Update on the treatment of advanced unresectable melanoma - 2021/2022

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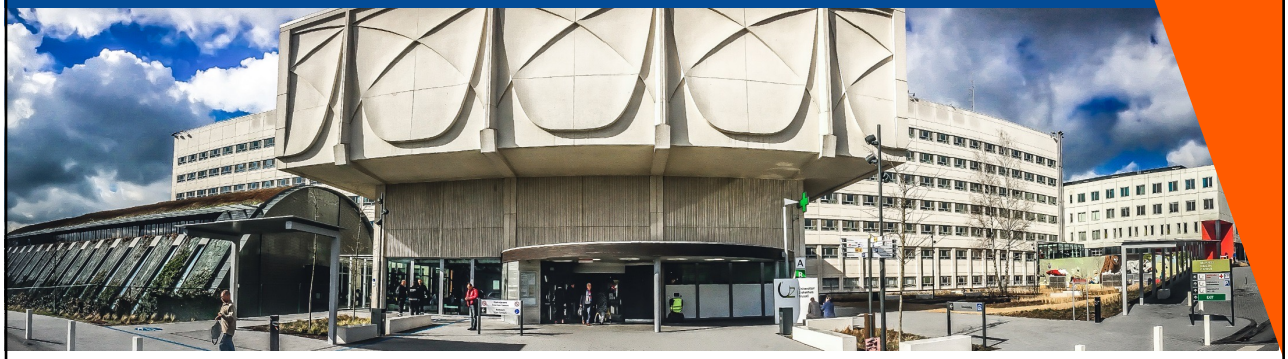
Brussels, Belgium



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DISCLOSURES

- Personal financial compensation from Novartis, Bristol-Myers Squibb, Roche, Merck Sharp & Dohme, AstraZeneca for public speaking, consultancy and participation in advisory board meetings
- My institution (UZ Brussel) received research funding related to projects conducted by my team from Pfizer, Novartis, Roche, Merck-Serono

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Topics

- State of the art
- Results of phase III trials in 2021
- Sequecing of available treatment options
- Emerging new treatment treatment options

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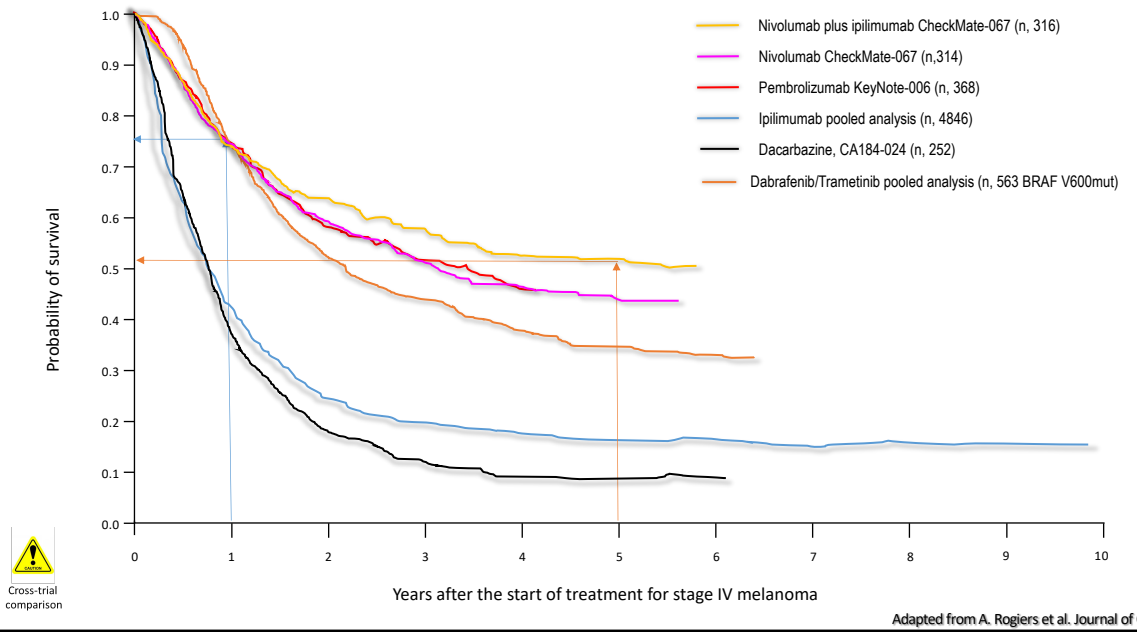
Overall Survival of Advanced Melanoma Patients According to First Line Therapy



Adapted from A. Rogiers et al. Journal of Oncology, 2019

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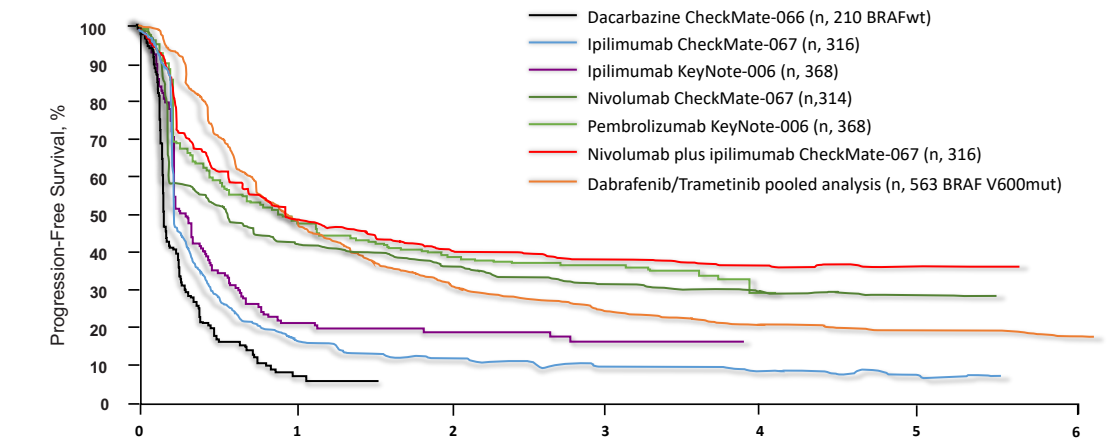
Progression-Free Survival of Advanced Melanoma Patients on First Line Therapy



Cross-trial comparison

Adapted from A. Rogiers et al. Journal of Oncology, 2019

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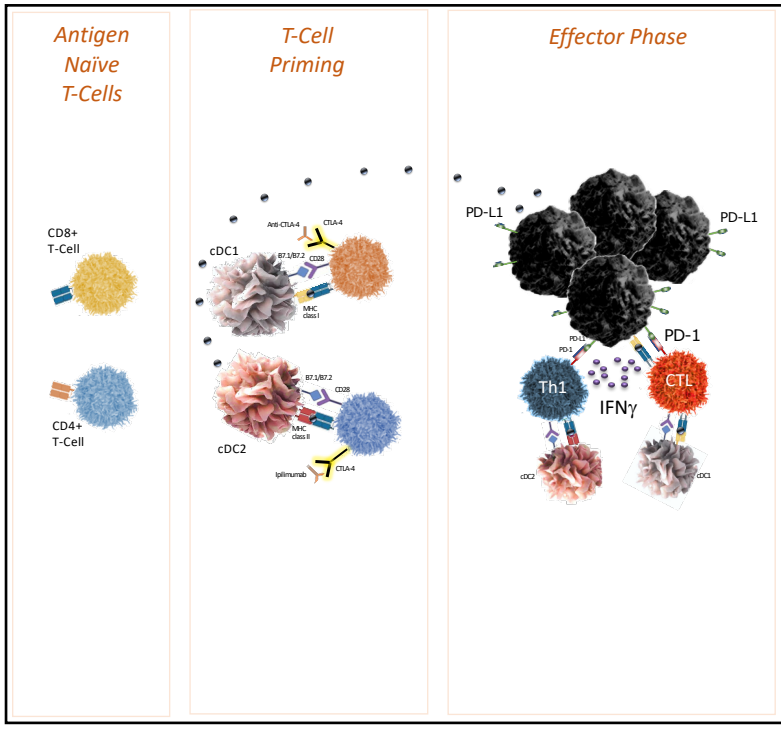

