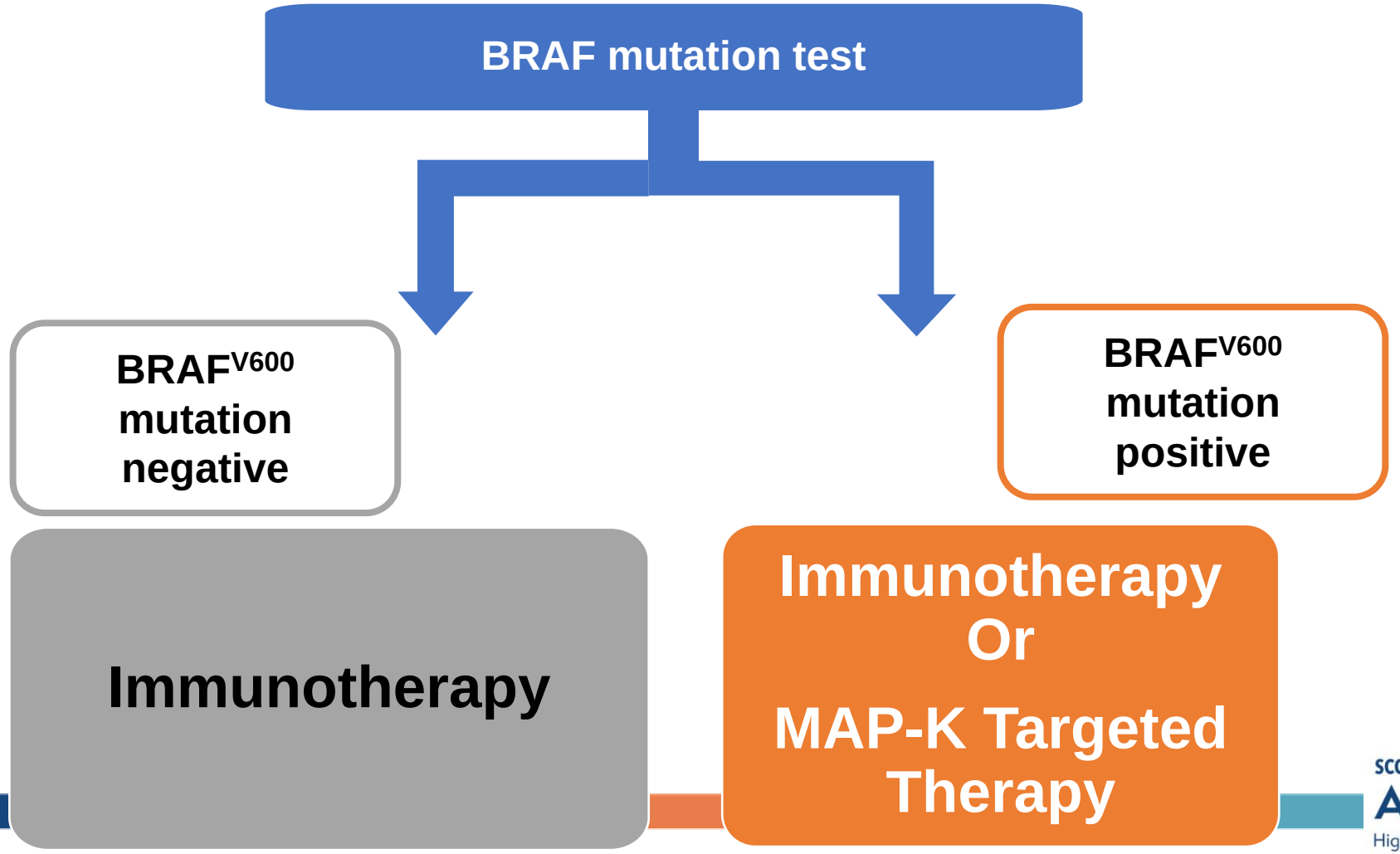




Long GV et al. *Lancet*. 2015.
Ascierto PA et al. *Lancet Oncol.* 2016.
Dummer R et al. *Lancet Oncol*. 2018.

# Melanoma Therapy Decision Point



# Is This a Marriage Made in Heaven?

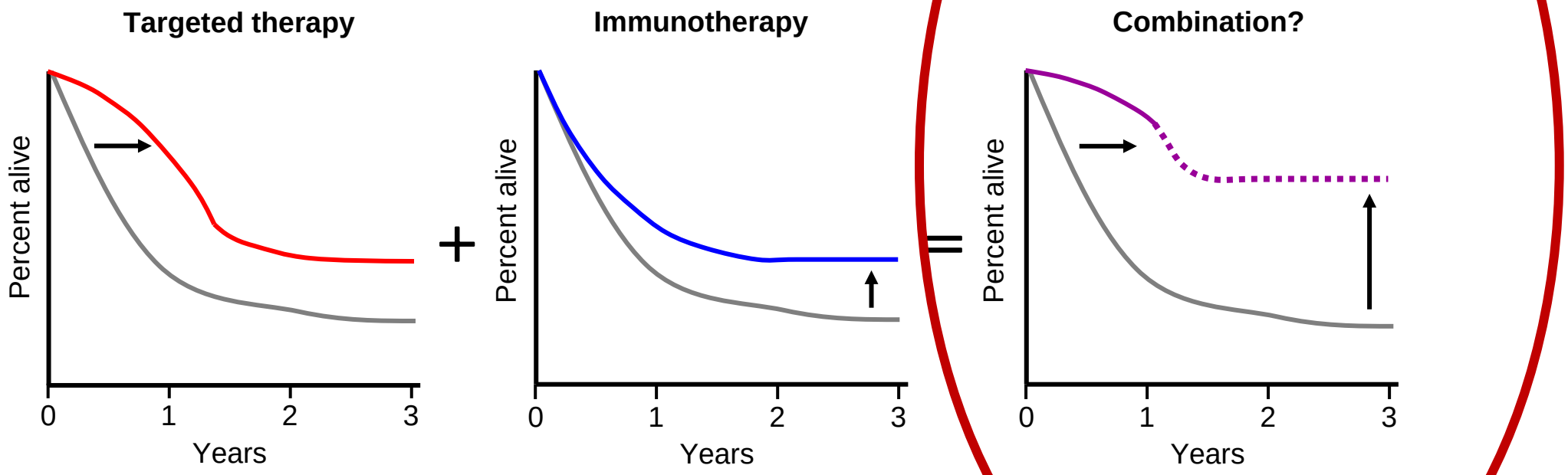



Figure modified from Ribas A et al. *Clin Cancer Res.* 2012, and Hamid O et al. SMR 2015.

# Evaluation of Atezolizumab, Cobimetinib, and Vemurafenib in Previously Untreated Patients With *BRAF*$^{V600}$ Mutation–Positive Advanced Melanoma: Primary Results From the Phase 3 IMspire150 Trial

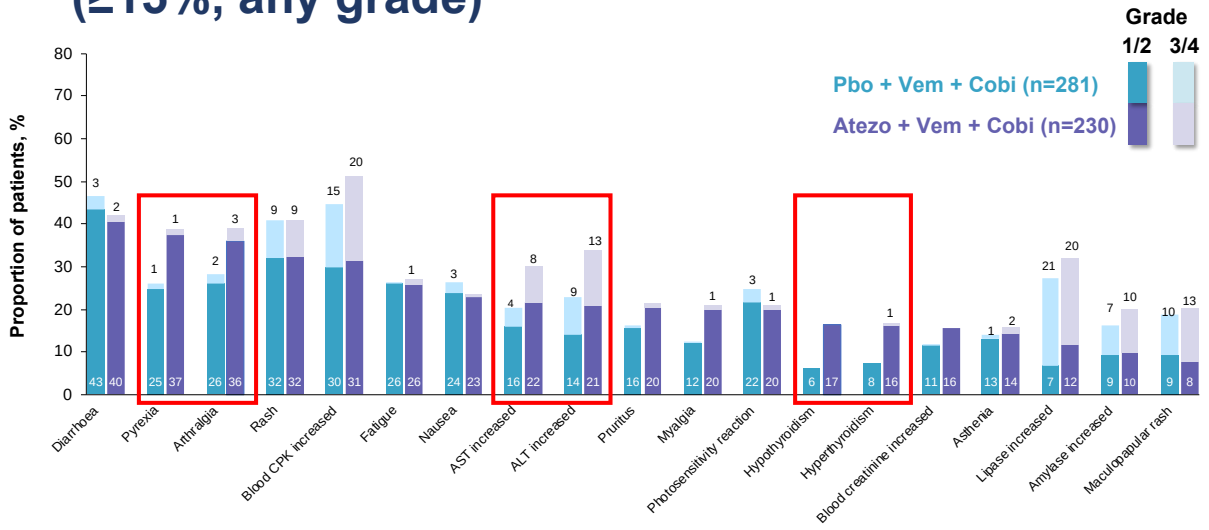
Grant A. McArthur, M.B., B.S., Ph.D.,[1] Daniil Stroyakovskiy, M.D.,[2] Helen Gogas, M.D., Ph.D.,[3] Caroline Robert, M.D., Ph.D.,[4] Karl Lewis, M.D.,[5] Svetlana Protsenko, M.D.,[6] Rodrigo Pereira, M.D.,[7] Thomas Eigentler, M.D.,[8] Piotr Rutkowski, M.D., Ph.D.,[9] Lev Demidov, M.D.,[10] Georgy Moiseevich Manikhas, M.D.,[11] Yibing Yan,[12] Kuan-Chieh Huang, Ph.D.,[12] Anne Uyei, M.D.,[12] Virginia McNally, Ph.D.,[13] Ralf Gutzmer, M.D.,[14] Paolo Ascierto, M.D.[15]

**AACR Annual Meeting 2020**

[1]Melanoma and Skin Service and Cancer Therapeutics Program, Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia; [2]Moscow City Oncology Hospital #62 of Moscow Healthcare Department, Moscow, Russia; [3]First Department of Medicine, Laiko General Hospital, National and Kapodistrian University of Athens, Greece; [4]Gustave Roussy and Université Paris-Saclay, Villejuif-Paris, France; [5]University of Colorado Comprehensive Cancer Center, Aurora, CO, USA; [6]Department of Chemotherapy and Innovative Technologies, N. N. Petrov National Medical Research Center of Oncology, St. Petersburg, Russia; [7]Hospital das Clinicas, Porto Alegre, Brazil; [8]University Hospital Tübingen, Tübingen, Germany; [9]Department of Soft Tissue/Bone Sarcoma and Melanoma, Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland; [10]N. N. Blokhin Russian Cancer Research Center, Ministry of Health, Moscow, Russia; [11]St. Petersburg Oncology Hospital, St. Petersburg, Russia; [12]Genentech, Inc., South San Francisco, CA, USA; [13]Roche Products Ltd., Welwyn Garden City, UK.; [14]Haut-Tumour-Zentrum Hannover (HTZH), Klinik für Dermatologie, Allergologie und Venerologie, Medizinische Hochschule Hannover (MHH), Hannover, Germany; [15]Istituto Nazionale Tumori IRCCS Fondazione "G. Pascale," Naples, Italy.

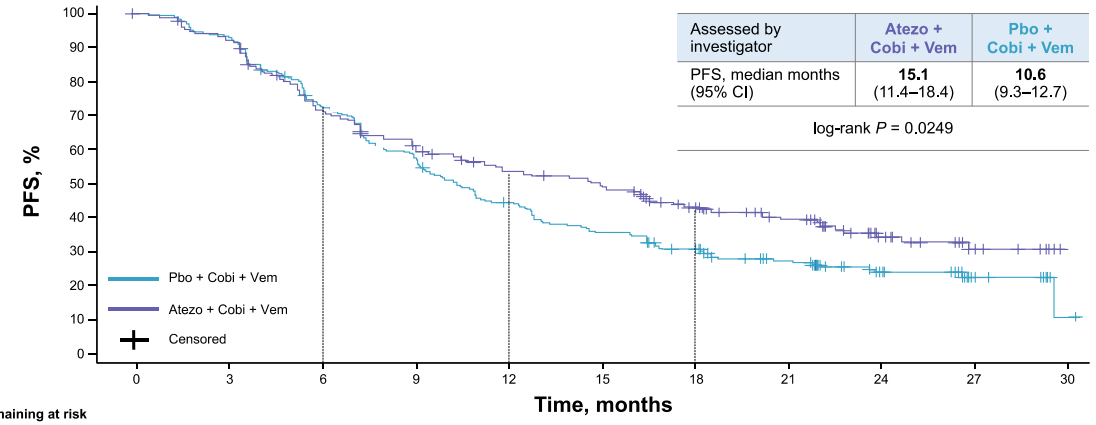
AACR Annual Meeting 2020

## Common Treatment-Related AEs (≥15%, any grade)




AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CPK, creatine phosphokinase.
Listed AEs were reported at a frequency of ≥15%, along with corresponding frequencies for grade 3/4 events.

