XVII JORNADAS ONCOLÓGICAS
ARAGÓN · NAVARRA · RIOJA
20 JUNIO 2024
Organizador:
Fundación Biomédica Miguel Servet

MELANOMA Y TUMORES CUTÁNEOS

Mónica Corral Subías
Hospital Clínico Universitario Zaragoza
20 de Junio de 2024

- NEOADYUVANCIA
- ADYUVANCIA
- MELANOMA METASTÁSICO
- MELANOMA UVEAL
- TUMOR CUTÁNEO ESCAMOSO

NEOADYUVANCIA

- The Phase 3 NADINA Trial

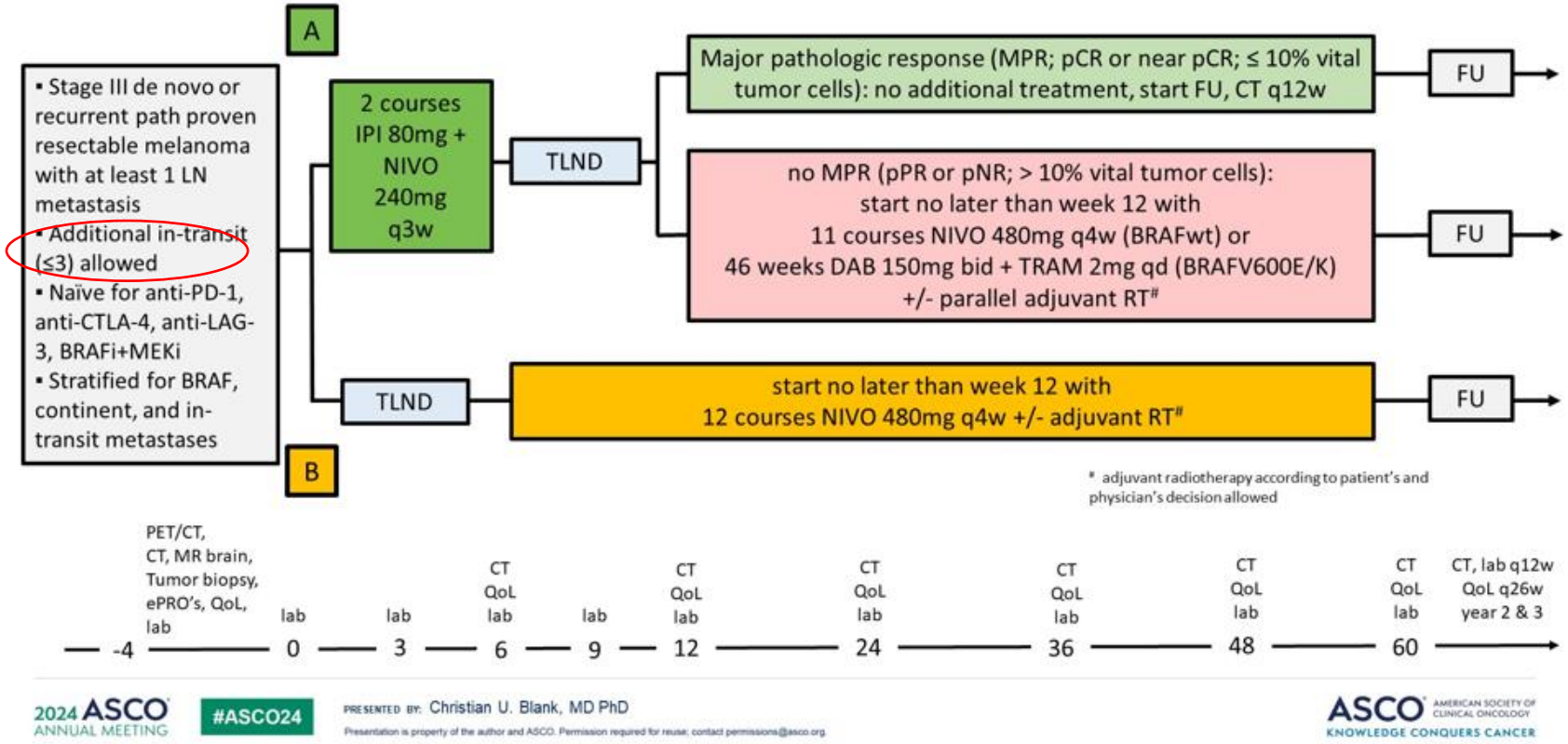
2024 ASCO ANNUAL MEETING

Neoadjuvant Nivolumab Plus Ipilimumab Versus Adjuvant Nivolumab in Macroscopic, Resectable Stage III Melanoma: The Phase 3 NADINA Trial

Christian U. Blank, M.W. Lucas, R.A. Scolyer, B.A. van de Wiel, A.M. Menzies, M. Lopez-Yurda, A.C.J. van Akkooi, W.J. van Houdt, R.P.M. Saw, A. Torres-Acosta, S.N. Lo, G.A.P. Hospers, M.S. Carlino, J.W.B. de Groot, E. Kapiteijn, K.P.M. Suijkerbuijk, P. Rutkowski, S. Sandhu, A.A.M. van der Veldt, G.V. Long

lay abstract

NADINA - Trial Design



2024 ASCO ANNUAL MEETING #ASCO24

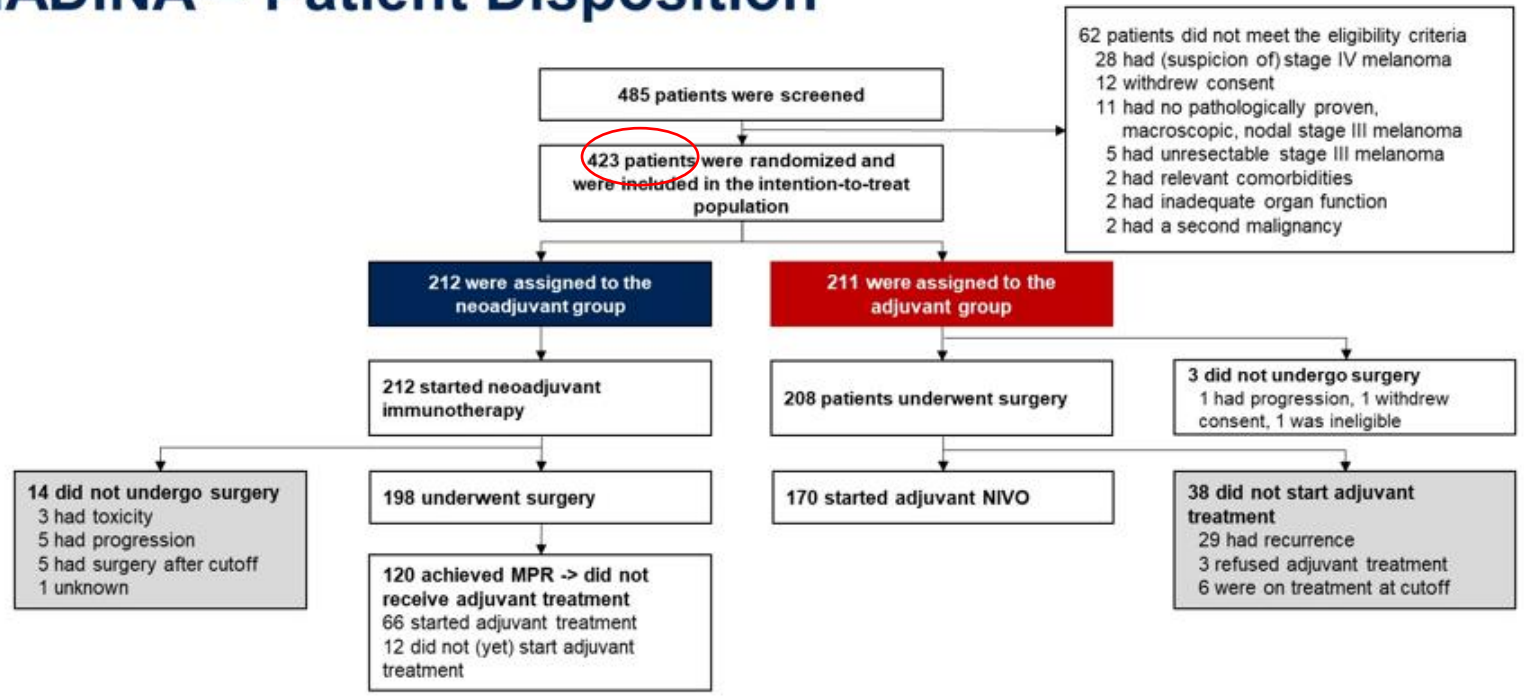
PRESENTED BY: Christian U. Blank, MD PhD

ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY
KNOWLEDGE CONQUERS CANCER

NADINA – Objectives and Endpoints

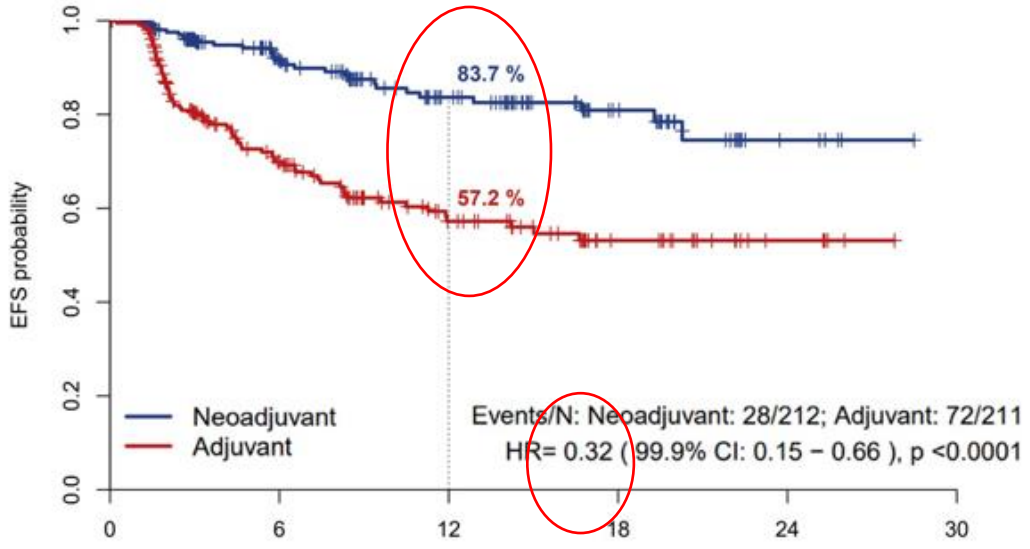
- **Primary endpoint**
  - Event-free survival: time from randomization until an event, being defined as progression, recurrence, or death due to melanoma/treatment.
- **Key secondary endpoint**
  - Overall survival
- **Secondary endpoints**
  - Pathological response rate: MPR (pCR + near pCR), pPR, pNR
  - Recurrence-free survival
  - Distant metastasis-free survival
  - Treatment related, and unrelated adverse events
  - Surgical complications
  - Health-related quality of life (ASCO 2024, LBA9584, poster #368)

NADINA – Patient Disposition



At data cut-off (January 12, 2024) with a median follow-up of 9.9 months, 99 patients were still on treatment (31 neoadjuvant, 68 adjuvant arm)

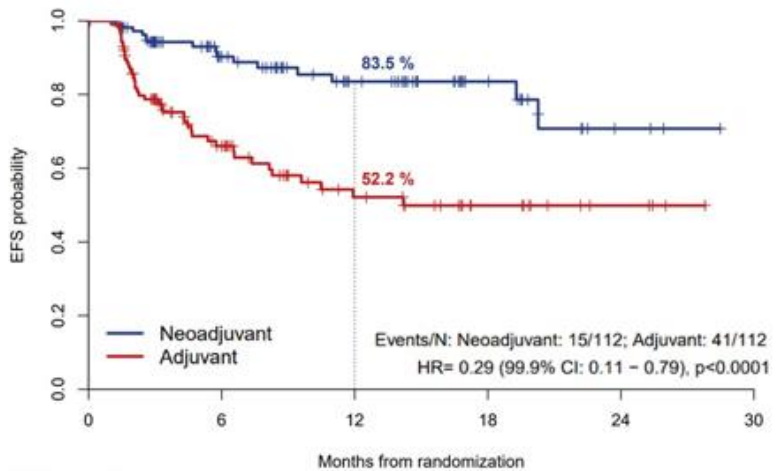
NADINA – Primary Endpoint: Event-Free Survival (EFS)