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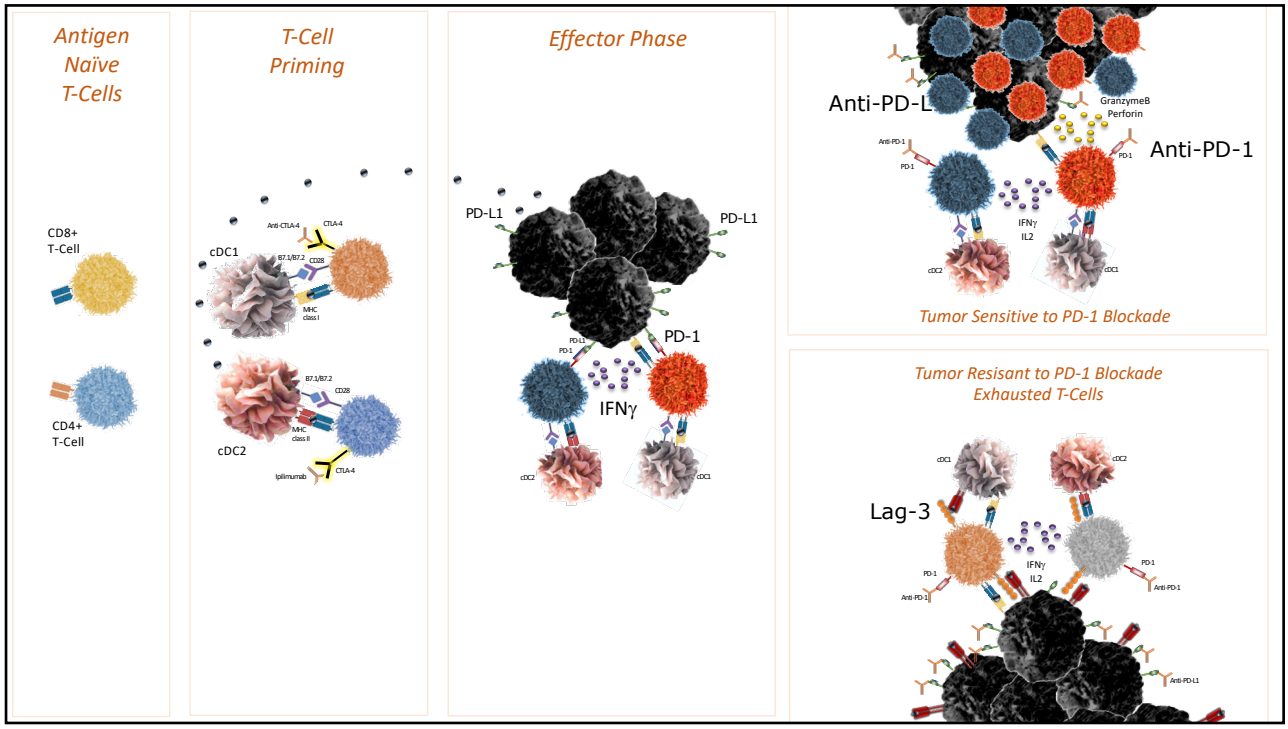
Antigen Naïve T-Cells
CD8+ T-Cell
CD4+ T-Cell
T-Cell Priming
cDC1
cDC2
Effector Phase
PD-L1
PD-L1
PD-1
IFNγ
Anti-PD-L1
Granzyme B
Perforin
Anti-PD-1
IFNγ
IL2
Tumor Sensitive to PD-1 Blockade
Tumor Resisant to PD-1 Blockade
Exhausted T-Cells
Lag-3
Anti-PD-L1

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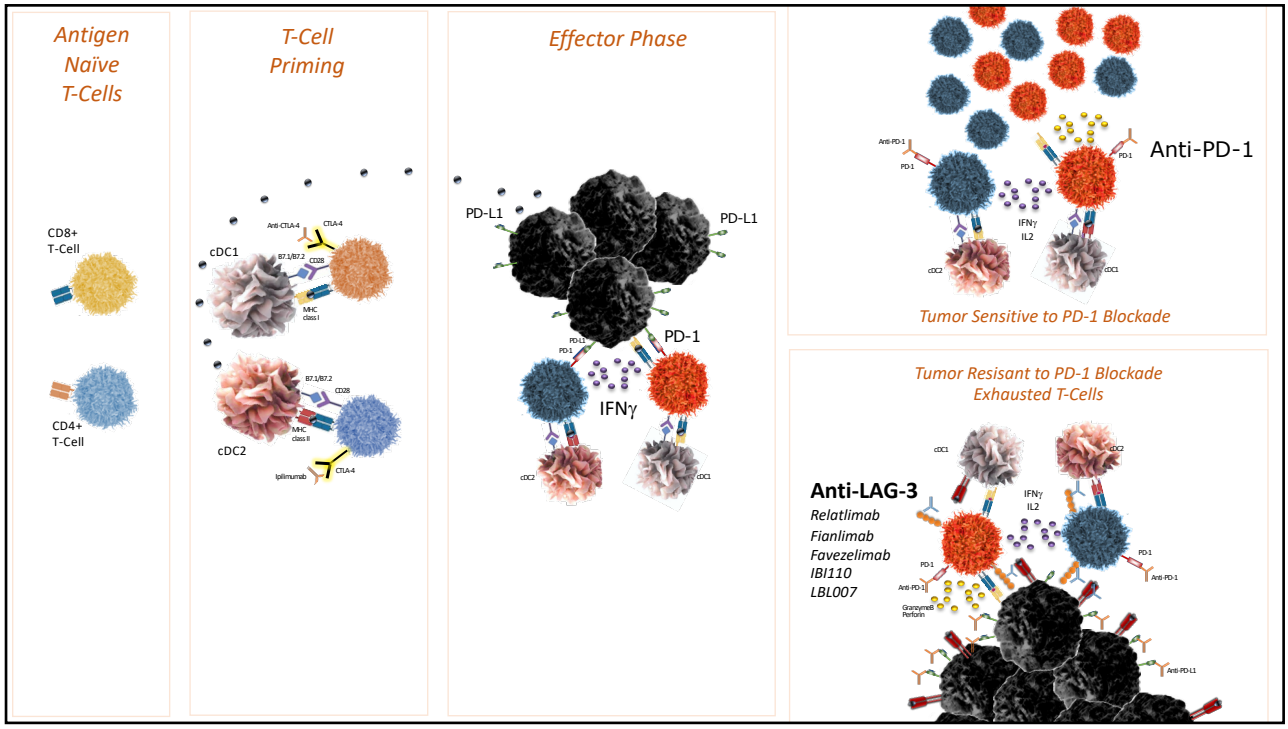
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Tumor Resisant to PD-1 Blockade
Exhausted T-Cells
Anti-LAG-3
Relatlimab
Fianlimab
Favezelimab
IBI110
LBL007

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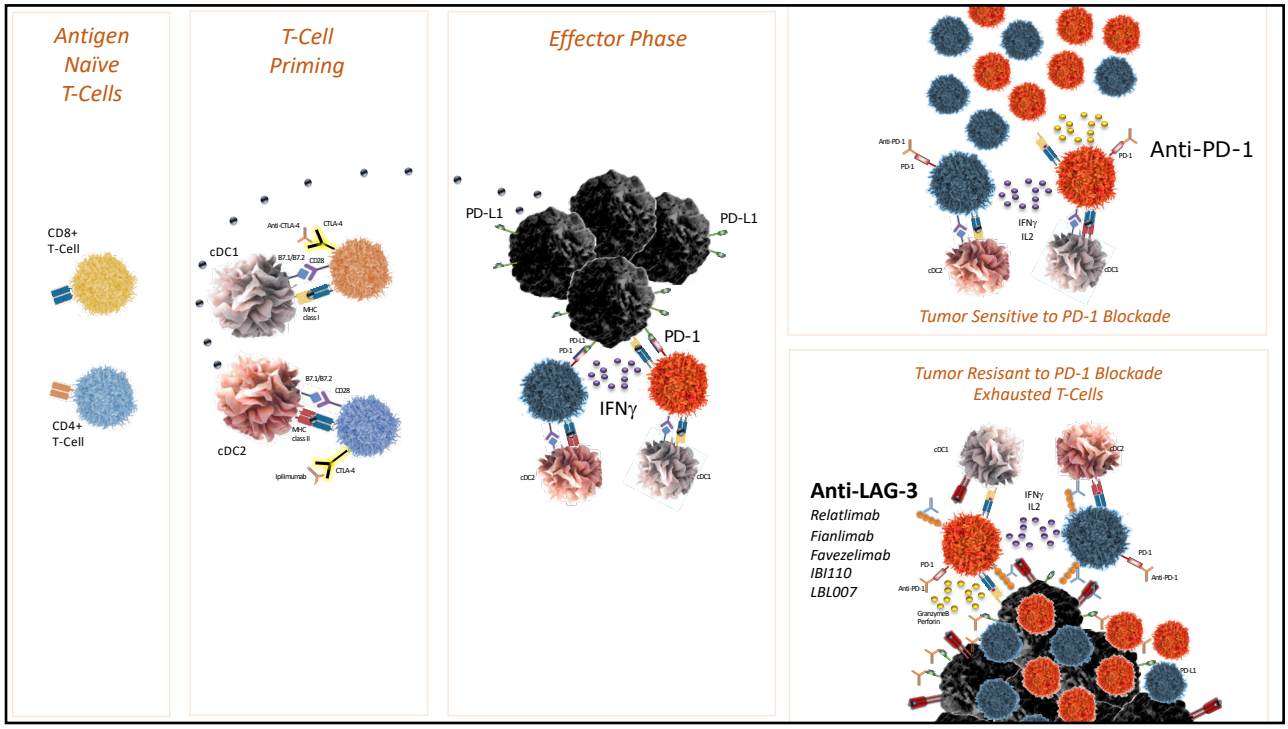
Antigen Naïve T-Cells
CD8+ T-Cell
CD4+ T-Cell
T-Cell Priming
cDC1
cDC2
Anti-CTLA-4
CTLA-4
B7.1/B7.2
CD28
MHC class I
MHC class II
Ipilimumab
Effector Phase
PD-L1
PD-1
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IFNγ
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IBI110
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Granzymes
Perforin

