

XXIII JORNADA DE REVISIÓN DEL

**CONGRESO
americano
DE
ONCOLOGÍA**

Miscelania II:
MELANOMA y SARCOMA

Dra. Eva Muñoz Couselo, MD, PhD
Oncología médica
Hospital Vall d'Hebrón, Barcelona



Conflictos de interés

Advisory board:

Amgen, Bristol-Myers Squibb, Merck Sharp & Dohme, Novartis, Pierre Fabre, Roche, Sanofi

Honoraria:

Amgen, Bristol-Myers Squibb, Merck Sharp & Dohme, Novartis, Pierre Fabre, Roche

Clinical trial participation (principal investigator):

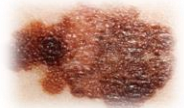
Amgen, Bristol-Myers Squibb, GlaxoSmithKline, Merck Sharp & Dohme, Novartis, Pierre Fabre, Roche, Sanofi



Algoritmo tratamiento del MELANOMA 2023



MELANOMA



Estadio III irresecable/IV

TRATAMIENTO SISTÉMICO

Estatus mutacional BRAF

iBRAF + iMEK

Anti-PD1 + Anti-CTLA4

FDA PFS +: TRIPLETE, Anti-PD1 + Anti-LAG3

(US only)
(US & EMA)
first-line treatment of advanced melanoma patients with tumor cell PD-L1 expression < 1%

1. Robert C et al. *N Engl J Med.* 2011;364:2517-2526. 2. Wolchok J et al. Presented at ASCO 2011; abstract LBA5. 3. Maio M et al. *J Clin Oncol.* 2015;33:1191-1196. 4. Robert C et al. *N Engl J Med.* 2015;372:320-323. 5. Atkinson V et al. Presented at SMR 2015. 6. Larkin J et al. *N Engl J Med.* 2015;373:23-34. 7. Larkin J et al. Presented at AACR 2017; abstract CT075. 8. Wolchok et al. *N Engl J Med.* 2017;377:1345-1356. 9. Hodi FS et al. Presented at ESMO 2018; abstract LBA44. 10. Robert C et al. *N Engl J Med.* 2015;372:2521-2532. 11. Schachter J et al. *Lancet.* 2017;390:1853-1862. 12. Robert C et al. ASCO 2017; abstract 9504. 13. Long GV et al. Presented at ASCO 2018; abstract 9503. 14. Hodi FS et al. Presented at AACR 2016; abstract CT00. 15. Hamid O et al. Presented at ASCO 2018; abstract 9516. 16. Dummer R et al SMR 2016. 17. Dummer R. et al Lancet Oncol 2018. 18. Dummer R. et al ASCO 2018. 19. Long G.V. et al. NEJM 2014. 20. Long G.V. et al Lancet 2015. 21. Long G.V. Ann Oncol 2017. 22.. Robert C. et al NEJM 2014,. 23. Robert C. et al ESMO 2016. 24.Larkin J. et al NEJM 2014. 25. Ascierto P.A. et al Lancet Oncol 2016; 26. Tawbi et al. NEJM 2022. 27. Mc Arthur AACR 2020;

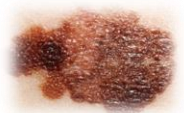
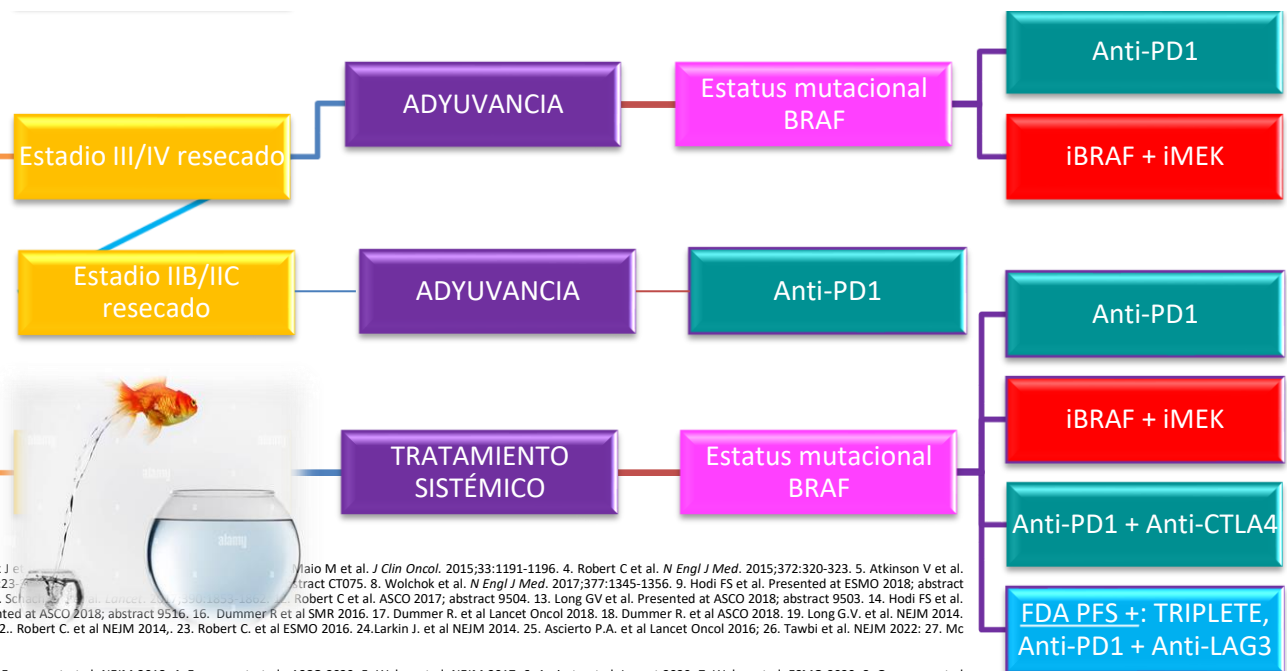
1. Zimmer et al. lancet 2020; 2. Dummer et al. NEJMM 2020; 3. Eggermont et al. NEJM 2018; 4. Eggermont et al. ASCO 2020; 5. Weber et al. NEJM 2017; 6. Ascierto et al. Lancet 2020; 7. Weber et al. ESMO 2020; 8. Grossman et al. Cancer discovery 2021; 9. Menzies et al. Nature medicina 2021, 8. Rutkowski wt al. Lancet 2022



Algoritmo tratamiento del MELANOMA 2023



MELANOMA



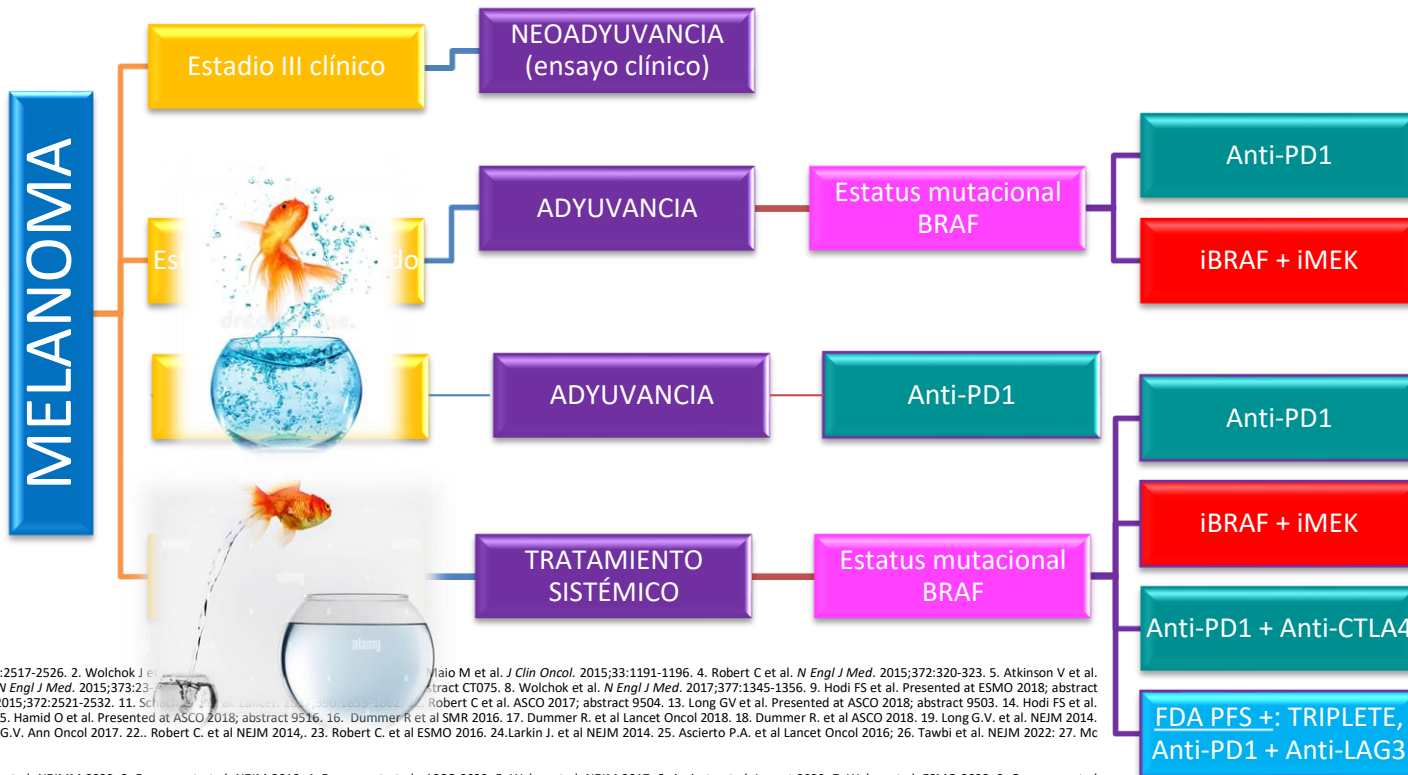
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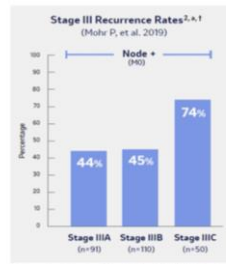
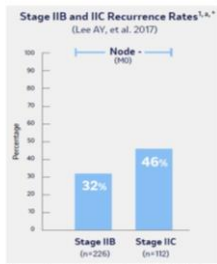
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MELANOMA DE ALTO RIESGO:

¿Qué objetivos busco con la elección del tratamiento?



Recurrence Rates for High-Risk Resected Melanoma^{1,2}



Objetivo 1º: RFS

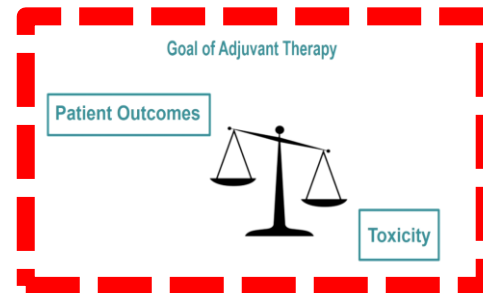


Objetivo 2º: DMFS

Objetivo 2º: OS, PFS



Toxicidades
Calidad de vida

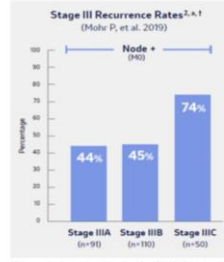
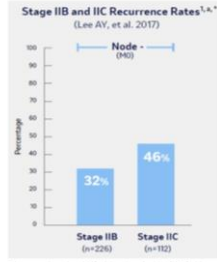




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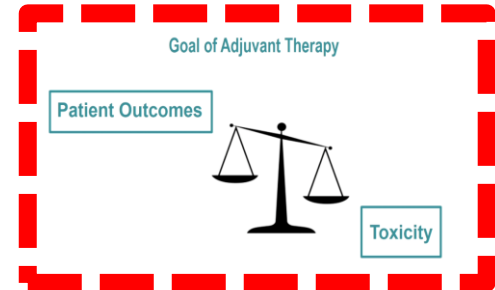
Objetivo 2º: DMFS
Objetivo 2º: OS, PFS



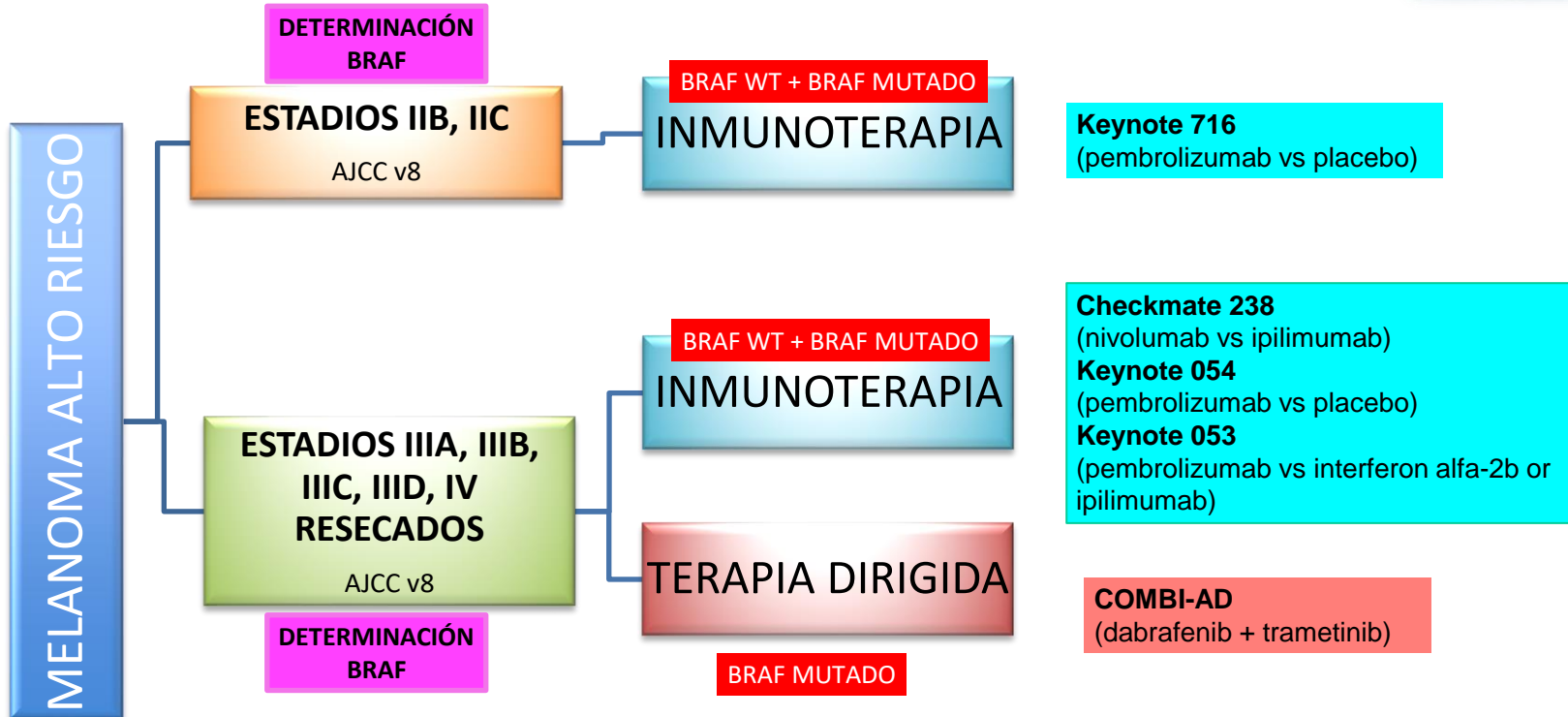
Toxicidades
Calidad de vida



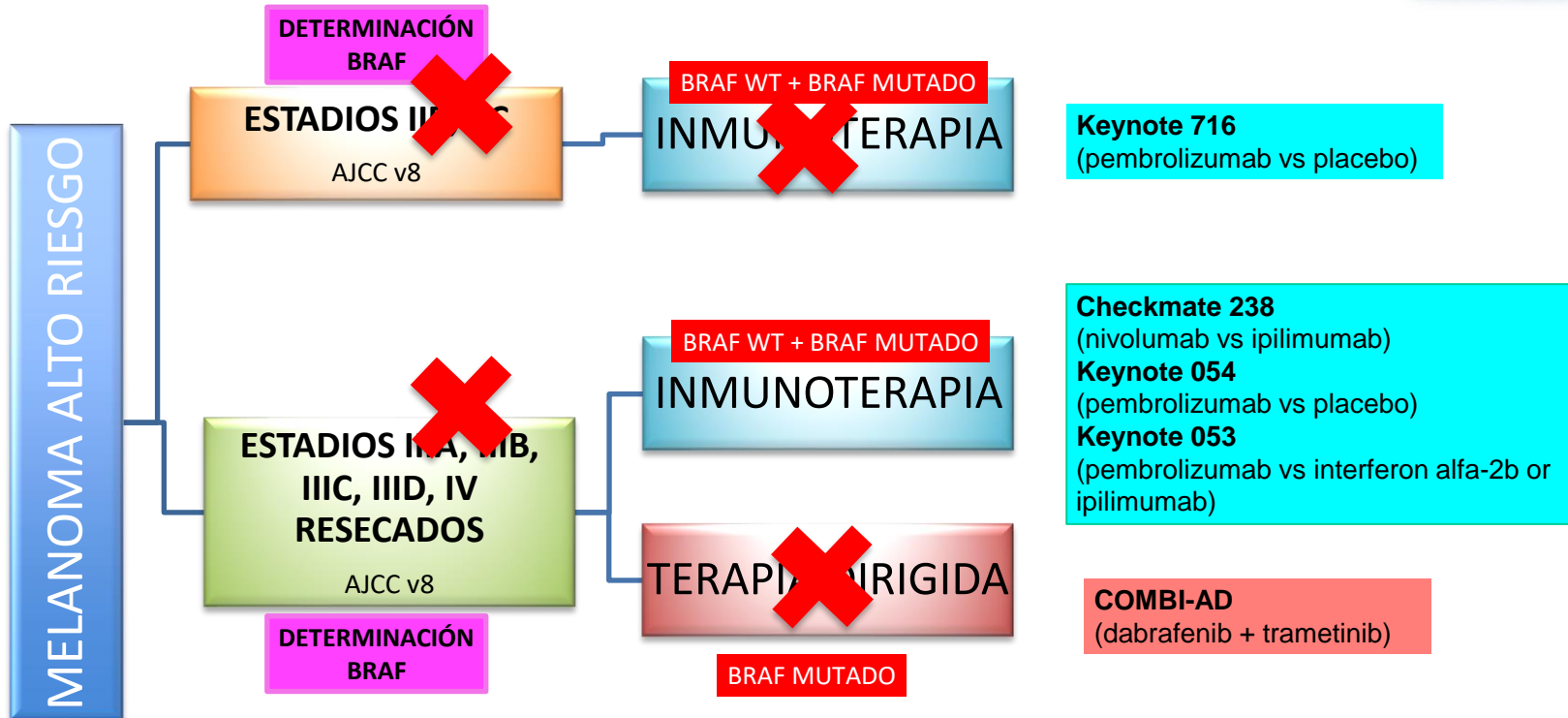
CURACIÓN



Tratamiento del MELANOMA ADYUVANTE 2023



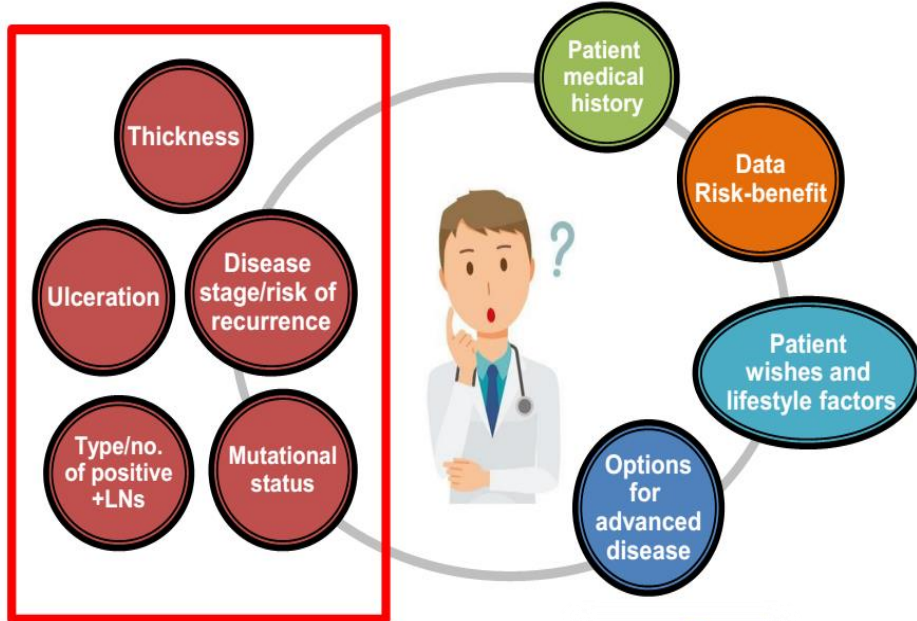
Tratamiento del MELANOMA ADYUVANTE 2023



Tratamiento del MELANOMA ADYUVANTE 2023



MELANOMA ALTO RIESGO



eficacia vs toxicidad



Keynote 716
(pembrolizumab vs placebo)

Checkmate 238
(nivolumab vs ipilimumab)
Keynote 054
(pembrolizumab vs placebo)
Keynote 053
(pembrolizumab vs interferon alfa-2b or ipilimumab)

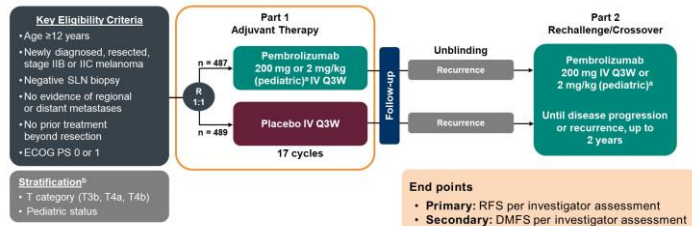
COMBI-AD
(dabrafenib + trametinib)