# at risk (censored)										
Neoadjuvant	212	(0)	126	(71)	77	(111)	34	(152)	5	(179)
Adjuvant	211	(0)	100	(57)	53	(89)	23	(116)	6	(133)

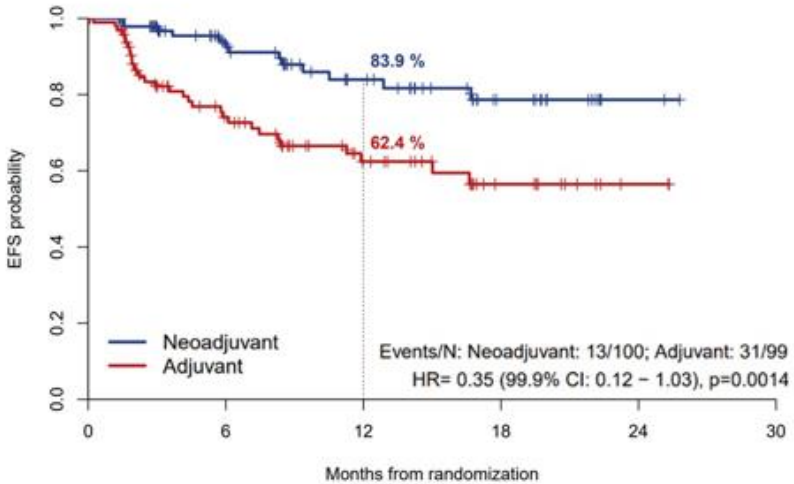
NADINA – EFS According to BRAF Mutational Status

BRAF$^{V600E/K}$ mutation



# at risk (censored)										
Neoadjuvant	112	(0)	63	(40)	38	(61)	18	(81)	3	(94)
Adjuvant	112	(0)	48	(32)	25	(47)	11	(60)	4	(67)

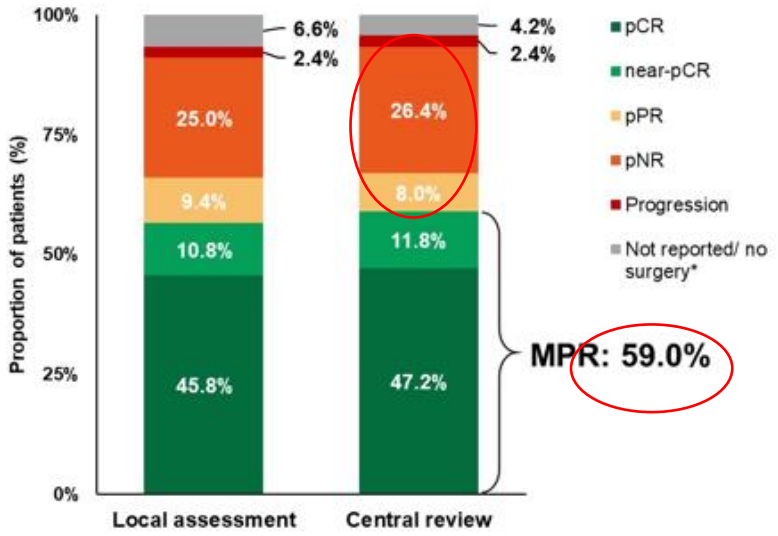
BRAF wildtype



# at risk (censored)										
Neoadjuvant	100	(0)	63	(31)	39	(50)	16	(71)	2	(85)
Adjuvant	99	(0)	52	(25)	28	(42)	12	(56)	2	(66)

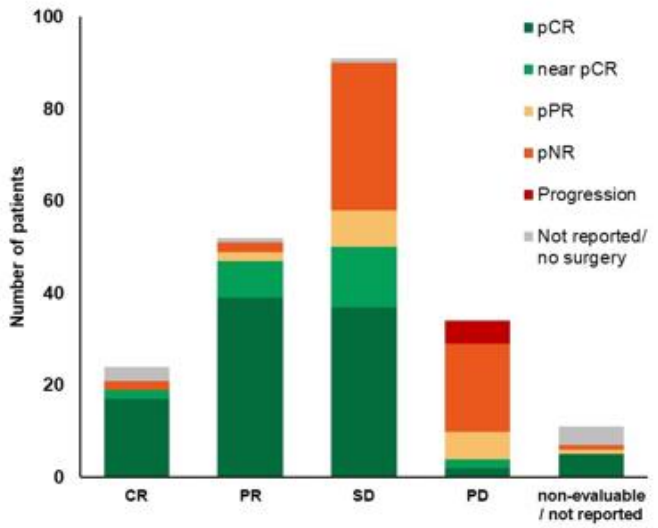
NADINA – Pathologic and Radiologic Response

Pathologic Response

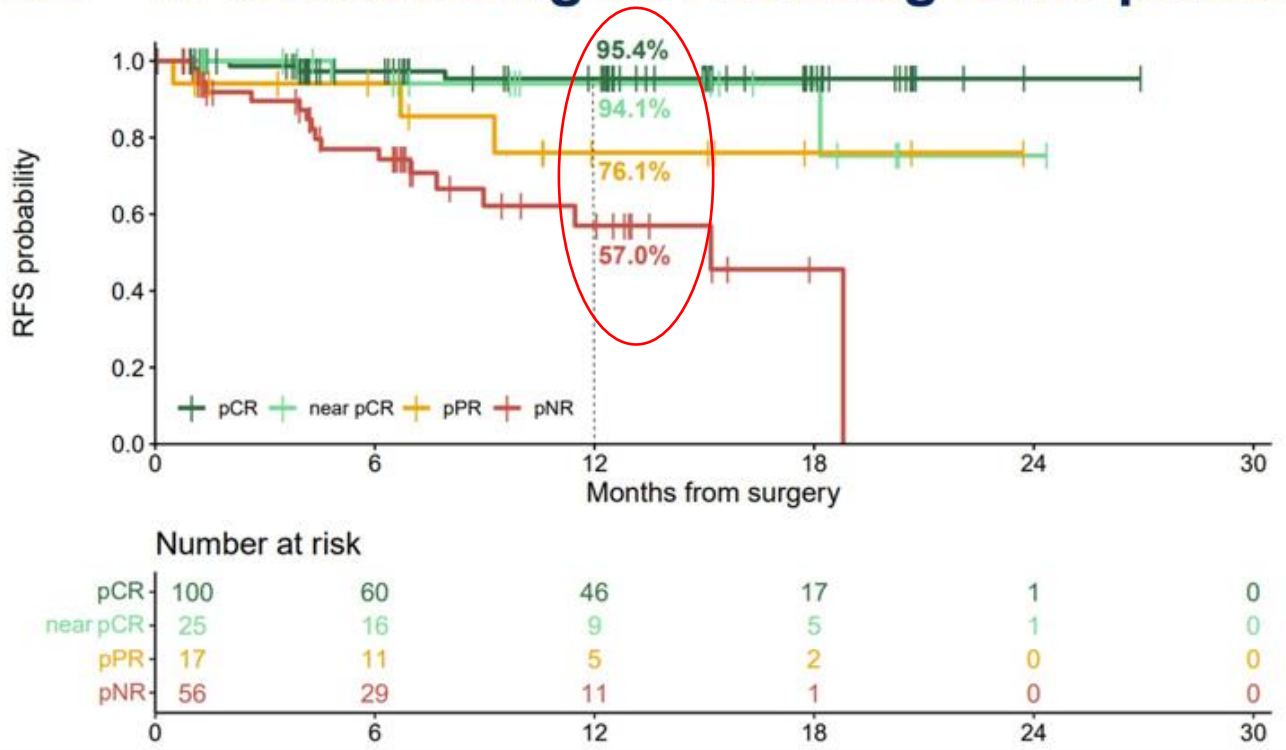


* Central review was completed for all patients who underwent surgery. At data cutoff, 9 patients had not (yet) undergone surgery (4.2%); 5 patients had surgery after data cutoff.

Radiologic- versus Pathologic Response



NADINA – RFS According to Pathologic Response



NADINA – No Novel Safety Observations

	Neoadjuvant n=212	Adjuvant n=208
Any adverse event	204 (96.2%)	194 (93.3%)
Any grade ≥3 AE	100 (47.2%)	71 (34.1%)
Surgery related AE [1]	120 (60.6%)	151 (72.6%)
Surgery related grade ≥3 AE [1]	28 (14.1%)	30 (14.4%)
Systemic treatment related AE [2]	181 (85.4%)	123 (72.4%)
Systemic treatment related grade ≥3 AE [2]	63 (29.7%)	25 (14.7%)
Death due to treatment related AE	0	1 (0.5%)

[1] The surgery safety population included all patients that underwent surgery (neoadjuvant n=198, adjuvant n=208).
[2] The systemic treatment safety population included all patients that received at least one dose of systemic treatment (neoadjuvant n=212, adjuvant n=170).

Conclusions

- Together with SWOG 1801, NADINA defines neoadjuvant immunotherapy as the new standard of care for macroscopic stage III melanoma
- NADINA is the new template for other malignancies implementing a neoadjuvant immunotherapy regimen followed by response-driven adjuvant therapy

ADYUVANCIA

- COMBI-AD study. Actualización a los 96 meses.

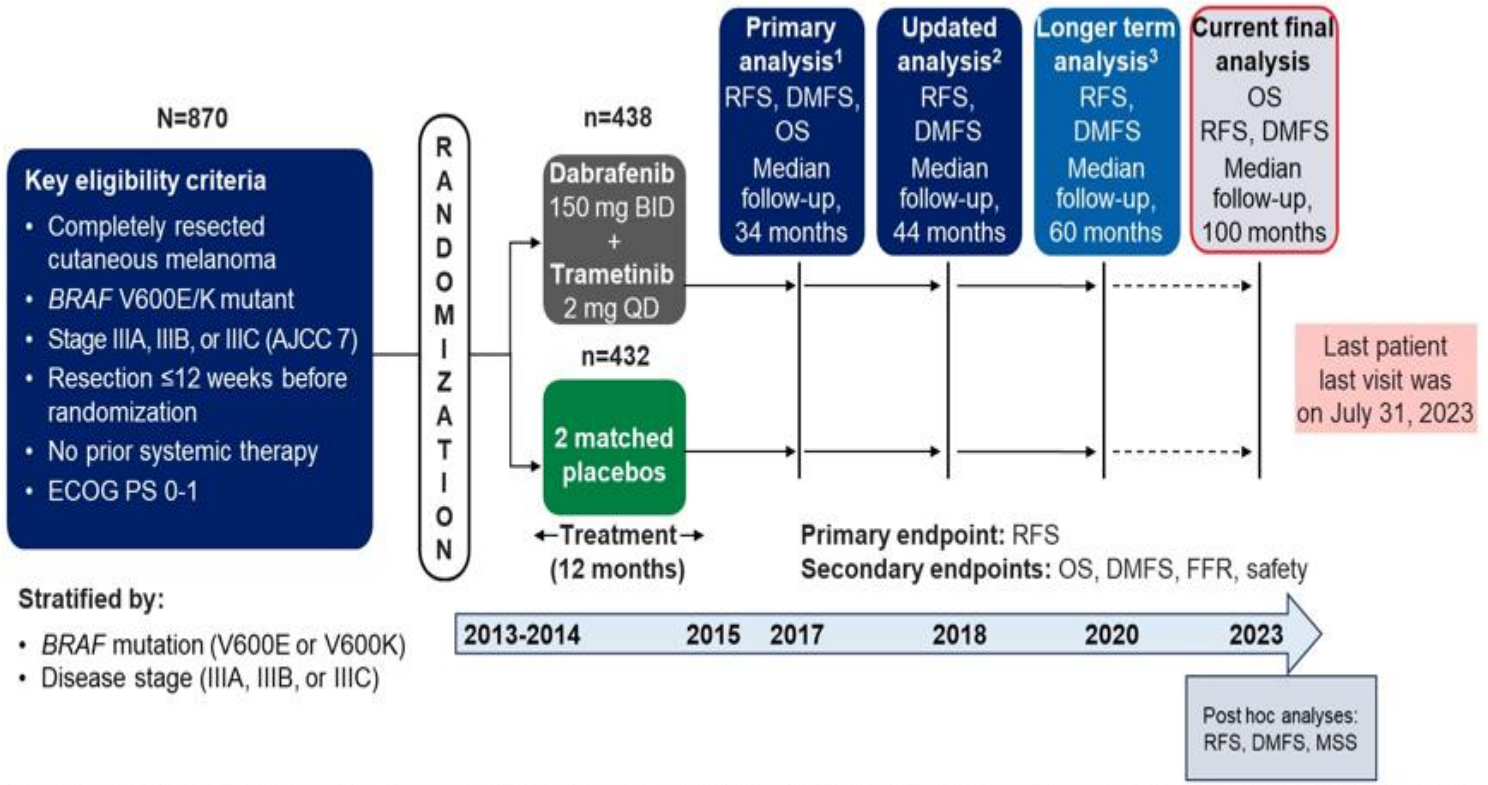
- KEYNOTE-942. Actualización a 3 años.