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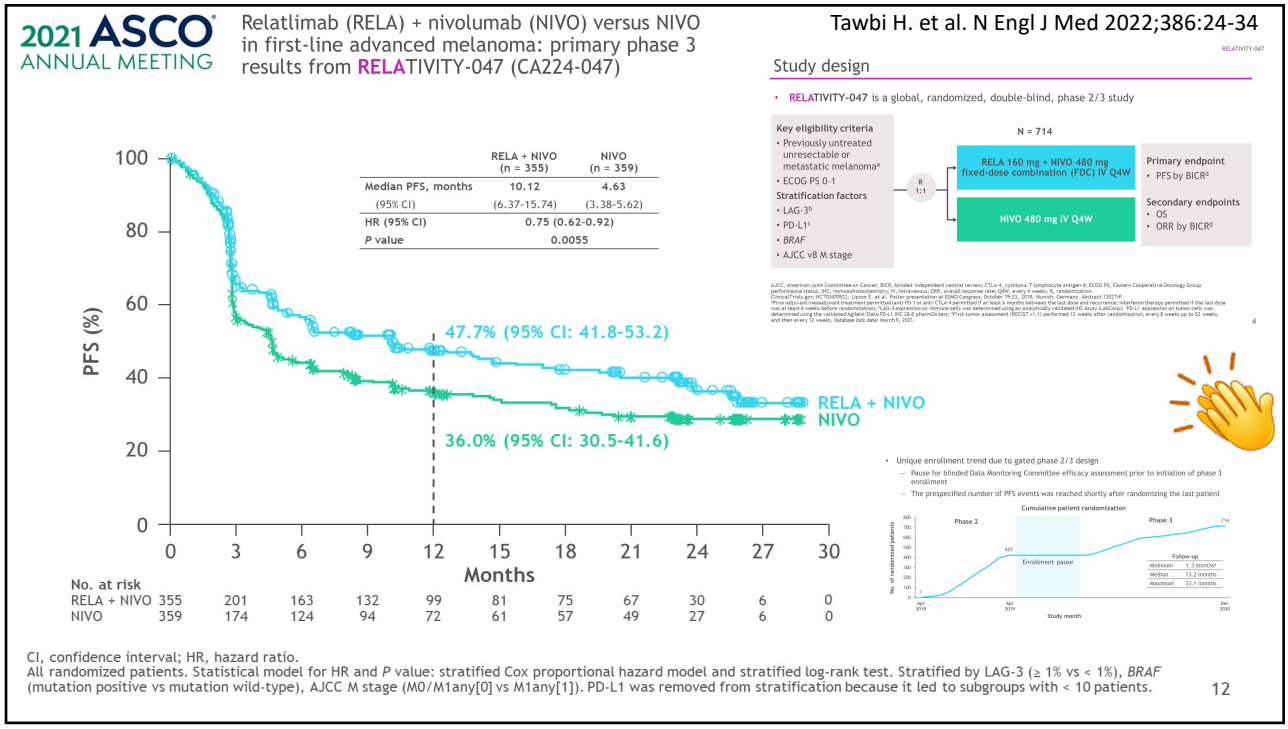
2021 ASCO ANNUAL MEETING
Relatlimab (RELA) + nivolumab (NIVO) versus NIVO in first-line advanced melanoma: primary phase 3 results from RELATIVITY-047 (CA224-047)
Tawbi H. et al. N Engl J Med 2022;386:24-34
Study design
RELATIVITY-047 is a global, randomized, double-blind, phase 2/3 study
Key eligibility criteria
Previously untreated unresectable or metastatic melanoma
ECOG PS 0-1
Stratification factors
LAG-3
PD-L1
BRAF
AJCC v8 M stage
N = 714
RELA 160 mg + NIVO 480 mg fixed-dose combination (FDC) IV Q4W
NIVO 480 mg IV Q4W
Primary endpoint
PFS by BICR
Secondary endpoints
OS
ORR by BICR
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
PFS (%)
47.7% (95% CI: 41.8-53.2)
36.0% (95% CI: 30.5-41.6)
RELA + NIVO
NIVO
Months
No. at risk
RELA + NIVO 355 201 163 132 99 81 75 67 30 6 0
NIVO 359 174 124 94 72 61 57 49 27 6 0
Unique enrollment trend due to gated phase 2/3 design
Pause for blinded Data Monitoring Committee efficacy assessment prior to initiation of phase 3 enrollment
The prespecified number of PFS events was reached shortly after randomizing the last patient
Cumulative patient randomization
Phase 2
Phase 3
Enrollment pause
Study month
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.

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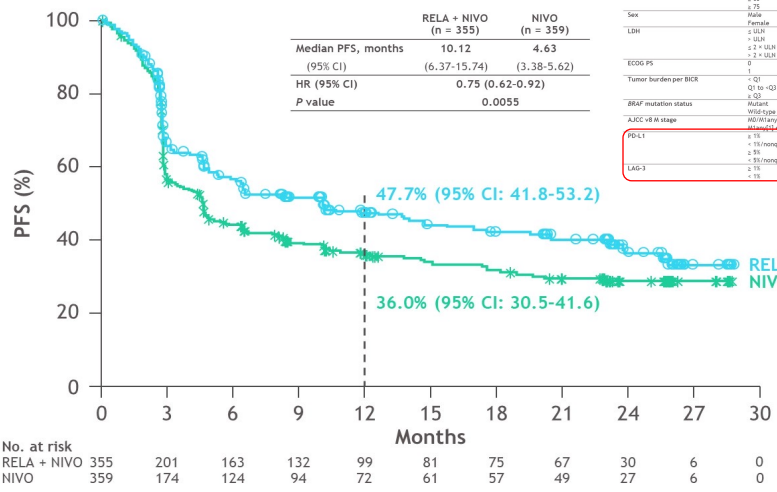
2021 ASCO ANNUAL MEETING

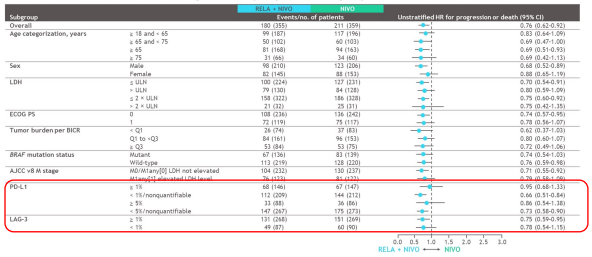
Relatlimab (RELA) + nivolumab (NIVO) versus NIVO in first-line advanced melanoma: primary phase 3 results from RELATIVITY-047 (CA224-047)

Tawbi H. et al. N Engl J Med 2022;386:24-34

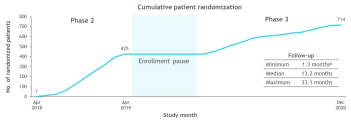


	RELA + NIVO (n = 355)	NIVO (n = 359)
Median PFS, months	10.12	4.63
(95% CI)	(6.37-15.74)	(3.38-5.62)
HR (95% CI)	0.75 (0.62-0.92)	
P value	0.0055	

- RELA + NIVO FDC extended PFS regardless of prespecified subgroups and stratification factors



- Unique enrollment trend due to gated phase 2/3 design
  - Pause for blinded Data Monitoring Committee efficacy assessment prior to initiation of phase 3 enrollment
  - The prespecified number of PFS events was reached shortly after randomizing the last patient



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.