## IMspire150: Primary Endpoint: Investigator-Assessed PFS




| Assessed by investigator | Atezo + Cobi + Vem | Pbo + Cobi + Vem |
|---|---|---|
| PFS, median months (95% CI) | **15.1** (11.4–18.4) | **10.6** (9.3–12.7) |

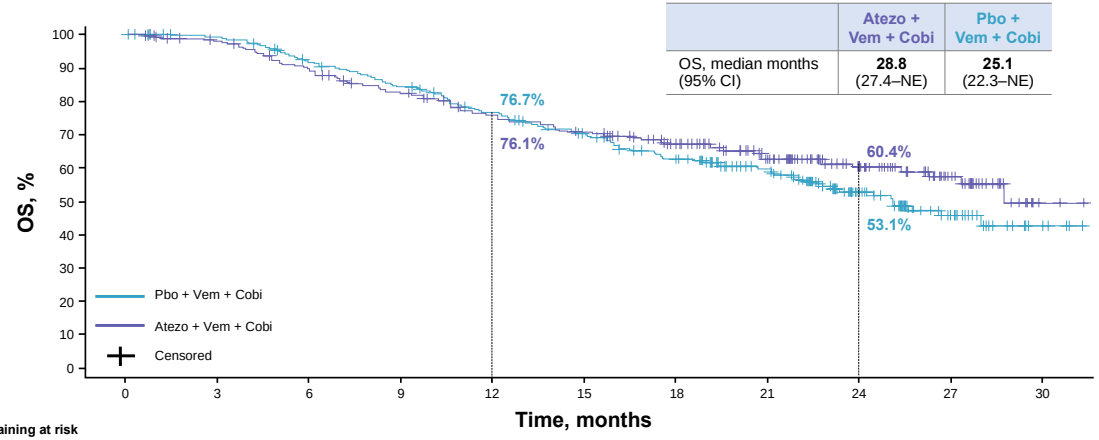
log-rank $P = 0.0249$

**Patients remaining at risk**

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Pbo + Cobi + Vem | 258 | 230 | 179 | 143 | 107 | 86 | 71 | 51 | 27 | 11 | 1 |
| Atezo + Cobi + Vem | 256 | 229 | 174 | 149 | 123 | 114 | 90 | 66 | 34 | 11 | |

Atezo, atezolizumab; CI, confidence interval; Cobi, cobimetinib; Pbo, placebo; Vem, vemurafenib.

## IMspire150: Overall Survival




| | Atezo + Vem + Cobi | Pbo + Vem + Cobi |
|---|---|---|
| OS, median months (95% CI) | **28.8** (27.4–NE) | **25.1** (22.3–NE) |

**Patients remaining at risk**

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Pbo + Vem + Cobi | 258 | 249 | 225 | 206 | 175 | 161 | 139 | 105 | 57 | 26 | 5 |
| Atezo + Vem + Cobi | 256 | 242 | 220 | 198 | 173 | 165 | 144 | 105 | 66 | 28 | 2 |

# Adjuvant Therapy

- Immunotherapy
  - Anti-PD1 (nivolumab, pembrolizumab)
- Targeted Therapy
  - BRAF/MEK combinations

# CheckMate 238: Study Design

**Patients with:**

- **High-risk, completely resected stage IIIB/IIIC or stage IV[a] melanoma**
- **No prior systemic therapy**
- **ECOG PS 0/1**

**1:1**

**n = 453**

**NIVO 3 mg/kg IV Q2W and IPI placebo IV Q3W for 4 doses, then Q12W from week 24**

**n = 453**

**IPI 10 mg/kg IV Q3W for 4 doses, then Q12W from week 24 and NIVO placebo IV Q2W**

**Follow-up**

**Maximum treatment duration of 1 year**

**Stratified by:**

1) Disease stage: IIIB/IIIC vs IV M1a or M1b vs IV M1c
2) Tumor PD-L1 status at a 5% cutoff

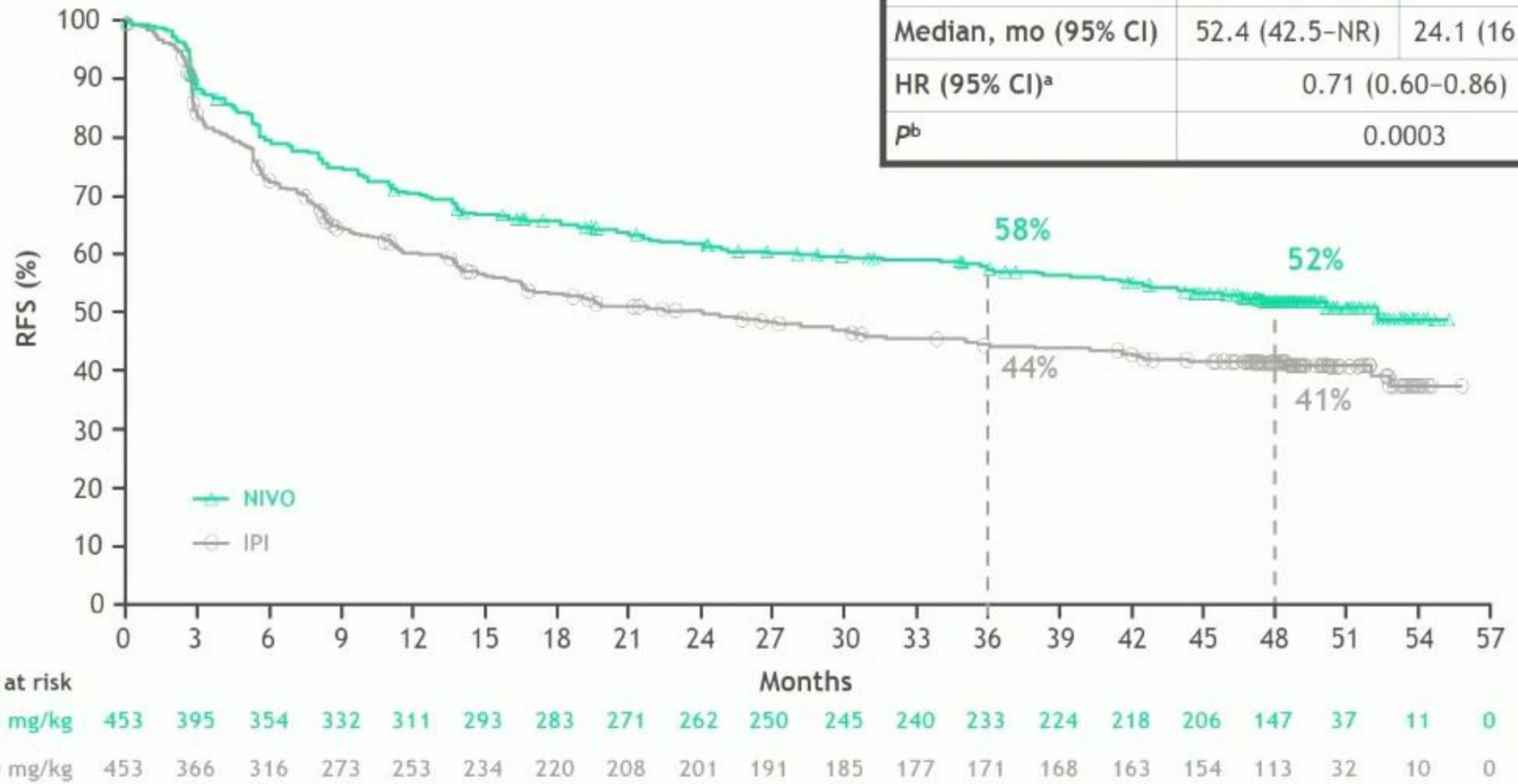
**Primary endpoint: RFS**

**Database lock: January 31, 2019; minimum follow-up of 36 months for all patients**

NCT02388906.[a]Per American Joint Committee on Cancer (AJCC) Cancer Staging Manual, seventh edition.

# Primary endpoint: 48-month RFS in all patients

| | NIVO (n = 453) | IPI (n = 453) |
|---|---|---|
| Events, n | 212 | 253 |
| Median, mo (95% CI) | 52.4 (42.5–NR) | 24.1 (16.6–35.1) |
| HR (95% CI)[a] | 0.71 (0.60–0.86) | |
| *P*[b] | 0.0003 | |




[a]Stratified; [b]Log-rank test. NR, not yet reached.

# KEYNOTE-054: Adjuvant Pembrolizumab vs Placebo for Stage III Melanoma (Part 1)

- Randomized, double-blind phase III study

Patients with resected high-risk stage IIIA, B, C melanoma (N = 1019)

**Pembrolizumab**
200 mg IV Q3W*
(n = 514)

**Placebo**
IV Q3W*
(n = 505)

***Treatment administered 18 doses (~ 1 yr) or until recurrence, unacceptable toxicity, or withdrawal***

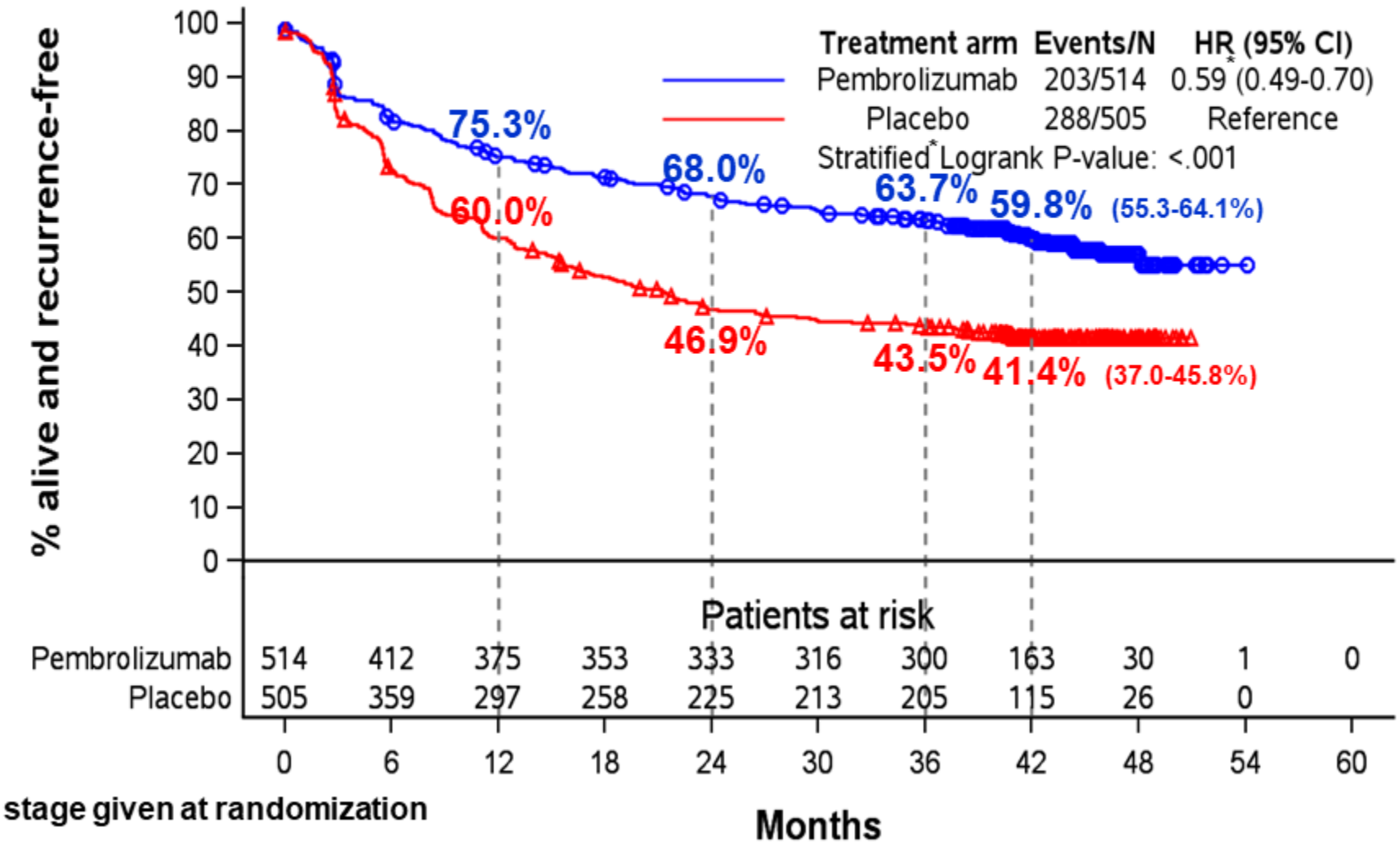
*Patients with recurrence eligible for crossover or repeat treatment with pembrolizumab.

- Coprimary endpoints: RFS in ITT population, RFS in PD-L1+ subgroup
- Secondary endpoints: DMFS, OS, safety, QoL

Eggermont. NEJM. 2018;378:1789.