2024 ASCO ANNUAL MEETING

Long-Term Follow-Up for Adjuvant Dabrafenib Plus Trametinib in Stage III BRAF-Mutated Melanoma: Final Results of the COMBI-AD Study

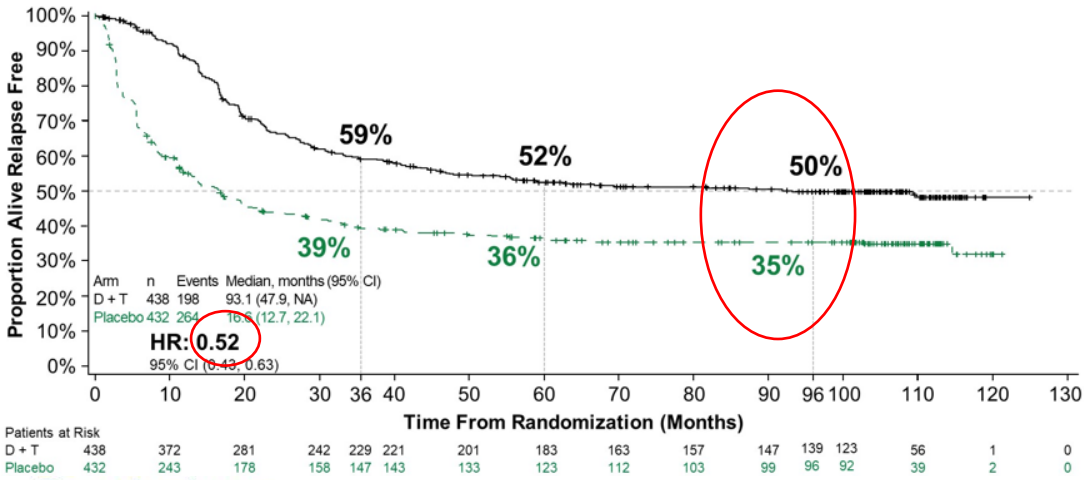
Axel Hauschild, Reinhard Dummer, Mario Santinami, Victoria Atkinson, Mario Mandala, Barbara Merelli, Vanna Chiarion-Sileni, Andrew Mark Haydon, Jacob Schachter, Dirk Schadendorf, Thierry Lesimple, Elizabeth Ruth Plummer, James Larkin, Monique Tan, Sachin Bajirao Adnaik, Paul Burgess, Tarveen Jandoo, Georgina V. Long

COMBI-AD: A Double-Blind, Placebo-Controlled, Phase 3 Study

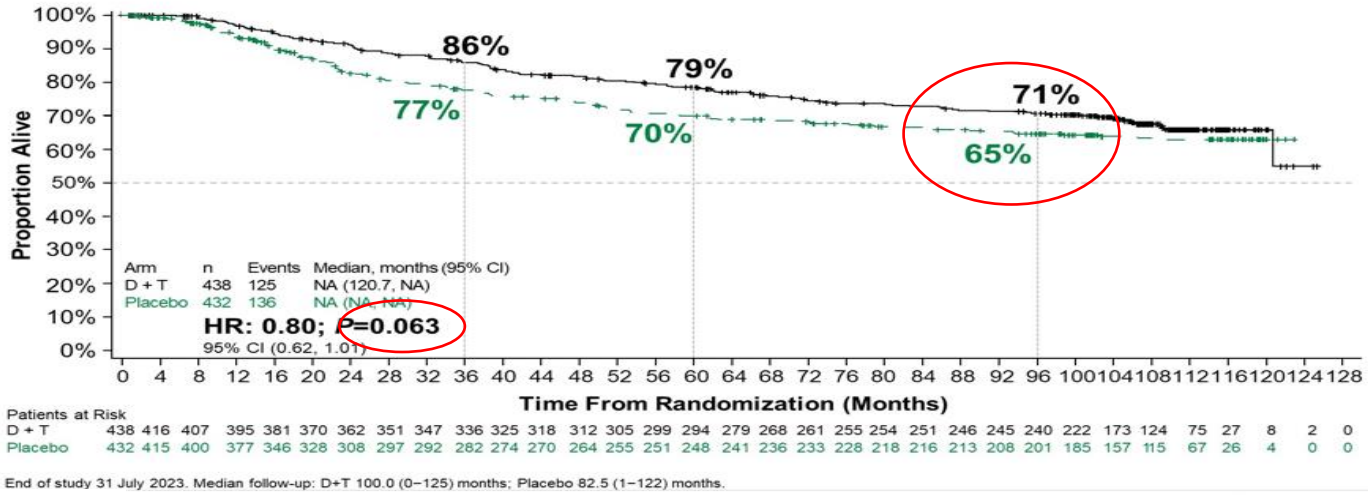


1. Long GV, et al. *N Engl J Med*. 2017;377:1813-1823; 2. Hauschild A, et al. *J Clin Oncol*. 2018;4:1382-1388; 3. Dummer R, et al. *N Engl J Med*. 2020;383:1139-1148.

Relapse-Free Survival (ITT)



Overall Survival (ITT)



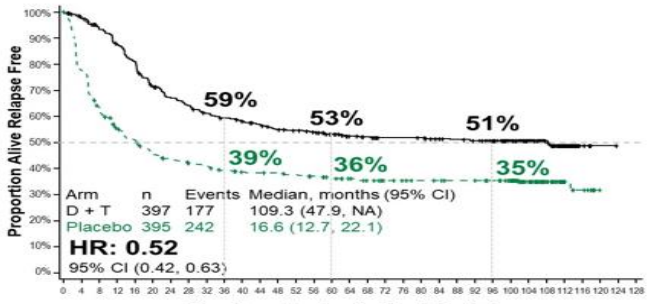
End of study 31 July 2023. Median follow-up: D+T 100.0 (0–125) months; Placebo 82.5 (1–122) months.

Conclusions

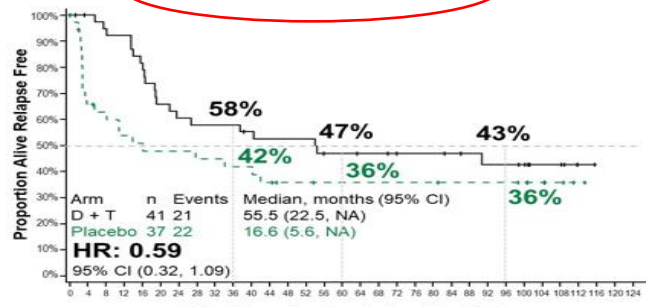
- **Longest follow-up (up to 10 years)** in adjuvant treatment of stage III melanoma
- **Durable improvements in RFS and DMFS** with dabrafenib plus trametinib over placebo
- **Overall survival and melanoma-specific survival** were numerically improved (not statistically significant) with D+T vs placebo, despite post-relapse systemic therapy
  - **20% risk reduction for death** with dabrafenib plus trametinib over placebo (***P*=0.063**)
  - **22% reduction for risk of death due to melanoma** with dabrafenib plus trametinib over placebo
- ***BRAF* V600E** showed a **benefit for OS** with dabrafenib plus trametinib over placebo
  - ***BRAF* V600K** population did not appear to have an OS benefit from adjuvant dabrafenib plus trametinib although caution warranted given this small subgroup
- **No new safety concerns**
  - No irreversible toxicities during the long-term follow-up
  - Skin and other cancers incidence was similar in each arm

Subgroup Analysis: Effect of Treatment on RFS by *BRAF* V600 Mutations (ITT)

***BRAF* V600E Mutations**



***BRAF* V600K Mutations**



One patient had a *BRAF* V600E mutation and a *BRAF* V600K mutation and is included in the *BRAF* V600K subset

End of study 31 July 2023. Median follow-up: D+T 100.0 (0–125) months; Placebo 82.5 (1–122) months.

2024 ASCO ANNUAL MEETING

Individualized neoantigen therapy mRNA-4157 (V940) plus pembrolizumab in resected melanoma: 3-year update from the mRNA-4157-P201 (KEYNOTE-942) trial

Jeffrey S. Weber,[1] Muhammad Adnan Khattak,[2] Matteo S. Carlino,[3] Tarek Meniawy,[4] Matthew H. Taylor,[5] George Ansstas,[6] Kevin B. Kim,[7] Meredith McKean,[8] Ryan J. Sullivan,[9] Mark B. Faries,[10] Thuy Tran,[11] C. Lance Cowey,[12] Theresa M. Medina,[13] Jennifer M. Segar,[14] Victoria Atkinson,[15] Geoffrey T. Gibney,[16] Jason J. Luke,[17] Elizabeth I. Buchbinder,[18] Georgina V. Long,[19] INT Research and Development Author Group,[20,21,a] Robert S. Meehan[20]

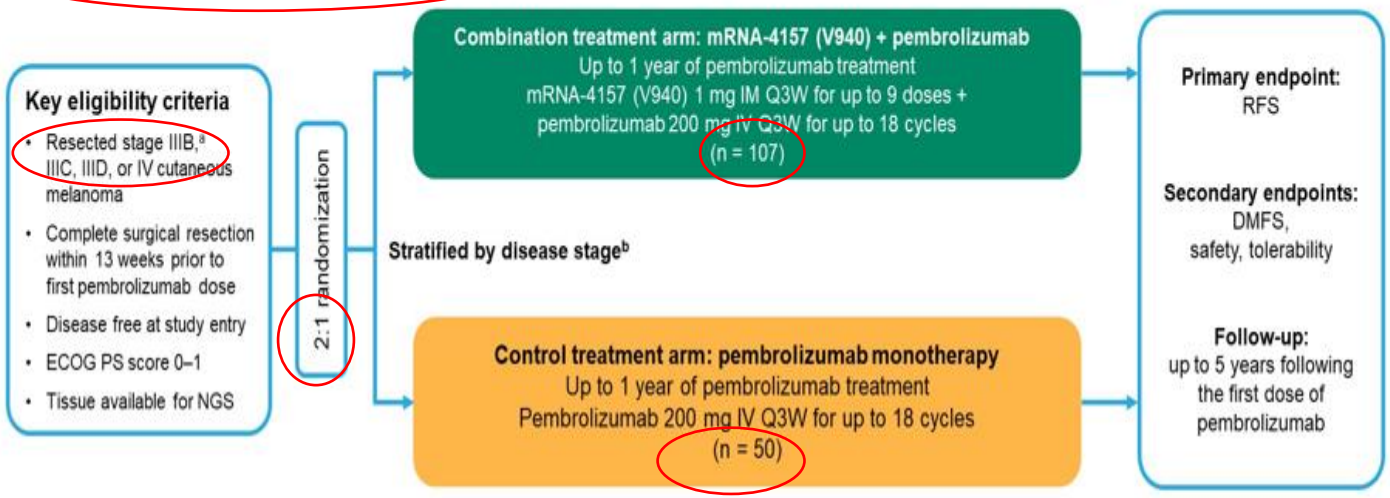
[a]Manju Morrissey,[20] Igor Feldman,[20] Vasudha Sehgal,[20] Huzhang Mao,[20] Jia Guo,[20] Min Liu,[20] Anjali Rao,[20] Wei Zheng,[20] Praveen Aanur,[20] Lakshmi Srinivasan,[20] Mo Huang,[21] Tal Zaks,[20] Michelle Brown,[20] Tracey Posadas[20]

[1]Laura and Isaac Perlmutter Cancer Center at NYU Langone Health, New York, NY, USA; [2]Hollywood Private Hospital and Edith Cowan University, Perth, Australia; [3]Melanoma Institute Australia and Westmead Hospital, Sydney, Australia; [4]Saint John of God Subiaco Hospital, Subiaco, Australia; [5]Earle A. Chiles Research Institute, Portland, OR, USA; [6]Washington Univer School of Medicine, St Louis, MO, USA; [7]California Pacific Medical Center Research Institute, San Francisco, CA, USA; [8]Sarah Cannon Research Institute, Nashville, TN, USA; [9]Massachi General Hospital, Boston, MA, USA; [10]The Angeles Clinic and Research Institute, Los Angeles, CA, USA; [11]Yale-New Haven Hospital, New Haven, CT, USA; [12]Baylor Charles A. Sammon Cancer Center, Dallas, TX, USA; [13]University of Colorado, Aurora, CO, USA; [14]University of Arizona Cancer Center, Tucson, AZ, USA; [15]Princess Alexandra Hospital, Woolloongabba, Au [16]Lombardi Comprehensive Cancer Center, Washington, DC, USA; [17]UPMC Hillman Cancer Center, Pittsburgh, PA, USA; [18]Dana-Farber Cancer Institute, Boston, MA, USA; [19]Melanoma Institute Australia, Sydney, Australia; [20]Moderna, Inc., Cambridge, MA, USA; [21]Merck & Co., Inc., Rahway, NJ, USA.