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2021 ASCO ANNUAL MEETING

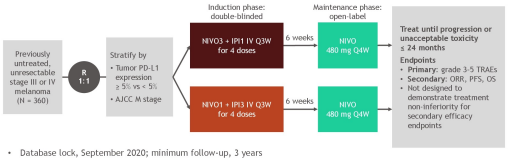
Two dosing regimens of nivolumab plus ipilimumab for advanced melanoma: 3-year results of CheckMate 511

Céleste Lebbé,[1] Nicolas Meyer,[2] Laurent Mortier,[3] Iván Márquez-Rodas,[4] Caroline Robert,[5] Piotr Rutkowski,[6] Marcus O. Butler,[7] Thomas Eigentler,[8] Alexander M. Menzies,[9] Michael Smylie,[10] Ana M. Arance,[11] Paolo A. Ascierto,[12] Inge M. Svane,[13] Mazhar Ajaz,[14] Nikhil I. Khushalani,[15] Maurice Lobo,[16] Jesus Zoco,[17] Jacopo Pigozzo[18]

[1]Université de Paris AP-HP Dermatology CIC Departments, Saint-Louis Hospital, INSERM U976, Paris, France; [2]Institut Universitaire du Cancer, Toulouse, France; [3]Université de Lille, INSERM U1189, Lille, France; [4]Hospital General Universitario Gregorio Marañon, Madrid, Spain; [5]Gustave Roussy and Université Paris-Saclay, Villejuif, France; [6]Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland; [7]Princess Margaret Cancer Centre, Toronto, ON, Canada; [8]University Hospital Tübingen, Tübingen, Germany; [9]Melanoma Institute Australia, The University of Sydney, and Royal North Shore and Mater Hospitals, Sydney, NSW, Australia; [10]Cross Cancer Institute, Edmonton, AB, Canada; [11]Hospital Clinic de Barcelona-IDIBAPS, Barcelona, Spain; [12]Istituto Nazionale Tumori Fondazione G. Pascale, Naples, Italy; [13]Herlev Hospital, University of Copenhagen, Herlev, Denmark; [14]Royal Surrey County Hospital, Guildford, UK; [15]H. Lee Moffitt Cancer Center, Tampa, FL, USA; [16]Bristol Myers Squibb, Princeton, NJ, USA; [17]Syneos Health, Braine l'Alleud, Belgium; [18]Istituto Oncologico Veneto-IRCCS, Padua, Italy

Abstract Number 9516

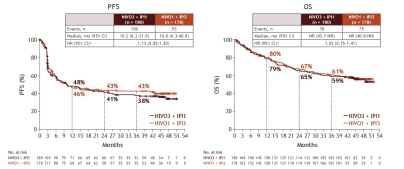
Phase 3b/4 CheckMate 511 study: 3-year analysis



- 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.

Survival outcomes



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

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.

Evaluation of Two Dosing Regimens for Nivolumab in Combination With Ipilimumab in Patients With Advanced Melanoma: Results From the Phase IIIb/IV CheckMate 511 Trial

Response per investigator assessment

	NIVO3 + IPI1 (n = 180)	NIVO1 + IPI3 (n = 178)
Best overall response, n (%)		
Complete response	40 (22)	41 (23)
Partial response	45 (25)	53 (30)
Stable disease	17 (9)	16 (9)
Progressive disease	63 (35)	48 (27)
Unknown	15 (8)	20 (11)
ORR, % (95% CI)	47.2 (39.8-54.8)	52.8 (45.2-60.3)
Difference, % (95% CI)	−5.5 (−15.8 to 4.8)	
Median time to response, months (range)	2.8 (2.0-25.3)	2.8 (2.3-31.4)
Median duration of response, months (range)	NR	NR
Median reduction in tumor volume, %	−42.2	−58.9

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. NR, not reached.

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)*	0
Treatment-related serious AEs, n (%)		
Grade 3-4	35 (19)	60 (34)
Grade 5	1 (1)*	0
TRAEs leading to discontinuation, n (%)	43 (24)	60 (34)
Grade 3-4	30 (17)	50 (28)
Grade 5	1 (1)*	0

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

*Rhabdomyolysis and autoimmune myocarditis.
AE, adverse event; CI, confidence interval.

Concerning ipilimumab-dose in combination with nivolumab: less-seems-more (: safety)
Also in patients with brain metastases?

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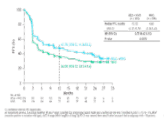
2021 ASCO ANNUAL MEETING

The question may become: aPD-1/aCTLA-4 *or* aPD-1/aLAG-3 ?

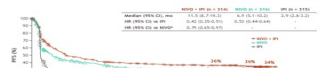
Relatlimab (RELA) + nivolumab (NIVO) versus NIVO in first-line advanced melanoma: primary phase 3 results from RELATIVITY-047 (CA224-047)

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] Stephane Dalle,[11] Ana Arance,[12] Jean-Jacques Grob,[13] Shivani Srivastava,[14] Reza Abdelrahman,[14] Kelly L. Sherman,[14] Bin Li,[14] Georgina V. Long,[15,16] F. Stephen Hodi[17,18]



CheckMate 067: 6.5-year outcomes in patients with advanced melanoma

Jedd D. Wolchok,[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 Francesco Ferrucci,[11] Michael Smylie,[12] Marcus O. Butler,[13] Andrew Hill,[14] Ivan Márquez-Rodas,[15] John B.A.G. Haanen,[16] Tuba Bas,[17] Wen-Van Dijck,[17] James Larkin,[18,19] F. Stephen Hodi[20,21]



Safety summary

- RELA + NIVO FDC was associated with a manageable safety profile and without unexpected safety signals

AE, n (%)	RELA + NIVO (n = 355) Any grade	RELA + NIVO (n = 355) Grade 3-4	NIVO (n = 359) Any grade	NIVO (n = 359) Grade 3-4
Any AE	345 (97.2)	143 (40.3)	339 (94.4)	120 (33.4)
TRAE	288 (81.1)	67 (18.9)	251 (69.9)	35 (9.7)
Leading to discontinuation	52 (14.6)	30 (8.5)	24 (6.7)	11 (3.1)

- Treatment-related deaths: RELA + NIVO (n = 3) - hemophagocytic lymphohistiocytosis, acute edema of the lung, and pneumonitis; NIVO (n = 2) - sepsis and myocarditis, and worsening pneumonia

AE, adverse event. Includes events reported between first dose and 30 days after last dose of study therapy. Other grade 3/4 TRAEs that were associated with any grade TRAEs occurring in <10% of patients not shown.

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	NIVO + IPI (n = 313) Any grade	NIVO + IPI (n = 313) Grade 3-4	NIVO (n = 313) Any grade	NIVO (n = 313) Grade 3-4	IPI (n = 311) Any grade	IPI (n = 311) Grade 3-4
Treatment-related AE, %	96	59	87	24	86	28
Treatment-related AE leading to discontinuation, %	42	31	14	8	15	13
Treatment-related death,[a] n (%)	2 (1)		1 (< 1)		1 (< 1)	

CheckMate 511

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 (%)		
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Grade 5	1 (1)*	0
Treatment-related serious AEs, n (%)		
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- The most common TRAEs in both groups were diarrhea, fatigue, and pruritus

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Outstanding Questions
- *Upfront combination or "add-on" strategy (29% 5y PFS on nivo monotherapy) ?*
- *Optimal sequencing of available ICI? Now also including adjuvant setting.*
- *Better predictive (or surrogate) biomarkers ? aLAG-3 vs aCTLA-4? (HLA class I & II ?)*

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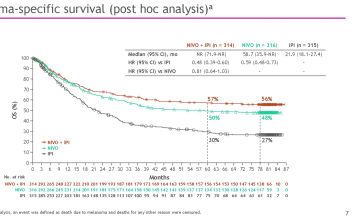
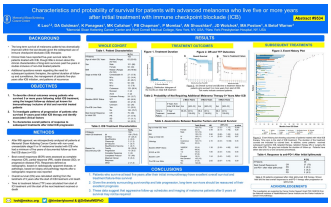
2021 ASCO ANNUAL MEETING