# Updated RFS analysis (ESMO 2020)

- **Cut-off date** (3-Apr-2020); median duration of follow-up: **3.5** years; **491** RFS events




**HR 0.59**

*Stratified by stage given at randomization

# Adjuvant Therapy: Combi-AD: Study Design

**Key eligibility criteria**

- Completely resected stage IIIA (lymph node metastasis > 1 mm), IIIB, or IIIC cutaneous melanoma
- *BRAF* V600E/K mutation
- ECOG performance status 0 or 1
- No prior radiotherapy or systemic therapy
- Tissue collection was mandatory at baseline and optional upon recurrence

**Stratification**

- ***BRAF* mutation status (V600E, V600K)**
- **Disease stage (IIIA, IIIB, IIIC)**

RANDOMIZATION

**N = 870**

**1:1**

**Dabrafenib 150 mg BID + trametinib 2 mg QD (n = 438)**

**2 matched placebos (n = 432)**

**Treatment duration: 12 months**

**Primary analysis** D+T median FU, 33 months

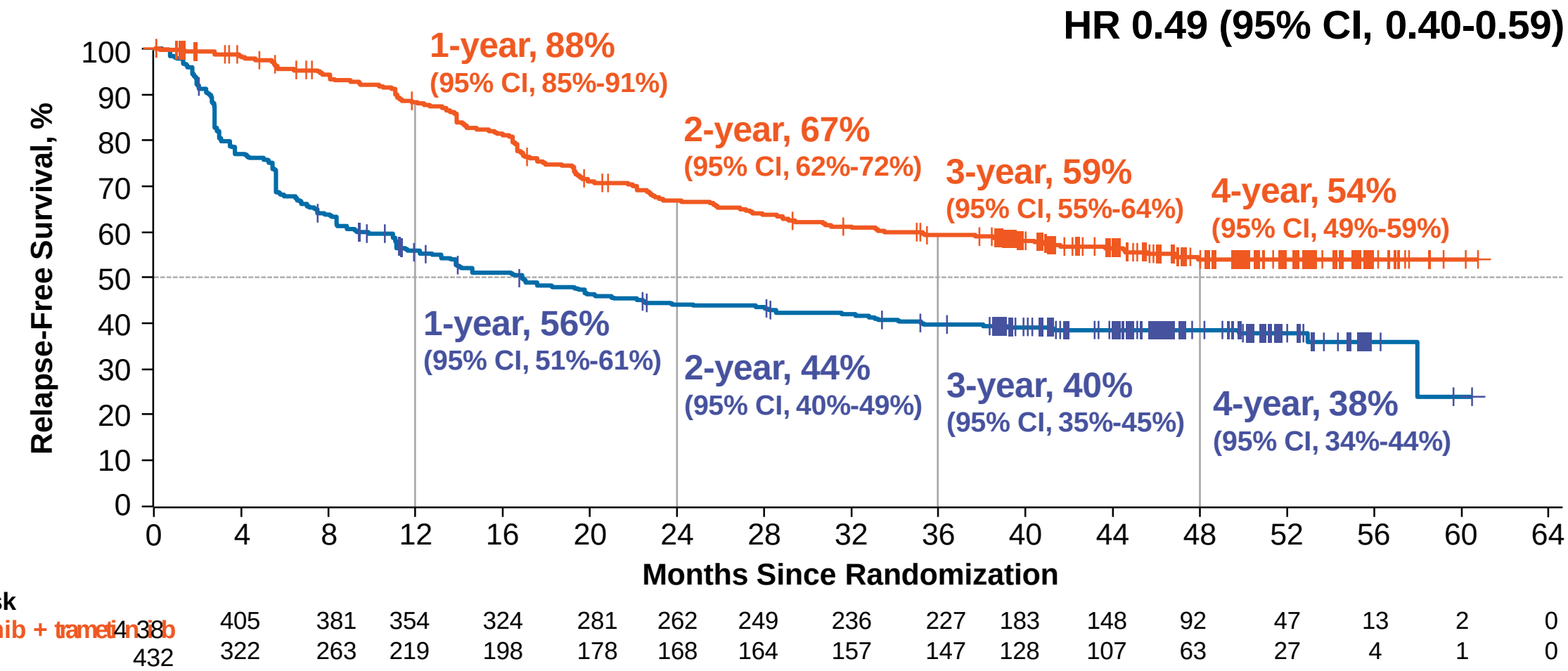
**Updated analysis** D+T median FU, 44 months

- **Primary endpoint: RFS**
- **Secondary endpoints: OS, DMFS, FFR, safety**

BID, twice daily; DMFS, distant metastasis–free survival; D+T, dabrafenib + trametinib; ECOG, Eastern Cooperative Oncology Group; FFR, freedom from relapse; FU, follow-up; QD, once daily.

Long GV, et al. *N Engl J Med*. 2017;377:1813-1823.

# COMBI-A/D: RELAPSE-FREE SURVIVAL



# Overview

- Current Status of Melanoma Therapy
- Learnings from ASCO 2021

# Learnings from ASCO 2021

- Front line therapy
  - Any new options?
- Data after immunotherapy failure
  - Major unmet need
- Neoadjuvant therapy

# Learnings from ASCO 2021

- Front line therapy
  - Any new options?
- Data after immunotherapy failure
  - Major unmet need
- Neoadjuvant therapy

2021 ASCO ANNUAL MEETING

# Relatlimab (RELA) + nivolumab (NIVO) versus NIVO in first-line advanced melanoma: primary phase 3 results from RELATIVITY-047 (CA224-047)

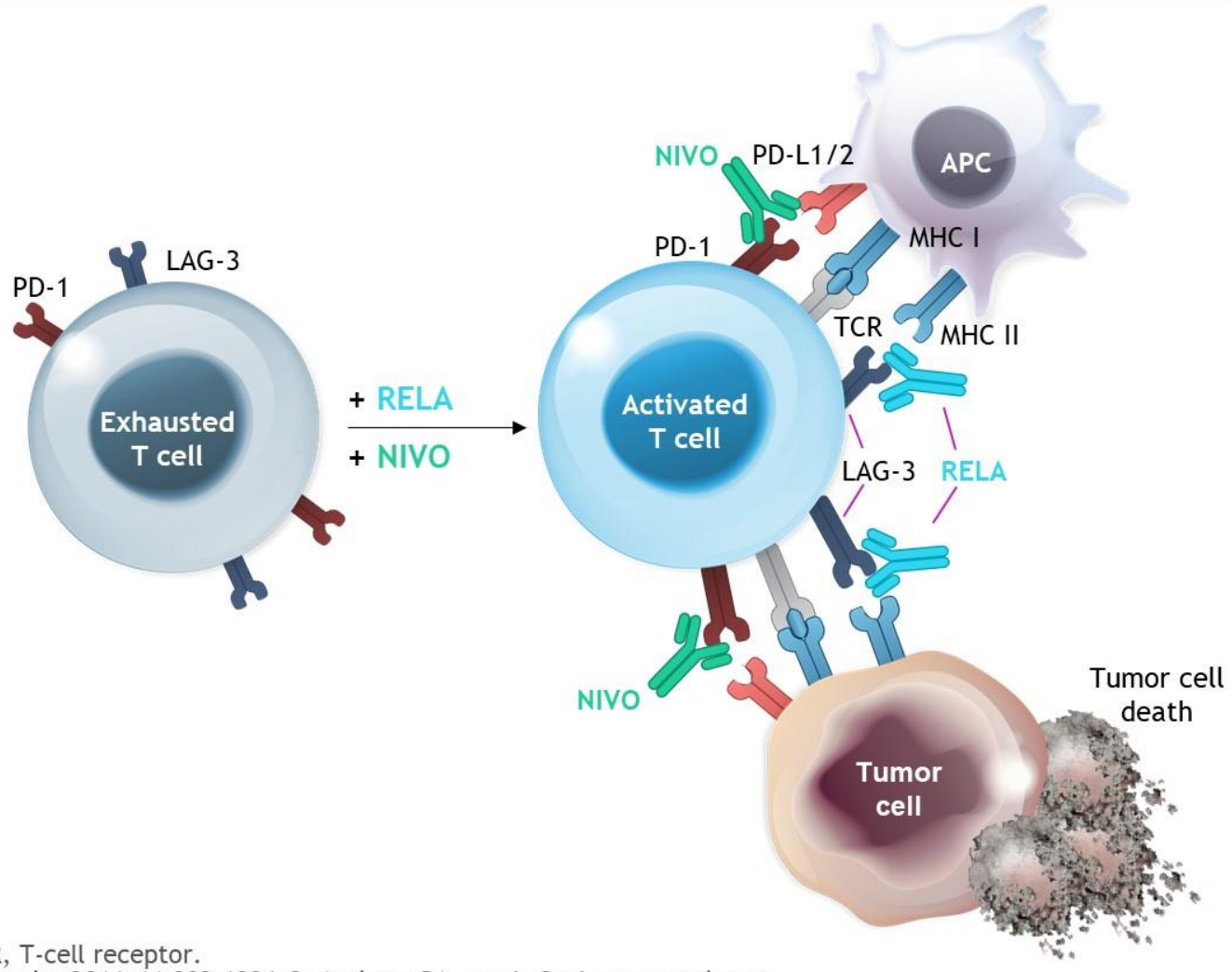
Evan J. Lipson,[1] Hussein A. Tawbi,[2] Dirk Schadendorf,[3] Paolo A. Ascierto,[4] Luis Matamala,[5] Erika Castillo Gutiérrez,[6] Piotr Rutkowski,[7] Helen J. Gogas,[8] Christopher D. Lao,[9] Juliana Janoski De Menezes,[10] Stéphane Dalle,[11] Ana Arance,[12] Jean-Jacques Grob,[13] Shivani Srivastava,[14] Mena Abaskharoun,[14] Katy L. Simonsen,[14] Bin Li,[14] Georgina V. Long,[a,15] F. Stephen Hodi[a,16]

[1]Bloomberg Kimmel Institute for Cancer Immunotherapy, Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD, USA; [2]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [3]University Hospital Essen, Essen, Germany; [4]Istituto Nazionale Tumori Fondazione "G. Pascale", Napoli, Italy; [5]Instituto Oncologico Fundacion Arturo Lopez Perez, Santiago, Chile; [6]FAICIC Clinical Research, Veracruz, Mexico; [7]Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland; [8]National and Kapodistrian University of Athens, Athens, Greece; [9]University of Michigan, Ann Arbor, MI, USA; [10]Hospital Nossa Senhora da Conceição, Porto Alegre, Brazil; [11]Hospices Civils de Lyon, Cancer Research Center of Lyon, Pierre-Bénite, France; [12]Hospital Clinic Barcelona, Barcelona, Spain; [13]Aix-Marseille University, CHU Timone, Marseille, France; [14]Bristol Myers Squibb, Princeton, NJ, USA; [15]Melanoma Institute Australia, The University of Sydney, and Royal North Shore and Mater Hospitals, Sydney, Australia; [16]Dana-Farber Cancer Institute, Boston, MA, USA [a]Co-senior author

*Presentation Number 9503*

# Rationale for RELA + NIVO

- LAG-3 and PD-1 are distinct immune checkpoints, often co-expressed on tumor-infiltrating lymphocytes, and contribute to tumor-mediated T-cell exhaustion[1,2]
- In preclinical models, LAG-3 and PD-1 blockade demonstrated synergistic antitumor activity[1]
- RELA + NIVO demonstrated clinically meaningful antitumor activity including durable objective responses and was well tolerated in patients with melanoma that was relapsed/refractory to anti-PD-1 therapy[3,4]




APC, antigen-presenting cell; MHC, major histocompatibility complex; TCR, T-cell receptor.

1. Woo S-R, et al. *Cancer Res* 2012;72:917-927; 2. Anderson AC, et al. *Immunity* 2016;44:989-1004; 3. Ascierto PA, et al. Oral presentation at ASCO Annual Meeting; June 2-6, 2017; Chicago, IL. Abstract 9520; 4. Ascierto PA, et al. Oral presentation at ESMO Congress; September 8-12, 2017; Madrid, Spain. Abstract LBA18.