Sponsored by Moderna, Inc., in collaboration with Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

mRNA-4157-P201/KEYNOTE-942 (NCT03897881) study design

Randomized, phase 2, open-label study in patients with adjuvant resected melanoma at high risk of recurrence

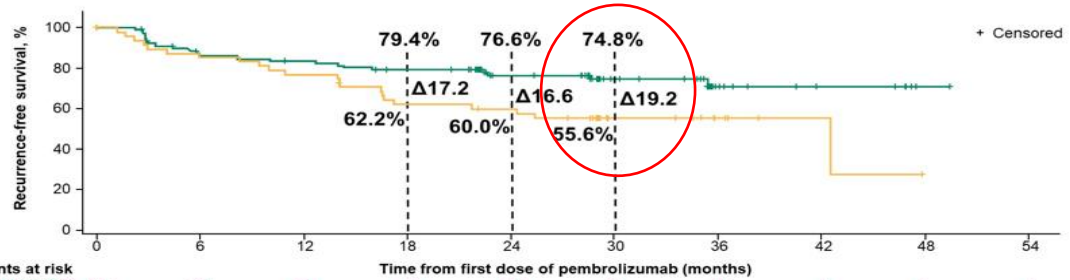


Designed with 80% power to detect a hazard ratio of 0.5 with 40 RFS events (with a 1-sided alpha of 0.1 per protocol)
Primary analysis **triggered after a minimum of 1-year planned follow-up[c]** (November 14, 2022 data cut) and at least 40 RFS events have been observed. DMFS analysis was prespecified for testing following positive RFS in the ITT population

Supportive analysis was **triggered after a minimum of 2 years of planned follow-up[c]** (November 3, 2023 data cut)
Median planned follow-up[c]: ~3yrs

[a]Patients with stage IIB disease were eligible only if relapse occurred within 3 months of prior surgery of curative intent; [b]According to the 8th edition of the American Joint Committee on Cancer Staging Manual [c]Defined as the time from the first dose date (or date of randomization if not treated) to date of clinical cut-off.
ECOG PS, Eastern Cooperative Oncology Group performance status; IM, intramuscular; ITT, intent-to-treat; IV, intravenous; NGS, next-generation sequencing; Q3W, every 3 weeks.

Sustained improvement of RFS primary efficacy endpoint



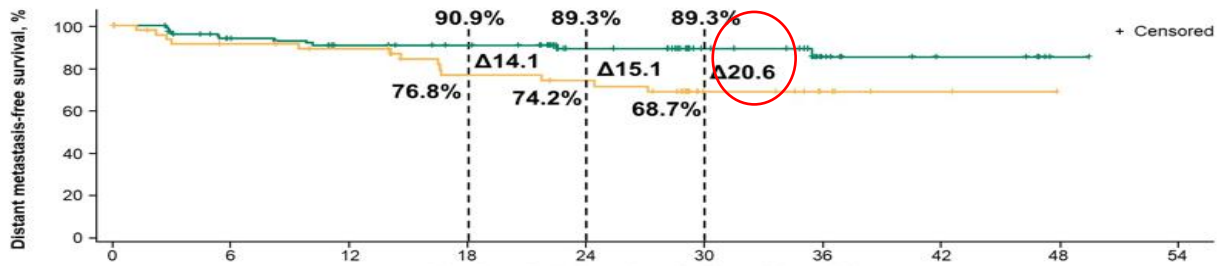
Patients at risk

mRNA-4157 (V940) + pembrolizumab	107	87	83	77	52	29	12	6	1	0
Pembrolizumab	50	41	37	29	27	10	5	2	0	0

	Median (95% CI), months	Events, % (n/N)	Hazard ratio (95% CI)[a]
mRNA-4157 (V940) + pembrolizumab	NE	23.4 (25/107)	0.510 (0.288–0.906) $P = 0.019$[b]
pembrolizumab	42.51 (16.59–NE)	44.0 (22/50)	

[a]The hazard ratio and 95% CI for mRNA-4157 (V940) + pembrolizumab versus pembrolizumab were estimated using a Cox proportional hazards model with treatment group as a covariate, stratified by disease stage (stages IIIB or IIIC or IIID vs stage IV) used for randomization. The *P* value is based on a 2-sided log-rank test stratified by disease stage (stages IIIB or IIIC or IIID vs stage IV) used for randomization. [b]Formal hypothesis testing of RFS was performed using November 2022 data cut. *P* value reported above used the November 2023 data cut. It's nominal and not for formal hypothesis testing. NE, not estimable.

Sustained improvement of DMFS secondary endpoint



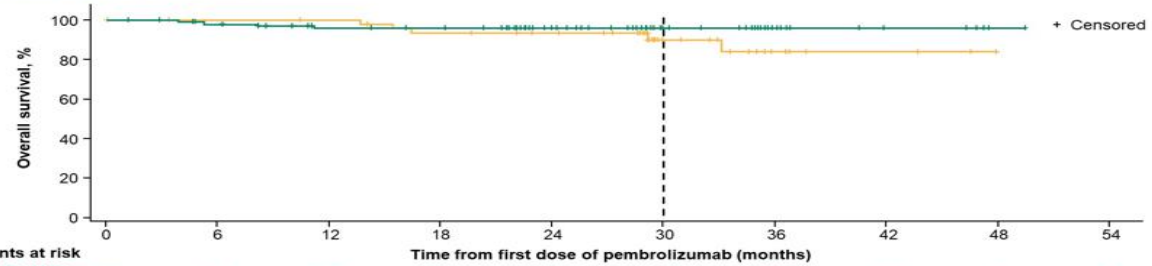
Patients at risk

mRNA-4157 (V940) + pembrolizumab	107	89	82	78	52	30	12	6	1	0
Pembrolizumab	50	42	39	30	27	10	5	2	0	0

	Median (95% CI), months	Events, % (n/N)	Hazard ratio (95% CI)[a]
mRNA-4157 (V940) + pembrolizumab	NE	10.3 (11/107)	0.384 (0.172–0.858) $P = 0.015$[b]
Pembrolizumab	NE	26.0 (13/50)	

[a]The hazard ratio and 95% CI for mRNA-4157 (V940) plus pembrolizumab versus pembrolizumab were estimated using a Cox proportional hazards model with treatment group as a covariate, stratified by disease stage (stages IIIB or IIIC or IIID vs stage IV) used for randomization. The *P* value is based on a 2-sided log-rank test stratified by disease stage (stages IIIB or IIIC or IIID vs stage IV) used for randomization. [b]Formal hypothesis testing of DMFS was performed using November 2022 data cut. *P* value reported above used the November 2023 data cut. It's nominal and not for formal hypothesis testing.

Overall survival shows encouraging trend with mRNA-4157 (V940) + pembrolizumab



Patients at risk

mRNA-4157 (V940) + pembrolizumab	107	100	92	90	65	35	14	6	1	0
Pembrolizumab	50	48	47	43	40	18	7	3	0	0

	Median (95% CI), Months	Events, % (n/N)	Hazard ratio (95% CI)[a]
mRNA-4157 (V940) + pembrolizumab	NE	3.7 (4/107)	0.425 (0.114–1.584)
Pembrolizumab	NE	10.0 (5/50)	

[a]The hazard ratio and 95% CI for mRNA-4157 (V940) plus pembrolizumab versus pembrolizumab were estimated using a Cox proportional hazards model with treatment group as a covariate, stratified by disease stage (stages IIIB or IIIC or IIID vs stage IV) used for randomiz

Conclusions

mRNA-4157 (V940) + pembrolizumab demonstrated a durable **clinically significant improvement in RFS & DMFS** compared with standard of care pembrolizumab in high-risk resected melanoma, with a **49% reduction in the risk of recurrence or death** and a **62% reduction of distant recurrence or death** with 3 years of follow-up

3-year exploratory endpoint showed an **encouraging trend in overall survival** with the combination versus pembrolizumab monotherapy

mRNA-4157 (V940) + pembrolizumab has a **manageable safety profile** without potentiation of immune-related AEs compared with pembrolizumab monotherapy

Translational analyses suggest mRNA-4157 (V940) + pembrolizumab may benefit a **broad patient** population **irrespective of the status of PD-L1, TMB, ctDNA, and HLA heterozygosity**

MELANOMA METASTASICO

- EBIN. Primer análisis. Mediana de seguimiento de 21 meses.
- IOV-COM-202. Resultados cohorte IA.
- RELATIVITY-047. Actualización a 3 años. Mediana de seguimiento de 34 meses.

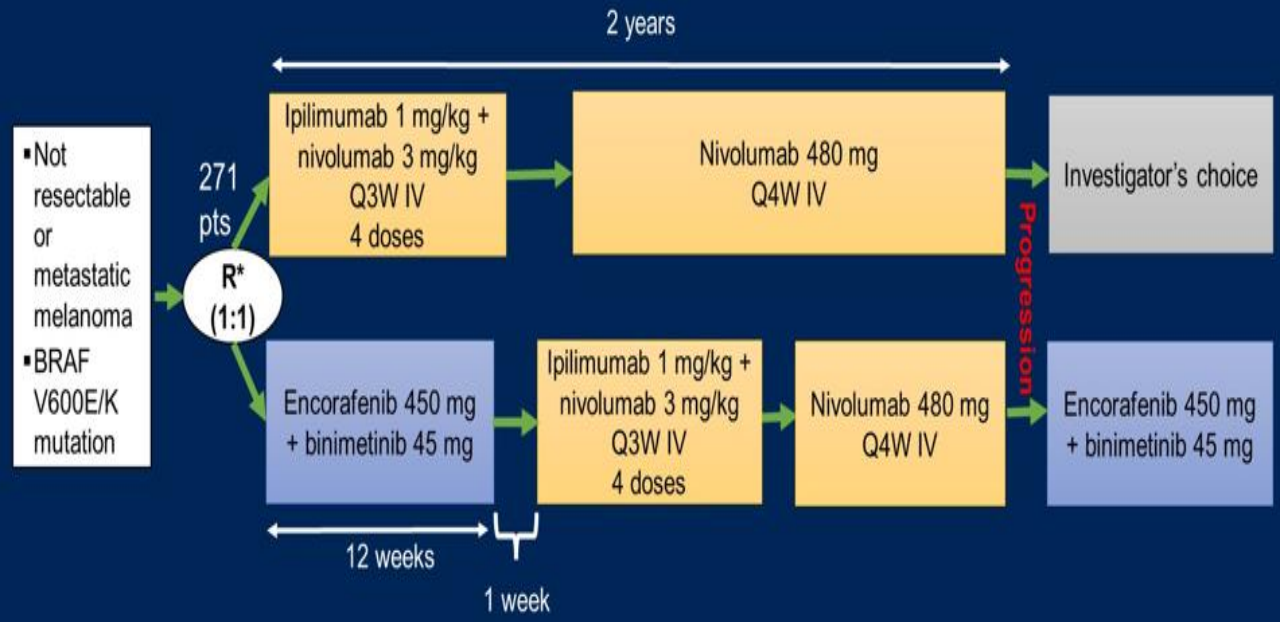
2024 ASCO ANNUAL MEETING

Combination of encorafenib and binimetinib followed by ipilimumab and nivolumab versus ipilimumab and nivolumab in patients with advanced BRAF-V600E/K melanoma: the primary analysis of an EORTC randomized phase II study (EBIN)

Caroline Robert, Caroline Dutriaux, Felix Oppong, Michal Kicinski, Émilie Routier, Eve-Marie Neidhardt, Xavier Durando, Barouyr Baroudjian, Philippe Saiag, Caroline Gaudy-Marqueste, Paolo A. Ascierto, Ana Arance, Michelangelo Russillo, Jean-Luc Perrot, Anne-sophie Govaerts, Emanuel Bührer, Bastian Schilling, Mario Mandalà, Paul Lorigan, Alexander C.J. van Akkooi