Pembrolizumab Versus Placebo as Adjuvant Therapy in Stage IIB or IIC Melanoma: Final Distant Metastasis-Free Survival Analysis in the Phase 3 KEYNOTE-716 Study

Jason J. Luke¹; Paolo A. Ascierto²; Muhammad A. Khattak³; Luis de la Cruz Merino⁴; Michele Del Vecchio⁵; Piotr Rutkowski⁶; Francesco Spagnolo⁷; Jacek Mackiewicz⁸; Vanna Chiarion-Sileni⁹; John M. Kirkwood¹; Caroline Robert¹⁰; Jean-Jacques Grob¹¹; Federica de Gallitiis¹²; Dirk Schadendorf¹³; Matteo S. Carlino¹⁴; Xi Lawrence Wu¹⁵; Mizuho Fukunaga-Kalabis¹⁵; Clemens Krepler¹⁵; Alexander M. M. Eggermont¹⁶; Georgina V. Long¹⁷

¹UPMC Hillman Cancer Center and University of Pittsburgh, Pittsburgh, PA, USA. ²Istituto Nazionale Tumori IRCCS Fondazione Pascale, Naples, Italy. ³Fiona Stanley Hospital and Edith Cowan University, Perth, WA, Australia. ⁴Hospital Universitario Virgen Macarena, Seville, Spain. ⁵Fondazione IRCCS Istituto Nazionale dei Tumori, Milano, Italy. ⁶Maria Skłodowska-Curie National Research Institute of Oncology, Warsaw, Poland. ⁷IRCCS San Martino Polyclinic Hospital, Genoa, Italy. ⁸Poznan University of Medical Sciences and Greater Poland Cancer Center, Poznan, Poland. ⁹Istituto Oncologico Veneto, IOV-IRCCS, Padova, Italy. ¹⁰Gustave Roussy, Villejuif, and Paris-Saclay University, Paris, France. ¹¹AP-HP Hospital, Aix-Marseille University, Marseille, France. ¹²Dermatologic Institute of the Immaculate (DI-IRCCS), Rome, Italy. ¹³University Hospital Essen and German Cancer Consortium Partner Site, Essen, Germany. ¹⁴Melanoma Institute Australia, The University of Sydney, Sydney, NSW, Australia, and Westmead and Blacktown Hospitals, Sydney, NSW, Australia. ¹⁵Merck & Co., Inc., Rahway, NJ, USA. ¹⁶University Medical Center Utrecht and Princess Maxima Center, Utrecht, Netherlands, and Comprehensive Cancer Center Maastricht, Maastricht, Germany. ¹⁷Melanoma Institute Australia, The University of Sydney, Sydney, NSW, Australia, and Royal

KEYNOTE-716 Study Design (NCT03553836)



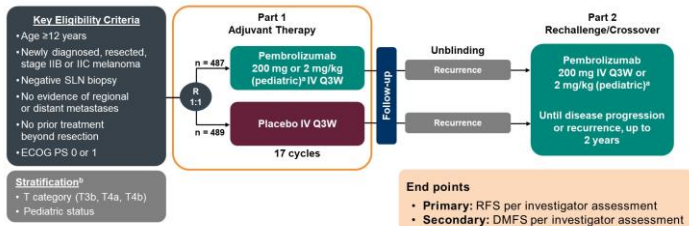
^aUp to a maximum of 200 mg for pediatric (aged 12 to 17 years) patients.
^bRFS: mutation and PD-L1 expression status were not pre-specified stratification factors because of tissue availability.

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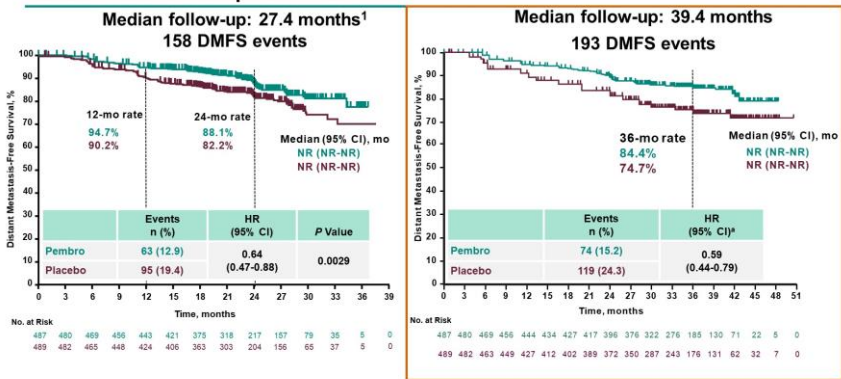
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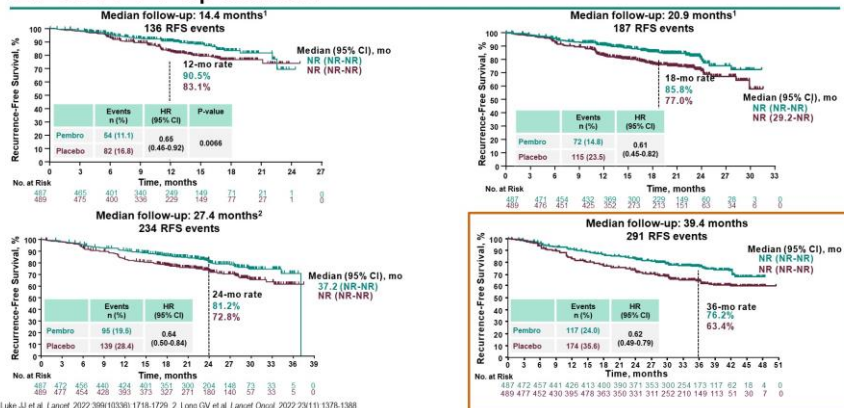
*Up to a maximum of 200 mg for pediatric (aged 12 to 17 years) patients.
*RFS, median and PD-L1 expression status were not pre-specified stratification factors because of issues availability.

DMFS: ITT Population



Long GV et al. *Lancet Oncol*. 2022;23(11):1378-1386.

RFS: ITT Population



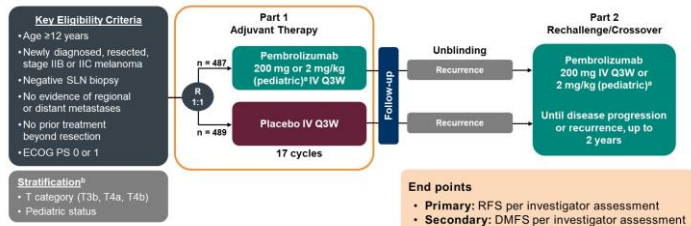
1. Luke JJ et al. *Lancet*. 2022;399(10330):1718-1729. 2. Long GV et al. *Lancet Oncol*. 2022;23(11):1378-1386.

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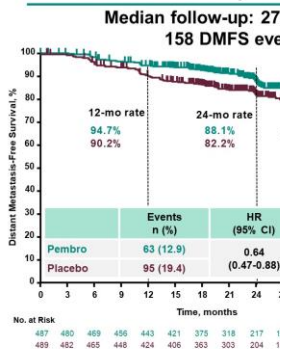
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KEYNOTE-716 Study Design (NCT03553836)



Summary and Conclusion

DMFS: ITT Popul

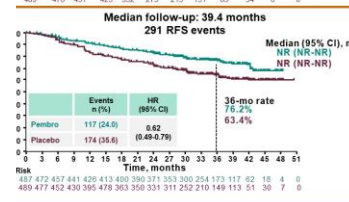
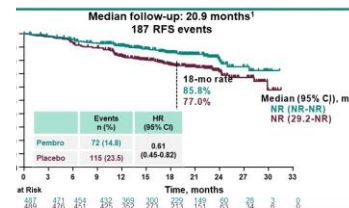


Long GV et al. *Lancet Oncol.* 2022;23(11):1378-1388.

- With a median follow-up of 39.4 months, adjuvant pembrolizumab continued to demonstrate a DMFS and RFS benefit compared with placebo in patients with resected stage IIB or IIC melanoma

- DMFS: HR, 0.59 (95% CI, 0.44-0.79)
- RFS: HR, 0.62 (95% CI, 0.49-0.79)

- Safety was similar to that reported at previous analyses^{1,2}
- Data from Part 2 and overall survival analysis remain immature and planned biomarker analyses are pending
- The results of the protocol-specified final DMFS analysis of KEYNOTE-716 support the use of pembrolizumab as adjuvant therapy in patients with resected stage IIB or IIC melanoma



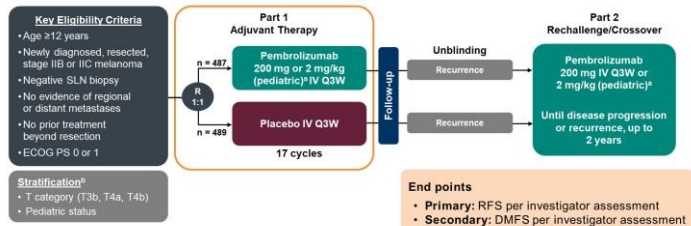
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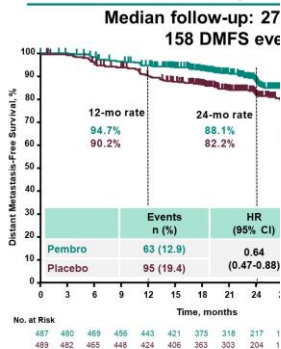


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Summary and Conclusion

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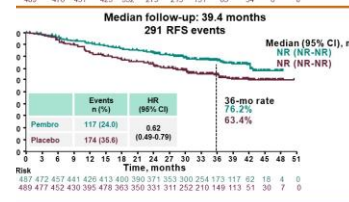
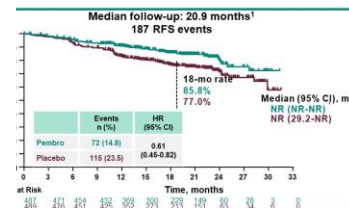


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CheckMate 76K study design^{1,2}

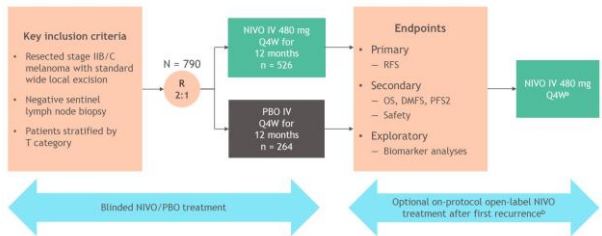


Association of biomarkers with efficacy of adjuvant nivolumab vs placebo in patients with resected stage IIB/C melanoma (CA209-76K)

Georgina V. Long,¹ John M. Kirkwood,² Christoph Hoeller,³ Jean-Jacques Grob,⁴ Jeffrey Weber,⁵ Janis Taube,⁶ Peter Mohr,⁷ Alexander van Akkooi,^{8,9,10} Carmen Loquai,¹¹ Caroline Dutriaux,¹² Vanna Chiarion-Sileni,¹³ Daniel J. Tenney,¹⁴ Sonia Dolfi,¹⁴ Hao Tang,¹⁴ Corey Ritchings,¹⁴ Maurice Lobo,¹⁴ Federico Campigotto,¹⁴ Wenjia Wang,¹⁴ Brian R. Gastman,^{15*} Michele Del Vecchio^{16*}

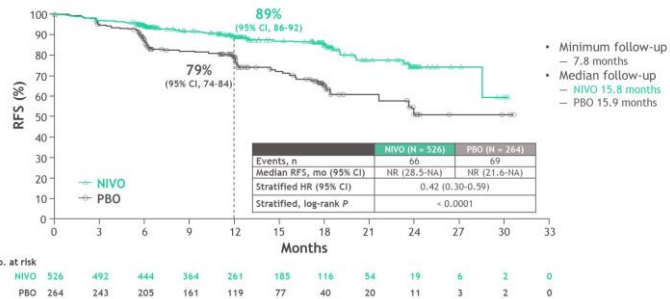
¹Melanoma Institute Australia, The University of Sydney, and Royal North Shore Mater Hospitals, Sydney, NSW, Australia; ²University of Pittsburgh Medical Center, Hillman Cancer Center, Pittsburgh, PA, USA; ³Medical University of Vienna, Vienna, Austria; ⁴Hôpital de la Timone, Marseille, France; ⁵Windermere Cancer Center at WVI Langone Health Medical Center, New York, NY, USA; ⁶Johns Hopkins University School of Medicine, Baltimore, MD, USA; ⁷EBC Klinikum Buxtehude, Buxtehude, Germany; ⁸Melanoma Institute Australia, Sydney, NSW, Australia; ⁹The University of Sydney, Sydney, NSW, Australia; ¹⁰Royal Prince Alfred Hospital, Sydney, NSW, Australia; ¹¹Department of Dermatology, Bremen-Ost Clinic, Gesundheitsfond GmbH, Bremen, Germany; ¹²Hôpital Saint André, Bordeaux, France; ¹³Istituto Oncologico Veneto-Istituto di Ricovero e Cura a Carattere Scientifico, Padova, Italy; ¹⁴Bristol Myers Squibb, Princeton, NJ, USA; ¹⁵The Cleveland Clinic Foundation, Cleveland, OH, USA; ¹⁶Istituto di Ricovero e Cura a Carattere Scientifico, Istituto Nazionale dei Tumori, Milan, Italy
*Co-senior authors

Abstract number 9504



*Per patient eligibility and choice. †For PBO patients, any time after recurrence, but within 3 years of last dose. For NIVO patients who experience recurrence, > 6 months since last dose and within 3 years after completing treatment. 1. ClinicalTrials.gov: NCT02809231. Accessed March 2023. <https://clinicaltrials.gov/ct2/show/study/NCT02809231>. 2. Long GV et al. Plenary presentation at SABR 2022, Edinburgh, Scotland, October 17-20.

CheckMate 76K primary endpoint: RFS^{1,2}



• Adjuvant NIVO significantly prolonged RFS and had a manageable safety profile¹

CheckMate 76K study design^{1,2}

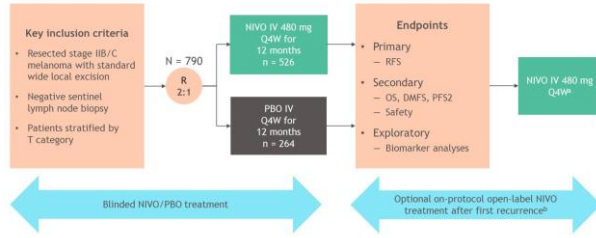


Association of biomarkers with efficacy of adjuvant nivolumab vs placebo in patients with resected stage IIB/C melanoma (CA209-76K)

Georgina V. Long,¹ John M. Kirkwood,² Christoph Hoeller,³ Jean-Jacques Grob,⁴ Jeffrey Weber,⁵ Janis Taube,⁶ Peter Mohr,⁷ Alexander van Akkooi,^{8,9,10} Carmen Loqui,¹¹ Caroline Dutriaux,¹² Vanna Chiarion-Sileni,¹³ Daniel J. Tenney,¹⁴ Sonia Dolfi,¹⁴ Hao Tang,¹⁴ Corey Ritchings,¹⁴ Maurice Lobo,¹⁴ Federico Campigotto,¹⁴ Wenjia Wang,¹⁴ Brian R. Gastman,^{15*} Michele Del Vecchio^{16*}

¹Melanoma Institute Australia, The University of Sydney, and Royal North Shore Mater Hospitals, Sydney, NSW, Australia; ²University of Pittsburgh Medical Center, Hillman Cancer Center, Pittsburgh, PA, USA; ³Medical University of Vienna, Vienna, Austria; ⁴Hôpital de la Timone, Marseille, France; ⁵Windermere Cancer Center at WVU Langone Health Medical Center, New York, NY, USA; ⁶Johns Hopkins University School of Medicine, Baltimore, MD, USA; ⁷EBC Klinikum Buxtehude, Buxtehude, Germany; ⁸Melanoma Institute Australia, Sydney, NSW, Australia; ⁹The University of Sydney, Sydney, NSW, Australia; ¹⁰Royal Prince Alfred Hospital, Sydney, NSW, Australia; ¹¹Department of Dermatology, Bremen-Ost Clinic, Gesundheitsord GmbH, Bremen, Germany; ¹²Hôpital Saint André, Bordeaux, France; ¹³Istituto Oncologico Veneto-Istituto di Ricovero e Cura a Carattere Scientifico, Treviso, Italy; ¹⁴Royal Bristol Myers Squibb, Princeton, NJ, USA; ¹⁵The Cleveland Clinic Foundation, Cleveland, OH, USA; ¹⁶Istituto di Ricovero e Cura a Carattere Scientifico, Istituto Nazionale dei Tumori, Milan, Italy

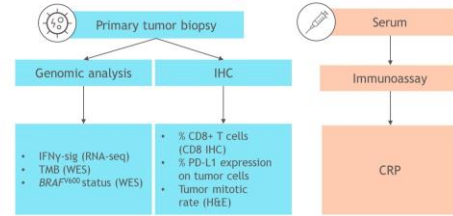
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Methods

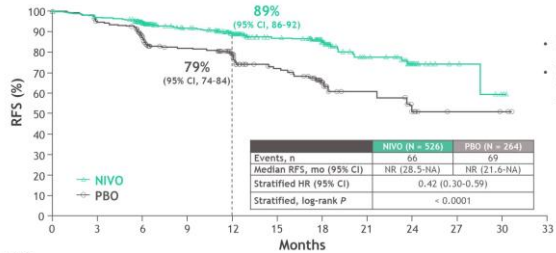
Baseline biomarker analyses conducted on the following:



Individual biomarkers and their association with treatment outcomes using RFS were evaluated

- As a continuous variable, by comparing higher (75th percentile) vs lower (25th percentile) groups from Cox proportional hazards model
 - Using median or other prespecified cutoffs
- Analyses were performed
- Within each treatment arm
 - Comparing NIVO vs PBO

CheckMate 76K primary endpoint: RFS^{1,2}



- Minimum follow-up – 7.8 months
- Median follow-up – NIVO 15.8 months – PBO 15.9 months

No. at risk	NIVO	264	492	444	364	261	185	116	54	19	6	2	0
PBO	264	243	205	161	119	77	40	20	11	3	2	0	0

Adjuvant NIVO significantly prolonged RFS and had a manageable safety profile¹

1. Long GV et al. Primary presentation at SMM 2023, Edinburgh, Scotland, October 17-20. 2. Gastman B et al. Oral presentation at SSO 2023, Boston, MA, USA, March 22-25.

Association between biomarkers and RFS within NIVO and PBO treatment arms: higher vs lower³ biomarker levels

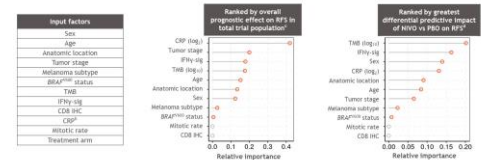
Biomarker	Events, n (patients, %)	Treatment	Events, n (patients, %)	Unstratified HR* (95% CI)	
				Higher vs lower	Favor higher level
IFNγ-slg	105 (63.8)	NIVO	48 (40.2)	0.38 (0.41-0.80)	+
		PBO	57 (21.3)	0.91 (0.65-1.27)	
TMB (log ₁₀ mut/exome)	112 (65.8)	NIVO	34 (44.1)	0.36 (0.49-0.90)	+
		PBO	38 (21.7)	1.20 (0.86-1.69)	
CD8 IHC (%)	117 (70.7)	NIVO	52 (66.6)	0.42 (0.30-0.59)	+
		PBO	60 (24.3)	0.97 (0.71-1.33)	
CRP (log ₁₀ μg/mL)	123 (73.9)	NIVO	10 (4.8)	1.37 (1.01-1.88)	-
		PBO	65 (24.6)	0.92 (0.69-1.24)	
Tumor PD-L1 (%)	51 (30.0)	NIVO	22 (1.9)	0.32 (0.40-1.12)	+
		PBO	29 (11.1)	0.99 (0.87-1.12)	
Mitotic rate (mitoses/mm ²)	123 (71.1)	NIVO	65 (47.2)	1.13 (0.87-1.47)	
		PBO	64 (24.1)	1.19 (0.94-1.51)	



Are associated with improved RFS in NIVO arm

Towards a composite biomarker model⁴

Multivariable analyses (Cox regression with group LASSO penalization) were performed to identify clinical and translational factors that predict RFS and differentiate NIVO and PBO treatment effects



- CRP had the strongest overall effect on RFS in the total population (across both treatment arms)
- TMB and IFNγ-slg had the largest independent effect on the relative benefit of NIVO over PBO

*Best final model did not include CD8 IHC and mitotic rate. Study did not adjust for interdependency between CD8 IHC and IFNγ-slg interaction coefficient (p = 0.7), and low independent predictive effect from mitotic rate. CRP shows some dependence of time from surgery to first disease. *Mean ± interquartile range. †Interaction term only.

Distant Metastasis-Free Survival Results From the Randomized, Phase 2 mRNA-4157-P201/KEYNOTE-942 Trial

Adnan Khattak,^{1,2} Jeffrey S. Weber,³ Tarek Menlawy,⁴ Matthew H. Taylor,⁵ George Anstas,⁶ Kevin B. Kim,⁷ Meredith McKean,⁸ Georgina V. Long,⁹ Ryan J. Sullivan,¹⁰ Mark B. Faries,¹¹ Thuy Tran,¹² C. Lance Cowey,¹³ Theresa M. Medina,¹⁴ Jennifer M. Segar,¹⁵ Victoria Atkinson,¹⁶ Geoffrey T. Gibney,¹⁷ Jason J. Luke,¹⁸ Elizabeth I. Buchbinder,¹⁹ Robert S. Meehan,²⁰ Matteo S. Carlino,^{2,21} Moderna Author's Group[†]

¹Hollywood Private Hospital, Netherlands; ²Edith Cowan University, Perth, Australia; ³NYU Langone Medical Center, New York, NY; ⁴St John of God Subiaco Hospital, Subiaco, Australia; ⁵Case Western Reserve University, Cleveland, OH, USA; ⁶Washington University School of Medicine, St. Louis, MO, USA; ⁷California Pacific Medical Center Research Institute, Oakland, CA, USA; ⁸Isaiah Cancer Research Institute, Nashville, TN, USA; ⁹Malcomson Institute Australia, Wollstonecraft, Australia; ¹⁰Massachusetts General Hospital, Boston, MA, USA; ¹¹The Angeles Clinic and Research Institute, Los Angeles, CA, USA; ¹²Franklin D. Roosevelt Hospital, New Haven, CT, USA; ¹³Bayar Charles A. Sproumeyer Cancer Center, Dallas, TX, USA; ¹⁴University of Colorado, Aurora, CO, USA; ¹⁵The University of Arizona Cancer Center, Tucson, AZ, USA; ¹⁶Princess Alexandra Hospital, Huddersfield, West Yorkshire, Australia; ¹⁷Leidos Cancer Center, Washington, DC, USA; ¹⁸UPMC Hillman Cancer Center, Pittsburgh, PA, USA; ¹⁹Dana-Farber Cancer Institute, Boston, MA, USA; ²⁰Moderna Inc., Cambridge, MA, USA; ²¹Westmead Hospital, Westmead, Australia.