# Study design

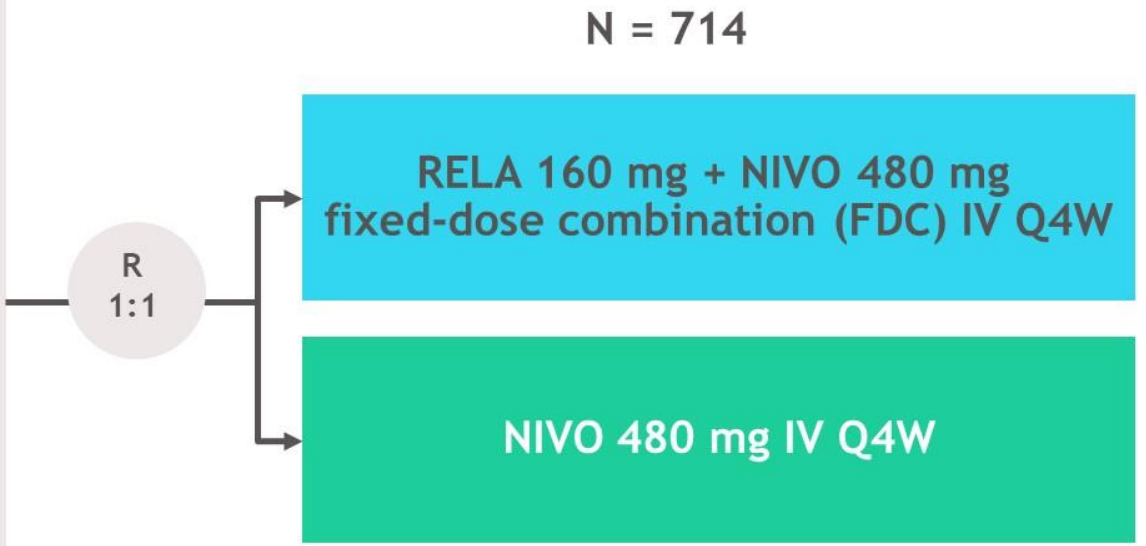
- **RELATIVITY-047** is a global, randomized, double-blind, phase 2/3 study

**Key eligibility criteria**

- Previously untreated unresectable or metastatic melanoma[a]
- ECOG PS 0–1

**Stratification factors**

- LAG-3[b]
- PD-L1[c]
- *BRAF*
- AJCC v8 M stage




**Primary endpoint**

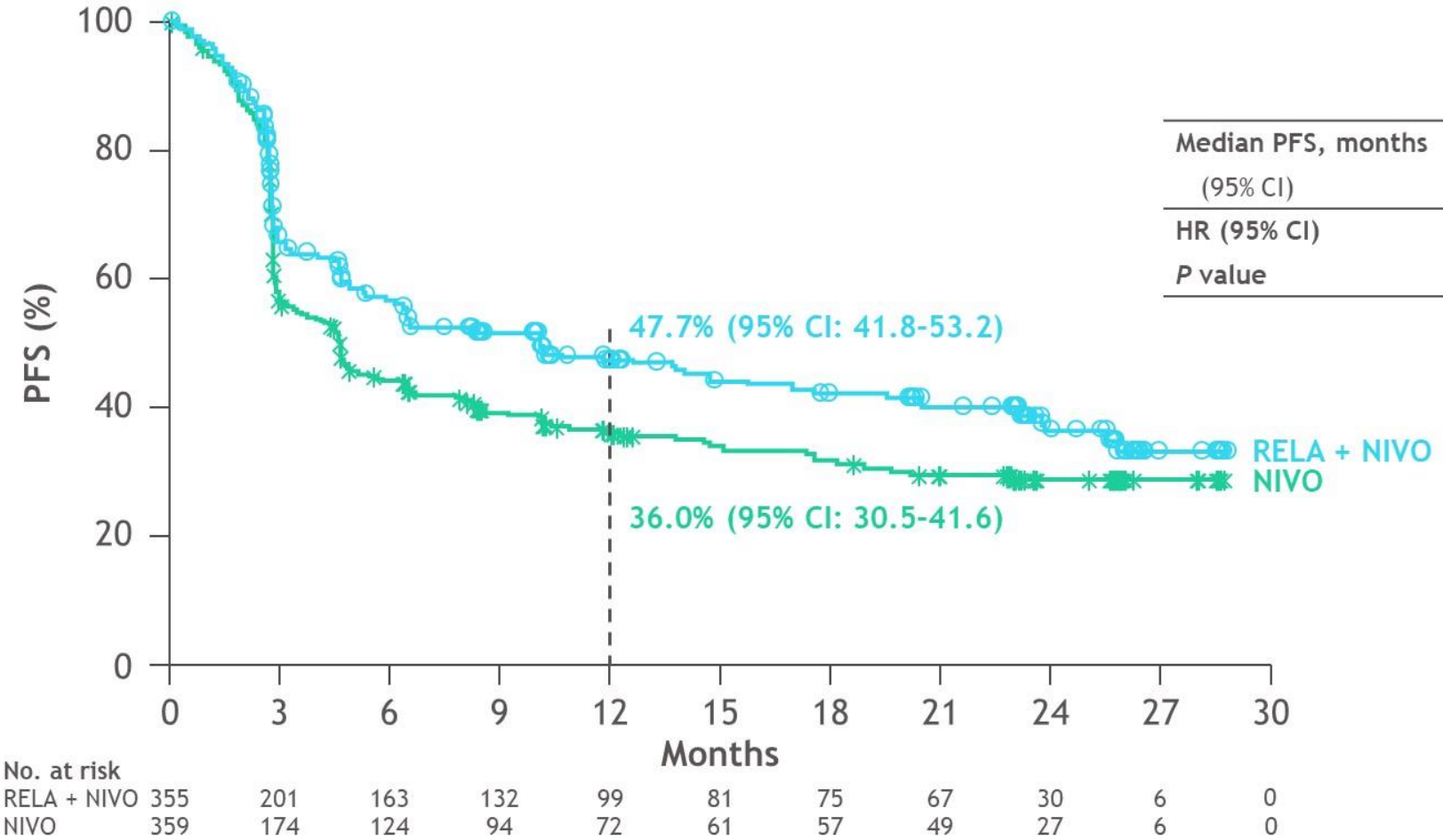
- PFS by BICR[d]

**Secondary endpoints**

- OS
- ORR by BICR[d]

AJCC, American Joint Committee on Cancer; BICR, blinded independent central review; CTLA-4, cytotoxic T lymphocyte antigen-4; ECOG PS, Eastern Cooperative Oncology Group performance status; IHC, immunohistochemistry; IV, intravenous; ORR, overall response rate; Q4W, every 4 weeks; R, randomization.
ClinicalTrials.gov: NCT03470922; Lipson E, et al. Poster presentation at ESMO Congress; October 19-23, 2018; Munich, Germany. Abstract 1302TiP.
[a]Prior adjuvant/neoadjuvant treatment permitted (anti-PD-1 or anti-CTLA-4 permitted if at least 6 months between the last dose and recurrence; interferon therapy permitted if the last dose was at least 6 weeks before randomization); [b]LAG-3 expression on immune cells was determined using an analytically validated IHC assay (LabCorp); [c]PD-L1 expression on tumor cells was determined using the validated Agilent/Dako PD-L1 IHC 28-8 pharmDx test; [d]First tumor assessment (RECIST v1.1) performed 12 weeks after randomization, every 8 weeks up to 52 weeks, and then every 12 weeks. Database lock date: March 9, 2021.

# RELATIVITY 047 demonstrated superior PFS benefit by BICR for RELA + NIVO FDC vs NIVO




| | RELA + NIVO (n = 355) | NIVO (n = 359) |
|---|---|---|
| Median PFS, months | 10.12 | 4.63 |
| (95% CI) | (6.37-15.74) | (3.38-5.62) |
| HR (95% CI) | 0.75 (0.62-0.92) | |
| *P* value | 0.0055 | |

CI, confidence interval; HR, hazard ratio.
All randomized patients. Statistical model for HR and *P* value: stratified Cox proportional hazard model and stratified log-rank test. Stratified by LAG-3 (≥ 1% vs < 1%), *BRAF* (mutation positive vs mutation wild-type), AJCC M stage (M0/M1any[0] vs M1any[1]). PD-L1 was removed from stratification because it led to subgroups with < 10 patients.

# Immune-mediated adverse events

| Immune-mediated AE category[a], n (%) | RELA + NIVO (n = 355) | | NIVO (n = 359) | |
|---|---|---|---|---|
| | Any grade | Grade 3-4 | Any grade | Grade 3-4 |
| Hypothyroidism/thyroiditis | 64 (18.0) | 0 | 50 (13.9) | 0 |
| Rash | 33 (9.3) | 2 (0.6) | 24 (6.7) | 5 (1.4) |
| Diarrhea/colitis | 24 (6.8) | 4 (1.1) | 11 (3.1) | 5 (1.4) |
| Hyperthyroidism | 22 (6.2) | 0 | 24 (6.7) | 0 |
| Hepatitis | 20 (5.6) | 14 (3.9) | 9 (2.5) | 4 (1.1) |
| Adrenal insufficiency | 15 (4.2) | 5 (1.4) | 3 (0.8) | 0 |
| Pneumonitis | 13 (3.7) | 2 (0.6) | 6 (1.7) | 2 (0.6) |
| Hypophysitis | 9 (2.5) | 1 (0.3) | 3 (0.8) | 1 (0.3) |
| Nephritis and renal dysfunction | 7 (2.0) | 4 (1.1) | 5 (1.4) | 4 (1.1) |
| Hypersensitivity | 4 (1.1) | 0 | 4 (1.1) | 0 |

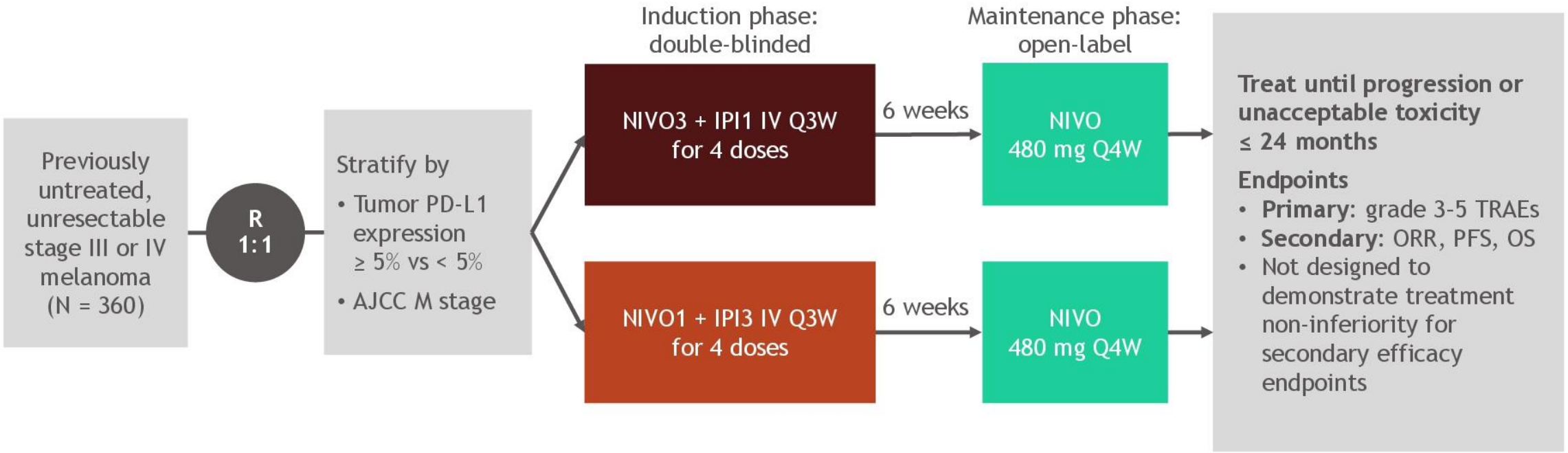
- Additional AE of interest: myocarditis (any grade) occurred in 5 (1.7%) patients with RELA + NIVO and 2 (0.6%) with NIVO. Troponin monitoring was performed for the first 2 months of treatment per protocol

[a]Includes AEs of any grade occurring in ≥ 1% of patients considered by investigators to be potentially immune-mediated that met the following criteria: occurred within 100 days of the last dose, regardless of causality, treated with immune-modulating medication with no clear alternate etiology, or had an immune-mediated component.

# Summary

- In RELATIVITY-047, RELA + NIVO as a fixed-dose combination (FDC) demonstrated superior PFS by BICR, with more than a doubling of improvement in median PFS compared with NIVO alone
  - Median PFS 10.12 vs 4.63 months (HR [95% CI] vs NIVO: 0.75 [0.62–0.92]; *P* = 0.0055)
  - PFS favored RELA + NIVO FDC across key prespecified subgroups
  - OS and ORR remain blinded
- RELA + NIVO FDC demonstrated a manageable safety profile without unexpected safety signals
  - Grade 3/4 TRAEs occurred in 18.9% with RELA + NIVO FDC vs 9.7% with NIVO
- RELATIVITY-047 is the first phase 3 study to validate dual LAG-3 and PD-1 inhibition
- **RELA + NIVO FDC is a potential new treatment option for patients with advanced melanoma, bringing the benefits of dual checkpoint inhibition to more patients**

# Phase 3b/4 CheckMate 511 study: 3-year analysis




- Database lock, September 2020; minimum follow-up, 3 years
- Median duration of therapy over both study phases: 4.4 months with NIVO3 + IPI1; 2.3 months with NIVO1 + IPI3
  - 20% and 15% of patients, respectively, completed the full 2 years of treatment
- Maintenance NIVO therapy was initiated by 57% and 42% of patients, respectively
- Baseline characteristics were generally well balanced

NCT02714218. AJCC, American Joint Committee on Cancer; IPI, ipilimumab; IV, intravenous; M stage, metastatic disease stage; NIVO, nivolumab; ORR, objective response rate; OS, overall survival; PD-L1, programmed death ligand 1; PFS, progression-free survival; Q3W, every 3 weeks; Q4W, every 4 weeks; TRAE, treatment-related adverse event.