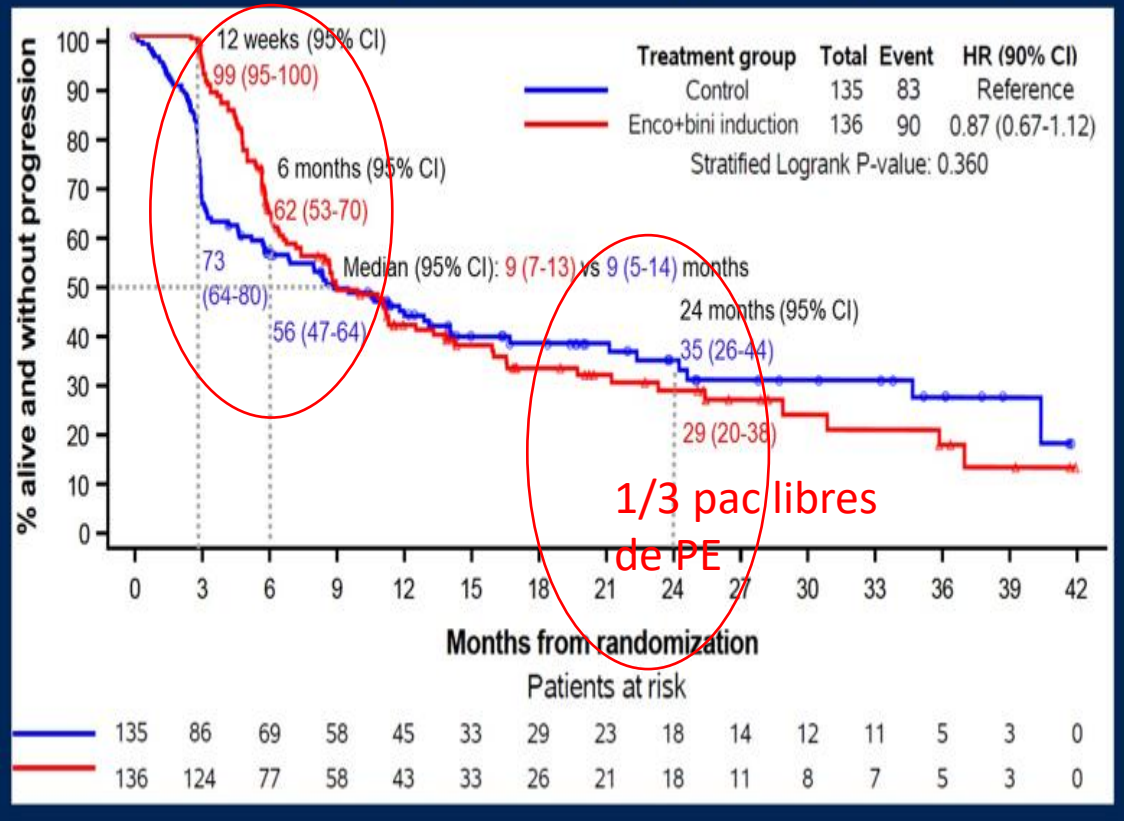
Funding: Bristol-Myers Squibb and Pierre Fabre

Study design



*Stratified by stage/LDH (unresectable stage III/M1a with LDH≤ULN vs M1b/M1c with LDH≤ULN vs ULN<LDH≤2ULN vs LDH>2ULN) and center

PFS in the ITT population (primary analysis)



Conclusions

- No difference in PFS between the two treatment arms in the unselected population of patients
- Data supports the hypothesis that patients with high LDH (>2ULN) and those with liver metastases benefit from the sequential approach in terms of PFS
- The primary overall survival analysis will be performed when the data is mature

2024 ASCO Annual Meeting
May 31–June 4, 2024 | Chicago, IL, USA

Efficacy and safety of lifileucel, an autologous tumor-infiltrating lymphocyte cell therapy, and pembrolizumab in patients with immune checkpoint inhibitor-naive unresectable or metastatic melanoma: updated results from IOV-COM-202 Cohort 1A

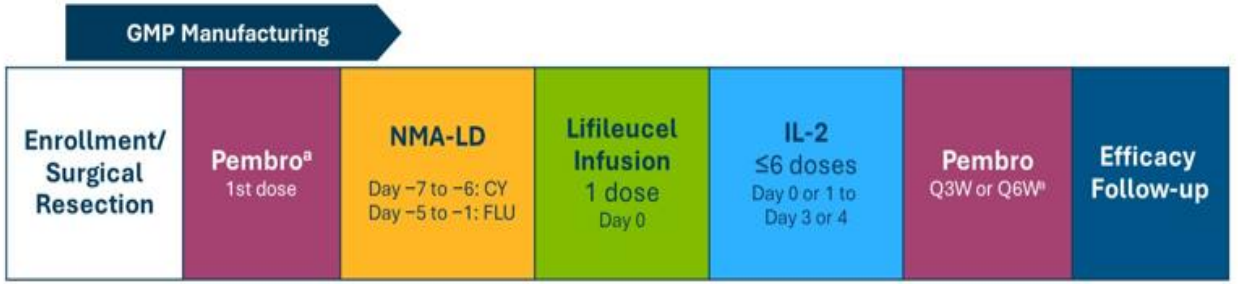
Sajeve Thomas,[1] Helen Gogas,[2] Young Ki Hong,[3] Gino K. In,[4] Bernard Doger de Speville Uribe,[5] Andrew J.S. Furness,[6] Almudena Garcia Castano,[7] Simon Häfliger,[8] Kai He,[9] Theresa Medina,[10] Donald Lawrence,[11] Sylvia Lee,[12] Juan Martin-Liberal,[13] Friedrich Graf Finckenstein,[14] Brian Gastman,[14] Jeffrey Chou,[14] Rana Fiaz,[14] Melissa Catlett,[14] Guang Chen,[14] Patrick Terheyden[15]

[1]Orlando Health Cancer Institute, Orlando, FL, USA; [2]Laiko General Hospital, School of Medicine, National and Kapodistrian University of Athens, Athens, Greece; [3]Cooper University Hospital, Camden, NJ, USA; [4]University of Southern California, Norris Comprehensive Cancer Center, Los Angeles, CA, USA; [5]START Madrid Fundación Jiménez Diaz, Madrid, Spain; [6]The Royal Marsden NHS Foundation Trust, London, UK; [7]Hospital Universitario Marqués de Valdecilla, Santander, Spain; [8]Inselspital, Bern University Hospital, Bern, Switzerland; [9]James Cancer Center, The Ohio State University, Columbus, OH, USA; [10]University of Colorado Cancer Center – Anschutz Medical Campus, Aurora, CO, USA; [11]Massachusetts General Hospital Cancer Center, Boston, MA, USA; [12]Fred Hutchinson Cancer Center, Seattle, WA, USA; [13]ICO L'Hospitalet – Hospital Duran i Reynals, Barcelona, Spain; [14]Iovance Biotherapeutics, Inc., San Carlos, CA, USA; [15]University of Lübeck, Lübeck, Germany

IOV-COM-202: Phase 2, Multicohort, Multicenter Study of Lifileucel + Pembrolizumab in Patients With Solid Tumors

- Cohort 1A of IOV-COM-202 (NCT03645928) assesses the efficacy and safety of lifileucel + pembrolizumab in patients with ICI-naive unresectable or metastatic melanoma
  - Patients may have received BRAF/MEK inhibitor treatment if they are *BRAF* mutation positive 13%
  - Eligible patients must have ≥1 resectable lesion (≥1.5-cm diameter) and ≥1 measurable lesion for response assessment per RECIST v1.1
- Trial designed as a proof-of-concept study to support a registrational study in the frontline treatment setting

Treatment Schema

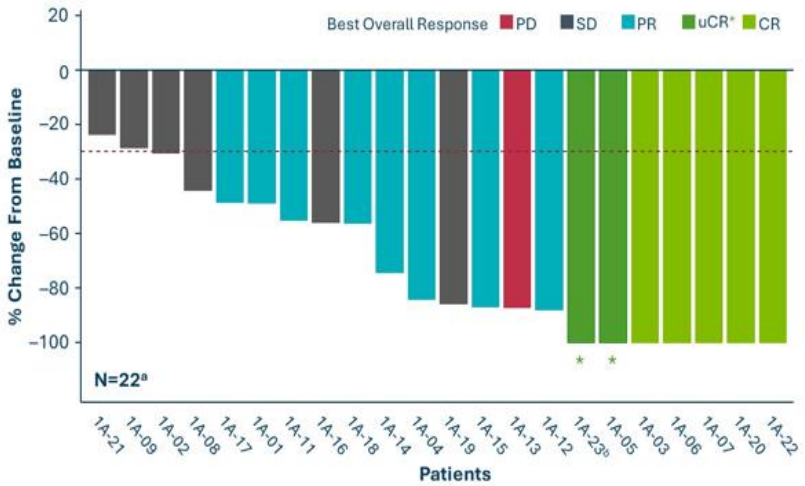


[a]First administration of single-dose pembrolizumab IV 200 mg or 400 mg, followed by pembrolizumab IV 200 mg Q3W or 400 mg Q6W for 24 months or until disease progression or unacceptable toxicity.
CY, cyclophosphamide; EOA, end of assessment; FLU, fludarabine; GMP, Good Manufacturing Practice; ICI, immune checkpoint inhibitor; IL-2, interleukin-2; NMA-LD, nonmyeloablative lymphodepletion; pembro, pembrolizumab; Q3W, every 3 weeks; Q6W, every 6 weeks; RECIST, Response Evaluation Criteria in Solid Tumors.

Efficacy

ORR was 65.2%; CR rate was 30.4%

Best Percentage Change From Baseline in Target Lesion SOD



Investigator-Assessed Response (RECIST v1.1)

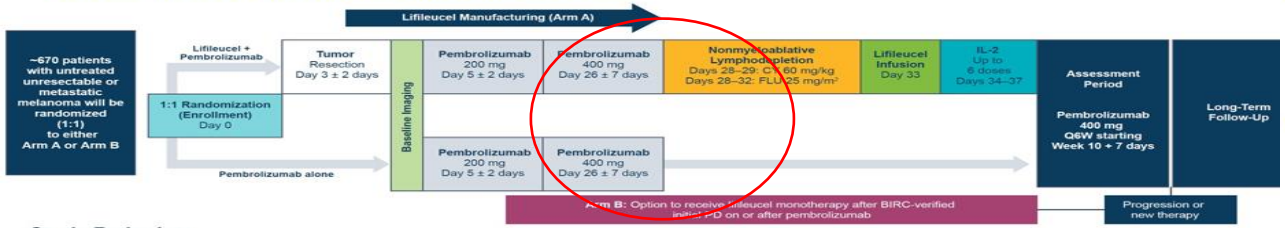
	N=23
ORR, n (%) (95% CI)	15 (65.2) (42.7, 83.6)
CR	7 (30.4)
PR	8 (34.8)
SD	6 (26.1)
PD	1 (4.3)
NE	1 (4.3)

All response-evaluable patients demonstrated regression of target lesions

* The two uCRs have been confirmed post-data cut

TILVANCE-301[a] Global Phase 3 and Confirmatory Trial

Randomized study to evaluate lifileucel + pembrolizumab in frontline advanced melanoma Enrolling in Europe, North America, and Australia



Study Endpoints

Dual primary efficacy endpoints

- BIRC-assessed ORR per RECIST v1.1
  - Potential for accelerated approval and confirmation of post anti-PD1 approval based on early interim analysis
- BIRC-assessed PFS per RECIST v1.1

Key secondary efficacy endpoint

- OS

Additional secondary endpoints

- BIRC-assessed CR rate, DOR, EFS per RECIST v1.1
- Investigator-assessed ORR, PFS, CR rate, DOR, EFS, PFS2 per RECIST v1.
- Safety

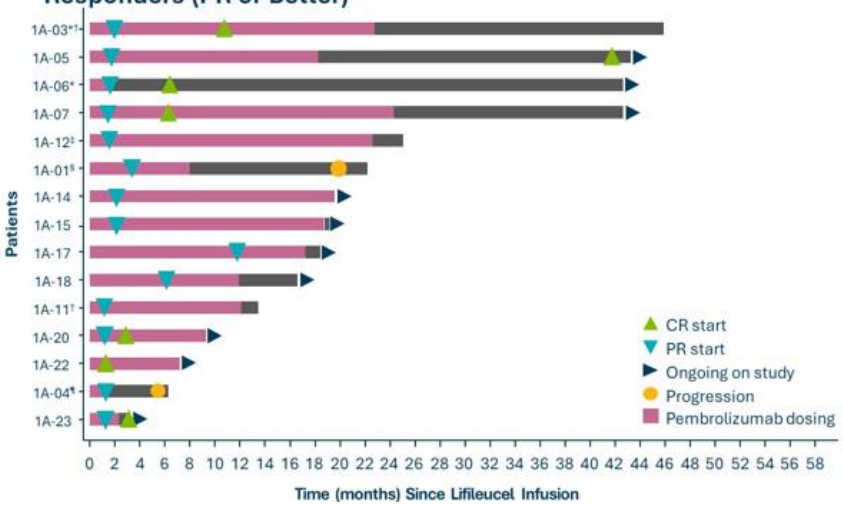
[a]NCT05727904.