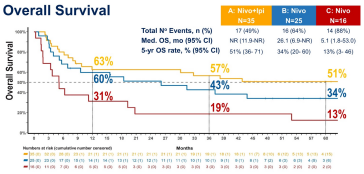
Overall Survival

Melanoma-specific survival (post hoc analysis)[a]





Overall Survival



CONCLUSIONS

1. Patients who survive at least five years after their initial immunotherapy have excellent overall survival and treatment failure-free survival
2. Given the anxiety surrounding survivorship and late progression, long-term survivors should be reassured of their excellent prognosis
3. These data suggest that aggressive follow-up schedules and imaging of melanoma patients after 5 years of survival may not be required

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2021 ESMO congress

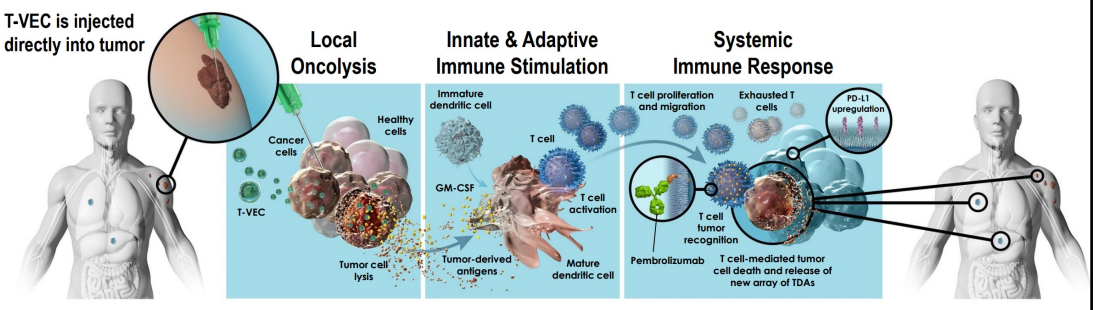
MASTERKEY-265: A phase 3, randomized, placebo-controlled study of talimogene laherparepvec plus pembrolizumab for unresectable stage IIIB–IVM1c melanoma

Antoni Ribas,[1*] Jason Chesney,[2*] Georgina V. Long,[3] John M. Kirkwood,[4] Reinhard Dummer,[5] Igor Puzanov,[6] Christoph Hoeller,[7] Thomas F. Gajewski,[8] Ralf Gutzmer,[9] Piotr Rutkowski,[10] Lev Demidov,[11] Petr Arenberger,[12] Sang Joon Shin,[13] Pier Francesco Ferrucci,[14] Scott J. Diede,[15] James Anderson,[16] Sheryl Treichel,[16] Edward L. Chan,[17] Frank Stephen Hodi,[18] Helen Gogas[19]

NCT02263508 trial is sponsored by Amgen Inc. and Merck & Co., Inc., Kenilworth, NJ, USA

*These authors contributed equally to this work

Talimogene laherparepvec (T-VEC) plus pembrolizumab proposed mechanism of action



- This schematic is based on data from a phase 1b, single-arm trial (MASTERKEY-265) testing the combination of talimogene laherparepvec (T-VEC)-pembrolizumab in 21 patients with advanced melanoma[1]

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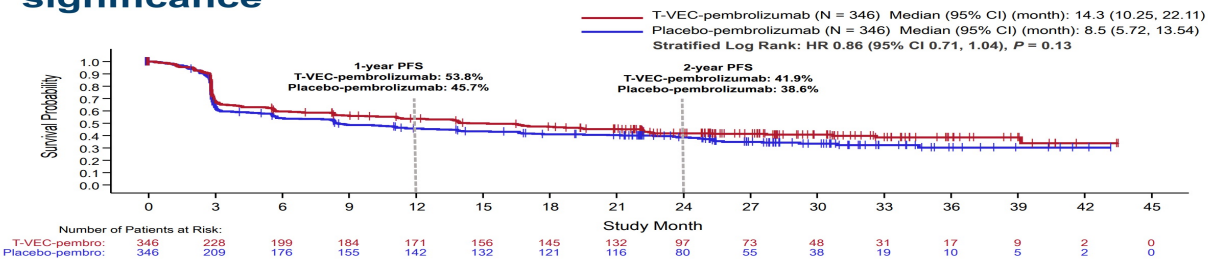
Primary PFS endpoint did not meet statistical significance

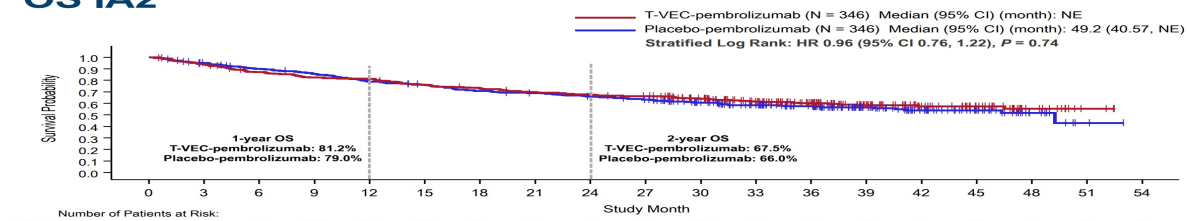


Number of Patients at Risk:

T-VEC-pembro:	346	228	199	184	171	156	145	132	97	73	48	31	17	9	2	0
Placebo-pembro:	346	209	176	155	142	132	121	116	80	55	38	19	10	5	2	0

- PFS triggered at 407 events in March 2020
- A 5.8-month difference was observed in median PFS between T-VEC-pembrolizumab (PFS = 14.3 months) and placebo-pembrolizumab (PFS = 8.5 months)

Futility boundary for overall survival was crossed at OS IA2



Number of Patients at Risk:

T-VEC-pembro:	346	322	295	279	275	256	245	233	225	219	193	158	125	80	51	35	14	3	0
Placebo-pembro:	346	322	302	286	264	252	235	227	216	205	177	150	121	77	49	31	11	2	0

- OS triggered after 282 events in October 2020
- Futility boundaries: HR = 0.89 (constant treatment effect), HR = 0.93 (non-constant treatment effect)
- Chance of achieving OS statistical significance at OS IA3/PA is extremely low

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2021 ESMO congress

962MO - A phase I clinical trial on intratumoral injection of autologous CD1c (BDCA-1)$^+$ / CD141 (BDCA-3)$^+$ myeloid dendritic cells in combination with talimogene laherparepvec (T-VEC) in patients with advanced pretreated melanoma

Schwarze JK, Tijtgat J, Awada G, Cras L, Dufait I, Forsyth R, Van Riet I, Tuyaerts S, Neyns B

Julia Katharina Schwarze, MD MSc
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VUB VRIJE UNIVERSITEIT BRUSSEL
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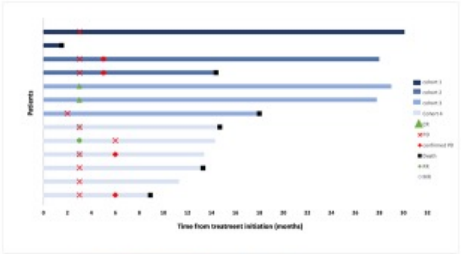
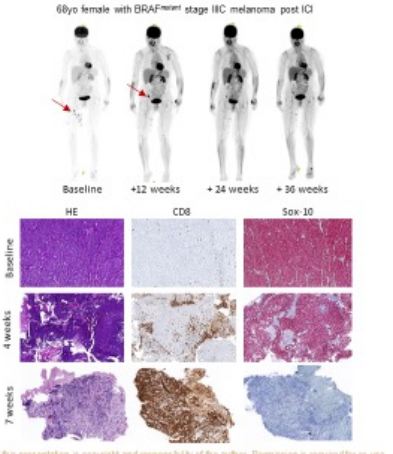
CLINICAL OUTCOME



Responses in injected lesions: CR n=3; PR n=3; SD n=2; PD n=5

BOR (RECIST): CR n=2; PR n=1; PD n=9 (MR n=2)



2021 ESMO congress

Julia Katharina Schwarze, MD MSc

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Sequencing of available treatment options in BRAF V600-mutant melanoma