# Safety summary

| TRAE | NIVO3 + IPI1 (n = 180) | NIVO1 + IPI3 (n = 178) |
|---|---|---|
| **Grade 3-5 TRAEs, n (%)** | **61 (34)** | **86 (48)** |
| **Difference (95% CI)** | **−14.4% (−24.5 to −4.3)** | |
| ***P* value (descriptive)** | **0.0059** | |
| **TRAEs, n (%)** | | |
| Grade 3-4 | 60 (33) | 86 (48) |
| Grade 5 | 1 (1)[a] | 0 |
| **Treatment-related serious AEs, n (%)** | | |
| Grade 3-4 | 35 (19) | 60 (34) |
| Grade 5 | 1 (1)[a] | 0 |
| **TRAEs leading to discontinuation, n (%)** | 43 (24) | 60 (34) |
| Grade 3-4 | 30 (17) | 50 (28) |
| Grade 5 | 1 (1)[a] | 0 |

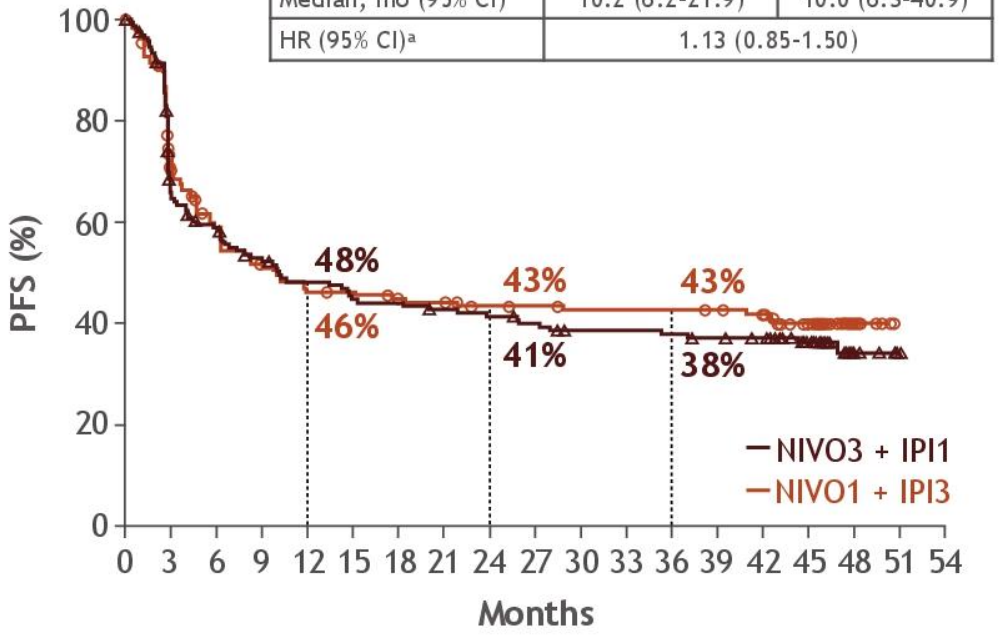
- The most common TRAEs in both groups were diarrhea, fatigue, and pruritus

[a]Rhabdomyolysis and autoimmune myocarditis.
AE, adverse event; CI, confidence interval.

# Survival outcomes

## PFS

| | NIVO3 + IPI1 (n = 180) | NIVO1 + IPI3 (n = 178) |
|---|---|---|
| Events, n | 100 | 93 |
| Median, mo (95% CI) | 10.2 (6.2-21.9) | 10.0 (6.3-40.9) |
| HR (95% CI)[a] | 1.13 (0.85-1.50) | |

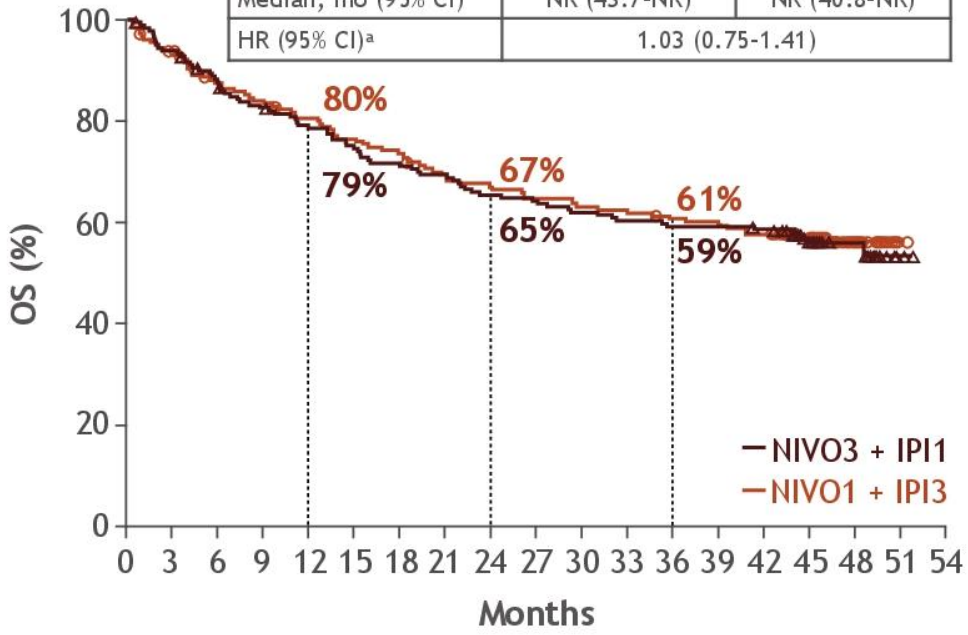



No. at risk

| | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| NIVO3 + IPI1 | 180 | 105 | 90 | 79 | 71 | 66 | 65 | 62 | 60 | 57 | 53 | 53 | 52 | 50 | 48 | 34 | 7 | 1 | 0 |
| NIVO1 + IPI3 | 178 | 111 | 88 | 75 | 68 | 67 | 64 | 62 | 58 | 57 | 55 | 55 | 55 | 53 | 48 | 36 | 10 | 0 | 0 |

## OS

| | NIVO3 + IPI1 (n = 180) | NIVO1 + IPI3 (n = 178) |
|---|---|---|
| Events, n | 78 | 75 |
| Median, mo (95% CI) | NR (43.7-NR) | NR (40.8-NR) |
| HR (95% CI)[a] | 1.03 (0.75-1.41) | |




No. at risk

| | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| NIVO3 + IPI1 | 180 | 168 | 156 | 145 | 138 | 131 | 125 | 121 | 114 | 112 | 108 | 105 | 103 | 103 | 101 | 82 | 29 | 3 | 0 |
| NIVO1 + IPI3 | 178 | 165 | 152 | 145 | 138 | 131 | 127 | 118 | 114 | 110 | 107 | 106 | 102 | 101 | 97 | 80 | 29 | 1 | 0 |

- Across patient subgroups, OS outcomes were generally similar with both regimens

[a]NIVO3 + IPI1 vs NIVO1 + IPI3. The study was not designed or powered to formally compare NIVO3 + IPI1 with NIVO1 + IPI3 for the secondary efficacy endpoints. All statistical analyses are descriptive only.

# Learnings from ASCO 2021

- Front line therapy
  - Any new options?
- Data after immunotherapy failure
  - Major unmet need
- Neoadjuvant therapy

# LEAP-004 Study Design (NCT03776136)

**Participants**

- Unresectable stage III or IV melanoma[a]
- Confirmed PD per iRECIST[1b] on or within 12 wk of last dose of anti–PD-1/L1 given alone or in combination (including with anti–CTLA-4) for ≥2 doses
  - ≤25% with PD on anti–CTLA-4 + anti–PD-1/L1
- No limit to number of previous therapies
- Measurable disease confirmed by blinded, independent central review (BICR)

N ≈ 100

**Pembrolizumab**
**200 mg IV Q3W**
**for up to 35 cycles**
**+**
**Lenvatinib**
**20 mg PO QD**

Continued until PD, unacceptable toxicity, or patient or physician decision[c]

**End Points**

- Primary: ORR per RECIST v1.1[d] by BICR
- Secondary: DOR and PFS per RECIST v1.1[d] by BICR, OS, and safety

[a]Per AJCC 8th edition. [b]In the absence of rapid clinical progression, initial evidence of radiologic PD required confirmation by a second assessment performed ≥4 weeks from first documented radiographic PD. [c]Eligible patients deriving clinical benefit can be treated beyond PD. Participants with CR can discontinue study treatment if they have received it for ≥24 weeks. [d]Modified to follow ≤10 target lesions total and ≤5 target lesions per organ. 1. Seymour L et al. *Lancet Oncol* 2017;18:e143-52.

# BICR-Confirmed Response by RECIST v1.1

| | Total Population N = 103 |
|---|---|
| **ORR, % (95% CI)** | **21.4% (13.9-30.5)** |
| DCR, % (95% CI) | 66.0% (56.0-75.1) |
| Best overall response, n (%) | |
| CR | 3 (2.9%) |
| PR | 19 (18.4%) |
| SD | 46 (44.7%) |
| PD | 30 (29.1%) |
| Not assessed[a] | 5 (4.9%) |

**Compared With Initial Analysis[1]**

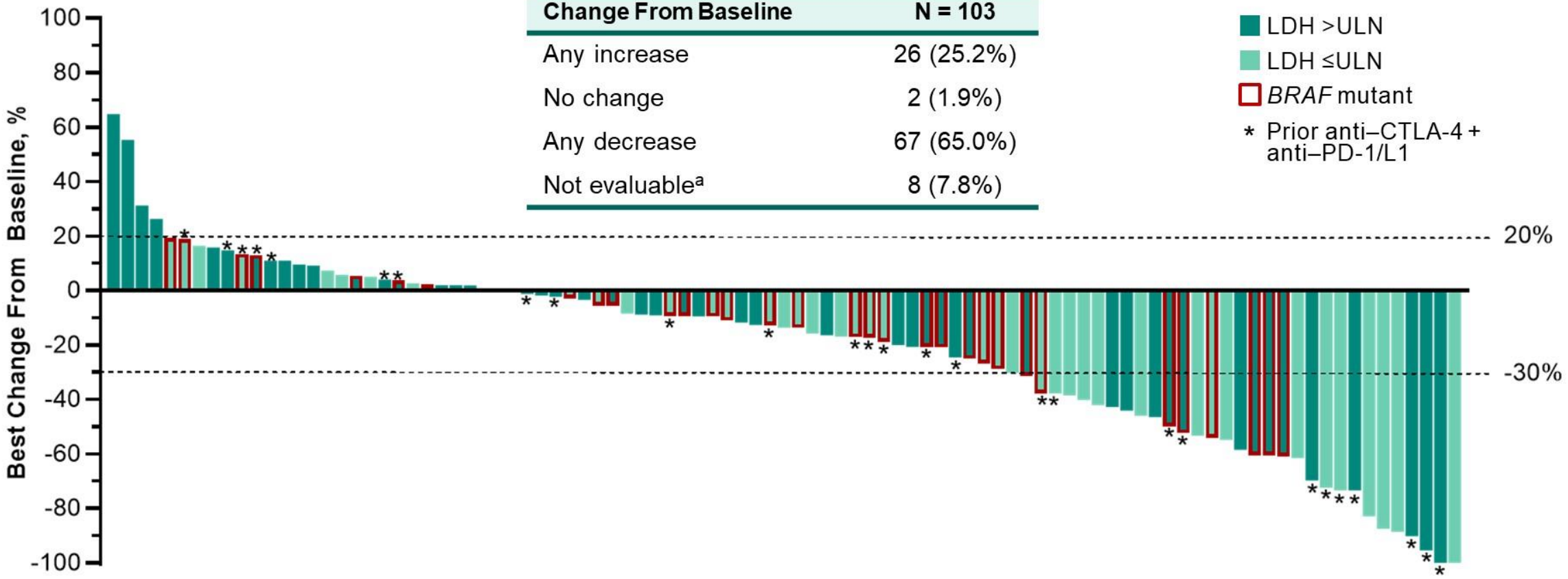
- ORR remained the same
  - 1 additional CR
- DCR increased from 65.0% to 66.0%
  - 1 additional SD

[a]Participants who had no post-baseline imaging assessments. Data cutoff date: Sep 18, 2020.