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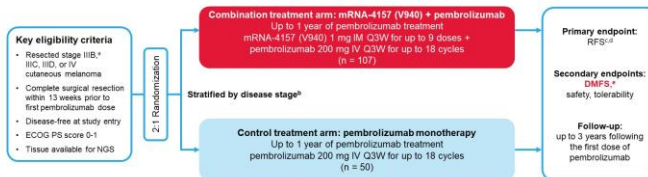
mRNA-4157 (V940) Mechanism of Action

- mRNA-4157 (V940) is an individualized neoantigen therapy designed to target an individual patient's unique tumor mutations and encodes up to 34 neoantigens^{1,2}



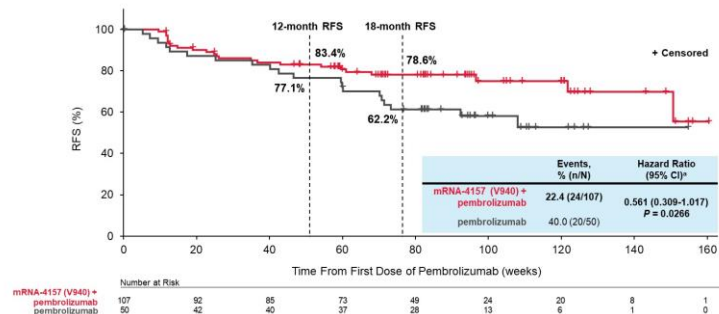
mRNA-4157-P201/KEYNOTE-942 (NCT03897881) Study Design

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



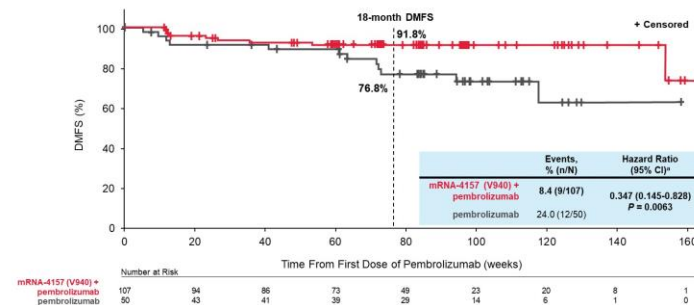
Designed with 80% power to detect an HR of 0.5 with ≥40 RFS events (with a 1-sided alpha of 0.1)
DMFS analysis was prespecified for testing following positive RFS in the ITT population[†]
Median follow-up[†]: 23 months for mRNA-4157 (V940) + pembrolizumab
24 months for pembrolizumab monotherapy

Primary Efficacy Endpoint: RFS¹



*The hazard ratio and 95% CI for mRNA-4157 (V940) plus pembrolizumab versus pembrolizumab is estimated using a Cox proportional hazards model with treatment group as a covariate, stratified by disease stage (stages IIB or IIC or IIID vs stage IV) used for randomization. The P value is based on a 1-sided log-rank test stratified by disease stage (stages IIB or IIC or IIID vs stage IV) used for randomization.

Secondary Efficacy Endpoint: DMFS



*The hazard ratio and 95% CI for mRNA-4157 (V940) plus pembrolizumab versus pembrolizumab is estimated using a Cox proportional hazards model with treatment group as a covariate, stratified by disease stage (stages IIB or IIC or IIID vs stage IV) used for randomization. The P value is based on a 1-sided log-rank test stratified by disease stage (stages IIB or IIC or IIID vs stage IV) used for randomization. At 18-months, the estimated DMFS rates were 91.8% (95% CI, 84.2-95.6) versus 76.8% (95% CI, 61.0-86.8) in the combination and monotherapy arms, respectively.

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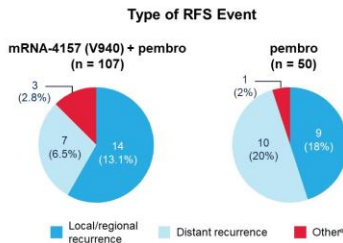
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Recurrence Type and Distant Recurrence Location

24/107 (22.4%) patients in the mRNA-4157 (V940) + pembro arm versus 20/50 (40.0%) in the pembro monotherapy arm experienced an RFS event



*Other: new primary cutaneous melanoma or death (n = 1); †Death from sepsis, unrelated to mRNA-4157 (V940) or pembro.

	mRNA-4157 (V940) + pembro (n = 107)	pembro (n = 50)
Patients with distant recurrence (with or without prior recurrence) or death, n (%)	9 (8.4)	12 (24.0)
Site of distant recurrence, n (%)		
Lymph node	2 (1.9)	4 (8.0)
Lung	2 (1.9)	4 (8.0)
Liver	3 (2.8)	1 (2.0)
Bone	1 (0.9)	2 (4.0)
Brain	1 (0.9)	3 (6.0)
Skin	0	4 (8.0)
Colon	1 (0.9)	1 (2.0)
Spleen	0	1 (2.0)
Soft tissue	1 (0.9)	0
Other site	2 (1.9)	1 (2.0)
Death not due to melanoma	1 (0.9)†	0

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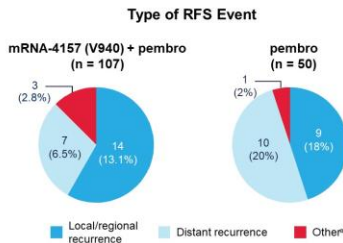
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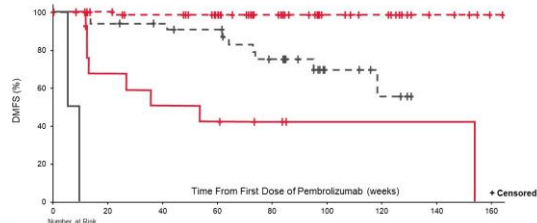
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Colon	1 (0.9)	1 (2.0)
Spleen	0	1 (2.0)
Soft tissue	1 (0.9)	0
Other site	2 (1.9)	1 (2.0)
Death not due to melanoma	1 (0.9)	0



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DMFS by ctDNA Status at Baseline



	mRNA-4157 (V940) + pembro vs pembro	mRNA-4157 (V940) + pembro	mRNA-4157 (V940) + pembro
	HR (95% CI)*	Events, % (n/N)	Events, % (n/N)
ctDNA-neg	0.048 (0.006, 0.386)	1.3 (1/77)	27.3 (9/33)
ctDNA-pos	NE	61.5 (8/13)	100 (2/2)

See LBA9815 presented by Matteo S. Carlino on 6/3 Jun

Minimal residual disease by circulating tumor DNA as a biomarker of recurrence-free survival in resected high-risk melanoma patients treated with mRNA-4157 (V940), iperfornated cancer vaccine, and pembrolizumab.

ctDNA was NE at baseline for 20.4% (32/157) patients from this study due to unavailability of the sample at baseline (mRNA-4157 (V940) + pembrolizumab, n = 115; pembrolizumab monotherapy, n = 14) or insufficient number of ctDNA⁺ variants identified by NGS (quality control flag mRNA-4157 (V940) + pembrolizumab, n = 2; pembrolizumab monotherapy, n = 1). Results limited by small sample size and event number. ctDNA, circulating tumor DNA.

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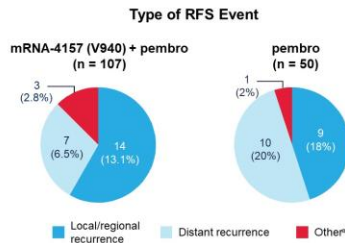
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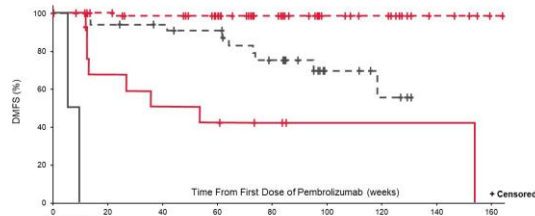


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Soft tissue	1 (0.9)	0
Other site	2 (1.9)	1 (2.0)
Death not due to melanoma	1 (0.9)	0



DMFS by ctDNA Status at Baseline



ctDNA-neg	mRNA-4157 (V940) + pembro	mRNA-4157 (V940) + pembro	mRNA-4157 (V940) + pembro	pembro	pembro
77	69	57	38	18	6
33	30	26	18	7	4
13	8	6	5	3	1
2	0	0	0	0	0

ctDNA-neg	mRNA-4157 (V940) + pembro vs pembro HR (95% CI)*	mRNA-4157 (V940) + pembro Events, % (n/N)	pembro Events, % (n/N)
ctDNA-neg	0.48 (0.006, 0.385)	1.3 (1/77)	27.3 (9/33)
ctDNA-pos	NE	61.5 (8/13)	100 (2/2)

ctDNA was AE at baseline for 20.4% (32/157) patients from this study due to unavailability of the sample at baseline (mRNA-4157 (V940) + pembro, n = 15; pembro monotherapy, n = 1) or insufficient number of ctDNA⁺ variants identified by NGS (quality control flag mRNA-4157 (V940) + pembro, n = 2; pembro monotherapy, n = 1). Results listed by small sample size and event number: ctDNA⁺, circulating tumor DNA.

mRNA-4157-P201/KEYNOTE-942 Safety and Tolerability¹

Event, n (%)	mRNA-4157 (V940) + pembro (n = 104)		pembro (n = 50)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Any AE	104 (100.0)	36 (34.6)	47 (94.0)	18 (36.0)
Any treatment-related AE	104 (100.0)	26 (25.0)	41 (82.0)	9 (18.0)
Serious AE ^a	15 (14.4)	13 (12.5%)	5 (10.0)	4 (8.0%)
mRNA-4157 (V940) or combination-related AEs^a occurring in >20% of patients				
Any	98 (94.2)	12 (11.5)	-	-
Fatigue	63 (60.6)	5 (4.8)	-	-
Injection site pain	56 (55.5)	0	-	-
Chills	52 (50.0)	0	-	-
Pyrexia	50 (48.1)	1 (1.0)	-	-
Headache	33 (31.7)	0	-	-
Injection site erythema	33 (31.7)	0	-	-
Influenza-like illness	32 (30.8)	0	-	-
Nausea	26 (25.0)	0	-	-
Myalgia	22 (21.2)	1 (1.0)	-	-
Pembro or combination related AEs^a occurring in >20% of patients				
Any	101 (97.1)	24 (23.1)	41 (82.0)	9 (18.0)
Fatigue	72 (69.2)	9 (8.8)	20 (40.0)	0
Diarrhea	31 (29.8)	2 (1.9)	5 (10.0)	0
Pruritus	30 (28.8)	0	10 (20.0)	0
Nausea	23 (22.1)	0	5 (10.0)	0
Chills	22 (21.2)	0	1 (2.0)	0
Pyrexia	22 (21.2)	0	0	0

Safety analyses were conducted in the safety population, which was defined as all randomly assigned patients who received ≥1 dose of treatment. Grading per National Cancer Institute Common Terminology Criteria for Adverse Events (version 5.0). ^aMinor AEs included grade 1 fever, attributed to mRNA-4157 (V940), and grade 2 influenza and grade 3 asthenia/fever, attributed to both mRNA-4157 (V940) and pembrolizumab. ^bAttributed to mRNA-4157 (V940) and pembrolizumab. ^cAttributed to mRNA-4157 (V940) and pembrolizumab. ^dAttributed to mRNA-4157 (V940) and pembrolizumab. ^eAttributed to mRNA-4157 (V940) and pembrolizumab. ^fAttributed to mRNA-4157 (V940) and pembrolizumab. ^gAttributed to mRNA-4157 (V940) and pembrolizumab. ^hAttributed to mRNA-4157 (V940) and pembrolizumab. ⁱAttributed to mRNA-4157 (V940) and pembrolizumab. ^jAttributed to mRNA-4157 (V940) and pembrolizumab. ^kAttributed to mRNA-4157 (V940) and pembrolizumab. ^lAttributed to mRNA-4157 (V940) and pembrolizumab. ^mAttributed to mRNA-4157 (V940) and pembrolizumab. ⁿAttributed to mRNA-4157 (V940) and pembrolizumab. ^oAttributed to mRNA-4157 (V940) and pembrolizumab. ^pAttributed to mRNA-4157 (V940) and pembrolizumab. ^qAttributed to mRNA-4157 (V940) and pembrolizumab. ^rAttributed to mRNA-4157 (V940) and pembrolizumab. ^sAttributed to mRNA-4157 (V940) and pembrolizumab. ^tAttributed to mRNA-4157 (V940) and pembrolizumab. ^uAttributed to mRNA-4157 (V940) and pembrolizumab. ^vAttributed to mRNA-4157 (V940) and pembrolizumab. ^wAttributed to mRNA-4157 (V940) and pembrolizumab. ^xAttributed to mRNA-4157 (V940) and pembrolizumab. ^yAttributed to mRNA-4157 (V940) and pembrolizumab. ^zAttributed to mRNA-4157 (V940) and pembrolizumab. ^{aa}Attributed to mRNA-4157 (V940) and pembrolizumab. ^{ab}Attributed to mRNA-4157 (V940) and pembrolizumab. ^{ac}Attributed to mRNA-4157 (V940) and pembrolizumab. ^{ad}Attributed to mRNA-4157 (V940) and pembrolizumab. ^{ae}Attributed to mRNA-4157 (V940) and pembrolizumab. ^{af}Attributed to mRNA-4157 (V940) and pembrolizumab. ^{ag}Attributed to mRNA-4157 (V940) and pembrolizumab. ^{ah}Attributed to mRNA-4157 (V940) and 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Distant Metastasis-Free Survival Results From the Randomized, Phase 2 mRNA-4157-P201/KEYNOTE-942 Trial

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Recurrence Type and Distant Recurrence Location

24/107 (22.4%) patients in the mRNA-4157 (V940) + pembro arm versus 20/50 (40.0%) in the pembro monotherapy arm experienced an RFS event

Type of RFS Event

	mRNA-4157 (V940) + pembro (n = 107)	pembro (n = 50)
Patients with distant recurrence (with or without prior recurrence) or death, n (%)	9 (8.4)	12 (24.0)
Site of distant recurrence, n (%)		



Conclusions

- mRNA-4157 (V940) and pembrolizumab demonstrated a **clinically significant improvement in RFS and DMFS** compared to standard of care pembrolizumab in high-risk resected melanoma, with a **44% reduction in the risk of recurrence or death** and a **65% reduction in the risk of distant metastasis or death** with a median of 2 years of follow-up
- mRNA-4157-P201/KEYNOTE-942 is the **first randomized trial to demonstrate improvement** in recurrence-free survival and distant metastasis-free survival with an **individualized neoantigen therapy approach**
- mRNA-4157 (V940) in combination with pembrolizumab was **well-tolerated without an increase in immune-mediated AEs** compared with pembrolizumab monotherapy
- mRNA-4157 (V940) in combination with pembrolizumab received **Breakthrough Therapy Designation** from FDA in February 2023 and **PRIME Designation** from EMA in April 2023

DMFS by c



ctDNA-neg: mRNA-4157 (V940) + pembrolizumab
 ctDNA-neg: pembrolizumab
 ctDNA-pos: mRNA-4157 (V940) + pembrolizumab
 ctDNA-pos: pembrolizumab

ctDNA was AE at baseline for 20 (19.1%)
 10 (9.4%) mRNA-4157 (V940) + pembrolizumab
 10 (20.0%) pembrolizumab

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Patients with distant recurrence (with or without prior recurrence) or death, n (%)	9 (8.4)	12 (24.0)
Site of distant recurrence, n (%)		

Type of RFS Event



Conclusions

Next Steps

- Additional analyses to include **protocol specified RFS with ≥51 events** and **other subpopulation and translational assessments including immunogenicity**
- Longer follow-up** with mRNA-4157-P201/KEYNOTE-942 to evaluate **durability of the treatment effect**
- A phase 3 study to confirm these results** will be initiated in patients with **high-risk resected melanoma in 2023**
- Expanded clinical studies to include **additional tumor types**, such as NSCLC

DMFS by c

cDNA-neg: mRNA-4157 (V940) + pembrolizumab
 cDNA-neg: pembrolizumab
 cDNA-pos: mRNA-4157 (V940) + pembrolizumab
 cDNA-pos: pembrolizumab

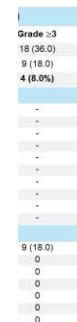
13

h-risk
65%
 w-up

in

apy
 2023

14



Version 5.0.0. Microscopic AEs included grade 1-4. Data by the investigator for mRNA-4157 (V940) and pembrolizumab (pembro).

cDNA was AE at baseline for 20/4% (3/21) for mRNA-4157 (V940) + pembrolizumab

MELANOMA METASTÁSICO:

¿Qué objetivos busco con la elección del tratamiento?



Objetivo 1º:
Alta tasa de
respuestas ORR



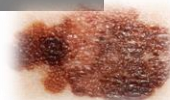
Objetivo 2º:
Respuestas
duraderas, PFS y
OS



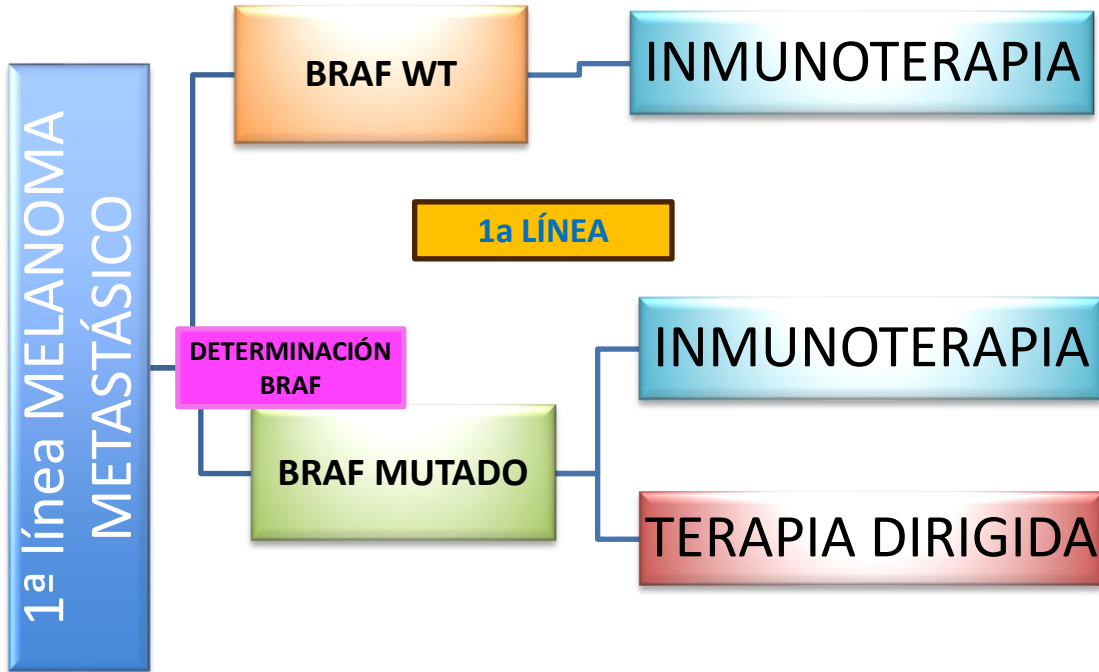
Toxicidades
Calidad de vida



**LARGOS RESPONDEDORES,
LARGOS SUPERVIVIENTES**



Tratamiento del MELANOMA METASTÁSICO



Keynote 006 (pembro vs Ipi 1^a/2^a línea)
Checkmate 066 (nivo vs QT BRAF WT)

Checkmate 067 (nivo o ipi/nivo vs ipi) -> PD-L1 -,
brain M1, mucosal

Checkmate 511 (nivo/ipi low dose vs nivo/ipi)
Keynote 029 (fase II, ipi low dose/pembro)

Relativity (nivo vs nivo/rela) -> PD-L1 -

Optim (T-VEC vs G-CSF)
- IIIB/C non resectable and M1a

coBRIM (vemurafenib/cobimetinib vs vemurafenib)
COMBI-D (dabrafenib/trametinib vs dabrafenib)
COMBI-V (dabrafenib/trametinib vs vemurafenib)
COLUMBUS (encorafenib/binimetinib vs encorafenib vs vemurafenib)

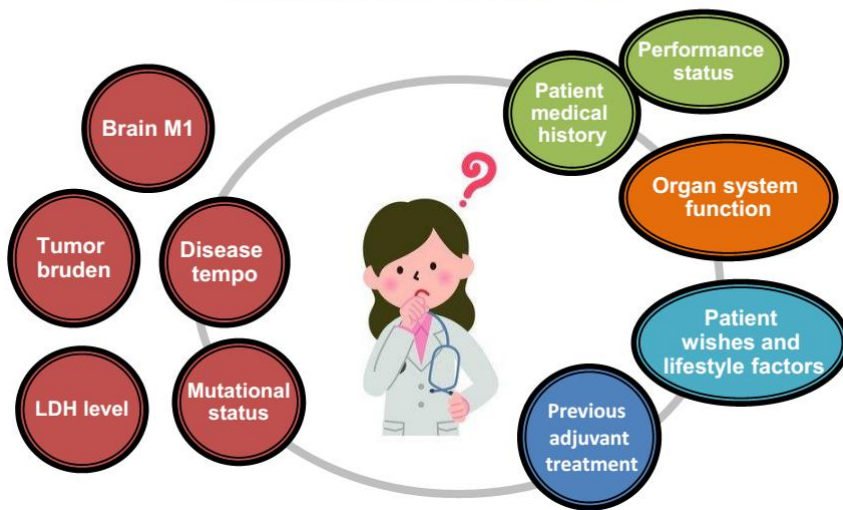
IMSPIRE 150 (vemurafenib + cobimetinib vs vemurafenib+cobimetinib+atezolizumab)

Tratamiento del MELANOMA METASTÁSICO



1ª línea MELANOMA METASTÁSICO

Factors for Consideration in Metastatic Treatment Decisions



Keynote 006 (pembro vs Ipi 1^a/2^a línea)
Checkmate 066 (nivo vs QT BRAF WT)

Checkmate 067 (nivo o ipi/nivo vs ipi) -> PD-L1 -, brain M1, mucosal)

Checkmate 511 (nivo/ipi low dose vs nivo/ipi)
Keynote 029 (fase II, ipi low dose/pembro)

Relativity (nivo vs nivo/rela) -> PD-L1 -

Optim (T-VEC vs G-CSF)
- IIIB/C non resectable and M1a

coBRIM (vemucobi vs vemu)
COMBI-D (dabra/trame vs dabra)
COMBI-V (dabra/trame vs vemu)
COLUMBUS (encorafenib/binimetinib vs encorafenib vs vemu)

IMSPIRE 150 (vemucobi vs vemucobi+atezo)



STEP 1

INMUNOTERAPIA

- Sistema terapéutico: sistema linfático
- Influencia crítica de valoración de respuesta
- Largos supervivientes
- Posibilidad de RC
- Oportunidad de múltiples combinaciones
- Oportunidad de secuenciar tratamientos con IO y TT
- Posibilidad de parar el tratamiento
- Posibilidad de reanunciar (parar IO)
- Eficacia en M1, SNC
- Posibilidad de tratamiento tras fallo a otra terapia dirigida
- Eficacia en adyuvancia
- Papel diferenciador de beneficio al tratamiento según el nivel de LDH
- Diferente perfil de toxicidad y de manejo de efectos adversos.