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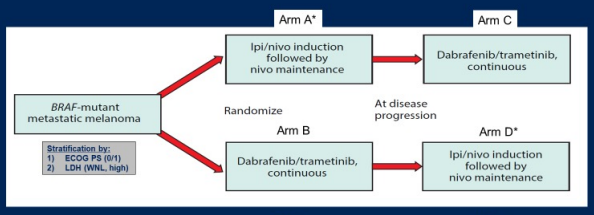
ASCO Plenary Series

DREAMseq (Doublet, Randomized Evaluation in Advanced Melanoma Sequencing) a Phase III Trial: ECOG-ACRIN EA6134

Michael B. Atkins[1], Sandra Lee[2], Bartosz Chmielowski[3], Antoni Ribas[3], Ahmad A. Tarhini[4], Thach-Giao Truong[5], Diwakar Davar[6], Mark O'Rourke[7], Brendan D. Curti[8], Joanna M. Brell[9], Kari L. Kendra[10], Alexandra P. Ikeguchi[11], Jedd D. Wolchok[12], John M. Kirkwood[6]

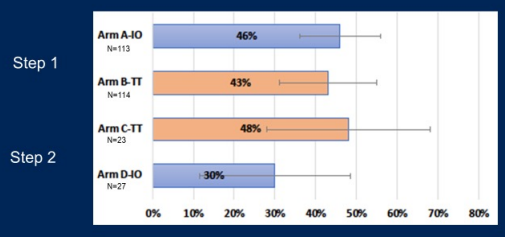
[1]Georgetown Lombardi Comprehensive Cancer Center, Washington DC; [2]Dana-Farber Cancer Institute, Boston MA; [3]Jonsson Comprehensive Cancer Center University of California Los Angeles, Los Angeles CA; [4]H. Lee Moffitt Cancer Center and Research Institute, Tampa FL; [5]Kaiser Permanente Northern California, Vallejo CA; [6]Pittsburgh Cancer Institute, Pittsburgh, PA; [7]Greenville Health System Cancer Institute, Greenville SC; [8]Providence Cancer Institute, Portland OR; [9]Metro-Health Medical Center, Cleveland OH; [10]Ohio State University Comprehensive Cancer Center, Columbus OH; [11]University of Oklahoma Medical Center, Oklahoma City OK; [12]Memorial Sloan Kettering Cancer Center, New York NY

DREAMseq Trial Treatment Schema



*Nivo/Ipi Induction = 12 wks; nivo maintenance = 72 wks

ORR (%) By Treatment Arm*



*Bars represent 95% CI Data missing on ~ 15% of pts

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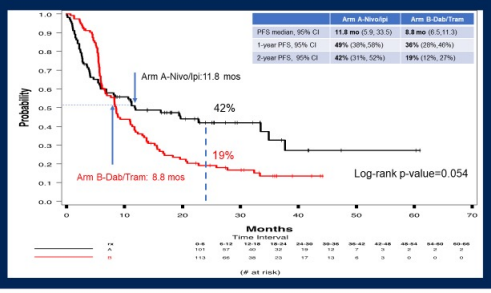
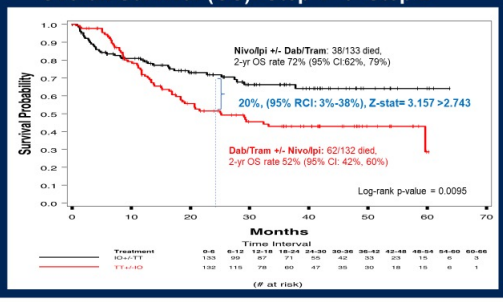
Progression Free Survival (PFS): Step1 (n=214)



	Arm A-Nivo/Ipi	Arm B-Dab/Tram
PFS median, 95% CI	**11.8 mo** (5.9, 33.5)	**8.8 mo** (6.5,11.3)
1-year PFS, 95% CI	**49%** (38%,58%)	**36%** (28%, 46%)
2-year PFS, 95% CI	**42%** (31%, 52%)	**19%** (12%, 27%)

Overall Survival (OS): Step 1 +/- Step 2



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Median Rx Duration < 6 weeks

Off Rx Reason
- PD= 39%
- AE = 30%
- Death= 26%
- Other= 4%

Crossover to Arm C-TT = 0

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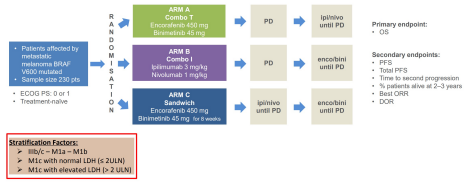
SECOMBIT: the best sequential approach with combo immunotherapy [ipilimumab (I) /nivolumab (N)] and combo target therapy [encorafenib (E)/binimetinib (B)] in patients with BRAF mutated metastatic melanoma. A phase II randomized study

Ascierto PA,[1] Mandalà M,[2] Ferrucci PF,[3] Rutkowski P,[4] Guidoboni M,[5] Arance AM,[6] Ferraresi V,[7] Maiello E,[8] Guida M,[9] Del Vecchio M,[10] Ferro MT,[11] Queirolo P,[12,13] Lebbe C,[14] Helgadottir H,[15] Matteo I,[16] Palmieri G,[16] Giannarelli D,[17] Grimaldi AM,[1] Dummer R,[18] Chiarion Sileni V,[19]

Abstract Number LBA#1997

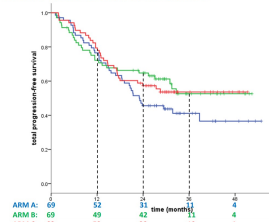
SEQUENTIAL COMBO IMMUNO AND TARGET THERAPY (SECOMBIT): STUDY DESIGN



DOR, duration of response; ECOG-PS, Eastern Cooperative Oncology Group performance status; LGX = encorafenib (BRAFi); MEK162 = binimetinib (MEKi); ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PD, progressive disease.

Clinicaltrials.gov: NCT02631447.

SEQUENTIAL COMBO IMMUNO AND TARGET THERAPY (SECOMBIT) STUDY: TOTAL PROGRESSION FREE SURVIVAL



	Arm A	Arm B	Arm C
1y tot PFS (95% CI)	77% (67-87)	72% (61-83)	78% (68-88)
2y tot PFS (95% CI)	46% (34-58)	65% (54-76)	57% (45-69)
3y tot PFS (95% CI)	41% (29-53)	53% (43-63)	54% (42-66)
HR (95% CI) Arm B vs A Exploratory analysis	0.71 (0.44-1.14)	-	-
HR (95% CI) Arm C vs A Exploratory analysis	0.74 (0.46-1.18)	-	-

tot PFS: time from randomization until the date of the second progression

ARM A: Enco/Bini PD → Ipi/Nivo
ARM B: Ipi/Nivo PD → Enco/Bini
ARM C: Enco/Bini (8 weeks)→ Ipi/Nivo PD → Enco/Bini

Paolo A. Ascierto

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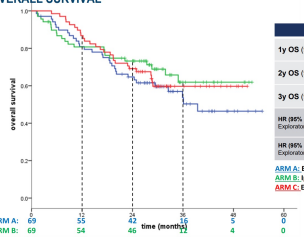
SEQUENTIAL COMBO IMMUNO AND TARGET THERAPY (SECOMBIT) STUDY: OVERALL SURVIVAL



	Arm A	Arm B	Arm C
1y OS (95% CI)	81% (72-90)	81% (72-90)	87% (69-95)
2y OS (95% CI)	65% (54-76)	73% (62-84)	69% (58-80)
3y OS (95% CI)	54% (41-67)	62% (48-76)	60% (58-72)
HR (95% CI) Arm B vs A Exploratory analysis	0.73 (0.42-1.26)	-	-
HR (95% CI) Arm C vs A Exploratory analysis	0.81 (0.48-1.37)	-	-

ARM A: Enco/Bini PD → Ipi/Nivo
ARM B: Ipi/Nivo PD→ Enco/Bini
ARM C: Enco/Bini (8 weeks)→ Ipi/Nivo PD→ Enco/Bini

Paolo A. Ascierto

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cancers

MDPI

Article

A Comprehensive Analysis of Baseline Clinical Characteristics and Biomarkers Associated with Outcome in Advanced Melanoma Patients Treated with Pembrolizumab

Gil Awada [1], Yanina Jansen [2], Julia Katharina Schwarze [1], Jens Tijtgat [1], Lennert Hellinckx [1], Odrade Gondry [3], Sim Vermeulen [3], Sarah Warren [4], Kelly Schats [5], Pieter-Jan van Dam [5], Mark Kockx [5], Marleen Keyaerts [3], Hendrik Everaert [3], Teofila Seremet [1], Anne Rogiers [6] and Bart Neyns [1,*]