1. Arance A et al. *Ann Oncol* 2020;31(suppl_4): S1142-S1215 [Abstr LBA44].

# Best Change From Baseline in Target Lesions (RECIST v1.1 by BICR)

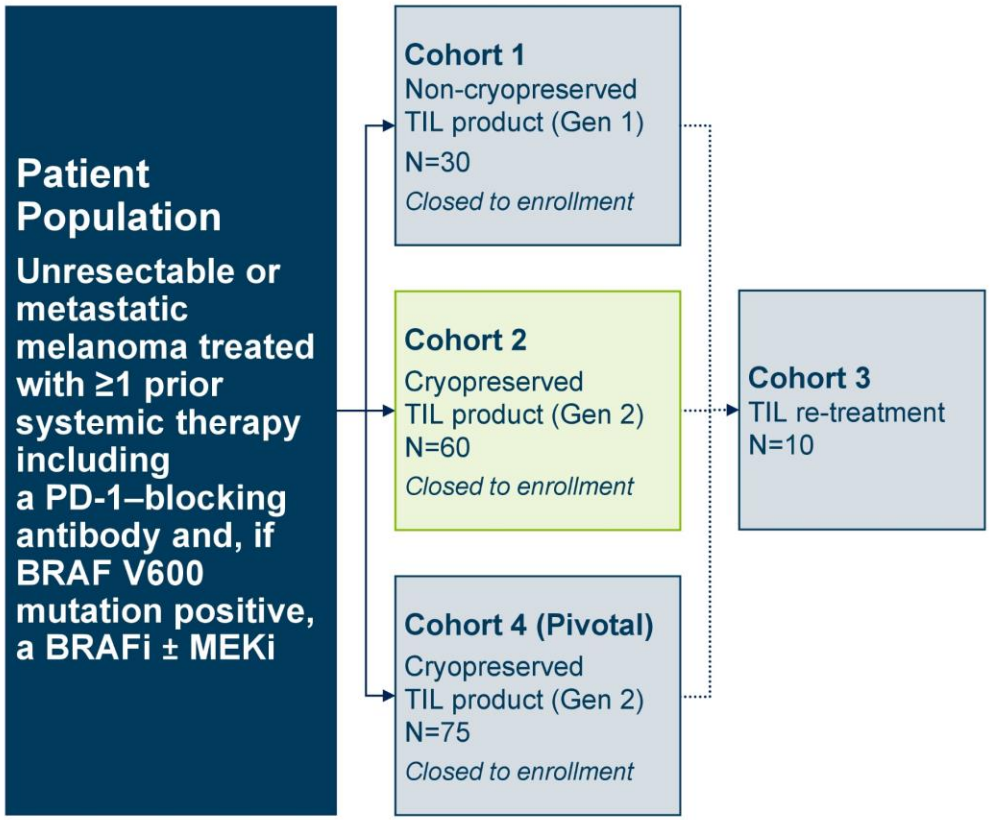
| Change From Baseline | N = 103 |
|---|---|
| Any increase | 26 (25.2%) |
| No change | 2 (1.9%) |
| Any decrease | 67 (65.0%) |
| Not evaluable[a] | 8 (7.8%) |




[a]The 8 participants who did not have ≥1 post-baseline imaging assessment evaluable for change from baseline in target lesions are excluded from the graph.
Data cutoff date: Sep 18, 2020.

# C-144-01 Study Design

## Phase 2, multicenter study to assess the efficacy and safety of autologous TIL (lifileucel) for treatment of patients with metastatic melanoma (NCT02360579)




### Cohort 2 Endpoints

- Primary: Efficacy per investigator-assessed ORR using RECIST 1.1 response criteria
- Secondary: Safety and additional parameters of efficacy

### Key Eligibility Criteria

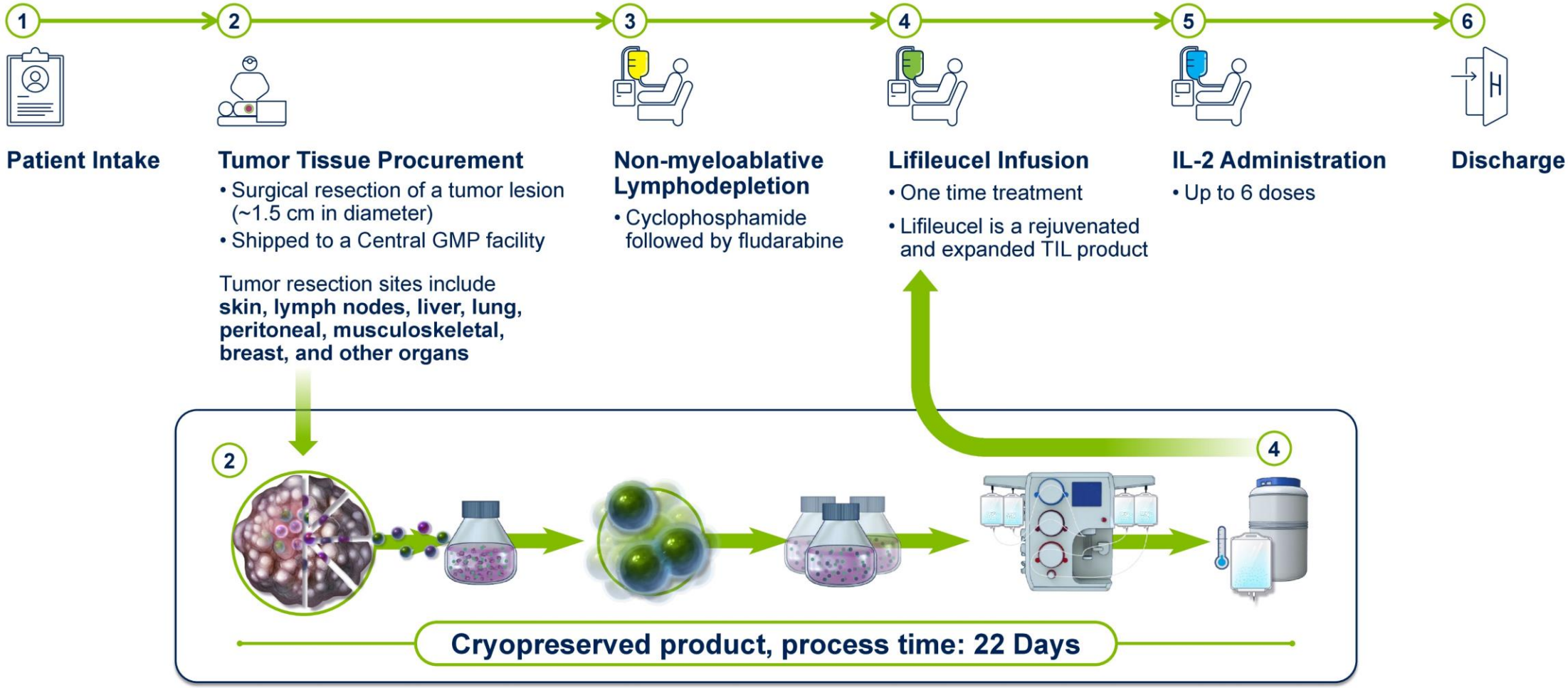
- Radiographic confirmation of progression
- One tumor lesion resectable for TIL generation (~1.5 cm in diameter) and ≥1 target tumor lesion for RECIST 1.1 response assessment
- Age ≥18 years at the time of consent
- ECOG performance status of 0–1

### Methods

- Patients were enrolled from April 2017 to January 2019 at 26 sites across the US and EU
- Concomitant anticancer therapy was not permitted
- Imaging-evaluable disease was required
- All responses required confirmation
- Data cutoff: 22 April 2021

BRAFi, BRAF inhibitor; ECOG, Eastern Cooperative Oncology Group; MEKi, MEK inhibitor; ORR, objective response rate; PD-1, programmed cell death protein 1; RECIST, Response Evaluation Criteria in Solid Tumors; TIL, tumor infiltrating lymphocytes.

# Patient Journey and TIL Manufacturing




GMP, good manufacturing practices; IL-2, interleukin-2; NMA-LD, non-myeloablative lymphodepletion; TIL, tumor infiltrating lymphocytes.

# Objective Response Rate

| Response, n (%) | N=66 |
|---|---|
| **Objective Response Rate** | **24 (36.4)** |
| Complete response | 3 (4.5) |
| Partial response | 21 (31.8) |
| Stable disease | 29 (43.9) |
| Progressive disease | 9 (13.6) |
| Non-evaluable* | 4 (6.1) |
| Disease control rate | 53 (80.3) |
| **Median Duration of Response** | **Not Reached** |
| Min, max (months) | 2.2, 38.5+ |

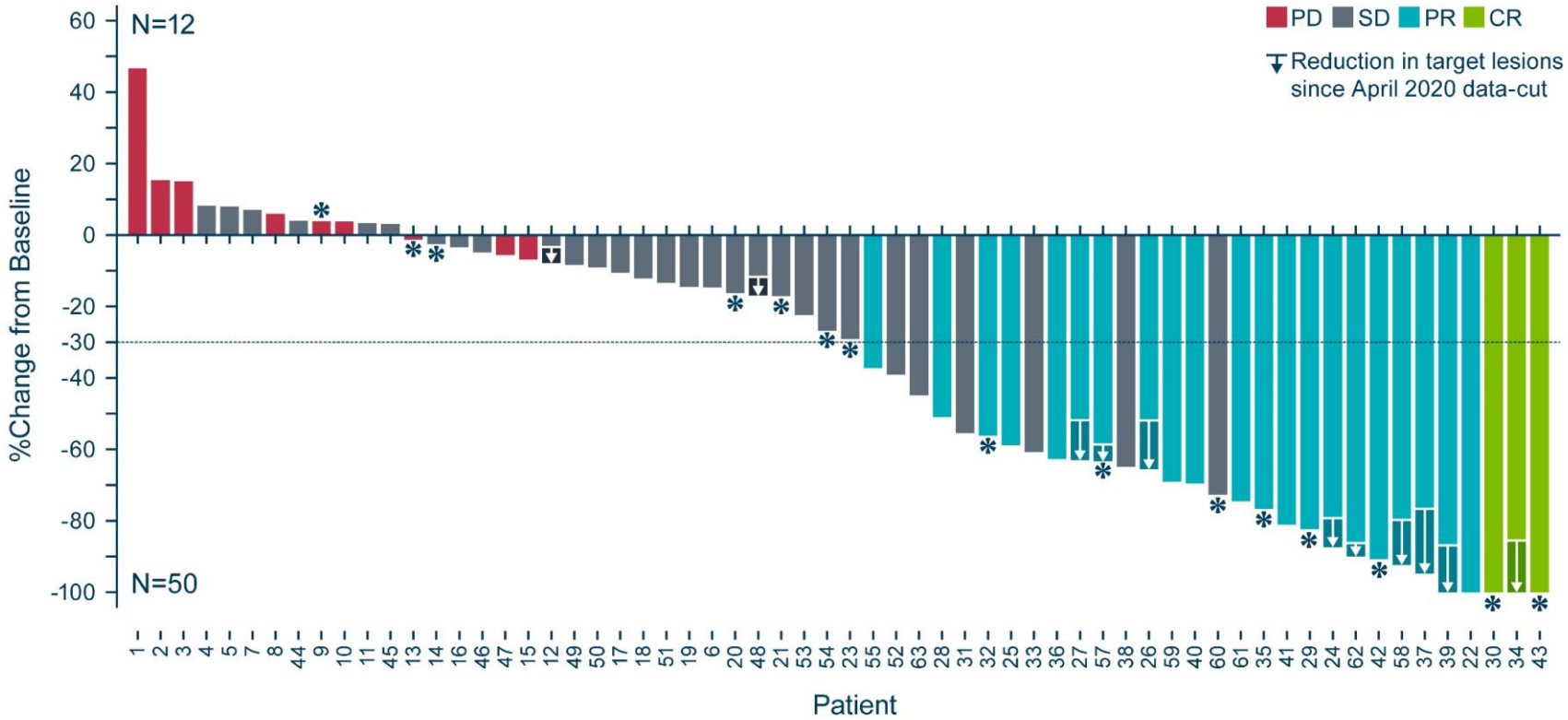
- Mean number of TIL cells infused: $27.3 \times 10^9$

- After a median study follow-up of 33.1 months, **median DOR was not reached** (range 2.2, 38.5+ months)

*Not evaluable due to not reaching first assessment.
DOR, duration of response; SOD, sum of diameters; TIL, tumor-infiltrating lymphocytes.

# Best Overall Response

- 81% (50/62) of patients had a reduction in tumor burden
- 11 patients (17.7%) had further SOD reduction since April 2020 datacut




*Patients with BRAF V600 mutation. 3 patients had no post-TIL disease assessment due to early death, and 1 due to start of new anticancer therapy.
DOR, duration of response; SOD, sum of diameters; TIL, tumor infiltrating lymphocytes.