TERAPIA DIRIGIDA

- Sistema terapéutico: BRAF
- Rápida velocidad de respuesta
- Largos supervivientes
- Posibilidad de RC
- Oportunidad de múltiples combinaciones
- Oportunidad de secuenciar tratamientos
- Imposibilidad de parar el tratamiento
- Posibilidad de reanunciar
- Eficacia en M1, SNC
- Posibilidad de tratamiento tras fallo a IO
- Papel diferenciador de beneficio al tratamiento según el nivel de LDH
- Eficacia en adyuvancia
- Perfil de toxicidad único y baja tasa de discontinuación

Mean survival curves created by weighted averaging of digitized Kaplan-Meier survival curves of metastatic melanoma patients treated in selected clinical trials

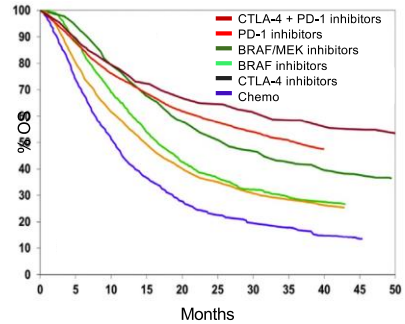


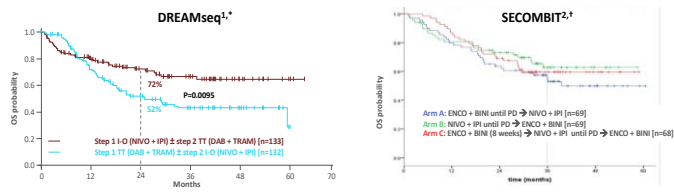
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OS rates, %	PD1 + CTLA4 inhibitors	PD-1 inhibitors	BRAF+MEK inhibitors		
Year	Nivo + ipi CM-067	Nivo CM-067	Enco/bini COLUMBUS	Dab/tram COMBI-v, COMBI-d	coBRIM ^{9,10}
1	-	-	76% ⁷	-	75% ⁹
2	64% ¹	59% ¹	58% ⁷	52% ⁸	49% ⁹
3	58% ²	52% ²	47% ⁷	44% ⁸	39% ⁹
4	53% ³	44% ³	39% ⁷	37% ⁸	35% ⁹
5	52% ⁴	44% ⁴	35% ⁷	34% ⁸	31% ¹⁰
6.5	49% ⁵	42% ⁵	-	-	-
7.5	48% ⁶	42% ⁶	-	-	-

Data overview deriving from different studies for the sole purpose of scientific discussions; direct comparative conclusions are not possible.

Two randomized clinical trials investigating sequential treatment strategies for BRAF-mutant metastatic melanoma

STEP 2



- Exploratory analyses from IMspire150 showed that adding ATEZO to 1L VEM + COBI resulted in a numerically lower rate for the development of CNS metastases among patients with advanced BRAF-mutant melanoma who had no CNS metastases at baseline⁵

Data overview deriving from different studies for the sole purpose of scientific discussions; direct comparative conclusions are not possible.

This slide may contain information related to therapies that are investigational and / or beyond their approved indication(s). *Median follow-up: 27.7 mo; †Median follow-up: 32.2 mo.

1b. First-line ATEZO, ipilimumab; BINI, binimetinib; COBI, cobimetinib; DAB, dabrafenib; ENCO, encorafenib; IO, immunotherapy; IPI, ipilimumab; NIVO, nivolumab; OS, overall survival; PD, progressive disease; TRAM, trametinib; TT, targeted therapy; VEM, vemurafenib.

1. Ashraf MB et al. Abstract 9565A. ASCO Monthly Meeting Series November 2021; 2. Ascierto PA et al. Poster 9535. ASCO Annual Meeting 3-7 June 2022; 3. Ascierto PA et al. Abstract 10023. ASCO Annual Meeting 29 May-2 June 2020.

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Three randomized clinical trials investigating combination treatment strategies for BRAF-mutant metastatic melanoma

STEP 2

KEYNOTE-022^{1,4}
Pembrolizumab plus dabrafenib and trametinib

Trial did NOT reach primary endpoint¹

- Two did not reach primary endpoint^{1,3}
- Clinically minor added benefit
- Toxicity ++

IMspire²
Atezolizumab plus vemurafenib and cobimetinib

Trial did NOT reach primary endpoint²

COMBI-³
Spartalizumab plus dabrafenib and trametinib

Trial did NOT reach primary endpoint³

1. Ribas A et al. Poster 9516. ASCO Annual Meeting 3-7 June 2022; 2. McGrath GA, et al. Poster 9547. ASCO Annual Meeting 3-7 June 2022; 3. Dummer R, et al. Poster 9521. ASCO Annual Meeting 3-7 June 2022; 4. Ferrucci PF, et al. *J Immunother Oncol*. 2020;8(2):82-89;10806.

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STEP 1

IO vs TT

INMUNOTERAPIA

- Sistema terapéutico: sistema inmune
- Ineficacia intrínseca de valoración de respuesta
- Largos supervivientes
- Posibilidad de RC
- Oportunidad de múltiples combinaciones
- Oportunidad de secuenciar tratamientos con IO y TT
- Posibilidad de parar el tratamiento
- Posibilidad de reanunciar Inmunoterapia
- Eficacia en M1, SNC
- Posibilidad de tratamiento tras fallo a IO
- Eficacia en adyuvancia
- Papel diferenciador de beneficio al tratamiento según el nivel de LDH
- Diferencia perfil de toxicidad y de manejo de efectos adversos.

TERAPIA DIRIDA

- Sistema terapéutico: BRAF
- Rápida velocidad de respuesta
- Largos supervivientes
- Posibilidad de RC
- Oportunidad de múltiples combinaciones
- Oportunidad de secuenciar tratamientos
- Imposibilidad de parar el tratamiento
- Posibilidad de reanunciar Inmunoterapia
- Eficacia en M1, SNC
- Posibilidad de tratamiento tras fallo a IO
- Papel diferenciador de beneficio al tratamiento según el nivel de LDH
- Eficacia en adyuvancia
- Perfil de toxicidad único y baja tasa de discontinuación

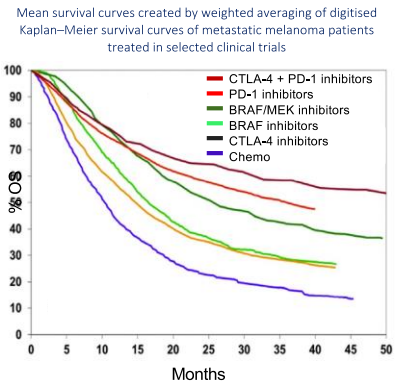


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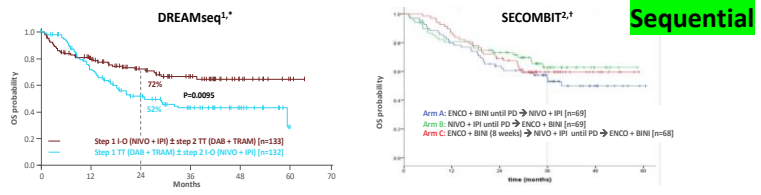
OS rates, %	PD1 + CTLA4 inhibitors	PD-1 inhibitors	BRAF+MEK inhibitors		
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STEP 2

Two randomized clinical trials investigating sequential treatment strategies for BRAF-mutant metastatic melanoma

STEP 2



• Exploratory analyses from IMspire150 showed that adding ATEZO to 1L VEM + COBI resulted in a numerically lower rate for the development of CNS metastases among patients with advanced BRAF-mutant melanoma who had no CNS metastases at baseline³

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Three randomized clinical trials investigating combination treatment strategies for BRAF-mutant metastatic melanoma

STEP 2

KEYNOTE-022^{1,4}
Pembrolizumab plus dabrafenib and trametinib

Trial did NOT reach primary endpoint⁴

- Primary end point: PFS
- Secondary end points: OS, duration of response, and ORR

IMspire²
Atezolizumab plus vemurafenib and cobimetinib

Trial did NOT reach primary endpoint²

- Primary end point: PFS
- Secondary end points: OS, duration of response, and ORR

COMBI-3³
Spartalizumab plus dabrafenib and trametinib

Trial did NOT reach primary endpoint³

- Primary end point: PFS
- Secondary end points: OS, duration of response, and ORR

- Two did not reach primary endpoint^{1,3}
- Clinically minor added benefit
- Toxicity ++

Combination

1. Ribas A et al. Poster 9516. ASCO Annual Meeting 3-7 June 2022; 2. McGrath GA, et al. Poster 9547. ASCO Annual Meeting 3-7 June 2022; 3. Dummer R, et al. Poster 9521. ASCO Annual Meeting 3-7 June 2022; 4. Ferrucci PF, et al. *J Immunother Oncol*. 2020;8(2):82-89.100606.
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STEP 1

IO vs TT

INMUNOTERAPIA

- Sistema terapéutico: sistema inmune
- Ineficacia intrínseca de valoración de respuesta
- Largos supervivientes
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- Posibilidad de parar el tratamiento
- Posibilidad de reanunciar Inhibidor PD
- Eficacia en M1 SNC
- Posibilidad de tratamiento tras fallo a IO
- Eficacia en subconjunto
- Papel diferenciador de beneficio al tratamiento según el nivel de ICMI
- Diferencia perfil de toxicidad y de manejo de efectos adversos.

TERAPIA DIRIDA

- Sistema terapéutico: BRAF
- Rápida velocidad de respuesta
- Largos supervivientes
- Posibilidad de IC
- Oportunidad de múltiples combinaciones
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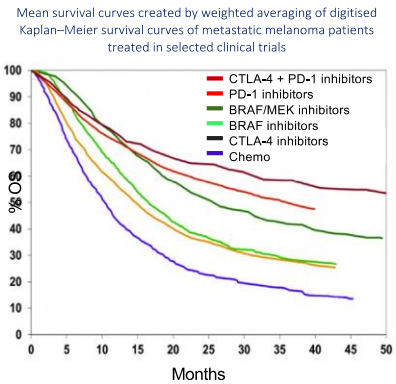


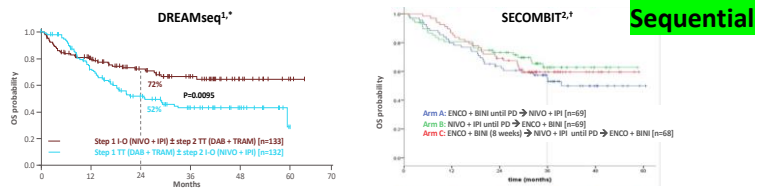
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Data overview deriving from different studies for the sole purpose of scientific discussions; direct comparative conclusions are not possible.

STEP 2

Two randomized clinical trials investigating sequential treatment strategies for BRAF-mutant metastatic melanoma



• Exploratory analyses from IMspire150 showed that adding ATEZO to 1L VEM + COBI resulted in a numerically lower rate for the development of CNS metastases among patients with advanced BRAF-mutant melanoma who had no CNS metastases at baseline³

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Three randomized clinical trials investigating combination treatment strategies for BRAF-mutant metastatic melanoma

KEYNOTE-022^{1,4}
Pembrolizumab plus dabrafenib and trametinib

IMspire²
Atezolizumab plus vemurafenib and cobimetinib

COMBI-³
Spartalizumab plus dabrafenib and trametinib

Key eligibility criteria:

- Age ≥ 18 years
- Histologically confirmed, unresectable metastatic melanoma with BRAF V600E
- No prior systemic anti-cancer therapy for unresectable or metastatic melanoma
- No clinically active brain metastases
- ECOG performance status ≤ 2

Primary endpoints:

- Investigator-assessed OS (n = 1,020)
- OS

Key secondary endpoints:

- Investigator-assessed PFS (n = 1,020)
- PFS
- ORR, ECR, DCR, SAEs, patient-reported outcomes

Key eligibility criteria:

- Age ≥ 18 years
- Histologically confirmed, unresectable metastatic melanoma with BRAF V600E
- No prior systemic anti-cancer therapy for unresectable or metastatic melanoma
- No clinically active brain metastases
- ECOG performance status ≤ 2

Primary endpoints:

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- OS

Key secondary endpoints:

- Investigator-assessed PFS (n = 1,020)
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Nivolumab (NIVO) plus relatlimab (RELA) vs NIVO in previously untreated metastatic or unresectable melanoma: 2-year results from RELATIVITY-047

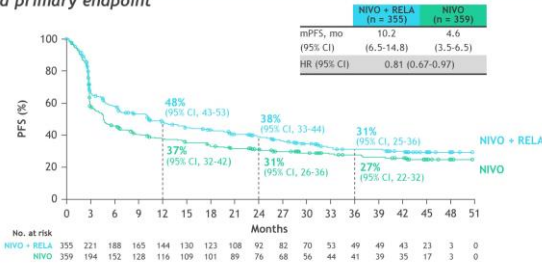
Hussein A. Tawbi,¹ F. Stephen Hodi,² Evan J. Lipson,³ Dirk Schadendorf,⁴ Paolo Antonio Ascierto,⁵ Luis Matamala,⁶ Erika Castillo Gutiérrez,⁷ Piotr Rutkowski,⁸ Helen Gogas,⁹ Christopher D. Lao,¹⁰ Juliana Janoski De Menezes,¹¹ Stéphane Dalle,¹² Ana Maria Arance,¹³ Jean-Jacques Grob,¹⁴ Barbara Ratto,¹⁵ Salma Rodriguez,¹⁶ Yuanfang Xu,¹⁷ Peter Wang,¹⁸ Sonia Dolfi,¹⁹ Georgina V. Long¹⁸

¹The University of Texas MD Anderson Cancer Center, Houston, TX; ²Dana-Farber Cancer Institute, Boston, MA; ³Bloomberg Kimmel Institute for Cancer Immunotherapy, Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD; ⁴University of Essen and the German Cancer Consortium, Essen, Germany; ⁵Istituto Nazionale dei Tumori IRCCS "Fondazione G. Pavesale", Naples, Italy; ⁶Instituto Oncológico Fundación Arturo López Pérez and Department of Oncology, Instituto Nacional del Cáncer, Santiago, Chile; ⁷INACIC Clinical Research, Viacruz, Mexico; ⁸Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland; ⁹National and Kapodistrian University of Athens, Athens, Greece; ¹⁰Michigan Medicine, Rogel Cancer Center, University of Michigan, Ann Arbor, MI; ¹¹Hospital Nossa Senhora da Conceição, Porto Alegre, Brazil; ¹²Hospices Civils de Lyon, Cancer Research Center of Lyon, Pierre-Benite, France; ¹³Hospital Clinic Barcelona and IDIBAP, Barcelona, Spain; ¹⁴Marseille University, CHU Timone, Marseille, France; ¹⁵Strokol Myers Squibb, Princeton, NJ; ¹⁶Melanoma Institute Australia, The University of Sydney, Royal North Shore and Mater Hospitals, Sydney, NSW, Australia

Abstract number 9502

PFS by BICR

Updated primary endpoint

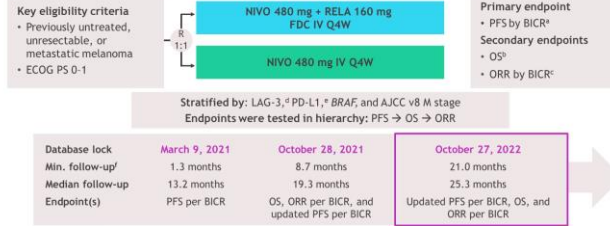


RELATIVITY-047 (NCT02470922). Median follow-up: 25.3 months. Descriptive analysis. Statistical model for HR: stratified Cox proportional hazard model. Stratified by LAG-3, BRAF mutation status, and AJCC v8 M stage. PD-L1 was removed from stratification because it led to subgroups with < 10 patients.

RELATIVITY-047

Study design

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

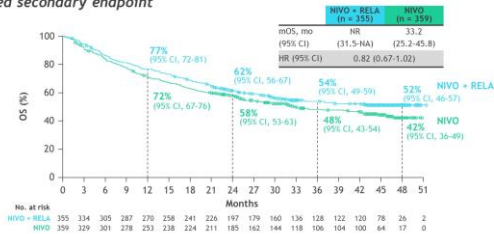


RELATIVITY-047 (NCT02470922). First cohort enrollment (RECCT 1-1) was performed 12 weeks after randomization, every 8 weeks up to 52 weeks, and then every 12 weeks. OS boundary for statistical significance was $P < 0.0420$. OS is not analyzed at 95% power; target HR, 0.75. ORR could not be formally tested and was descriptively analyzed. LAG-3 expression or tumor-infiltrating lymphocyte (TIL) expression or immune gene (IG) expression was determined by an analytical/clinical validation IHC assay (LabPath), Burlington, NC, USA. PD-L1 expression on tumor cells (TTC) was determined by a validated Agilent Data PD-L1 IHC 2B-8 platform test (Agilent, Santa Clara, CA, USA). Minimum potential follow-up was defined as the time from last patient randomized to last patient. Last visit.

RELATIVITY-047

OS

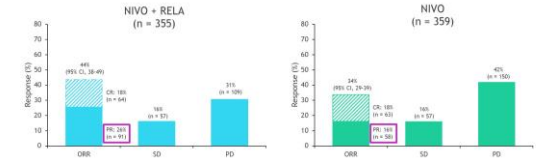
Updated secondary endpoint



RELATIVITY-047 (NCT02470922). Median follow-up: 25.3 months. Descriptive analysis. Statistical model for HR: stratified Cox proportional hazard model. Stratified by LAG-3, BRAF mutation status, and AJCC v8 M stage. PD-L1 was removed from stratification because it led to subgroups with < 10 patients.

Best overall response per BICR

Updated secondary endpoint



- NIVO + RELA vs NIVO ORR difference of 9.8% (95% CI, 2.8-16.8)
- Median duration of response was not reached in both the NIVO + RELA (NR [95% CI, 39.4-NA]) and NIVO (NR [95% CI, 39.8-NA]) arms

RELATIVITY-047 (NCT02470922). Median follow-up: 25.3 months. Descriptive analysis. 26 patients (7.3%) in the NIVO + RELA arm and 26 patients (7.2%) in the NIVO arm were classified as unable to determine.



Nivolumab (NIVO) plus relatlimab (RELA) vs NIVO in previously untreated metastatic or unresectable melanoma: 2-year results from RELATIVITY-047

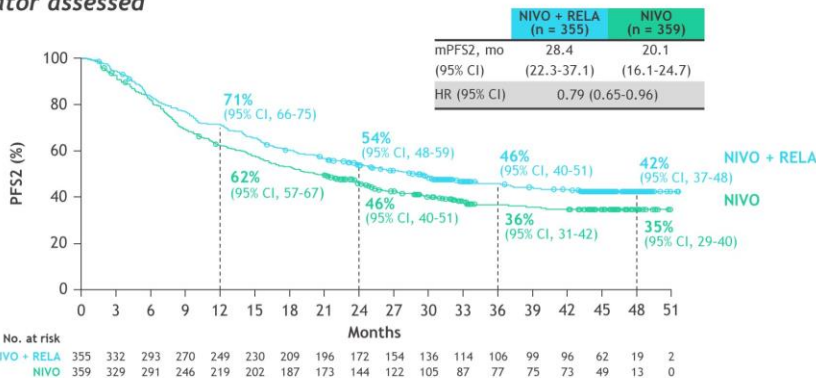
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Abstract number 9502

Progression-free survival 2 (PFS2)

Investigator assessed



RELATIVITY-047 (NCT03470922). Median follow-up: 25.3 months.

Progression-free survival 2 (PFS2) was an exploratory analysis and defined as the time from randomization to progression date after the next line of therapy, per investigator assessment, or to death from any cause.