2021, 13, 168. https://doi.org/10.3390/cancers13020168

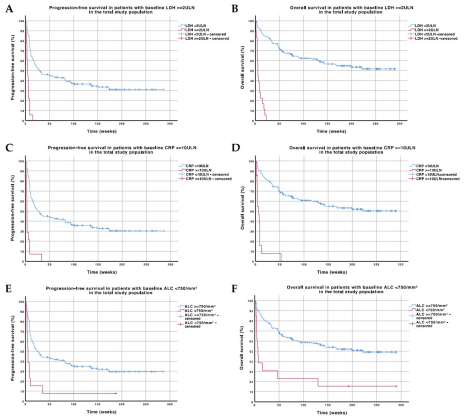
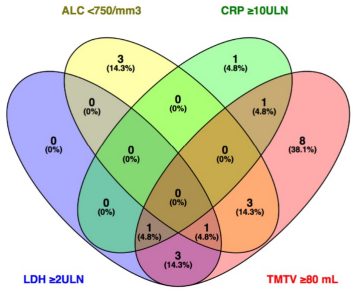


Figure 1. Progression-free and overall survival in subgroups of patients with LDH ≥ 2ULN (panels **A**,**B**), CRP ≥ 10ULN (panels **C**,**D**), and ALC < 750/mm^3 (panels **E**,**F**) in the total study population. Abbreviations: ALC—absolute lymphocyte count; CRP—C-reactive protein; LDH—lactate dehydrogenase; ULN—upper limit of normal.

Table 1. Baseline parameters investigated in this analysis.

Clinical Factors	Blood Values	Plasma ctDNA	Imaging	Tissue
- Age • - Sex • - World Health Organization Performance Status • - Tumor stage • - Presence of inactive/active brain metastases • - Number of affected organs • - Number of prior therapies • - Corticosteroid use •	- Albumin • (35–50 g/L) - Lactate dehydrogenase • (313–618 U/L) - C-reactive protein • (<5 mg/L) - Absolute lymphocyte count • (1200–3500/mm^3) - Absolute neutrophil count • (1200–7500/mm^3) - Neutrophil-to-lymphocyte ratio •	- Detection of $BRAF^{V600}$ or $NRAS^{Q61G/Q13}$ mutant ctDNA •*	- TMTV •*	- $BRAF^{V600}$ mutation status • - NanoString IO360 gene expression profiling scores •

Tumor stage was determined by the American Joint Committee on Cancer TNM 8th edition. Active brain metastases are defined as symptomatic brain metastases or brain metastases requiring corticosteroids for symptom control. Corticosteroid use was defined as the use of ≥8 mg of methylprednisolone (or equivalent). Normal institutional laboratory values are shown in the table. • analyzed as a categorical variable; * analyzed as a continuous variable. Abbreviations: ctDNA—circulating tumor DNA; TMTV—total metabolic tumor volume; U/L—units/liter.



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Emerging new treatment options

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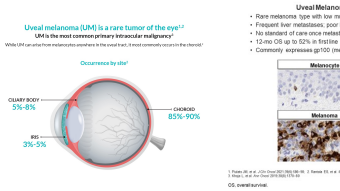
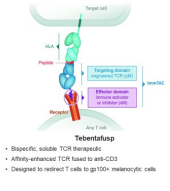
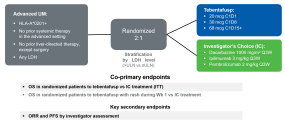
AACR ANNUAL MEETING 2021

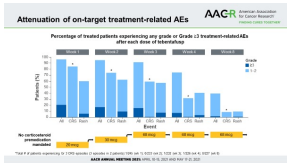
APRIL 10-15, 2021 AND MAY 17-21, 2021 ★ AACR.ORG ★ AACR.ORG/AACR2021

Phase 3 randomized trial comparing tebentafusp with investigator's choice in first-line metastatic uveal melanoma

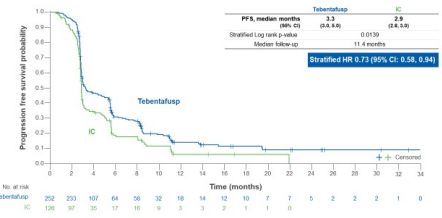








Progression free survival



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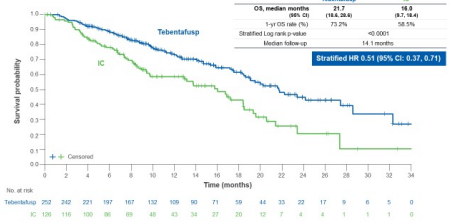
Primary endpoint: Overall survival



AACR ANNUAL MEETING 2021: APRIL 10-15, 2021 AND MAY 17-21, 2021

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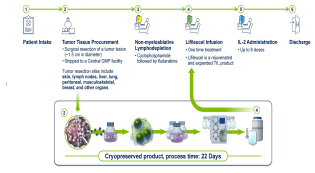
Cellular Immunotherapies in advanced melanoma

Lifileucel (LN-144), a Cryopreserved Autologous Tumor Infiltrating Lymphocyte (TIL) Therapy in Patients with Advanced Melanoma: Evaluation of Impact of Prior Anti–PD-1 Therapy

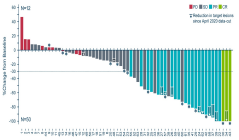
James M. G. Larkin,[1] Arnod Sarnaik,[2] Jason Alan Chesney,[3] Nikhil I Khushalani,[4] John M. Kirkwood,[5] Jeffrey S. Weber,[6] Kurt D. Lewis,[7] Theresa-Michelle Medina,[8] Hamel M. Kluger,[9] Sabina Sanchez Thomas,[10] Evelio Domingo-Musibay,[11] Judit Oláh,[12] Eric D. Whitman,[13] Salvador Martín-Algarra,[14] Philippe Dall Corso,[15] Jose Lutzky,[16] Wen Shi,[16] Renee Xiao Wu,[16] Maria Fardis,[16] Omid Hamid[16]

Patient Journey and TIL Manufacturing



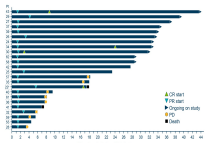
Best Overall Response

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

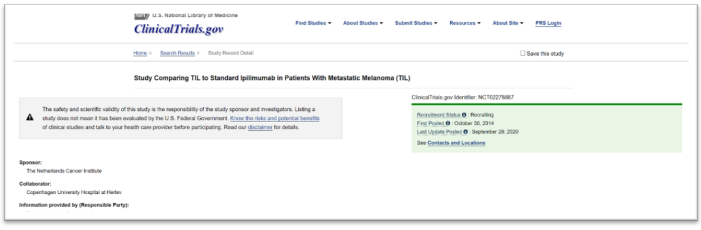


Time to Response for Evaluable Patients (PR or Better)

- 70% of responders received prior ipilimumab
  - 46% of responders received prior anti–PD-1 / anti–CTLA-4 combination
- Responses continued to deepen over time
  - 1 PR converted to CR after 24 months post-lifileucel



Lifileucel plus Pembrolizumab



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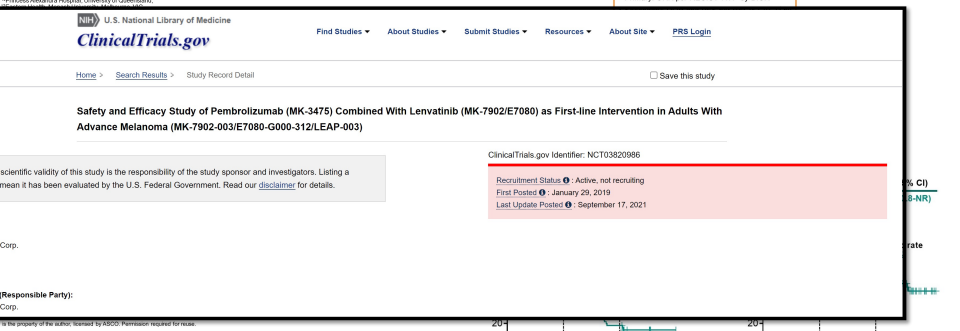
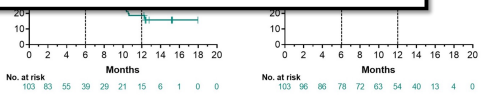
Lenvatinib Plus Pembrolizumab For Patients With Advanced Melanoma and Confirmed Progression on a PD-1 or PD-L1 Inhibitor: Updated Findings of LEAP-004