# Conclusions

- In heavily pretreated patients with advanced or metastatic melanoma who progressed on or after multiple prior therapies, including anti–PD-1 / anti–PD-L1 and BRAF/MEK inhibitors (if BRAF V600 mutant), lifileucel treatment resulted in:
  - 36.4% ORR
  - **Median DOR not reached at median 33.1 months of study follow-up**
- Responses deepened over time:
  - 11 patients (17.7%) demonstrated further reduction in SOD since April 2020 datacut
  - 1 patient converted from PR to CR at 24 months post lifileucel infusion
- Prior anti–PD-1 therapy:
  - Shorter duration of prior anti–PD-1 therapy maximizes DOR to lifileucel treatment
  - All newly diagnosed patients should be closely monitored for progression on anti–PD-1 therapy
  - **Early intervention with lifileucel at the time of initial progression on anti–PD-1 agents may maximize benefit**

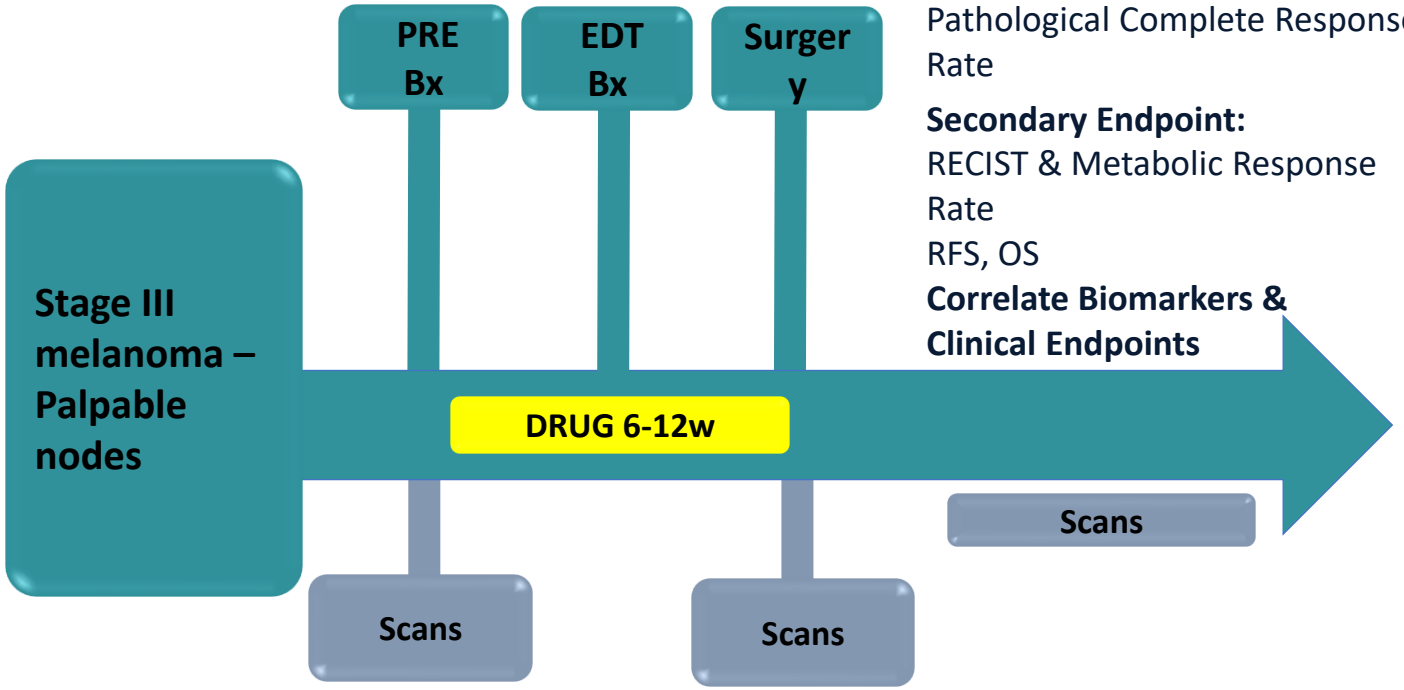
CR, complete response; DOR, duration of response; ORR, objective response rate; PD-1, programmed cell death protein-1; PD-L1, programmed death ligand-1; PR, partial response; SOD, sum of diameters; TIL, tumor-infiltrating lymphocytes.

# Learnings from ASCO 2021

- Front line therapy
  - Any new options?
- Data after immunotherapy failure
  - Major unmet need
- Neoadjuvant therapy

# Neoadjuvant model is well suited for melanoma

- Prototype tumor for drug development
- Accessible tissue
- Rapid results




**Primary Endpoint:**
Pathological Complete Response (pCR) Rate

**Secondary Endpoint:**
RECIST & Metabolic Response Rate
RFS, OS
**Correlate Biomarkers & Clinical Endpoints**

# Early Melanoma Treatment Landscape (Neoadjuvant Therapy)

| Agent | Trial [NCT] | Phase, N | Setting (Stage) | Endpoints | Topline Result | Key Takeaways |
|---|---|---|---|---|---|---|
| NIVO ± IPI or relatlimab[1] | [NCT02519322] | 2<br>N=53 | Neoadj/Adj (Stage IIIB/IV) | Pathologic response | NIVO + IPI: ORR 73%, pCR 45%, 73% gr 3 TRAEs;<br>nivo mono: ORR 25%, pCR 25%; 8% gr 3 TRAEs | First results to describe the feasibility of NAT immune checkpoint blockade in melanoma |
| Pembro[2] | [NCT02434354] | 1b<br>N=30 | Neoadj/Adj (Stage IV) | AEs | • On histologic assessment, 8 of 27 patients (29.6%) had a complete or major PR after 1 pembro dose<br>• OS at 2 years: 93% DFS: 63% | Despite the clinical success of checkpoint blockade, little is understood about the precise mechanism(s) of response or resistance to these treatments |
| NIVO + IPI[1] | OpACIN-neo (Arm B), PRADO extension cohort [NCT02977052] | 2<br>N=186 | Neoadj/Adj (Stage III) | RR, pRR | Stage III melanoma pts randomized 1:1:1<br>Arm B: IPI + NIVO | • pRR of 77%; 3-y RFS, NAT arm, 80% vs AT arm, 60%<br>• pCR and RFS surrogate endpoints are compelling, but validation of these endpoints are needed |

## Ongoing Clinical Studies

| Agent | Trial [NCT] | Phase, N | Setting (Stage) | Endpoints | Est. Completion |
|---|---|---|---|---|---|
| Atezo, cobimetinib, vemurafenib[3] | NeoACTIVE [NCT03554083] | 2<br>N=30 | Neoadj (Stage III) | • pCR (BRAFm and BRAFwt pts)<br>• median RFS | 06/2023 |
| Dabrafenib, trametinib and/or pembrolizumab[4] | NeoTrio [NCT02858921] | 2<br>N=60 | Neoadj (Stage IIIB/C) | pRR | 11/2020 |
| Domatinostat, NIVO, IPI[5] | DONIMI [NCT04133948] | 1b<br>N=45 | Neoadj/Adj (Stage III) | 2º: pPR, pCR | 06/2021 |
| Pembrolizumab +/- coxsackievirus A21 (V937)[8] | Substudy 02C [NCT04303169] | 1/2<br>N=65 | Neoadj/Adj (Stage III) | Percentage of AEs, pCR | 04/2030 |

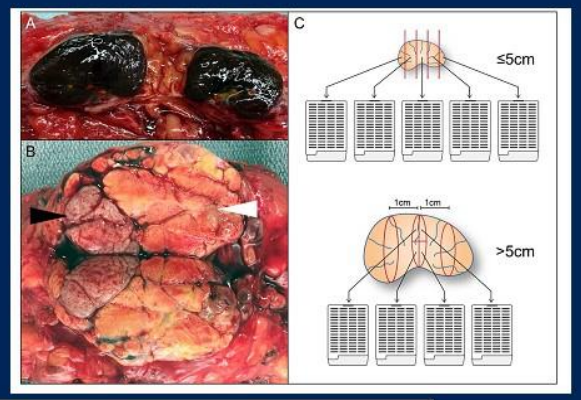
Adj, adjuvant; AEs, adverse events; AT, adjuvant therapy; atezo, atezolizumab; BRAFm, BRAF mutation; BRAFwt, BRAF wild-type; DFS, disease-free survival; IPI, ipilimumab; N, sample size; NAT, neoadjuvant therapy; Neoadj, neoadjuvant; NIVO, nivolumab; ORR, objective response rate; OS, overall survival; pCR, pathologic(al) complete response; Pembro, pembrolizumab; pPR, partial pathologic response; PR, pathologic(al) response; pRR, pathologic(al) response rate; RFS, relapse-free survival; RR, response rate; TRAEs, treatment-related adverse events.

1. Amaria RN, et al. *Nat Med.* 2018;24(11):1649-1654. doi:10.1038/s41591-018-0197-1. 2. Huang AC, et al. *Nat Med.* 2019;25:454-461. doi:10.1038/s41591-019-0357-y. 3. ClinicalTrials.gov. Published November 20, 2019. Accessed October 18, 2020. https://clinicaltrials.gov/ct2/show/NCT03554083. 4. ClinicalTrials.gov. Published December 16, 2019. Accessed October 18, 2020. https://clinicaltrials.gov/ct2/show/NCT02858921. 5. ClinicalTrials.gov. Published June 1, 2020. Accessed October 19, 2020. https://clinicaltrials.gov/ct2/show/NCT04133948. 6. ClinicalTrials.gov. Published October 20, 2020. Accessed October 22, 2020. https://clinicaltrials.gov/ct2/show/NCT02362594. 7. ClinicalTrials.gov. Published November 6, 2020. Accessed November 6, 2020. https://clinicaltrials.gov/ct2/show/NCT03553836. 8. Helwick C. ASCO Post. Published April 25, 2020. Accessed October 19, 2020. https://ascopost.com/issues/april-25-2020/what-s-the-current-status-of-neoadjuvant-immunotherapy/. 8. ClinicalTrials.gov. Published November 6, 2020. Accessed November 11, 2020. https://www.clinicaltrials.gov/ct2/show/NCT04303169.

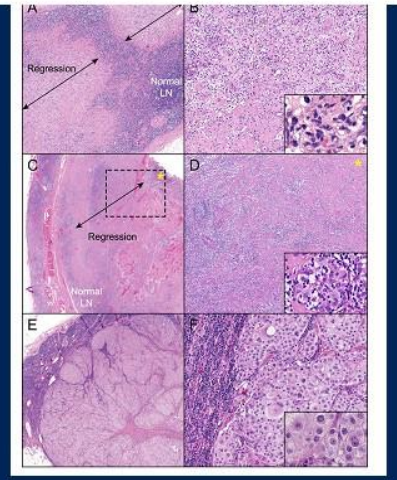
# International Neoadjuvant Melanoma Consortium has guided best practices for neoadjuvant trials

## Pathological assessment of resection specimens after neoadjuvant therapy for metastatic melanoma

M. T. Tetzlaff[1,2*], J. L. Messina[3], J. E. Stein[4], X. Xu[5], R. N. Amaria[6], C. U. Blank[7], B. A. van de Wiel[7], P. M. Ferguson[8], R. V. Rawson[8], M. I. Ross[9], A. J. Spillane[10], J. E. Gershenwald[9,11], R. P. M. Saw[8], A. C. J. van Akkooi[7], W. J. van Houdt[7], T. C. Mitchell[12], A. M. Menzies[10], G. V. Long[13], J. A. Wargo[9,14], M. A. Davies[2,6,15], V. G. Prieto[1,16], J. M. Taube[4†] & R. A. Scolyer[8†]




Ann Oncol. 2018;29(8):1861-8.