Study design

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



RELATIVITY-047 (NCT03470922).

PFS2 was investigator assessed (RECIST v1.1) was performed 12 weeks after randomization, every 8 weeks up to 52 weeks, and then every 12 weeks. OS boundary for statistical significance was $P < 0.0400$. OS is being analyzed at 80% power, target HR, 0.75. ORR could not be formally tested and was descriptively analyzed. *LAG-3 expression on immune cells (1%) was determined by an analytically validated IHC assay (Labview, Burlington, NC, USA). PD-L1 expression on tumor cells (1%) was determined by a validated Agilent Data PD-L1 IHC 2B-8 platform test (Agilent, Santa Clara, CA, USA). Minimum potential follow-up was defined as the time from last patient randomized to last patient. Last visit.

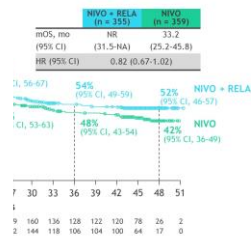
RELATIVITY-047

RELATIVITY-047

Subsequent therapy

Characteristic	NIVO + RELA (n = 355)	NIVO (n = 359)
Any subsequent therapy, n (%)	163 (46)	166 (46)
Subsequent systemic therapy (≥ 2L), n (%)	131 (37)	136 (38)
Radiotherapy, n (%)	57 (16)	51 (14)
Surgery, n (%)	28 (8)	34 (9)

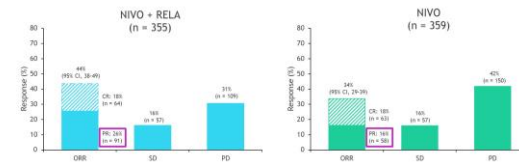
RELATIVITY-047



BRAF mutation status, and AJCC v8 M stage. PD-L1 was removed from stratification.

Best overall response per BICR

Updated secondary endpoint



NIVO + RELA vs NIVO ORR difference of 9.8% (95% CI, 2.8-16.8)

Median duration of response was not reached in both the NIVO + RELA (NR [95% CI, 39.4-NA]) and NIVO (NR [95% CI, 39.8-NA]) arms

RELATIVITY-047 (NCT03470922). Median follow-up: 25.3 months.

Descriptive analysis. 26 patients (7.3%) in the NIVO + RELA arm and 26 patients (7.2%) in the NIVO arm were classified as unable to determine.

Nivolumab (NIVO) plus relatlimab (RELA) vs NIVO in previously untreated metastatic or unresectable melanoma: 2-year results from RELATIVITY-047

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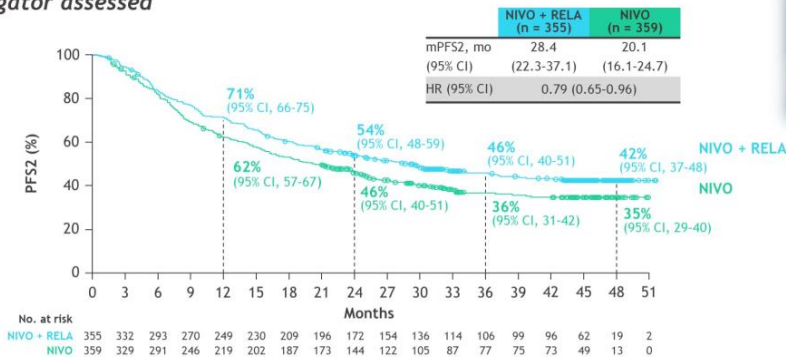
¹The University of Texas MD Anderson Cancer Center, Houston, TX; ²Dana-Farber Cancer Institute, Boston, MA; ³Bloomberg Kimmel Institute for Cancer Immunotherapy, Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD; ⁴University of Essen and the German Cancer Consortium, Essen, Germany; ⁵Istituto Nazionale dei Tumori IRCCS "Fondazione G. Pascale", Naples, Italy; ⁶Instituto Oncológico Fundación Arturo López Pérez and Department of Oncology, Instituto Nacional del Cáncer, Santiago, Chile; ⁷PAIC Clinical Research, Wrzaw, Mexico; ⁸Maria Skłodowska-Curie National Research Institute of Oncology, Warsaw, Poland; ⁹National and Kapodistrian University of Athens, Athens, Greece; ¹⁰Michigan Medicine, Rogel Cancer Center, University of Michigan, Ann Arbor, MI; ¹¹Hospital Nossa Senhora da Conceição, Porto Alegre, Brazil; ¹²Hospices Civils de Lyon, Cancer Research Center of Lyon, Pierre-Bénite, France; ¹³Hospital Clinic Barcelona and IDIBAP, Barcelona, Spain; ¹⁴Nantes Université, CHU Tirone, Nantes, France; ¹⁵Bristol Myers Squibb, Princeton, NJ; ¹⁶Melanoma Institute Australia, The University of Sydney, Royal North Shore and Mater Hospitals, Sydney, NSW, Australia

Abstract number 9502

RELATIVITY-047

Progression-free survival 2 (PFS2)

Investigator assessed



RELATIVITY-047 (NCT03470922). Median follow-up: 25.3 months.

Progression-free survival 2 (PFS2) was an exploratory analysis and defined as the time from randomization to progression date after the next line of therapy, per investigator assessment, or death from any cause.

RELATIVITY-047

TY-047

Efficacy on 2L systemic therapy following progression

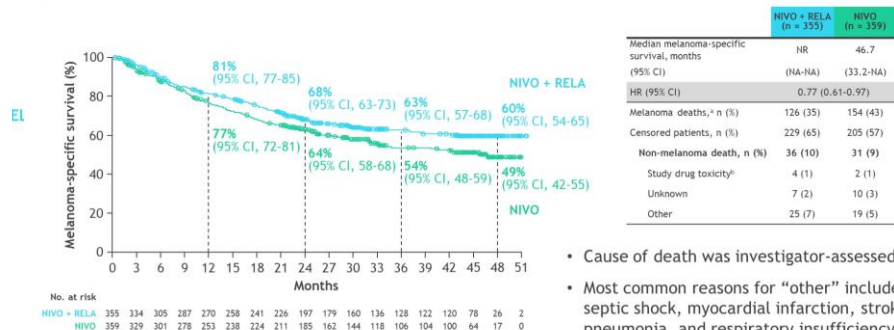
Investigator reported

	NIVO + RELA arm			NIVO arm		
	NIVO + IPI (n = 16)	IPI (n = 9)	BRAFI/MEKi (n = 43)	NIVO + IPI (n = 16)	IPI (n = 14)	BRAFI/MEKi (n = 45)
Subsequent 2L therapy						
BOR on subsequent 2L therapy, n (%)	4 (25)	2 (22)	7 (16)	3 (19)	0	7 (16)
CR	2 (12)	0	2 (5)	0	0	0
PR	2 (12)	2 (22)	5 (12)	3 (19)	0	7 (16)
SD	4 (25)	0	1 (2)	0	1 (7.1)	9 (20)
Unk/not reported/UTD ^a	4 (25)	3 (33)	24 (56)	7 (44)	2 (14)	17 (38)
Median time to next treatment, months (range)	8.1 (1.8-18.1)	4.2 (2.1-38.1)	9.7 (0.6-46.4)	4.5 (1.1-30.2)	5.3 (2.5-37.6)	10.6 (<0.1-46.5)
Median PFS, ^b months (95% CI)	8.4 (3.0-NA)	3.4 (1.7-22.3)	15.4 (6.9-NA)	2.9 (1.9-11.6)	2.9 (1.9-3.7)	10.6 (6.0-14.9)
6-month PFS, %	54	33	71	28	7	65
12-month PFS, %	45	22	56	21	0	43

RELATIVITY-047 (NCT03470922). Median follow-up: 25.3 months. Progression-free survival 2 (PFS2) was an exploratory analysis and defined as the time from randomization to progression date after the next line of therapy, per investigator assessment, or death from any cause.

RELATIVITY-047

Melanoma-specific survival



RELATIVITY-047 (NCT03470922). Median follow-up: 25.3 months.

Melanoma-specific survival (MSS) was a post hoc exploratory analysis and defined as time from randomization to death due to melanoma; deaths for any other reason were censored. Patients who were alive were censored at their last known alive date. ^aReasons for death were determined by the investigator. ^bDeath due to toxicity was considered non-melanoma death.

	NIVO + RELA (n = 355)	NIVO (n = 359)
Median melanoma-specific survival, months (95% CI)	NR (NA-NA)	46.7 (33.2-NA)
HR (95% CI)	0.77 (0.61-0.97)	
Melanoma deaths, ^a n (%)	126 (35)	154 (43)
Censored patients, n (%)	229 (65)	205 (57)
Non-melanoma death, n (%)	36 (10)	31 (9)
Study drug toxicity ^b	4 (1)	2 (1)
Unknown	7 (2)	10 (3)
Other	25 (7)	19 (5)

- Cause of death was investigator-assessed
- Most common reasons for "other" included septic shock, myocardial infarction, stroke, pneumonia, and respiratory insufficiency



RELATIVITY-047



Significant durable response with fiantlimab (anti-LAG-3) and cemiplimab (anti-PD-1) in advanced melanoma: post adjuvant PD-1 analysis

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Study design: three serial expansion cohorts in advanced melanoma setting

Treatment:
Fiantlimab 1600 mg + cemiplimab 350 mg IV every 3 weeks, for up to 51 weeks

Initial cohort MM1^a (n=40)
1L or 2L advanced melanoma patients who have never received anti-PD-(L)1

Confirmatory cohort MM2^b (n=40)
1L advanced melanoma patients who have never received anti-PD-(L)1

PD-1 experienced cohort MM3^c (n=18)
1L advanced melanoma patients with prior (neo)adjuvant systemic therapy^d, including 13/18 patients who received anti-PD-1

Primary endpoint
• ORR per RECIST 1.1 criteria

Secondary endpoints

- PFS
- DoR
- DCR
- Safety
- PK

Key inclusion criteria

- Metastatic or inoperable locally advanced non-visceral melanoma
- ≥18 years of age
- ECOG PS of 0 or 1
- At least one lesion measurable by RECIST 1.1

Key exclusion criteria

- Uveal melanoma
- Prior treatment with a LAG-3 targeting agent
- Radiation therapy within 2 weeks prior to enrollment

MM1^a, Cohort 1; MM2^b, Cohort 2; MM3^c, Cohort 3. ^aSee also abstract 4005. ^bSee also abstract 4006. ^cSee also abstract 4007. ^dIncludes adjuvant systemic therapy (including anti-PD-1) with recurrence ≥6 months after adjuvant therapy. ^eSee also abstract 4008. ^fSee also abstract 4009. ^gSee also abstract 4010. ^hSee also abstract 4011. ⁱSee also abstract 4012. ^jSee also abstract 4013. ^kSee also abstract 4014. ^lSee also abstract 4015. ^mSee also abstract 4016. ⁿSee also abstract 4017. ^oSee also abstract 4018. ^pSee also abstract 4019. ^qSee also abstract 4020. ^rSee also abstract 4021. ^sSee also abstract 4022. ^tSee also abstract 4023. ^uSee also abstract 4024. ^vSee also abstract 4025. ^wSee also abstract 4026. ^xSee also abstract 4027. ^ySee also abstract 4028. ^zSee also abstract 4029. ^{aa}See also abstract 4030. ^{ab}See also abstract 4031. ^{ac}See also abstract 4032. ^{ad}See also abstract 4033. ^{ae}See also abstract 4034. ^{af}See also abstract 4035. ^{ag}See also 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Significant durable response with fianlimab (anti-LAG-3) and cemiplimab (anti-PD-1) in advanced melanoma: post adjuvant PD-1 analysis

Omid Hamid,¹ Karl D Lewis,² Amy Weise,³ Meredith McKean,⁴ Kyriakos P Papadopoulos,⁵ John Crown,⁶ Sajeve S Thomas,⁷ Eugenia Girda,⁸ John Kaczmarz,⁹ Kevin B Kim,¹⁰ Nehal J Lakhani,¹¹ Melinda Yushak,¹² Tae Min Kim,¹³ Guillaume Rabinowitz,¹⁴ Alexander Spirin,¹⁵ Jayakumar Mani,¹⁶ Fang Fang,¹⁷ Shuang Chen,¹⁸ Juan Wang,¹⁹ Laura Brennan,¹⁴ Vladimir Jankovic,¹⁶ Anne Paccaly,¹⁶ Sheila Masinde,¹⁶ Mark Salvati,¹⁶ Matthew G Fury,¹⁶ Israel Lowy,¹⁶ Giuseppe Gulfo¹⁶

¹The Agency for Chronicall Research Institute, a Division of Oncology, Los Angeles, CA, USA; ²Harvard Medical School, Dana-Farber Cancer Institute, Boston, MA, USA; ³University of Colorado Cancer Center, Aurora, CO, USA; ⁴Harvard Medical School, Dana-Farber Cancer Institute, Boston, MA, USA; ⁵University of Colorado Cancer Center, Aurora, CO, USA; ⁶University of Colorado Cancer Center, Aurora, CO, USA; ⁷University of Colorado Cancer Center, Aurora, CO, USA; ⁸University of Colorado Cancer Center, Aurora, CO, USA; ⁹University of Colorado Cancer Center, Aurora, CO, USA; ¹⁰University of Colorado Cancer Center, Aurora, CO, USA; ¹¹University of Colorado Cancer Center, Aurora, CO, USA; ¹²University of Colorado Cancer Center, Aurora, CO, USA; ¹³University of Colorado Cancer Center, Aurora, CO, USA; ¹⁴University of Colorado Cancer Center, Aurora, CO, USA; ¹⁵University of Colorado Cancer Center, Aurora, CO, USA; ¹⁶University of Colorado Cancer Center, Aurora, CO, USA; ¹⁷University of Colorado Cancer Center, Aurora, CO, USA; ¹⁸University of Colorado Cancer Center, Aurora, CO, USA; ¹⁹University of Colorado Cancer Center, Aurora, CO, USA

Study design: three serial expansion cohorts in advanced melanoma setting

Treatment:
Fianlimab 1600 mg + cemiplimab 350 mg IV every 3 weeks, for up to 51 weeks

Initial cohort MM1* (n=40)

1L or 2L advanced melanoma patients who have never received anti-PD-(L)1

Confirmatory cohort MM2* (n=40)

1L advanced melanoma patients who have never received anti-PD-(L)1

PD-1 experienced cohort MM3* (n=18)

1L advanced melanoma patients with prior (neo)adjuvant systemic therapy¹, including 13/18 patients who received anti-PD-1

Primary endpoint

• ORR per RECIST 1.1 criteria

Secondary endpoints

- PFS
- DoR
- DCR
- Safety
- PK

Key inclusion criteria

- Metastatic or inoperable locally advanced non-visceral melanoma
- ≥18 years of age
- ECOG PS of 0 or 1
- At least one lesion measurable by RECIST 1.1

Key exclusion criteria

- Uveal melanoma
- Prior treatment with a LAG-3 targeting agent
- Radiation therapy within 2 weeks prior to enrollment



Conclusions

- A consistent and reproducible high clinical activity was observed in three independent cohorts of patients who were naïve to anti-PD-1 in the advanced melanoma setting:

- ORR: 61%, 95% CI: 51–71
- KM estimation of PFS: 15 months (95% CI: 9–NE)

- Similar clinical activity was observed in patients treated with prior adjuvant therapies including anti-PD-1
- Clinical activity was observed in:

- Poor prognosis subgroups (high LDH, liver/visceral metastases)
- Patients with high and low PD-L1/LAG-3 expression levels

- The fianlimab + cemiplimab combination demonstrated an acceptable safety profile that appears similar to that observed with cemiplimab monotherapy and other anti-PD-1 agents
- Phase 3 trials of fianlimab + cemiplimab in patients with advanced melanoma (NCT05352672) and in adjuvant setting (NCT05608291) are ongoing

Tumor re

Response endpoints

Median follow-up, months

ORR, (95% CI)

DCR

DoR, median (95% CI) months

KM-estimated PFS, (95% CI), months

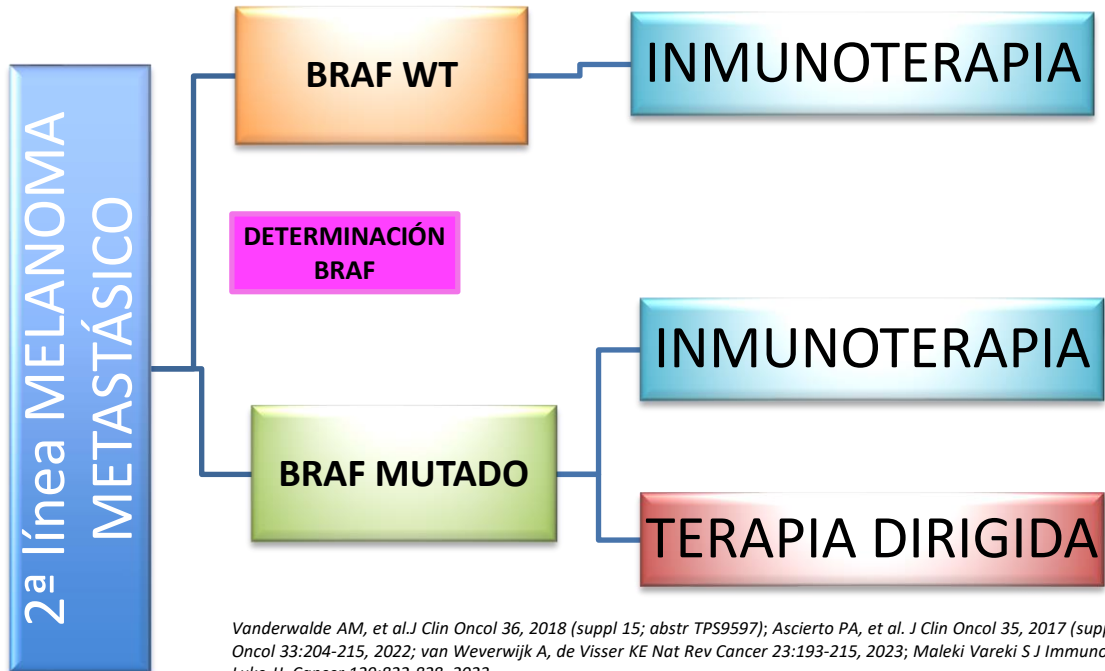
MEP, Cohort 1; MEP, Cohort 2; MEP, Cohort 3; PFS, progression-free survival; DoR, duration of response; 1, low; 2, high; 3, low and high

verall, the safety profile of fianlimab + cemiplimab treatment was generally consistent with the safety profile of single agent cemiplimab and other anti-PD-1 agents. Only adrenal insufficiency (11%) appeared to be higher than with cemiplimab monotherapy. 7/11 cases were grade 1–2. All cases were successfully managed with steroid replacement. Only one case was associated with treatment discontinuation.