Ana Arance,[1] Luis de la Cruz Merino,[2] Teresa M. Petrella,[3] Rahima Jamal,[4] Lars Ny,[5] Ana Carneiro,[6] Alfonso Berrocal,[7] Ivan Márquez-Rodas,[8] Anna Spreafico,[9] Victoria Atkinson,[10] Fernanda Costa Svedman,[11] Andrew Mant,[12] Alan D. Smith,[13] Ke Chen,[14] Scott J. Diede,[14] Clemens Krepler,[14] Georgina V. Long[15]

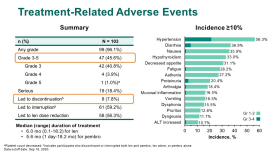
[1]Hospital Clinic Barcelona, Barcelona, Spain; [2]Hospital Universitario Virgen Macarena, Seville, Spain; [3]Sunnybrook Health Sciences Centre, Toronto, ON, Canada; [4]Centre hospitalier de l'Université de Montréal, Montréal, QC, Canada; [5]University of Gothenburg and Sahlgrenska University Hospital, Gothenburg, Sweden; [6]Skåne University Hospital and Lund University, Lund, Sweden; [7]Hospital General Universitario de Ciudad Real, Ciudad Real, Spain; [8]Hospital General Universitario Gregorio Marañón and CIBERONC, Madrid, Spain; [9]Princess Margaret Cancer Centre, University Health Network, University of Toronto, Toronto, ON, Canada; [10]Princess Alexandra Hospital, University of Queensland, Brisbane, QLD, Australia; [11]Karolinska Institutet, Stockholm, Sweden; [12]Royal Melbourne Hospital, Melbourne, VIC, Australia; [13]Eisai Ltd., Hatfield, United Kingdom; [14]Eisai Inc., Woodcliff Lake, NJ, USA; [15]Melanoma Institute Australia and The University of Sydney, and Royal North Shore and Mater Hospitals, Sydney, NSW, Australia

LEAP-004 Study Design (NCT03776136)





Treatment-Related Adverse Events



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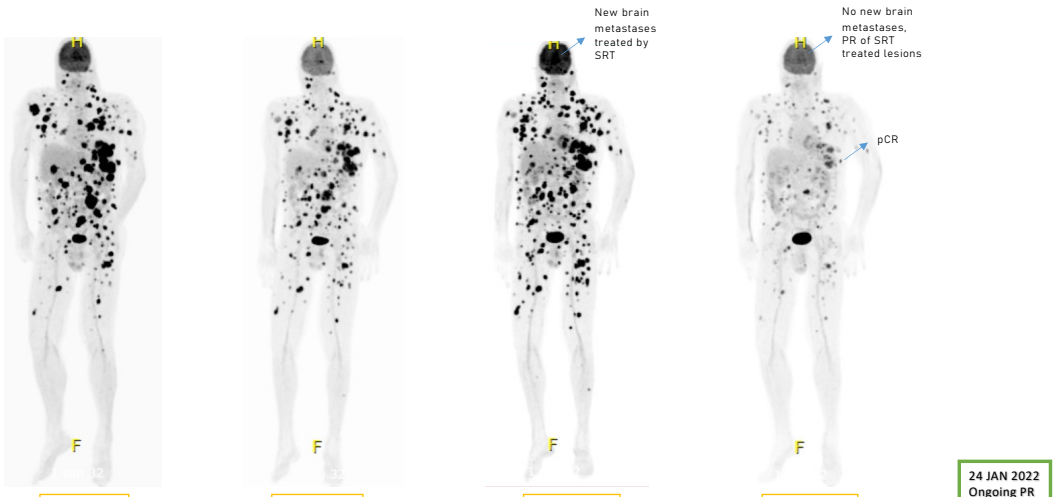
62y M, stage IV-M1d NRAS Q61R, progressive following: nivolumab, ipilimumab, temozolomide, trametinib/low-dose dabrafenib (TRAMEL-WT study)



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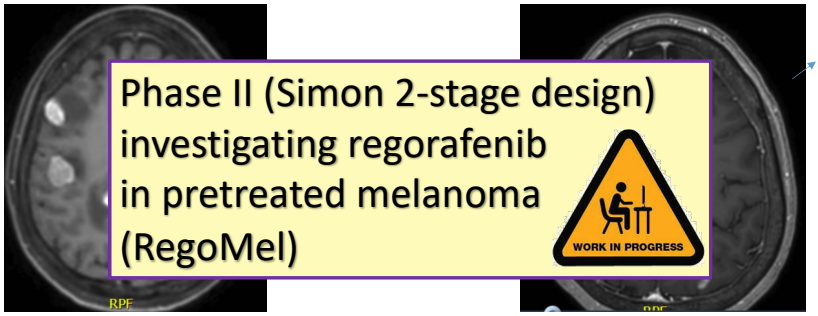
52y F, stage IV-M1d BRAF V600E, progressive brain and leptomeningeal metastases following: nivolumab+ipilimumab, trametinib/dabrafenib and binimetinib/encorafenib



Regorafenib 80 mg QD
Binimetinib 15 mg BID
Encorafenib 300 mg QD

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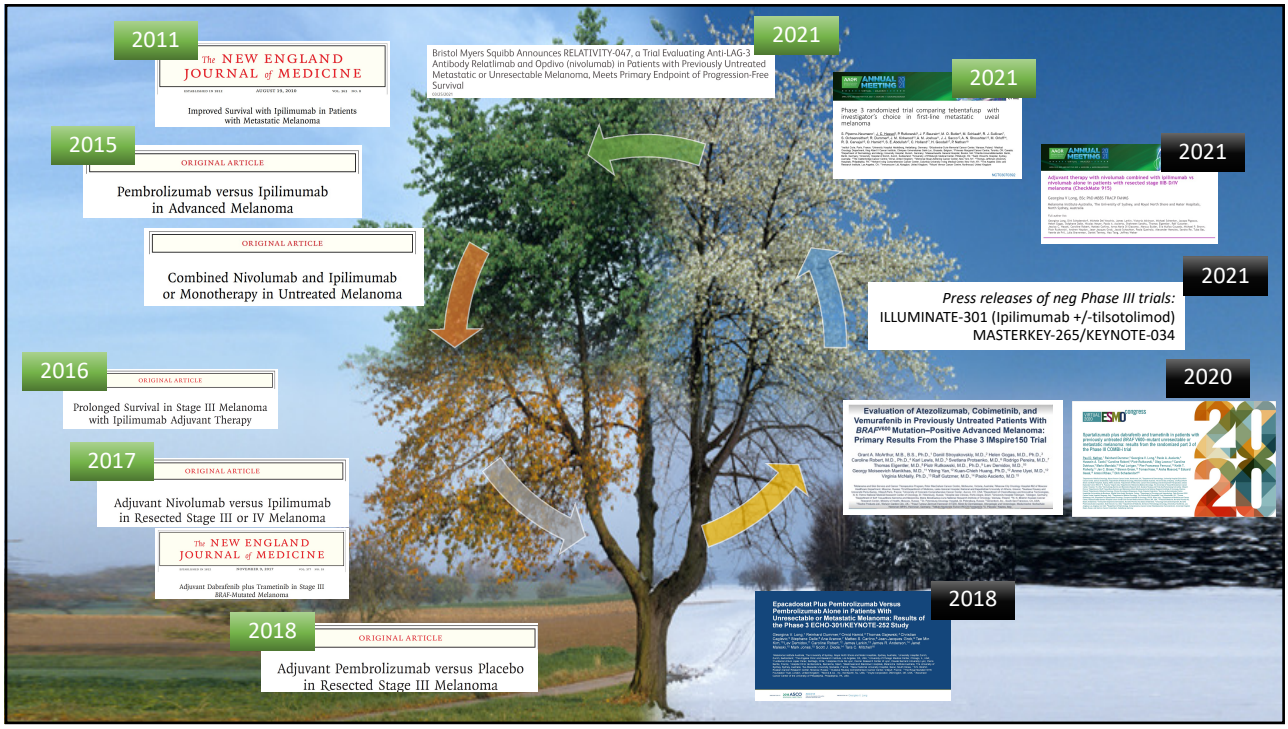

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