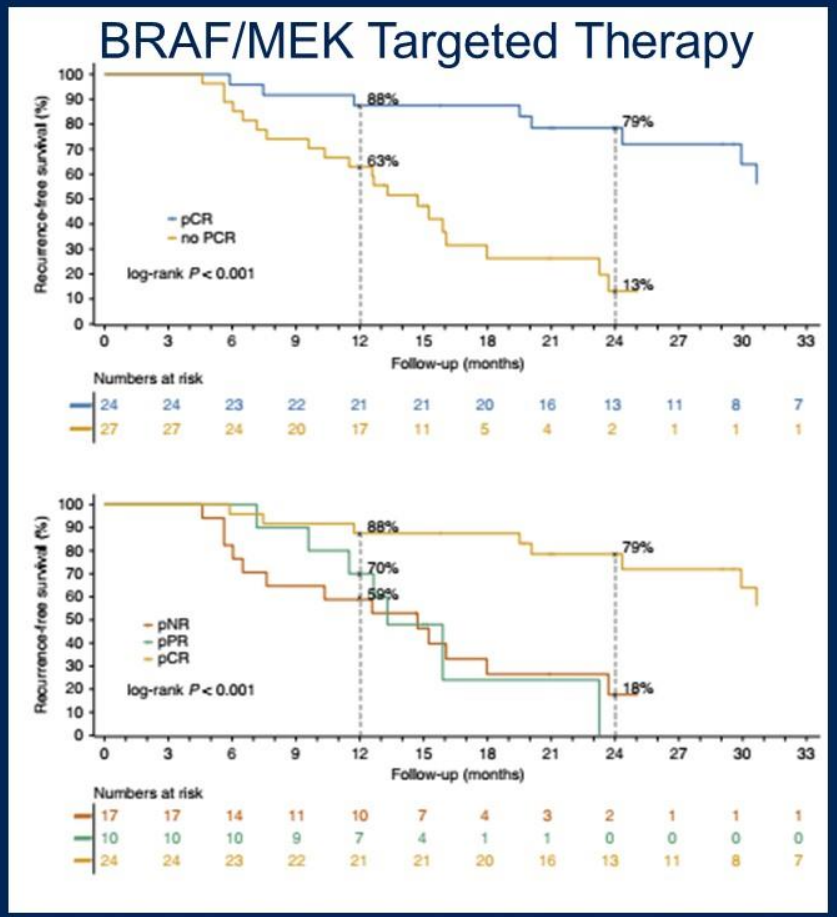


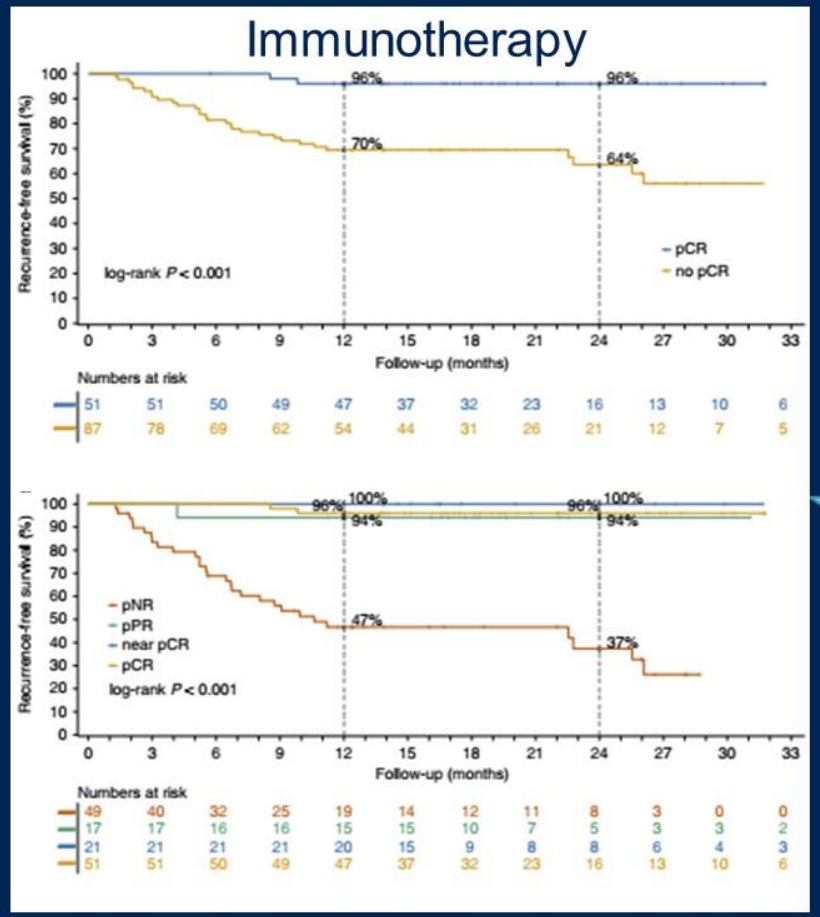

## Neoadjuvant systemic therapy in melanoma: recommendations of the International Neoadjuvant Melanoma Consortium

*Rodabe N Amaria*, Alexander M Menzies*, Elizabeth M Burton*, Richard A Scolyer*, Michael T Tetzlaff*, Robert Antdbacka, Charlotte Ariyan, Roland Bassett, Brett Carter, Adil Daud, Mark Faries, Leslie A Fecher, Keith T Flaherty, Jeffrey E Gershenwald, Omid Hamid, Angela Hong, John M Kirkwood, Serigne Lo, Kim Margolin, Jane Messina, Michael A Postow, Helen Rizos, Merrick I Ross, Elisa A Rozeman, Robyn P M Saw, Vernon Sondak, Ryan J Sullivan, Janis M Taube, John F Thompson, Bart A van de Wiel, Alexander M Eggermont, Michael A Davies, The International Neoadjuvant Melanoma Consortium members†, Paolo A Ascierto‡, Andrew J Spillane‡, Alexander C J van Akkooi‡, Jennifer A Wargo‡, Christian U Blank‡, Hussein A Tawbi‡, Georgina V Long‡*

Lancet Oncol 20019; 20: e378-89

# Any pathologic response from neoadjuvant immunotherapy results in better RFS

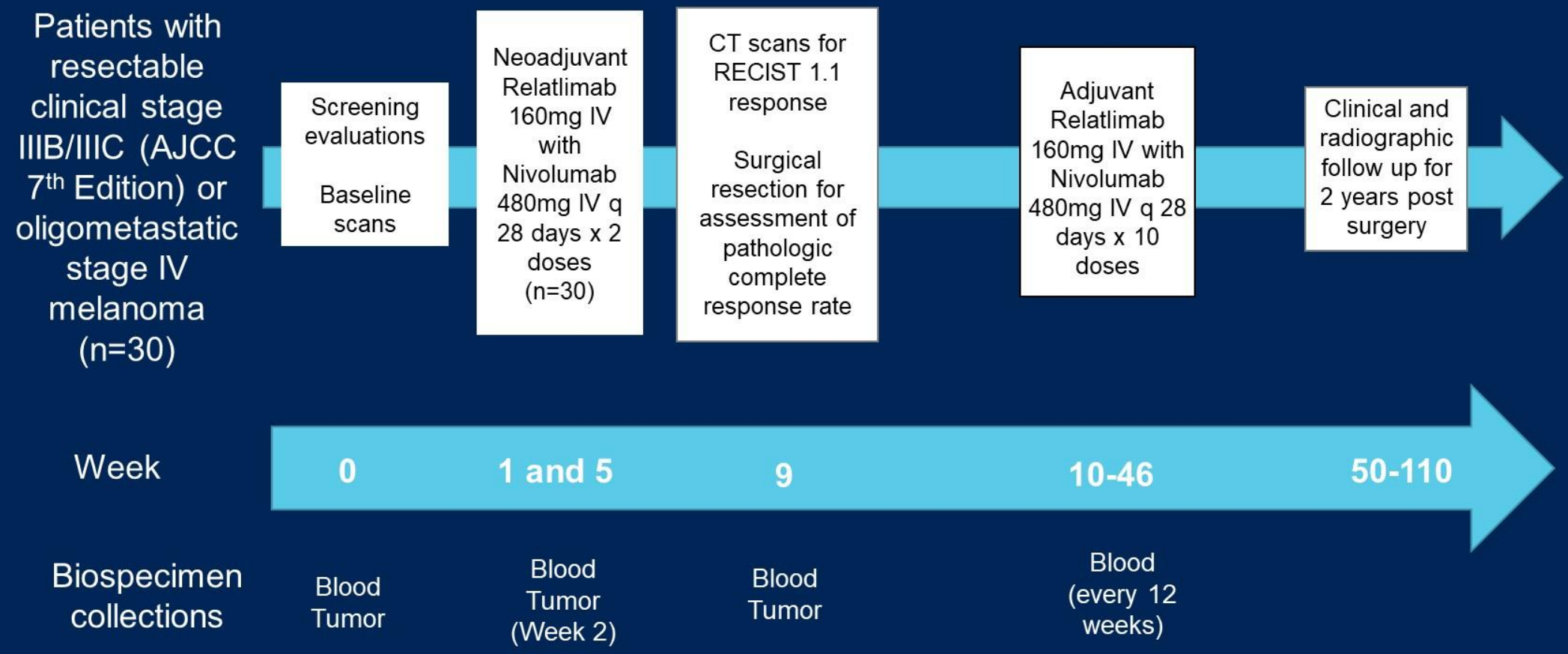



Menzies et al.
Nat Med 2021;
27: 301-09

pCR: 0% viable tumor  near pCR: 1-10% viable tumor  pPR: 11-49% viable tumor  pNR:≥ 50% viable tumor

# Study Design and Treatment Plan



**30 pts initiated treatment**

**RECIST 1.1 ORR 57%**

17 pts with PR | 10 pts with SD | 3 pts with PD

No surgery

- 1 pt due to new metastatic disease

29 pts underwent surgery

- 1 delay due to concern for toxicity[1]
- 1 delay due to Covid restrictions

**pCR rate 59%**

## Participant Disposition

- 11 completed treatment
- 6 treatment ongoing
- 8 stopped due to toxicity in adjuvant setting
- 2 stopped treatment due to preference
- 3 disease progression with median 16.2 mo f/up
  - 1 local recurrence
  - 2 distant disease

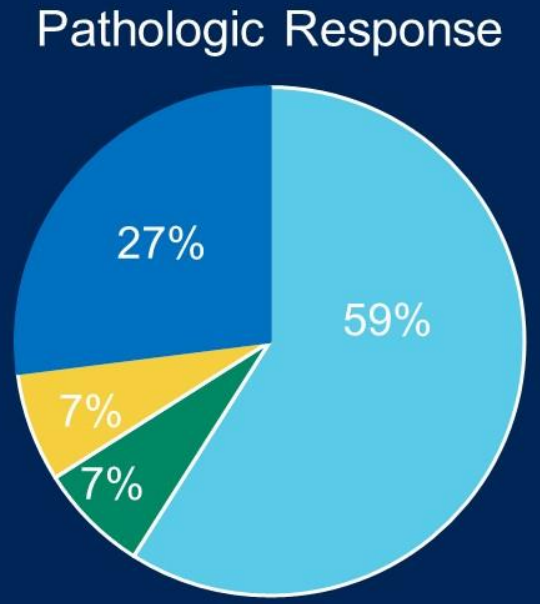
1: concern for myocarditis which was ruled out on endomyocardial biopsy and patient went to surgery 6 weeks later

# 59% Pathologic Complete Response Rate

| | Total cohort N=29 |
|---|---|
| pCR | 17 (59%) |
| Near pCR | 2 (7%) |
| pPR | 2 (7%) |
| pNR | 8 (27%) |

MPR: 66%

Any path response: 73%



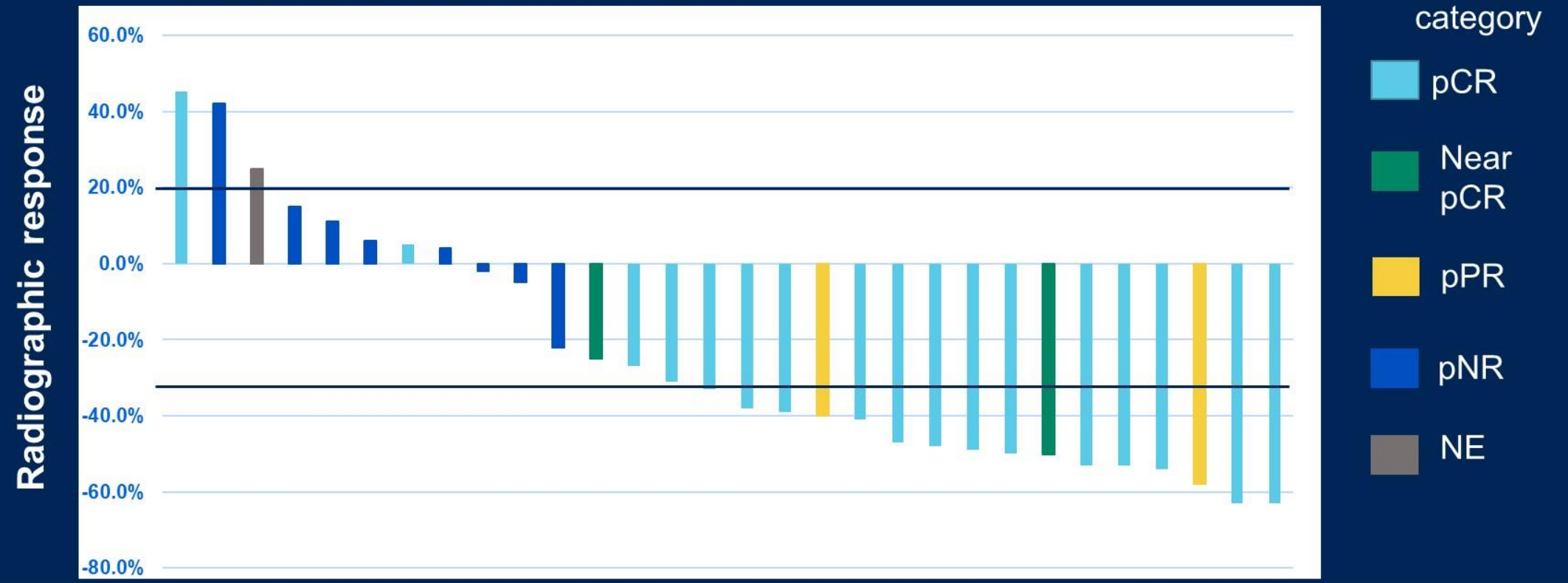

pCR: 0% viable tumor
pPR: 11-49% viable tumor
MPR: pCR + near pCR

near pCR: 1-10% viable tumor
pNR:≥ 50% viable tumor
Any path response: pCR + near pCR + pPR

pCR | Near pCR | pPR | pNR

# Radiographic Response can Underestimate Pathologic Response

- Of 19 patients with pCR/near pCR, 1 had radiographic PD, 3 SD, 15 PR
- Of 8 patients with pNR, only 1 had radiographic PD, 7 had SD
- No patients achieved a RECIST 1.1 CR



# Conclusions

- Neoadjuvant nivolumab + relatlimab achieved high rates of pCR (59%) and MPR (66%)
- Patients with MRP have improved RFS compared to those without MPR with no relapses observed to date with median 16.2 mo follow up
- Nivolumab + relatlimab is well tolerated with no high-grade toxicities in the neoadjuvant setting
- Translational studies demonstrate increased effector CD8 T cell population and decreased immunosuppressive M2 macrophages in tumors of MPR patients
- Compared to other neoadjuvant regimens, nivolumab + relatlimab produces similar efficacy but reduced toxicity
- Neoadjuvant trials continue to provide invaluable insights into novel therapies/combinations and represents an important tool in drug development

# Learnings from ASCO 2021

- Front line therapy
  - Anti-LAG3 plus nivolumab maybe a new front-line option
  - Low dose (1 mg/kg) of ipi+nivo as effective as higher dose (3mg/kg) ipi?
- Data after immunotherapy failure
  - Lenvatinib plus pembro – promising but toxic
  - Lifileucel – promising but practical considerations
- Neoadjuvant Therapy
  - Neoadjuvant therapy remains promising; randomized trials are underway
  - No change in clinical practice for adjuvant therapy
    - Relapsed patients have similar outcomes as front-line metastatic patients