BIRC, blinded independent review committee; CR, complete response; CY, cyclophosphamide; EFS, event-free survival; FLU, fludarabine; IL-2, interleukin-2; ORR, objective response rate; OS, overall survival; PD, progressive disease; PD-1, programmed cell death protein-1; PFS, progression-free survival; PFS2, progression-free survival 2; Q6W, every 6 weeks; RECIST, Response Evaluation Criteria in Solid Tumors.

Efficacy

Lifileucel + pembrolizumab demonstrated durable and deepening responses

Time to Response and Time of Efficacy Assessment for Confirmed Responders (PR or Better)



Duration of Response

	Responders (N=15/23)
mDOR, months (95% CI)	Not reached (NR) (16.8, NR)
DOR, n (%)	
≥6 months	11 (73.3)
≥12 months	8 (53.3)

- Median follow-up was 21.7 months
- **mDOR was NR**
- Median time to initial response was 2.6 months
- 10 of 15 responders (66.7%) continue on study with ongoing response and 3 additional patients (20%) discontinued follow-up while in response

Conclusions

A single administration of lifileucel combined with pembrolizumab demonstrated:

- Manageable and expected safety profile
  - TEAEs consistent with the underlying disease and known, manageable safety profiles of single administration of the lifileucel regimen and continued pembrolizumab
  - Late AEs consistent with anti-PD-1 monotherapy, differentiated from ICI combination therapies
- Efficacy and durability of responses in patients with ICI-naive advanced melanoma
  - ORR was 65.2% and CR rate was 30.4%
  - All evaluable patients demonstrated regression of target lesions
  - mDOR was not reached, with a high proportion of ongoing responses (median follow-up of 21.7 months)
  - Rate and depth of responses compare favorably with ICI mono- and combination-regimens for first-line melanoma patients

These results serve as rationale for TILVANCE-301, an ongoing registrational, randomized trial assessing lifileucel + pembrolizumab in frontline advanced melanoma

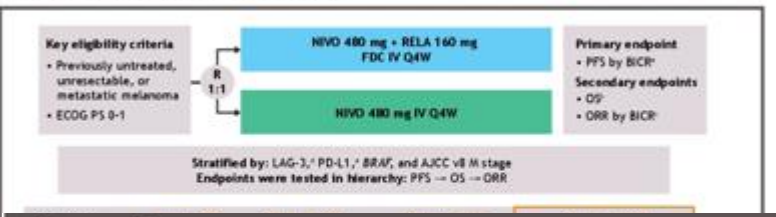
Nivolumab plus relatlimab vs nivolumab in previously untreated metastatic or unresectable melanoma (RELATIVITY-047): overall survival and melanoma-specific survival outcomes at 3 years

Hussein A. Tawbi,[1] F. Stephen Hodi,[2] Evan J. Lipson,[3] Dirk Schadendorf,[4] Paolo Antonio Ascierto,[5] Luis Matamala,[6] Erika Castillo Gutiérrez,[7] Piotr Rutkowski,[8] Juliana Janoski De Menezes,[11] Stéphane Dalle,[12] Ana María Arance,[13] Jean-Jacques Grob,[14] Barbara Ratto,[15] Salma Rodriguez,[15] Antonella Mazzei,[15] Sonia Do

Methods

- RELATIVITY-047 is a global, randomized, double-blind, phase 2/3 study in patients with previously untreated, histologically confirmed, unresectable stage III or stage IV melanoma (**Figure 1**)

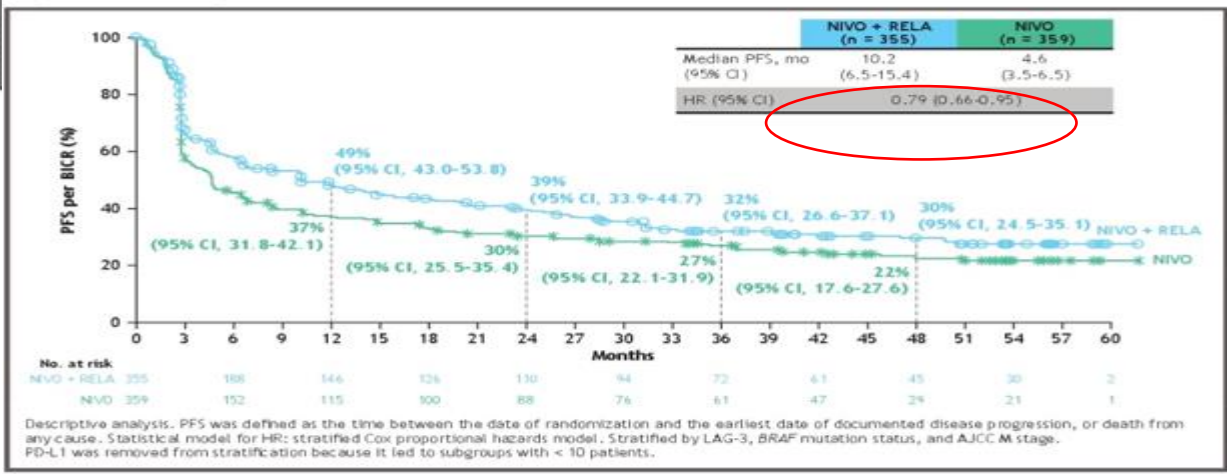
Figure 1. RELATIVITY-047 study design



Results

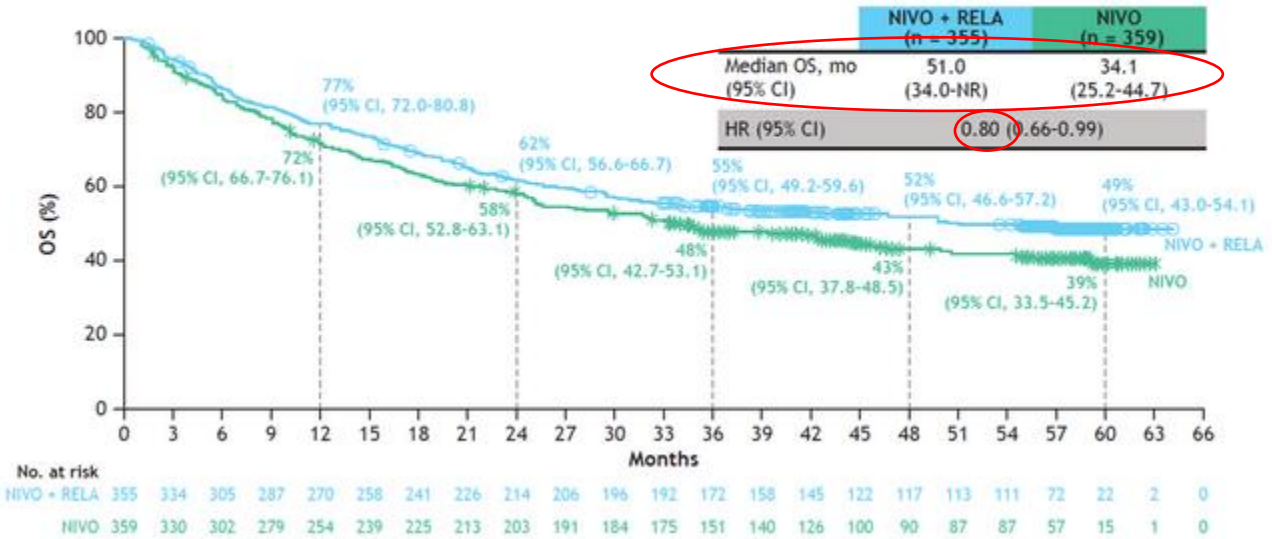
- At 3 years of follow-up, the efficacy benefit (PFS per BICR, OS, and confirmed ORR per BICR) with NIVO + RELA vs NIVO in patients with advanced melanoma was sustained (**Figures 2-4**)

Figure 2. PFS per BICR



Descriptive analysis. PFS was defined as the time between the date of randomization and the earliest date of documented disease progression, or death from any cause. Statistical model for HR: stratified Cox proportional hazards model. Stratified by LAG-3, *BRAF* mutation status, and AJCC M stage. PD-L1 was removed from stratification because it led to subgroups with < 10 patients.

RELA-047: Updated OS (secondary endpoint)



Conclusions

- At 3 years of follow-up, descriptive analyses continued to show benefit for patients with previously untreated metastatic or unresectable melanoma who were treated with NIVO + RELA vs NIVO
  - PFS per BICR HR 0.79 (95% CI, 0.66-0.95)
  - OS HR 0.80 (95% CI, 0.66-0.99), with the 95% CI upper bound of the HR for OS now less than 1
  - Sustained ORR difference of 9.8% (95% CI, 2.8-16.8)
  - MSS HR 0.75 (95% CI, 0.60-0.94)
- NIVO + RELA had sustained benefit vs NIVO beyond initial treatment and first progression
  - The therapeutic benefit of 2L therapy did not appear to be negatively impacted by prior treatment with NIVO + RELA vs NIVO
- No new or unexpected safety signals were identified at this 3-year update

MELANOMA UVEAL

- Phase II multi-center study of adyuvant nivolumab in combination with ipilimumab in patients with high-risk uveal melanoma (HCRNMEL17-309).Mediana de seguimiento de 3 años.
- A phase 2 safety and efficacy study of neoadjuvant/adjuvant darovasertib for localized ocular melanoma.

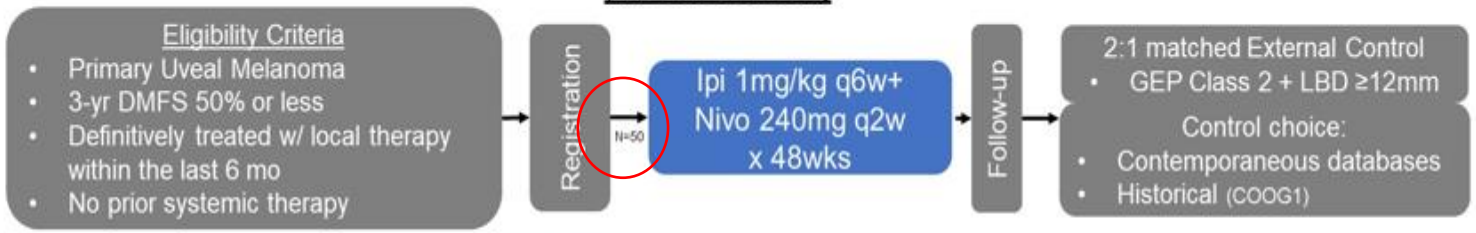
2024 ASCO ANNUAL MEETING

Phase II single-arm multi-center study of adjuvant nivolumab in combination with ipilimumab in patients with high-risk uveal melanoma (UM) (HCRN MEL17-309)

Suthee Rapisuwon, Richard D. Carvajal, George Ansstas, Katy K. Tsai, Leonel F. Hernandez-Aya, Shaheer Khan, Sunandana Chandra, J. William Harbour, Jeffrey A. Sosman, Adil Daud, Christina Decatur, Deniz, Ozisik, Ming T. Tan, Michael B. Atkins, Sapna P. Patel*

Lombardi Comprehensive Cancer Center, Northwell Health Cancer Institute, Washington University in St. Louis, University of California Sanfrancisco, University of Miami Sylvester Comprehensive Cancer Center, Columbia University, Northwestern University, University of Texas Southwestern Medical Center, The University of Texas MD Anderson Cancer Center *as of July 1: The University of Colorado