Tratamiento del MELANOMA METASTÁSICO



La 2ª LINEA es ARTE



SWOG S1616 (ipi/nivo post anti-PD1) -> 6m PFS 34%

CA 224020 (nivo /rela without SNC M1) -> ORR 21%, disease control rate 45%

Keynote 006 (pembro vs Ipi 1ª/2ª línea) -> **2ª línea TERAPIA DIRIGIDA** ORR 30'5%

M14TIL (TILS) -> ORR 49%, mPFS 7'2m

KEYNOTE-D36 EVX-01 + anti-PD1

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Vanderwalde AM, et al. J Clin Oncol 35, 2017 (suppl 15; abstr 9520); Menzies AM, et al. N Engl J Med 386:1668-1669, 2022; Long GV, et al. Ann Oncol 33:204-215, 2022; van Weverwijk A, de Visser KE. Nat Rev Cancer 23:199-215, 2023; Maleki Vareki S. J Immunother Cancer 6:157, 2018; Long GV, et al. Future Oncol 18:3473-3480, 2022; Augustin RC, Luke JJ. Cancer 129:822-828, 2023

Initial efficacy and safety of RP1 + nivolumab in patients with anti-PD-1–failed melanoma from the ongoing phase 1/2 IGNYTE study

Melanoma/Skin Cancers Poster Discussion Session

Safety



Treatment related adverse events for patients treated with RP1 combined with nivolumab (n=91)

Preferred term, n (%)	Grade 1–2 (>10%)	Grade 3	Grade 4	Grade 5	Total (n=91)
Chills	34 (37.4)	0	0	0	34 (37.4)
Fatigue	31 (34.1)	2 (2.2)	0	0	32 (35.2)
Pyrexia	28 (28.6)	0	0	0	28 (28.6)
Nausea	24 (26.4)	0	0	0	24 (26.4)
Influenza like illness	12 (13.2)	0	0	0	12 (13.2)
Diarrhoea	10 (11.0)	1 (1.1)	0	0	10 (11.0)

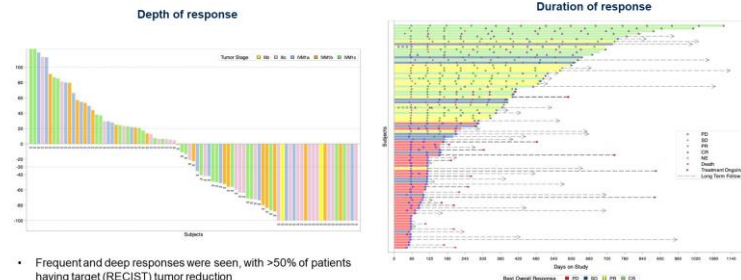
- Mostly grade 1 or 2 side effects which are indicative of systemic immune activation, combined with the underlying safety profile of nivolumab
 - Grade 3 events were one each of maculopapular rash, immune-mediated hepatitis, enterocolitis, immune-mediated enterocolitis, edema, paresthesia, memory impairment, aseptic meningitis, infusion-related reaction, abdominal pain, MALT lymphoma, increased amylase, increase LFT, arthritis, arthralgia, palmar-plantar erythrodysesthesia, muscular weakness and rash. One Grade 4 event each of lipase increased and cytokine release syndrome. There was no treatment-related Grade 5 event.
- RP1 combined with nivolumab is well tolerated, including when RP1 is injected into deep and/or visceral lesions

Objective response rates

BOR n (%)	All patients (n=91)	Prior adjuvant anti-PD-1 only (n=32)	Prior anti-PD-1 other than adjuvant (n=59)	Prior anti-PD-1 & anti-CTLA-4 (n=32)	Stage IIIb/IIIc/IVa (n=45)	Stage IVb/IVc (n=46)	Primary resistance to anti-PD1 (n=50)**	Secondary resistance to anti-PD1 (n=38)**
CR	17 (18.7)	9 (28.1)	8 (13.6)	3 (9.4)	13 (28.9)	4 (8.7)	12 (24.0)	5 (13.2)
PR	17 (18.7)	7 (21.9)	10 (16.9)	8 (25.0)	8 (17.8)	9 (19.6)	6 (12.0)	11 (28.9)
SD	14 (15.4)	6 (18.8)	8 (13.6)	5 (15.6)	5 (11.1)	9 (19.6)	7 (14.0)	7 (18.4)
PD	39 (42.9)	10 (31.3)	29 (49.2)	13 (40.6)	19 (42.2)	20 (43.5)	24 (48.0)	12 (31.6)
ORR	37.4%	50.0%	30.5%	34.4%	46.7%	28.3%	36.0%	42.1%

- The overall objective response rate (ORR) was 37.4%
- ORR of at least 28.3% in all subgroups analyzed, including in patients:
 - Having failed anti-CTLA-4 therapy as well as anti-PD1 therapy (34.4% ORR)
 - With Stage IVm1b/c disease (28.3% ORR)
 - Who progressed while on prior adjuvant anti-PD1 therapy (50% ORR)
 - With both primary resistance (36.0% ORR) and secondary resistance (42.1% ORR) disease
 - Activity seen in both BRAF wild-type & mutant patients, and patients with PD-L1 positive & negative disease (see poster)

Depth, duration & kinetics of response



- Frequent and deep responses were seen, with >50% of patients having target (RECIST) tumor reduction
- Responses were seen across disease stages, including complete responses in patients with stage IVm1b/c disease
- Responses are generally durable, and often deepen over time, indicative of systemic overall benefit
- 85% of responses are ongoing, with 71% of responders out over 1 year from starting therapy

Initial efficacy and safety of RP1 + nivolumab in patients with anti-PD-1-failed melanoma from the ongoing phase 1/2 IGNYTE study

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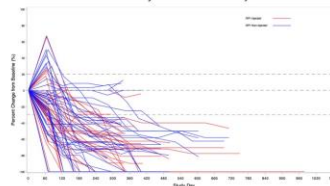
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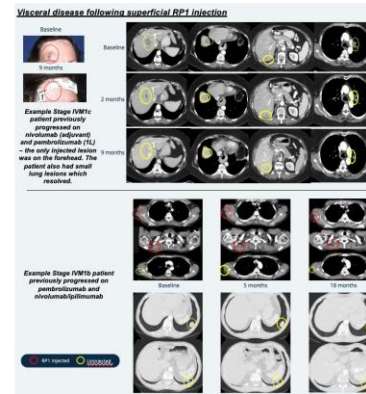
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Systemic responses & effects in uninjected lesions

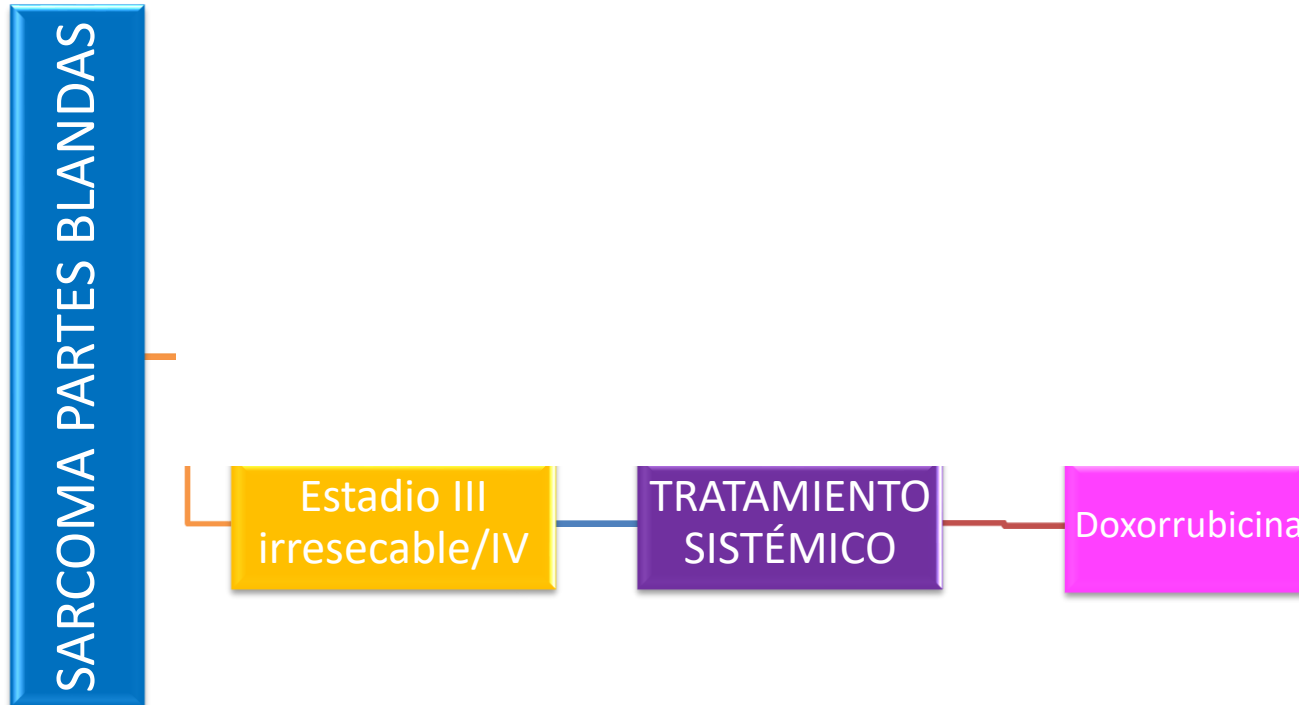
- Systemic effects were seen across the entire disease burden, with response of:
 - Visceral lesions following both deep and superficial injection
 - Bulky lesions
 - Up to >20cm of total tumor burden and up to >10cm of uninjected disease
- 70.4% of responding patients had lesions which were not injected, including patients where only a small minority of lesions were injected
- The ORR on the basis of non-injected lesions only was 25.9%



Response of individual injected (red lines) and uninjected lesions (blue lines) for responding patients, showing similar depth, durability and kinetics of response



Algoritmo tratamiento de los SARCOMAS 2023



ESMO Guidelines

There is no formal demonstration that multiagent chemotherapy is superior to single-agent chemotherapy with doxorubicin alone in terms of overall survival.

GEIS Guidelines

Polychemotherapy schemes should only be used in the context of a clinical trial.

Algoritmo tratamiento de los SARCOMAS 2023



SARCOMA PARTES BLANDAS

- ✓ **GIST** → IMATINIB
- ✓ **LIPO MIXOIDE / CLS REDONDAS** → TRABECTEDINA
- ✓ **TUMORES DESMOIDES** → SORAFENIB, PAZOPANIB, IMATINIB, MTX LD - VINBLASTINA
- ✓ **TUMOR FIBROSO SOLITARIO** → PAZOPANIB, SUNITINIB, TEMOZOLAMIDA + BEVACIZUMAB
- ✓ **DERMATOFS PROTUBERANS** → IMATINIB
- ✓ **PEComas** → INHIBIDORES mTOR
- ✓ **MIOFIBROBLÁST INFL ALK-TR** → CRIZOTINIB
- ✓ **SARC ALVEOLAR P BLANDAS** → CEDIRANIB, SUNITINIB – NIVOLUMAB
- ✓ **SARCOMA DE CÉLULAS CLARAS** → SUNITINIB + NIVOLUMAB
- ✓ **SARCOMA EPITELIOIDES** → TAZEMOSTAT
- ✓ **PNSMT** → TAXANOS



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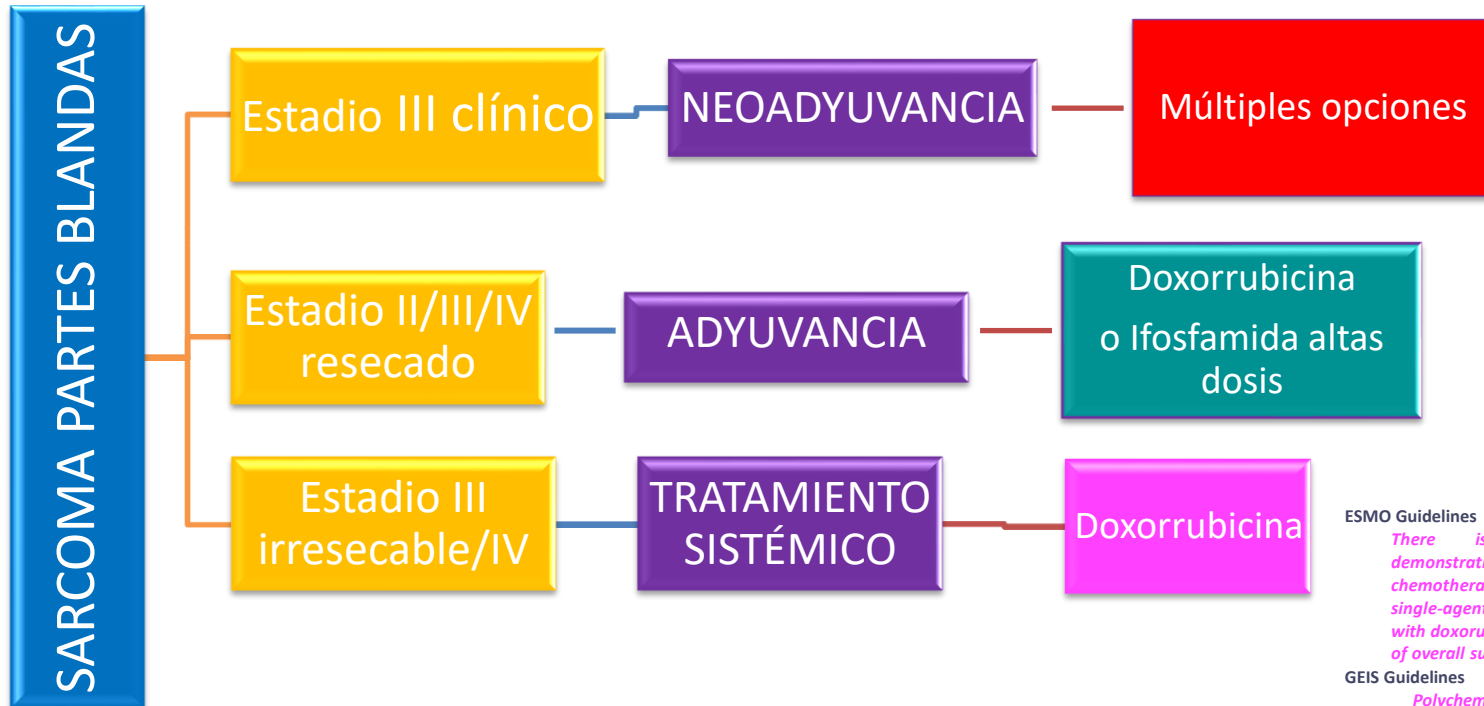
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Algoritmo tratamiento de los SARCOMAS 2023



SARCOMA PARTES BLANDAS

Estadio III clínico

NEOADYUVANCIA

Múltiples opciones

- ✓ **RADIOTERAPIA** → evitar la QT si solo es para control de márgenes
 - ✓ → CONSIDERARLA SIEMPRE QUE SE PLANEE RADIAR POSTOP
 - ✓ → PACIENTES INAPROPIADOS QT / GRADO BAJO-INTERMEDIO / HISTOLOGÍAS QUIMIORESISTENTES
- ✓ **TRATAMIENTOS ESPECÍFICOS** → potenciales opciones de tratamiento (stay tuned!)
- ✓ **TRABECTEDINA** → tratamiento específico para LIPOSARCOMA MIXOIDE / DE CÉLULAS REDONDAS
- ✓ **DOXORRUBICINA + IFOSFAMIDA-HD** → tratamiento neoadyuvante "estándar" si se pretende reducir el volumen
- ✓ **DOXORRUBICINA 75** → en el caso de pacientes inapropiados para IFOSFAMIDA HD
- ✓ **QUIMIO-RADIOTERAPIA** → parece que es mejor que DOXORRUBICINA/DOXORRUBICINA-IFOSFAMIDA HD en grado alto quimiosensibles
 - ✓ → "sandwich" con DOXORRUBICINA + IFOSFAMIDA HD
 - ✓ → concomitante con GEMCITABINA
 - ✓ → concomitante con IFOSFAMIDA HD
 - ✓ → concomitante con TRABECTEDINA

SARCOMA LOCALMENTE AVANZADO: ¿Qué objetivos busco con la elección del tratamiento?



Objetivo 1º:
reseabilidad,
evitar amputación,
márgenes
correctos, menor
morbilidad

Objetivo 1º pCR

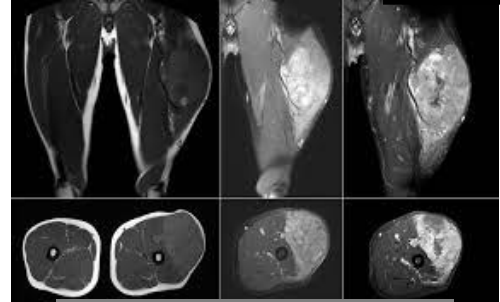


Objetivo 2º PFS:
evitar/retrasar M1

Objetivo 2º OS:
evitar/retrasar muerte



Toxicidades
Calidad de vida



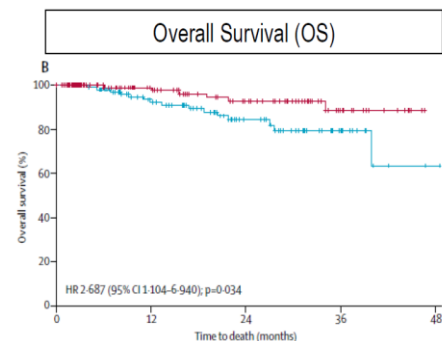
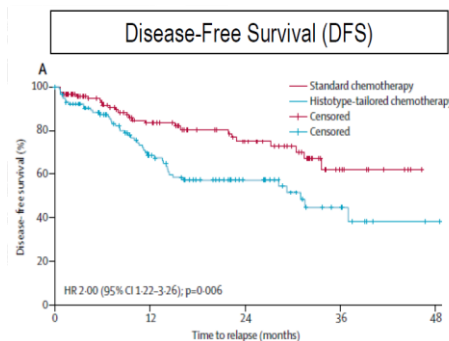
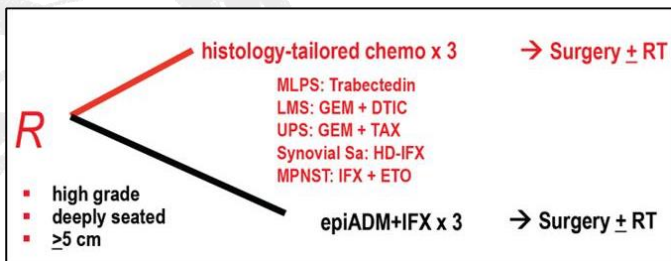
RESECABILIDAD

Tratamiento del SARCOMA NEOADYUVANTE



Histotype-tailored neoadjuvant chemotherapy versus standard chemotherapy in patients with high-risk soft-tissue sarcomas (ISG-ST5 1001): an international, open-label, randomised, controlled, phase 3, multicentre trial

Alessandro Gronchi, Stefano Ferrasi, Vittorio Quagliuolo, Javier Martin Breta, Antonio Lopez Poveda, Giovanni Grignani, Umberto Basso, Jean-Yves Blay, Oscar Tondora, Robert Diaz Beveridge, Virginia Ferraresi, Ivona Lugowska, Domenico Franco Merlo, Valeria Fontana, Emanuela Marchesi, Davide Maria Donati, Elena Palassini, Emanuela Palmerini, Rita De Sanctis, Carlo Morosi, Silvia Stacchiotti, Silvia Baggi, Jean Michelle Coindre, Angelo Paolo Dei Tos, Piers Picci, Paolo Bruzzi, Paolo Giovanni Casali



NEOADYUVANCIA: decisión individual compartida con el paciente y determinada en un Comité multidisciplinar

- Nivel de evidencia de ESMO es IIB.
- Siempre basada en epirubicina-ifosfamida
- RT concomitante en casos seleccionados

Tratamiento del SARCOMA NEOADYUVANTE



- ✓ **RADIOTERAPIA:** sin quimioterapia si se pretende controlar márgenes; opción para pacientes *unfit* para QT, grado histológicos bajo- intermedio, histologías quimio resistentes
- ✓ **TRATAMIENTOS ESPECÍFICOS:** stay tuned!
- ✓ **QUIMIOTERAPIA:**
 - ✓ TRABECTEDINA : para liposarcoma mixoide/sarcoma de células redondas
 - ✓ DOXORRUCINA + IFOSFAMIDA-HD : tratamiento estándar si se pretende reducir el tamaño tumoral
 - ✓ DOXORUBINA 75 : para pacientes *unfit* para ifosfamida-HD
- ✓ **QUIMIO-RADIOTERAPIA:** probablemente mejor que doxorubicina o incluso que doxorubicina e ifosfamida-HD en tumores de alto grado quimiosensibles
 - ✓ opción de ‘sándwich’ con doxorubicina e ifosfamida_HD
 - ✓ concomitante con gemcitabina, ifosfamida-HD o trabectedina

RECIST radiological responses



A phase III randomized trial on neo-adjuvant chemotherapy in high-risk soft tissue sarcomas (ISG-STs 1001): feasibility and activity of concurrent chemotherapy and radiation therapy

Elena Palassini; Sara Pizzamiglio; Emanuela Palmerini; Vittorio Quagliuolo; Javier Martin Broto; Antonio Lopez Pousa; Giovanni Grignani; Antonella Brunello; Jean-Yves Blay; Oscar Tendero; Roberto Diaz Beveridge; Virginia Ferraresi; Iwonna Lugoowska; Valeria Fontana; Giuseppe Bianchi; Silvia Stacchiotti; Angelo Paolo Dei Tos; Paolo Verderio; Paolo Giovanni Casali and Alessandro Gronchi

	ALL (N=265) *		pre-op ChT and RT (N=133)	pre-op ChT alone and post-op RT (N=132)			
→ Partial response (PR)	40	15.1%	27	20.3%	13	9.8%	p=0.023
Stable disease (SD)	202	76.2%	92	69.2%	110	83.3%	
Progressive disease (PD)	23 **	8.7%	14 **	10.5%	9	6.8%	

Treatment received: surgery and RT

	ALL (N=287)		pre-op ChT and RT (N=146)	pre-op ChT alone and post-op RT (N=141)
Surgery				
→ yes	285	99.3%	144	98.6%
no	1*	0.3%	1	0.7%
NA	1**	0.3%	1	0.7%
Type of surgery				
→ conservative	278	96.9%	140	95.9%
destructive	7	2.4%	4	2.7%
NA	2	0.7%	2	1.4%
Margins				
R0	235	81.9%	119	81.5%
R1	47	16.4%	24	16.4%
R2	2	0.7%	0	0.0%
missing or NA	3	1.0%	3	2.1%
RT completion				
→ yes	275	95.8%	141	96.0%
no	12	4.2%	5	3.4%
RT dose				
→ median, Gy (IQR, Gy)	50 (50-50)		50 (50-50)	60 (54-64.8)

* Patient progressed with distant relapse during neo-ad ChT
** Patient lost to FU

Treatment received: ChT

	ALL (N=287)		pre-op ChT and RT (N=146)	pre-op ChT alone and post-op RT (N=141)
ChT completion				
ChT completed per protocol	260	90.6%	127	87%
ChT completed with >3 cycles	8	2.8%	7	4.8%
ChT discontinued	19	6.6%	12	8.2%
Reason for discontinuation				
→ toxicity (SAE)	13 (9)*	4.5% (3.1%)	8 (5)†	5.5% (3.4%)
consent/withdrawal	2	0.7%	1	0.7%
progression	4	1.4%	3	2%
ChT reduction (> 25%) **				
→ no	220	82.1%	104	77.6%
→ yes	48	17.9%	30	22.4%

* All SAE were related to haematological toxicities
** 19 patients who discontinued ChT were excluded

RECIST radiological responses



A phase III randomized trial on neo-adjuvant chemotherapy in high-risk soft tissue sarcomas (ISG-ST5 1001): feasibility and activity of concurrent chemotherapy and radiation therapy

Elena Palassini; Sara Pizzamiglio; Emanuela Palmerini; Vittorio Quagliuolo; Javier Martin Broto; Antonio Lopez Pousa; Giovanni Grignani; Antonella Brunello; Jean-Yves Blay; Oscar Tendero; Roberto Diaz Beveridge; Virginia Ferraresi; Iwonna Lugoowska; Valeria Fontana; Giuseppe Bianchi; Silvia Stacchiotti; Angelo Paolo Dei Tos; Paolo Verderio; Paolo Giovanni Casali and Alessandro Gronchi

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Stable disease (SD)	202	76.2%	92 (69.2%)	110 (83.3%)	
Progressive disease (PD)	23 **	8.7%	14 ** (10.5%)	9 (6.8%)	

Treatment received: surgery and RT

	ALL (N=287)		pre-op ChT and RT (N=146)	pre-op ChT alone and post-op RT (N=141)
Surgery				
→ yes	285	99.3%	144 (98.6%)	141 (100%)
no	1 *	0.3%	1 (0.7%)	0 (0.0%)
NA	1 **	0.3%	1 (0.7%)	0 (0.0%)
Type of surgery				
→ conservative	278	96.9%	140 (95.9%)	138 (97.9%)
destructive	7	2.4%	4 (2.7%)	3 (2.1%)
NA	2	0.7%	2 (1.4%)	0 (0.0%)
Margins				
RO	235	81.9%	119 (81.5%)	116 (82.3%)
R1	47	16.4%	24 (16.4%)	23 (16.3%)
R2	2	0.7%	0 (0.0%)	2 (1.4%)
missing or NA	3	1.0%	3 (2.1%)	0 (0.0%)
RT completion				
→ yes	275	95.8%	141 (96.0%)	134 (95.0%)
no	12	4.2%	5 (3.4%)	7 (5.0%)
RT dose				
→ median, Gy (IQR, Gy)	50 (50-50)		50 (50-50)	50 (50-50)

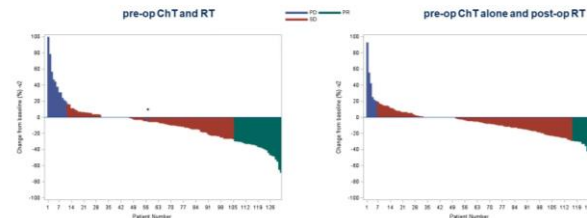
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ChT completed per protocol	260	90.6%	127 (87%)	133 (94.3%)
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ChT discontinued	19	6.6%	12 (8.2%)	7 (5.0%)
Reason for discontinuation				
→ toxicity (SAE)	13 (9) *	4.5% (3.1%)	8 (5)† (5.5% (3.4%))	5 (4) (3.5% (2.8%))
consent withdrawn	2	0.7%	1 (0.7%)	1 (0.7%)
progression	4	1.4%	3 (2.1%)	1 (0.7%)
ChT reduction (> 25%) **				
→ no	220	82.1%	104 (77.6%)	116 (86.6%)
→ yes	48	17.9%	30 (22.4%)	18 (13.4%)

* All SAE were related to haematological toxicities
** 19 patients who discontinued ChT were excluded

Dimensional change on maximum diameter



RECIST radiological responses



A phase III randomized trial on neo-adjuvant chemotherapy in high-risk soft tissue sarcomas (ISG-ST5 1001): feasibility and activity of concurrent chemotherapy and radiation therapy

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Stable disease (SD)	202	76.2%	92	69.2%	110	83.3%	
Progressive disease (PD)	23 **	8.7%	14 **	10.5%	9	6.8%	

In conclusion

- Concurrent pre-op ChT and RT was confirmed to be feasible, in terms of G3/G4 haematological toxicities and acute RT-related toxicities, with a limited increased rate of post-op local complications. A high ChT DI (>90%) was achieved.
- A modest, statistically significant, increased number of PRs was found with pre-op ChT and RT, with some differences across histologies
- When pre-op RT would be selected, ChT can be added safely, with a view to preservation of function, quality of margins and surgical ease

SARCOMA METASTÁSICO:

¿Qué objetivos busco con la elección del tratamiento?



Objetivo 1º:
Alta tasa de
respuestas
ORR, PFS



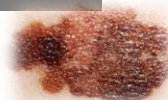
Objetivo 2º:
Respuestas
duraderas, OS



Toxicidades
Calidad de vida



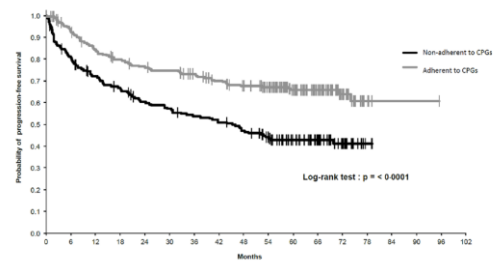
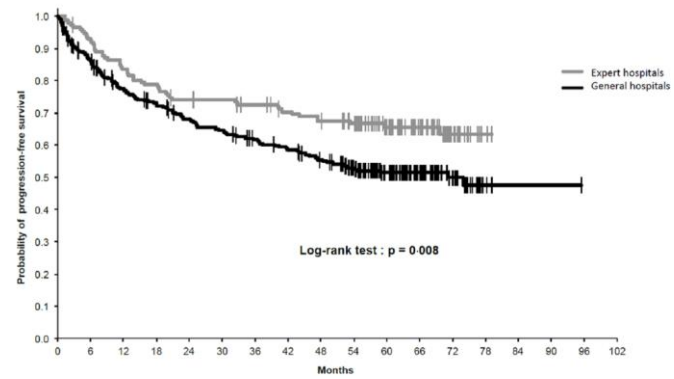
**LARGOS RESPONDEDORES,
LARGOS SUPERVIVIENTES**



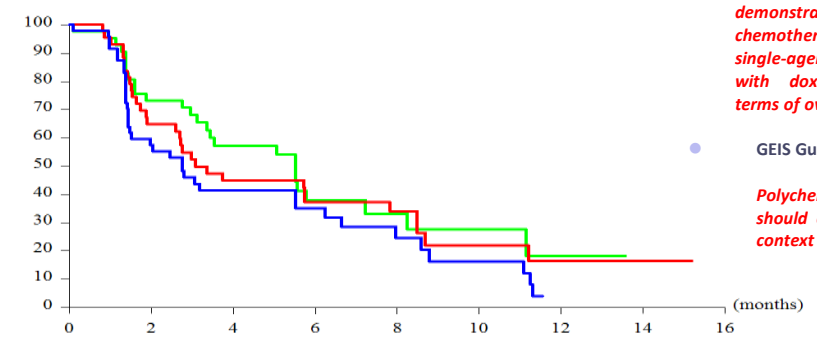


Tratamiento del SARCOMA METASTÁSICO

CENTROS DE REFERENCIA CON EXPERIENCIA



Progression free survival



O	N	Number of patients at risk :								Treatment
26	43	30	20	10	6	5	1	0	0	Green line
31	43	27	18	13	10	5	3	1	1	Red line
37	47	26	16	11	6	4	0	0	0	Blue line

● ESMO Guidelines

There is no formal demonstration that multiagent chemotherapy is superior to single-agent chemotherapy with doxorubicin alone in terms of overall survival.

● GEIS Guidelines

Polychemotherapy schemes should only be used in the context of a clinical trial.

1ª LINEA: DOXORRUBICINA (antraciclina + Ifosfamida en determinadas situaciones) sigue siendo el estándar de tratamiento para pacientes no tributarios de resección (ensayos en marcha para los diferentes subtipos).



Tratamiento del SARCOMA METASTÁSICO

FIRST LINE OF ADVANCED DISEASE (STS): Which is the therapeutic goal in each patient?

Is the patient **symptomatic**?

Is **surgery** potentially feasible?

Asymptomatic patient
No surgical rescue options

Maximize options of response → Chemo combinations

Epi/Doxo + ifosfamide (ORR 26%)¹
Doxo+ DTIC (LMS), (ORR 30.9%)²
Doxo+Trabectedin (LMS) (ORR 36%)³

Palliative RT
Palliative surgery
RT/ILP primary tumor

Surgery of residual disease

Doxorubicin monotherapy

Close follow-up

ESMO Guidelines

There is no formal demonstration that multiagent chemotherapy is superior to single-agent chemotherapy with doxorubicin alone in terms of overall survival.

GEIS Guidelines

Polychemotherapy schemes should only be used in the context of a clinical trial.

(months)
16
Treatment
Doxo
Trab_24hrs
Trab_3hrs

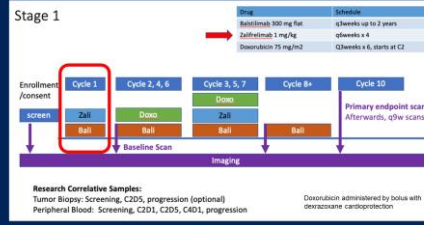
1. Judson I et al. Lancet Oncol 2014
2. D'Ambrosio L et al. Cancer 2020
3. Pautier P et al. Lancet Oncol 2022

...minadas situaciones)
...butarios de resección
...entes subtipos).

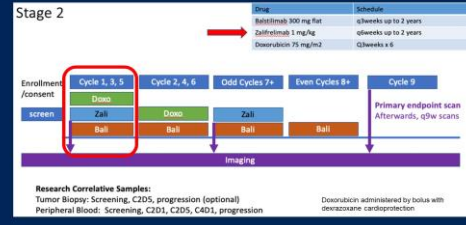
A single-arm, open-label phase 2 trial of doxorubicin plus zalifrelimab, a CTLA-4 inhibitor, with balstilimab, a PD-1 inhibitor in patients with advanced/metastatic soft tissue sarcomas

Breehyn A. Wilky, MD
University of Colorado School of Medicine

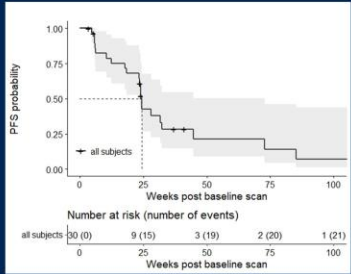
Treatment Schema – Stage 1



Treatment Schema – Stage 2



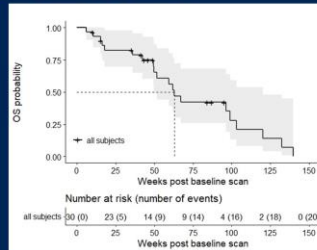
Results – Primary Endpoint



PFS rate at 6 months (N=28):
46.4% [95% CI 28-66]
* Fail to reject null

Median PFS:
24.4 weeks [23.4 – 72.9]

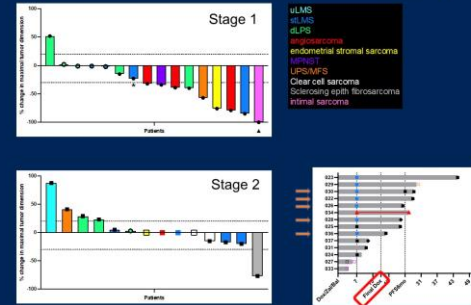
Results – Overall Survival



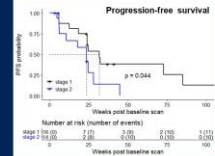
Median OS:
63 weeks [50-120]

Median follow up time:
95 weeks [84.3 – NA]

Impact of Treatment Schema (Stage 1 vs 2)



Variable	Stage 1	Stage 2
mPFS (weeks)	31.7 [24-NA]	23.5 [11-NA]
ORR	56.2 [30-80]	7 [0 – 34]
DCR	88 [62-98]	71 [42-92]



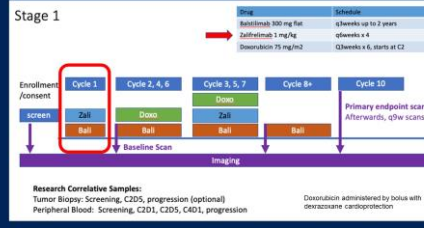
Treatment-Related Adverse Events

Category	Adverse Events	All grades	Grade 3+	Notes
Fever/febrile illness	ALL	4 (12)	4 (12)	PR #17 - colitis/pneumonia
	Cytitis	2 (6)	2 (6)	PR #17 - colitis/pneumonia
	Pharyngitis	1 (3)	1 (3)	PR #17 - colitis/pneumonia
	Diarrhea	2 (6)	1 (3)	PR #17 - colitis/pneumonia
	Upper respiratory tract infection	2 (6)	2 (6)	PR #17 - colitis/pneumonia
	Pyrexia	2 (6)	1 (3)	PR #17 - colitis/pneumonia
GI	ALL	26 (76)	4 (12)	Primary: Diarrhea/colitis/nausea/vomiting
	Diarrhea	19 (57)	2 (6)	
	Constipation	7 (21)	1 (3)	
Fatigue	ALL	22 (67)	0 (0)	Attributed to Dox and IO
	Diarrhea	17 (51)	0 (0)	Attributed to Dox and IO
Nausea	ALL	15 (45)	9 (27)	Primary: Dox-related
	Diarrhea	13 (39)	9 (27)	Diarrhea
Hypotension	ALL	4 (12)	0 (0)	Attributed to Dox and IO
	Diarrhea	4 (12)	0 (0)	Attributed to Dox and IO
Arthralgia/myalgia	ALL	4 (12)	0 (0)	Attributed to Dox and IO
	Diarrhea	2 (6)	0 (0)	Dox-related, no myocarditis

A single-arm, open-label phase 2 trial of doxorubicin plus zalifrelimab, a CTLA-4 inhibitor, with balstilimab, a PD-1 inhibitor in patients with advanced/metastatic soft tissue sarcomas

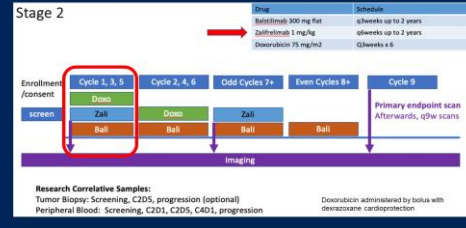
Breejyn A. Wilky, MD
University of Colorado School of Medicine

Treatment Schema – Stage 1



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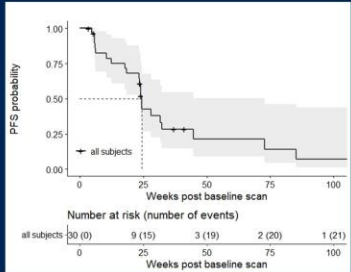
Treatment Schema – Stage 2



ASCO 2023 ANNUAL MEETING #ASCO23 Research by Breejyn A. Wilky, MD, University of Colorado



Results – Primary Endpoint



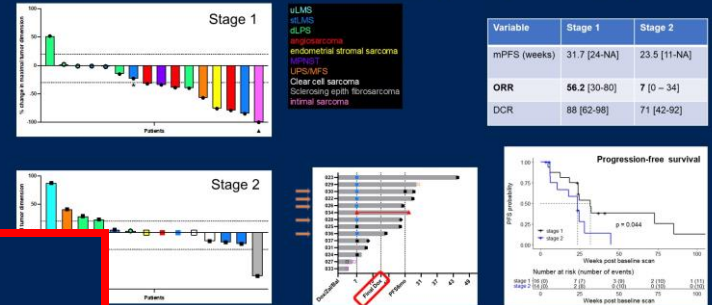
PFS rate at 6 months (N=28):
46.4% [95% CI 28-66]
* Fail to reject null

Median PFS:
24.4 weeks [23.4 – 72.9]

Conclusions

- Combination doxorubicin/zalifrelimab/balstilimab demonstrates intriguing early efficacy signals and expected toxicity
- CTLA-4 appears to impart benefit in combination with chemotherapy and PD1 therapy
- Additional work is critical to understand impact of ICI “priming” cycle, biomarkers/mechanism of response/resistance
 - Preclinical modeling and patient correlates

Impact of Treatment Schema (Stage 1 vs 2)



Treatment-Related Adverse Events

Category	Adverse Events	All grades	Grade 3+	Notes
Immune-related AEs requiring steroids/ICU	ALL	4 (12)	4 (12)	PR #1 - colitis
	Colitis	2 (6)	2 (6)	PR #17 - colitis
	Pneumonitis	1 (3)	1 (3)	PR #2 - colitis/colitis/colitis
	Diarrhea	2 (6)	1 (3)	PR #10 - hypophysitis
	Myocarditis	2 (6)	2 (6)	PR #18 - colitis/colitis/colitis
GI	ALL	26 (78)	4 (12)	Primary/Secondary/colitis/colitis/colitis/colitis
	Colitis	1 (3)	1 (3)	
	Diarrhea	11 (33)	1 (3)	
	Pharyngitis/tonsillitis	13 (39)	1 (3)	
Fatigue	ALL	22 (67)	0 (0)	Attributed to Dox and IO
	Diarrhea	1 (3)	0 (0)	Attributed to Dox and IO
Nausea	ALL	15 (45)	9 (27)	Primary/Dox-related
	Diarrhea	1 (3)	0 (0)	
Thrombocytopenia	ALL	4 (12)	0 (0)	Attributed to Dox and IO
	Diarrhea	1 (3)	0 (0)	Attributed to Dox and IO
Decreased appetite/nausea	ALL	2 (6)	0 (0)	Dox-related, no myocarditis
	Diarrhea	1 (3)	0 (0)	

ImmunoSarc2: A Spanish Sarcoma Group (GEIS) phase Ib trial of doxorubicin and dacarbazine plus nivolumab in first line of advanced leiomyosarcoma

Javier Martín-Broto¹, Roberto Díaz-Beveridge², David Moura³, Rafael Ramos³, Javier Martínez-Trufero⁴, Irene Carrasco⁵, Antonio Lopez-Pousa⁶, Enrique González⁷, Antonio Gutierrez², Claudia Valverde⁸, Josefina Cruz², Nadia Hindi⁹

¹ Hospital Universitario Fundación Jiménez Díaz; ² Hospital Universitario I Péllico; ³ Hospital Universitario San Espasa; ⁴ Hospital Universitario Miguel Servet; ⁵ Hospital Universitario Virgen del Rocío; ⁶ Hospital de la Santa Cruz y San Pablo; ⁷ Hospital Universitario 12 de Octubre; ⁸ Hospital Universitario Vall d'Hebron; ⁹ Hospital Universitario de Cáncer

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METHODS

IMMUNOSARC TRIAL cohort 7b



- Phase Ib trial with 2 dose-levels: (3+3 design¹ with a minimum of 20 evaluable patients in RP2D)
 - Level 0: Doxorubicin 75 mg/m²/d d1+ DTIC 400 mg/m²/d d1-2 + Nivolumab 360 mg on day 2 / 21d + GCSF
 - Level -1: Doxorubicin 75 mg/m²/d d1+ DTIC 400 mg/m²/d d1-2 + Nivolumab 240 mg on day 2 / 21d + GCSF
- After 6 cycles, Nivolumab/21d during 1 year as maintenance phase
- Main Inclusion/Exclusion criteria:
 - Anthracycline naïve; Advanced centrally confirmed LMS; ECOG 0-1; Measurable disease
- Main Endpoint: To determine the MTD/RP2D based on DLTs observed during the first 21-day cycle
- Secondary Objectives: Safety profile (CTCAE 5.0); ORR (RECIST 1.1); mPFS; mOS; Translational

RESULTS-2 Toxicity Evaluation: TREAES (n=20, but 3 too early)

TREAES	Any grade	Grade 1-2	Grade 3	Grade 4	Grade 5
Anemia	15 (50.0%)	6 (30.0%)	4 (20.0%)	0	0
Neutropenia	8 (40.0%)	2 (10.0%)	3 (15.0%)	3 (15.0%)	0
Leukopenia	6 (30.0%)	3 (15.0%)	2 (10.0%)	1 (5.0%)	0
Thrombocytopenia	4 (20.0%)	3 (15.0%)	0	0	0
Lymphocytosis	1 (5.0%)	1 (5.0%)	0	0	0
Febrie neutropenia	1 (5.0%)	0	1 (5.0%)	0	0
Fatigue	9 (45.0%)	8 (40.0%)	1 (5.0%)	0	0
Alopecia	8 (40.0%)	7 (35.0%)	1 (5.0%)	0	0
Nausea	7 (35.0%)	7 (35.0%)	0	0	0
Skin/mucosal alterations	4 (20.0%)	4 (20.0%)	0	0	0
ALT increased	4 (20.0%)	4 (20.0%)	0	0	0
Dysphagia	3 (15.0%)	3 (15.0%)	0	0	0
Diarrhea	3 (15.0%)	3 (15.0%)	0	0	0
Constipation	3 (15.0%)	3 (15.0%)	0	0	0
Vomiting	2 (10.0%)	2 (10.0%)	0	0	0
Pain	2 (10.0%)	2 (10.0%)	0	0	0
Mucositis oral	2 (10.0%)	2 (10.0%)	0	0	0
Dry mouth	2 (10.0%)	2 (10.0%)	0	0	0
Blood bilirubin increased	2 (10.0%)	1 (5.0%)	0	0	0
Anorexia	2 (10.0%)	2 (10.0%)	0	0	0
AST increased	2 (10.0%)	2 (10.0%)	0	0	0
Pneumonitis	1 (5.0%)	1 (5.0%)	0	0	0
GGT increased	1 (5.0%)	0	1 (5.0%)	0	0
Fever	1 (5.0%)	1 (5.0%)	0	0	0

No DLTs were reported. No toxic deaths. 2 drug-related SAEs (hospitalization): G2 fever and G3 febrile neutropenia. 1 nivolumab-related event: G1 (asymptomatic) pneumonitis.

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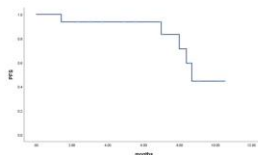
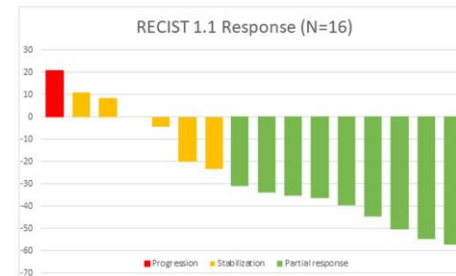
Conclusions

- The combination of Doxorubicin 75 mg/m²/d1+ DTIC 400 mg/m²/d1-2 + Nivolumab 360 mg on day2 + GCSF every 21 days (RP2D) is **feasible and well tolerated**.
- The preliminary **activity is encouraging** (seemingly improving historical efficacy/outcomes) as systemic upfront line in advanced LMS patients.
- A **significant correlation** is found between % increase of HMGB1 and a longer PFS, probably indicating an activation of ICD.
- Future designs will be focused on the **improvement of the maintenance strategy**.