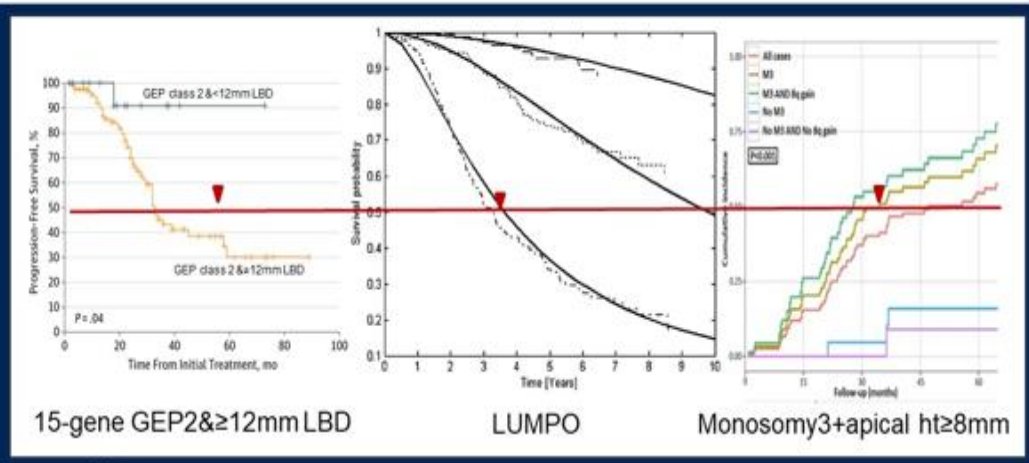
HCRN MEL17-309 Phase II Investigator-Initiated Adjuvant Nivo/Ipi in High-Risk Uveal Melanoma Schema (NCT03528408)



Definition of high-risk uveal melanoma

- GEP Class 2 + LBD ≥12mm
- Monosomy 3 + apical tumor height ≥8mm
- LUMPO calculator 3-yr DMFS ≤50%

(any one of the three definitions is eligible)



15-gene GEP2&≥12mm LBD | LUMPO | Monosomy3+apical ht≥8mm

Primary Endpoint: 3-yr DMFS rate

Secondary Endpoints: mDMFS, mOS, 3-yr OS rate, AEs

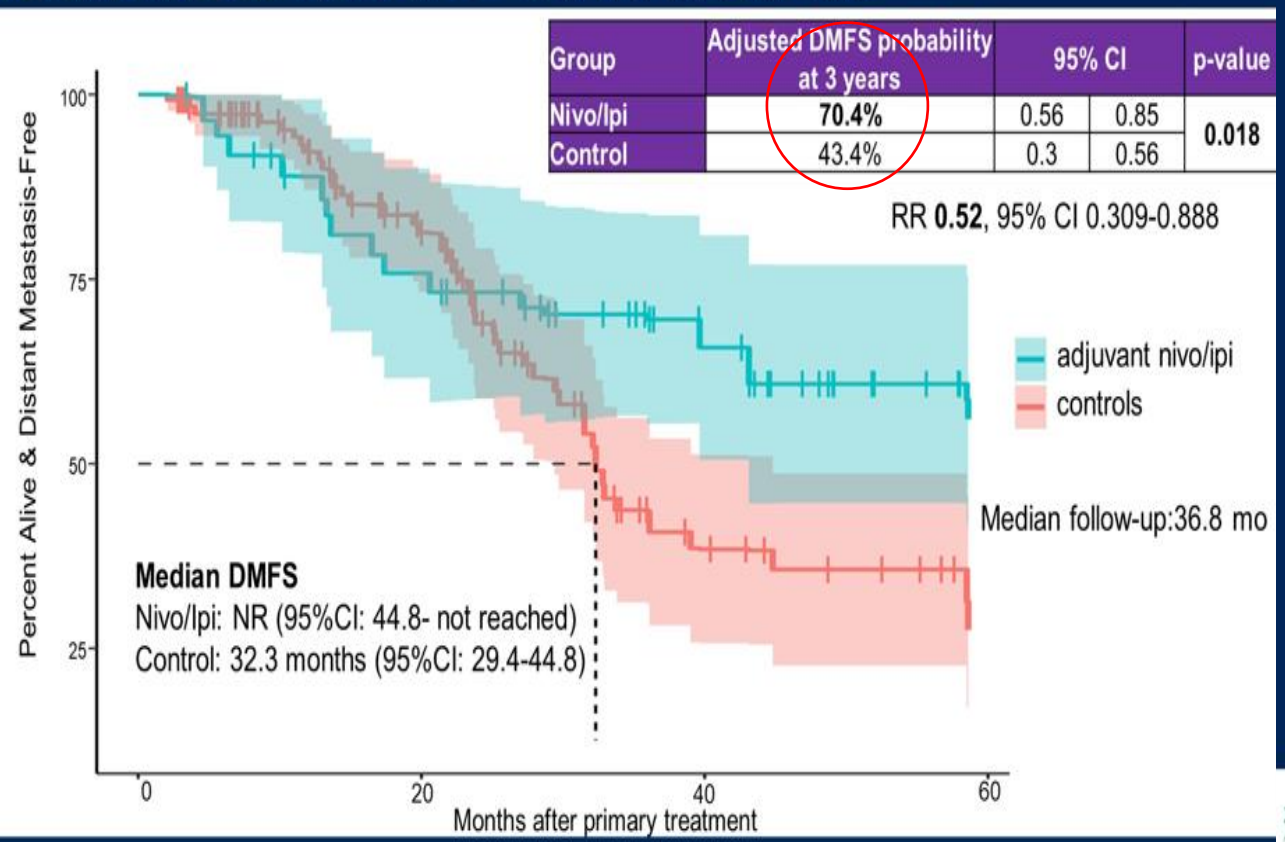
Statistical Plan: Kaplan-Meier estimation with augmented inverse probability of treatment weighting (AIPTW)

Abbreviations: DMFS, distant metastatic-free survival, Ipi, ipilimumab; Nivo, nivolumab; GEP, gene expression profile; COOG1, cooperative ocular oncology group study No.1; LUMPO, Liverpool Uveal Melanoma Prognosticator Online;LBD: largest basal tumor diameter

Eluteri Int Biomed Eng Technol 2012
Walter JAMA Ophthalmol 2016
Dogrusoz Invest Ophthalmol Vis Sci 2017

Distant metastatic-free survival-AIPTW

Group	Adjusted DMFS probability at 3 years	95% CI		p-value
Nivo/Ipi	**70.4%**	0.56	0.85	**0.018**
Control	43.4%	0.3	0.56	



Conclusions

- Adjuvant Nivo+Ipi resulted in statistically significant improvement in 3-year DMFS in patients with high-risk UM compared to historical control
  - 3-year DMFS: 70.4% vs 43.4% (RR:0.52; 95% CI: 0.31-0.88, 2-sided p:0.018)
- Higher than expected incidence of TRAEs with the regimen
  - Grade≥3 TRAEs: 48%
  - 22 patients (44%) discontinued treatment due to AEs
  - No new safety signal compared to cutaneous melanoma (CheckMate915)
- Further investigation of the regimen as adjuvant therapy of high-risk UM is warranted
- Tissue, blood, and other correlative biomarkers were collected and studies are ongoing

2024 ASCO ANNUAL MEETING #ASCO24 PRESENTED BY: Suthee Rapisuwon, MD
ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY KNOWLEDGE CONQUERS CANCER

2024 ASCO ANNUAL MEETING

IDEAYA BIOSCIENCES

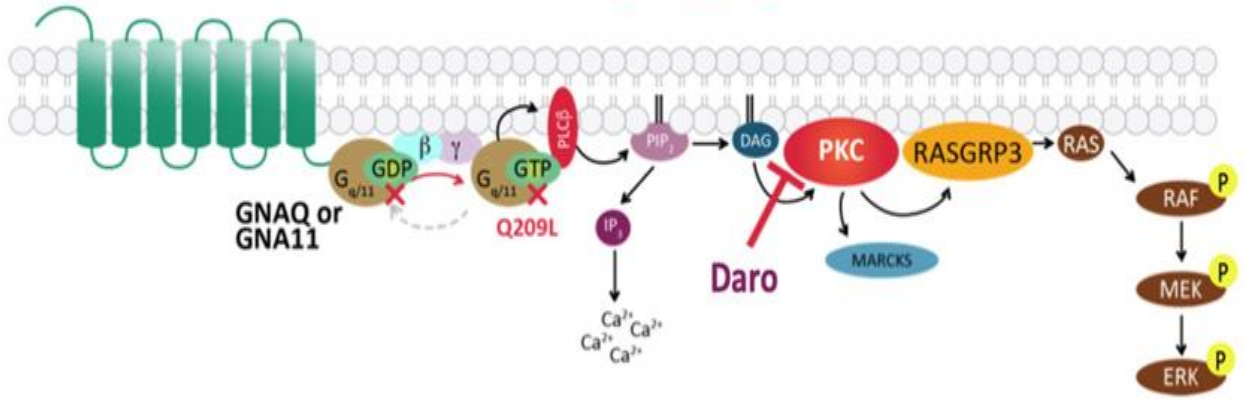
Abstract 9510: A phase 2 safety and efficacy study of neoadjuvant/adjuvant darovasertib for localized ocular melanoma (NADOM).

Shackleton, M; O'Day, R; McGrath, L; Lim, L; Conway, M; Glasson, W; Sia, D; Fung, AT; Isaacs, T; McKay, D; McKenzie, J; Ameratunga, M; Cosman, R; Cherepanoff, S; Brooks, C; Yousif, J; Psaroulis, T; O'Quigley, M; Beaupre, D; Joshua, A.M

Prof. Anthony Joshua BSc(Med) MBBS PhD FRACP
Kinghorn Cancer Centre, St Vincents Hospital, Sydney, Australia

Background

Mutations in GNAQ / GNA11 activate PKC Signaling, a genetic driver of Uveal Melanoma



- Darovasertib is a potent Protein Kinase C (PKC) inhibitor
- Documented activity in metastatic uveal melanoma (11% PR; 67% SD)[1]

Study Design

Safety Cohort (n=3)

Eligible patient identified* → Neoadjuvant Darovasertib for 1 month → Enucleation → Optional adjuvant Darovasertib for 6 months

DSMB review

Treatment Cohort (n=12)

Eligible patient identified* → Neoadjuvant Darovasertib for up to 6months → Definitive treatment → Optional adjuvant Darovasertib for 6 months

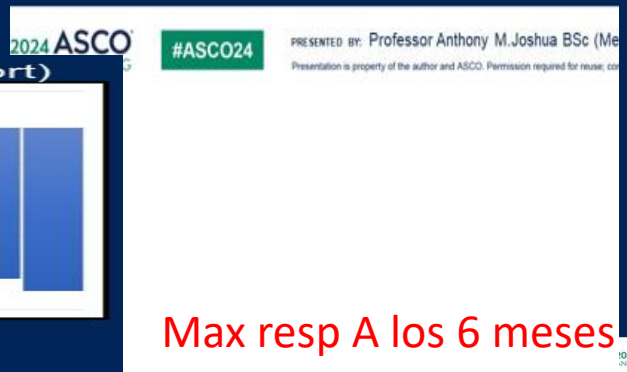
*Planned to undergo enucleation or unsuitable for plaque brachytherapy due to size, location

Male =7, Female = 8
62 (33-76)
T3a (5)
T3b (4)
T4a (4)
T4b (2)

Outcomes (Treatment Cohort) (May 14, 2024)

Treatment Parameter (n=12)	Median (Range in months)
Duration of Neoadjuvant Treatment	6 (2-6)
Follow-up	8.6 (6-21.5)
Duration of Adjuvant Treatment	4.6 (1-6)
Patients with Metastatic Disease	1

Primary Treatment	Type
Eye Preservation 75% (9/12)	Iodine-based plaques 3
	Ruthenium plaques 5
	EBRT 1
Enucleation 25% (3/12)	



Max resp A los 6 meses

Key Points

- NADOM provides the first prospective evidence that a neoadjuvant treatment strategy in UM is feasible, tolerable and safe.
- Protein Kinase C inhibition with darovasertib can induce tumor shrinkage and facilitate eye preservation in suitable patients.
- Larger trials are in now progress (NCT05907954) to further quantify visual and oncological outcomes.

TUMOR CUTANEO ESCAMOSO

- Keynote-629. Actualización.Mediana de seguimiento > 5 años.
- De-Squamate

Pembrolizumab for Locally Advanced or Recurrent/Metastatic Cutaneous Squamous Cell Carcinoma: Long-Term Results of the Phase 2 KEYNOTE-629 Study

J. Schachter[1], A. Arance[2], F. Grange[3], N. Meyer[4], A. Joshi[5], S. Bilan[6], S. E. Ogawa[7], J. Yuan[8], D. Gumuscu[8], A. Boland[8]
[1]Hospital Clínic of Barcelona and Clínic Barcelona Institute of Oncology (ICO), Barcelona, Spain; [2]Royal Brisbane and Women's Hospital, Herston, and University of Queensland, Brisbane, QLD, Australia; [3]CHRU Lille Hôpital Claude Huriez, Lille, France; [4]Ann Romedise University, Marseille, France; [5]Johannes Gutenberg Medical Center, Mainz University Medicine, Mainz, Germany; [6]Meir Medical Center, Kfar Saba, Israel; [7]Hospital Universitario Montreal, CIF, Canada; [8]Centro Estatal de Canceriología de Chihuahua, Chihuahua, Mexico; [9]Sheba Medical Center, Tel Hashomer, Ramat Gan, Israel; [10]Hospital Clínic i Provincial de Barcelona, Barcelona, Spain; [11]Centre Hospitalier Universitaire de Reims-Hôpital Robert Debré, Reims, France; [12]Institut Universitaire du Cancer Toulouse Oncopole, Toulouse, France; [13]Townsville University Hospital, Townsville, QLD, Australia; [14]Thomson Health Care Campus, Haifa, Israel; [15]Merck & Co., Inc., Rahway, NJ, USA; [16]Data Connect Bioanalytics, Oslo, Norway

Methods

Figure 1. Study design

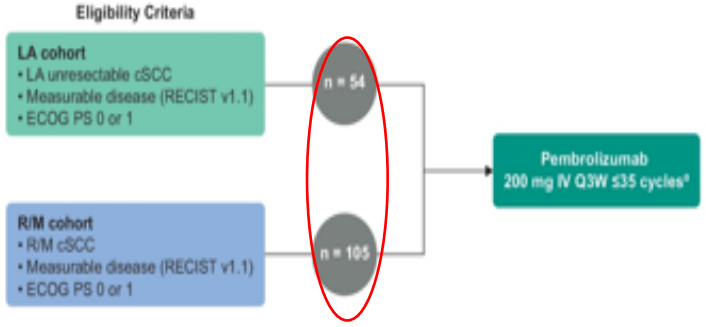
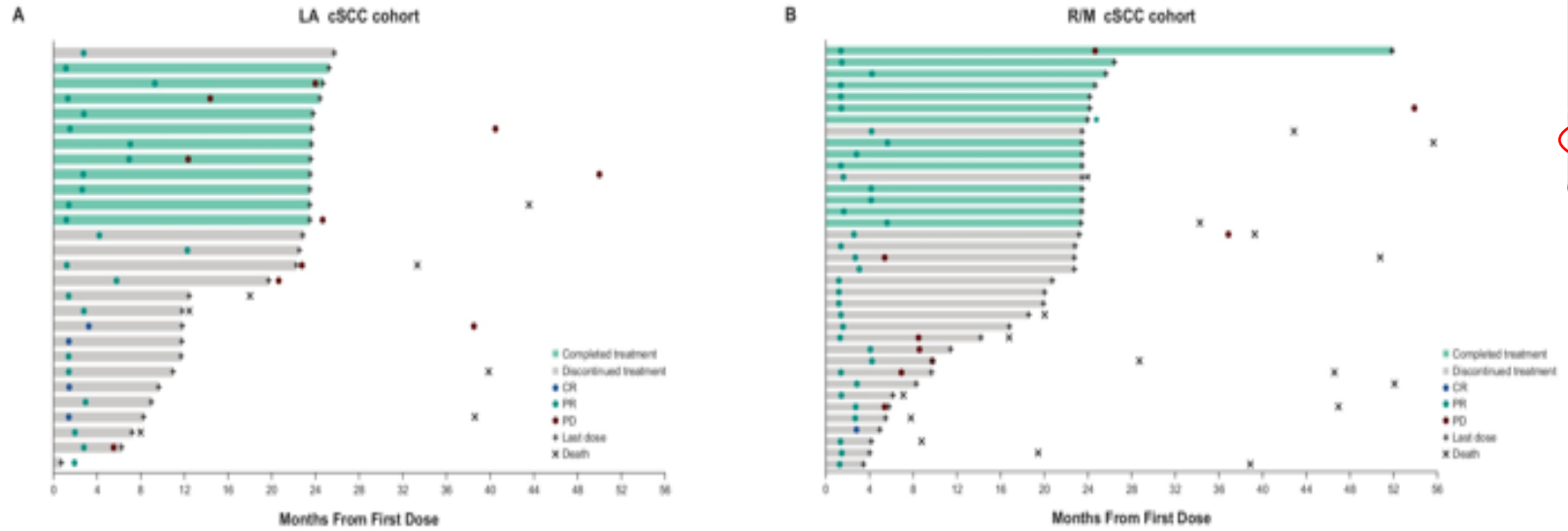


Table 2. ORR per RECIST v1.1 by BICR in the LA cohort, R/M cohort, and total population

	LA cohort n = 54	R/M cohort n = 105	Total population N = 159
ORR, % (95% CI)	51.9 (37.8-65.7)	35.2 (26.2-45.2)	40.9 (33.2-48.9)
DCR, % (95% CI)	64.8 (50.6-77.3)	52.4 (42.4-62.2)	56.6 (48.5-64.4)
Best overall response, n (%)			
CR	12 (22.2)	13 (12.4)	25 (15.7)
PR	16 (29.6)	24 (22.9)	40 (25.2)
SD	12 (22.2)	30 (28.6)	42 (26.4)
SD ≥12 weeks	7 (13.0)	18 (17.1)	25 (15.7)
PD	9 (16.7)	28 (26.7)	37 (23.3)
NE/NA[a]	5 (9.3)	10 (9.5)	15 (9.4)

NA, not available; NE, not evaluable.
[a]Postbaseline assessment not evaluable or no postbaseline assessment available.

Figure 4. Duration of treatment and time to response in patients with a confirmed response per RECIST v1.1 by BICR in the (A) LA cSCC cohort and the (B) R/M cSCC cohort



Conclusions

- With an additional 38 months of follow-up (median follow-up 63.1 months in the total population), pembrolizumab monotherapy continued to demonstrate durable antitumor activity in patients with LA or R/M cSCC
- In the current analysis, ORR, median PFS, and median OS are consistent with the initial analysis at a median time from first dose to data cutoff of approximately 15 months[4]
  - 1 additional patient in the LA cohort achieved a CR since the last data cutoff
- Responses were durable, with a median DOR of 52.5 months and 61.2% of responders by Kaplan-Meier estimate having extended responses that lasted ≥36 months

Se confirma beneficio clínico y respuestas duraderas

2024 ASCO ANNUAL MEETING

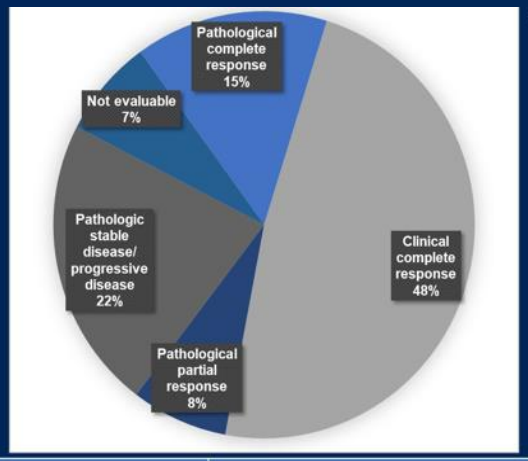
A phase 2 study of de-escalation in resectable, locally advanced cutaneous squamous cell carcinoma (cSCC) with the use of neoadjuvant pembrolizumab.

The De-Squamate study

Ladwa R, Lee J, Porceddu SV, McGrath M, Cooper C, Liu H, Gupta R, Cuscaden C, Nottage M, Clark J, Le D, Pauley M, Gonzalez-Cruz J, Frazer I, Hughes BGM, Panizza B.

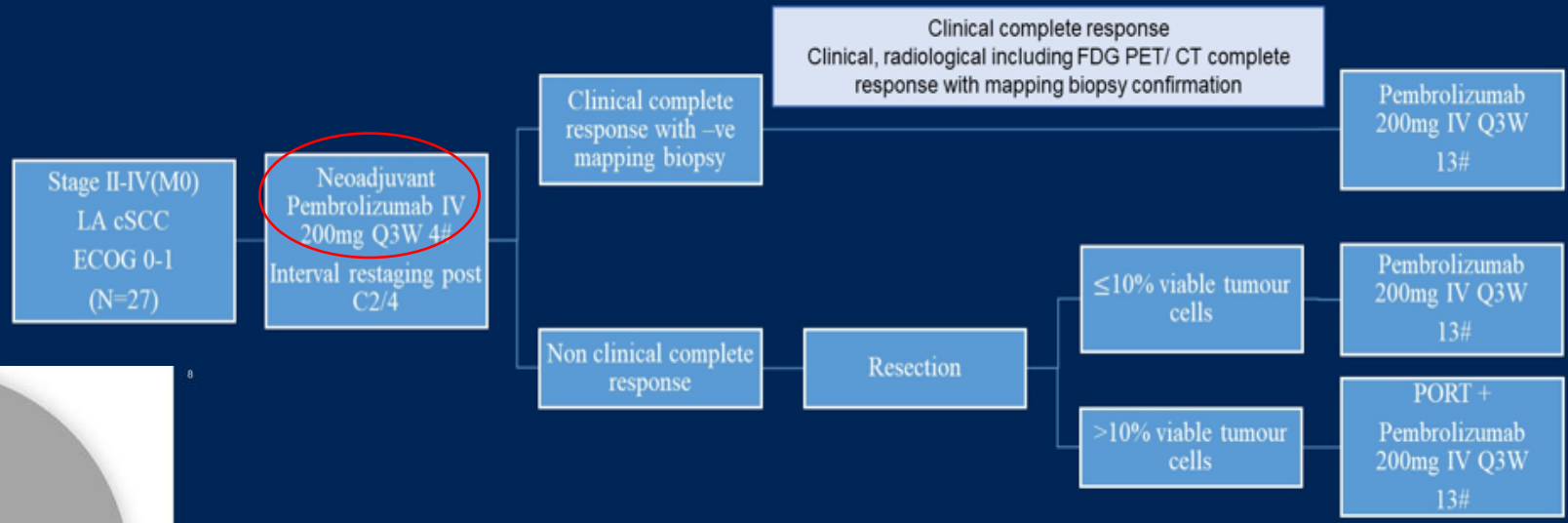
Primary endpoint

- The primary endpoint was observed in 17 patients (63%, 95% CI: 42-80)
  - PCR (15%)
  - MPR (0%)
  - CCR (48%)
- Treatment de-escalation occurred in 63%
  - De-escalation of both surgery and PORT was achieved in 48%
  - De-escalation of PORT alone was achieved in 15%.



Response	Definition
Pathological CR (pCR)	No residual viable tumour cells
Major pathological response (MPR)	≤10% viable tumour cells
Pathological PR (PPR)	11-50% viable tumour cells
Pathological SD/ PD (PPD)	>50% viable tumour cells
Clinical CR (CCR)	Radiological complete response with negative biopsy

De-Squamate Study Design



Primary Endpoint

Histopathological response as determined by a combination of pCR: (no viable tumour cells) + mPR: (≤10% viable tumour cells) + Clinical CR following up to 4 cycles of neoadjuvant therapy

- CONCLUSIONES

- NEOADYUVANCIA

-El ensayo fase III NADINA, muestra beneficio de tratamiento neoadyuvante con inmunoterapia en un subgrupo de pacientes con melanoma estadio III.

- ADYUVANCIA

-A los 8 años de seguimiento, se mantiene beneficio de DABRAFENIB-TRAMETINIB.

-mRNA 4157 + Pembrolizumab adyvante vs Pembrolizumab, sigue manteniendo beneficio clínico en RFS, incluso tendencia a beneficio en SG.Pendiente Fase III.

- MELANOMA METASTASICO

-EBIN: Pacientes con LDH elevada o metástasis hepáticas, se pueden beneficiar de recibir terapia dirigida primero.

-IOV-COM-202: Lifileucel + pembrolizumab eficaz y respuestas duraderas en 1ª Línea. Pendiente Fase III.

-RELATIVITY-047:Nivolumab+Relatlimab vs Nivolumab en 1ª L, mantiene beneficio y con toxicidad aceptable.

- MELANOMA UVEAL

-Darovasertib neoadyuvante→ Favorece preservar globo ocular.

-Nivo + Ipi adyuvante aumenta DMFS comparado con control histórico, pero se necesita estudio aleatorizado.

- TUMOR ESCAMOSO CUTÁNEO

-Keynote 629: Confirma la eficacia de Pembrolizumab.

-De-Squamate: Pembrolizumab neoadyuvante puede desescalar tratamientos en una población vulnerable.

XVII JORNADAS ONCOLÓGICAS

ARAGÓN · NAVARRA · RIOJA

20 JUNIO 2024

Organizador:

Fundación Biomédica Miguel Servet