RESULTS-3

Efficacy Variables

- Median follow-up: 8 months (2-12)
- #Cycles (combo): 94. Median: 6 (1-6)
- ORR from 16 evaluable patients:
 - 9 PR (56.2%); 6 SD (37.5%); 1 PD (6.3%)
- mPFS 8.67 months (95% CI: 7.96-9.37)
- Median to response: 1.7 months (95% CI 1.1-9)



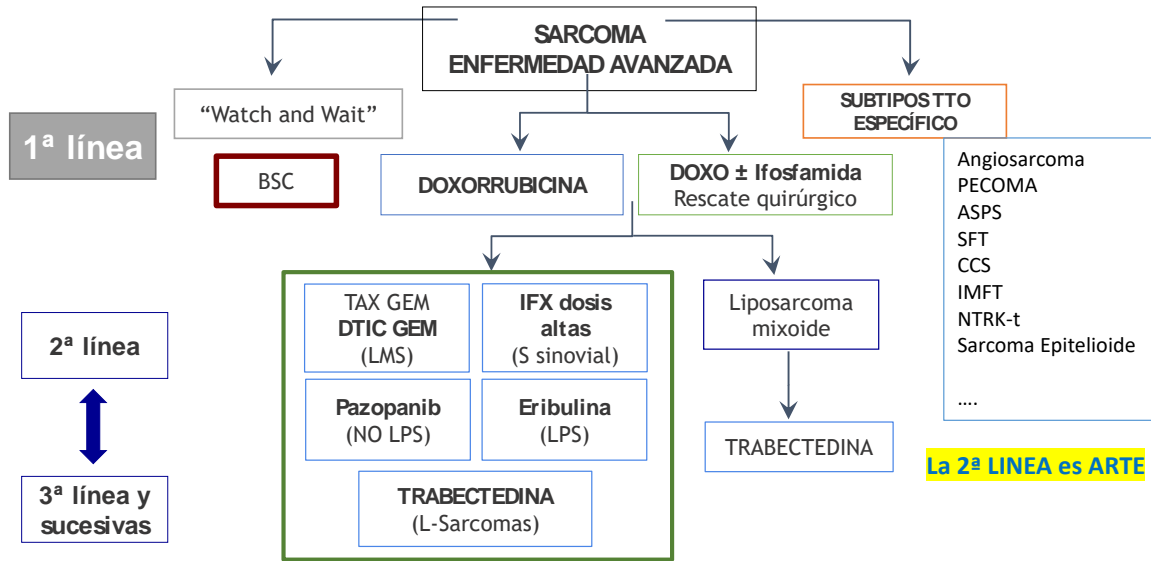
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Tratamiento del SARCOMA METASTÁSICO



- EFICACIA
- TOXICIDAD
- CALIDAD DE VIDA
- COSTE
- DISPONIBILIDAD
- ESTABILIZACIÓN
- NECESIDAD DE RESPUESTA
- TRATAMIENTO DE MANTENIMIENTO
- PREFERENCIAS DEL PACIENTE

Tratamiento del SARCOMA METASTÁSICO



BEYOND FIRST LINE OF THERAPY: In which scenarios could we incorporate local therapies?

Is **surgery** potentially feasible?

Short DFI, multiple nodules

Disease control with systemic therapy

Surgery

Is the patient **symptomatic**?

Maximize response options

Trabectedin + RT
or
Selected histotype-directed chemo

Is there an **oligoprogression** during systemic therapy?

Local therapy on progressing lesion (surgery, RT)

Trabectedin + RT

Maintain systemic therapy

EFICACIA

TOXICIDAD

CALIDAD DE VIDA

COSTE

DISPONIBILIDAD

ESTABILIZACIÓN

NECESIDAD DE RESPUESTA

TRATAMIENTO DE MANTENIMIENTO

PREFERENCIAS DEL PACIENTE

Tratamiento del SARCOMA METASTÁSICO



BEYOND FIRST LINE OF THERAPY: In which scenarios could we incorporate local therapies?

Is **surgery** potentially feasible?

Short DFI, multiple nodules

Disease control with systemic therapy

Surgery

Is the patient **symptomatic**?

Maximize response options

Trabectedin + RT
or
Selected histotype-directed chemo

Is there an **oligoprogression** during systemic therapy?

Local therapy on progressing lesion (surgery, RT)

Trabectedin + RT

Maintain systemic therapy

EFICACIA

TOXICIDAD

CALIDAD DE VIDA

COSTE

DISPONIBILIDAD

ESTABILIZACIÓN

NECESIDAD DE RESPUESTA

TRATAMIENTO DE MANTENIMIENTO

PREFERENCIAS DEL PACIENTE

- Immunotherapy in NOT approved in sarcomas
- Some clue of efficacy has been described, specially in specific histologic subtypes
- Lack of validated predictive factors of efficacy
 - Histologic subtype? (ASPS, Angio)
 - TLS?
 - UV induced sarcoma? (Angio of the scalp)
- Sarcoma → “cold” tumors
 - Several strategies to potentially enhance efficacy of immunotherapy (combos)



Tratamiento del SARCOMA METASTÁSICO



B
In

Immunotherapy, Cytotoxic, and Targeted Therapy in Sarcoma				
Regimen	ORR %	SD %	PD %	Reference
Nivolumab	5	26	69	D'Angelo et al. Lancet Oncology 2018
Ipi/Nivo + Cryoablation	11	26	63	Bui et al. Clinical Cancer Research 2023
Pembro/Cyclophosphamide	2	32	62	Toulmonde et al. JAMA Oncology 2018
Durvalumab/Tremelimumab	12	35	51	Somaiah et al. Lancet Oncology 2022
Nivolumab	0	50	50	Ben-Ami et al. Cancer 2017
Pembrolizumab	18	38	45	Tawbi et al. Lancet Oncology 2017
Ipilimumab/Nivolumab	16	41	43	D'Angelo et al. Lancet Oncology 2018
Gemcitabine/Docetaxel	18	47	36	Somaiah et al. Cancer 2021
Gemcitabine/Pazopanib	11	52	31	Somaiah et al. Cancer 2021
Pazopanib	6	67	23	van der Graaf et al. Lancet 2012
Gemcitabine/Docetaxel	20	39	21	Seddon et al. Lancet Oncology 2017
Doxorubicin/Placebo	18	57	21	Tap et al. JAMA 2020
Doxorubicin	20	47	19	Seddon et al. Lancet Oncology 2017
Cabozantinib	11	61	17	Coyne et al. Clinical Cancer Research 2022

?

Immunotherapy
 Cytotoxic/
 Targeted
 Therapy

PD >50%
 PD 40-50%
 PD <40%

- EFICACIA
- TOXICIDAD
- CALIDAD DE VIDA
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A Multicenter Phase II Study of Cabozantinib + Nivolumab for Patients with Advanced Angiosarcoma Previously Treated with a Taxane

Alliance A091902

Juneke Grillay-Olson, MD

Duke University

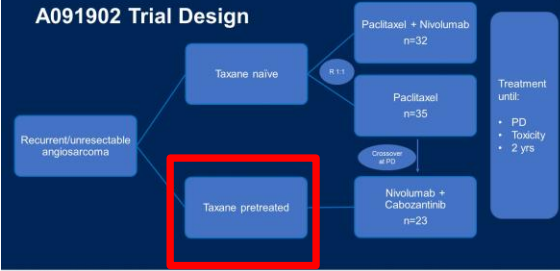
Authors: Juneke E. Grillay-Olson, Jacob B. Allred, Scott Schuetz, Elizabeth J. Davis, Michael J. Wagner, Andrew Stewart, Poklepow, Blake Waechter, Richard F. Riedel, Meng Xu, Welliver, Stephanie A. Berg, Suzanne George, Steven Ian Robinson, Paul B. Googe, Sandra P. D'Angelo, Gary K. Schwartz

Duke Cancer Institute, Duke University, Durham, NC; Alliance Statistics and Data Management Center, Mayo Clinic, Rochester, MN; University of Michigan, Ann Arbor, MI; Vanderbilt University Medical Center, Nashville, TN; University of Washington, Seattle, WA; Virginia Commonwealth University, Richmond, VA; Mayo Clinic, Rochester, MN; Duke Cancer Institute, Durham, NC; Mayo Clinic, Rochester, MN; Dana-Farber Partners, CancerCare, Boston, MA; Dana-Farber Cancer Institute, Boston, MA; Department of Dermatology, The University of North Carolina at Chapel Hill, Chapel Hill, NC; Memorial Sloan Kettering Cancer Center, New York, NY; Cleveland Clinic, Cleveland, OH



Abstract #11503

A091902 Trial Design



2023 ASCO ANNUAL MEETING #ASCO23 Presented at: Juneke Grillay-Olson, MD

ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY



Cabozantinib/Nivolumab in Angiosarcoma

Summary of Response n=22

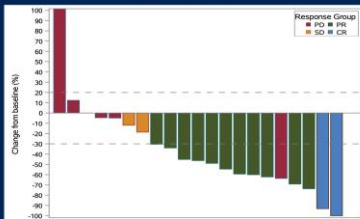
Best Objective Status (n, %)	
CR	2 (9%)
PR	11 (50%)
SD	3 (14%)
PD	6 (27%)
Death/No Assessment	0
ORR (CR + PR)	13 (59%; 95% CI 47 – 90%)
Cutaneous scalp/face (n=13)	7 of 13 (54%; 95% CI 25 – 81%)
Non-cutaneous (n=9)	6 of 9 (67%; 95% CI 30 – 93%)

Cabozantinib/Nivolumab in Angiosarcoma Best Overall Response: RECIST v1.1 Significant responses including 2 CRs

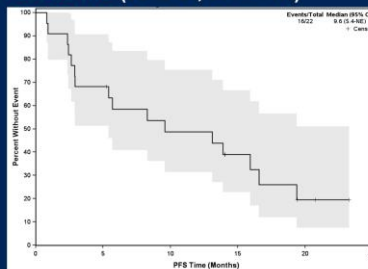
ORR 13/22 = 59%
(95% CI, 36 – 79%)

1st stage 8/9 (89%)

Overall CBR 16/22 (73%)

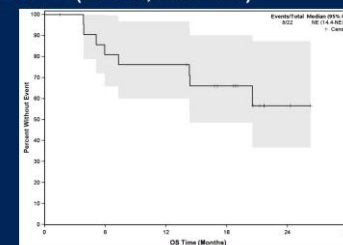


Cabozantinib/Nivolumab in Angiosarcoma Median PFS: 9.6 mo (95% CI, 5.4 – NR)



2023 ASCO ANNUAL MEETING #ASCO23 Presented at: Juneke Grillay-Olson, MD

Cabozantinib/Nivolumab in Angiosarcoma Median OS: NR (95% CI, 14.4 – NR)



2023 ASCO ANNUAL MEETING #ASCO23 Presented at: Juneke Grillay-Olson, MD

ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY

A Multicenter Phase II Study of Cabozantinib + Nivolumab for Patients with Advanced Angiosarcoma Previously Treated with a Taxane

Alliance A091902

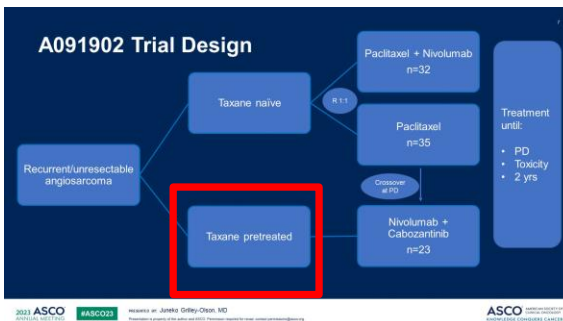
Juneko Grilløy-Olson, MD

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Authors: Juneko E. Grilløy-Olson, Jacob B. Allred, Scott Schuetz, Elizabeth J. Davis, Michael J. Wagnier, Andrew Stewart, Poklepow, Blake Waechter, Richard F. Riedel, Meng Xu, Welliver, Stephanie A. Berg, Suzanne George, Steven Ian Robinson, Paul B. Googe, Sandra P. D'Angelo, Gary K. Schwartz

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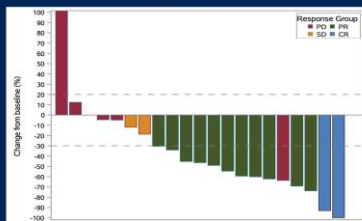
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ORR 13/22 = 59%
(95% CI, 36 – 79%)

1st stage 8/9 (89%)

Overall CBR 16/22 (73%)



Conclusions

- Cabozantinib + nivolumab has significant antitumor activity in taxane pretreated angiosarcoma
- Cabozantinib + Nivolumab exceeded its primary endpoint (planned 10 → 35% ORR improvement)
 - ORR 59%
 - CBR 73%
- Median PFS (9.6 mo) double that of historic controls (4.2 mo¹)
- Responses were similar in cutaneous and noncutaneous
- The combination was well tolerated without new safety signals
- Correlative analyses and PRO-CTCAE/FACT-G are ongoing
- Rare tumor trial accrued quickly (June – Oct 2021) through NCTN
 - A091902 taxane naïve cohorts have recently completed accrual

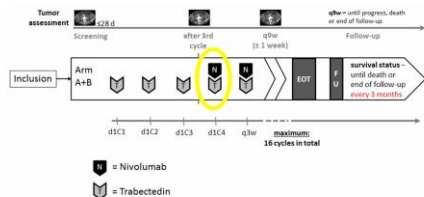
¹Jones JAMA Onc 2022

Efficacy and safety of nivolumab and trabectedin in pretreated patients with advanced soft tissue sarcomas (STS) - results of a phase II trial of the German Interdisciplinary Sarcoma Group (GISG-15, NitraSarc)

Peter Reichardt¹, Dimosthenis Andreou², Anne Flörcken³, Thorben Groß⁴, Stephan Richter⁵, Irgalen Kessler⁶, Martin Kortum⁷, Christian A Schmidt⁸, Bernd Kasper⁹, Eva Wardelmann¹⁰, Benedict Atzler¹⁰, Disorn Sookthai¹⁰, Daniel W Mueller¹¹, Daniel Pink^{8, 11}

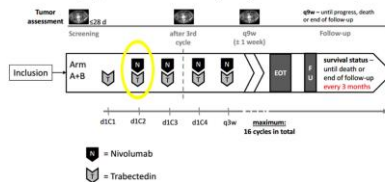
¹ Helios Klinikum Berlin-Buch, Medical School Berlin, Berlin, Germany; ² Medizinische Universität Graz, Austria; ³ Charité-Universitätsmedizin Berlin, Berlin, Germany; ⁴ Universitätsklinikum Tübingen, Tübingen, Germany; ⁵ Universitätsklinikum Carl Gustav Carus, Dresden, Germany; ⁶ Universitätsklinikum Münster, Münster, Germany; ⁷ Universitätsklinikum Würzburg, Würzburg, Germany; ⁸ Universitätsmedizin Greifswald, Greifswald, Germany; ⁹ Universität Heidelberg, Mannheim Cancer Center (MCC), Mannheim, Germany; ¹⁰ Institut für Klinische Krebsforschung IKF GmbH am Krankenhaus Nordwest, Frankfurt am Main, Germany; ¹¹ Helios Klinikum Bad Saarow, Bad Saarow, Germany

Study Design (late combination cohort; LCC)



Study Design (early combination cohort; ECC)

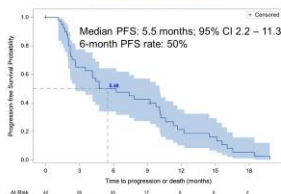
Amendment after preplanned interim safety analysis and with new published data*



*Chen D, Sestini G, Patel J, Tang Q, Li S, Asadun N, et al. Clinical Experience with Combination Chemotherapy using Trabectedin and Nivolumab for Advanced Soft Tissue Sarcoma. *Ann Oncol*. 2023;34:108.

L-Sarcoma (Group A): progression-free survival

Group A: overall

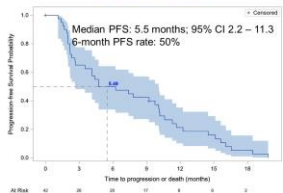


Statistical Design

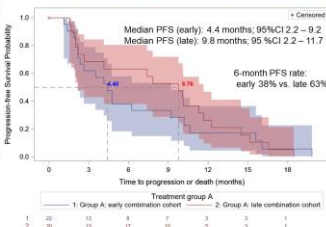
combination insufficient, if PFSR6 ≤ 35%
combination highly promising, if PFSR6 ≥ 55%

L-Sarcoma (Group A): progression-free survival

Group A: overall

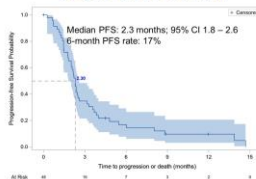


early combination vs. late combination

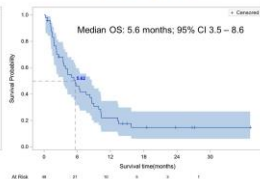


Non-L-Sarcoma (Group B): Survival

progression-free survival

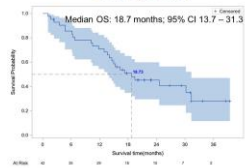


overall survival

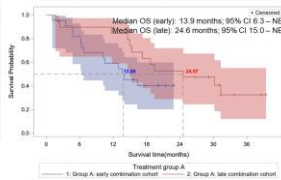


L-Sarcoma (Group A): overall survival

Group A: overall



early combination vs. late combination

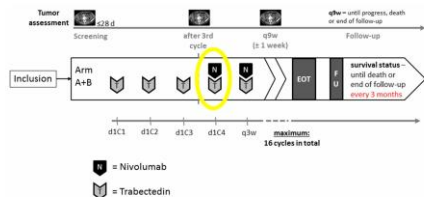


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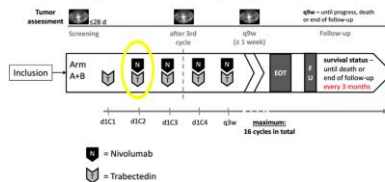
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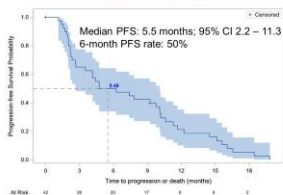
Study Design (early combination cohort; ECC)

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Group A: overall



Statistical Design

combination insufficient, if PFSR6 ≤ 35%
 combination highly promising, if PFSR6 ≥ 55%

L-Sarcoma (Group A): progression-free survival

Group A: overall



early combination vs. late combination



- the striking difference between ECC and LCC in terms of PFSR6, PFS and OS seen with the combination of trabectedin and nivolumab in L-Sarcomas suggests synergistic activity in LCC and could be explained by increased immunogenicity resulting from pretreatment with trabectedin
- this may lead to new concepts in combining chemotherapy and immunotherapy in different tumor types

Non-L-Sarcoma (Group B): Survival

progression-free survival

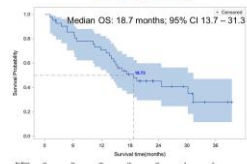


overall survival

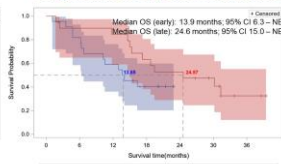


- results in group B do not justify further investigation of trabectedin plus nivolumab in non-L-sarcomas.
- study confirms the preferential activity of trabectedin in patients with LMS and LS

Group A: overall

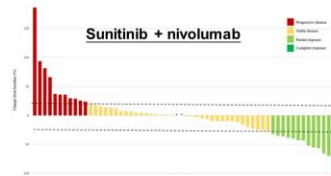
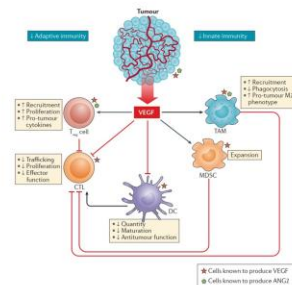


early combination vs. late combination

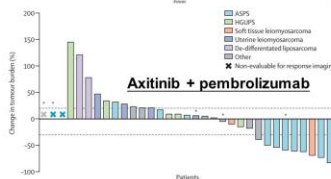


Lenvatinib plus pembrolizumab in patients with advanced sarcoma

Silvana Movva, Vaseelj Asutu, Ping Chi, Mark Andrew Dickson, Mitral M. Gounder, Clara Marie Kelly, Mary Louise Keohan, Paul A. Meyers, Seth M. Cohen, Marlee L. Hensley, Jason A. Kinnor, Alison M. Schrim, Robert A. Laskowitz, Joseph Patrick Empey, Li-Xuan Gu, Tiffany Sakito, Kenneth Seew, William D. Tap, Sandra P. D'Angelo

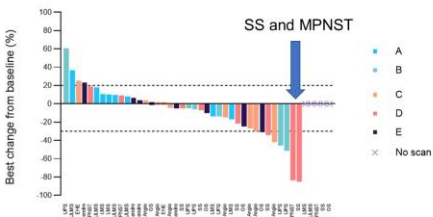


Martin-Broto et al. JTO 2020



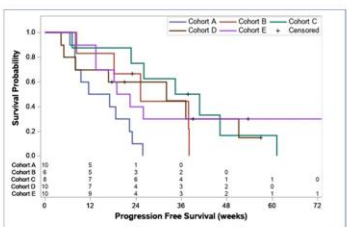
Wilky et al. Lancet Oncol 2016

Efficacy results



SS and MPNST

- PR noted in: **UPS, SS, MPNST and osteo**; 1 patient with **angio** had a PR after 27-weeks



- Median PFS \geq 20 weeks cohorts
 - UPS
 - Vascular
 - Other (SS and MPNST)
 - Bone

Adverse Events

- 46/47 (97.8%) of patients had at least one TRAE
- 26/47 (55.3%) of patients had a \geq Gr 3 TRAE
- 35/47 (74.4%) of patients required dose interruption of lenvatinib, pembrolizumab or both due to TRAE
- 24/47 (51.1%) of patients required at least one dose reduction of lenvatinib due to toxicity
- There was one grade 5 death event of respiratory failure due to steroid refractory pneumonitis and subsequent POD
- Two additional patients discontinued study due to toxicity: grade 3 htn, grade 3 LVEF dysfunction

Adverse Event	Number of Patients, (%)		SAE (n)
	Grade 1/2	Grade 3/4	
Blood and Lymphatic			
Anemia	9 (19.1)	2 (4.3)	0
Leucopenia	13 (27.7)	0	0
Thrombocytopenia	11 (23.4)	2 (4.3)	1
Cardiac Disorders			
Left ventricular dysfunction	0	1 (2.1)	1
Pericarditis	0	1 (2.1)	1
Endocrine			
Hypothyroidism	14 (29.8)	0	0
Gastrointestinal			
Colitis	2 (4.3)	0	1
Colonic Perforation	0	1 (2.1)	1
Constipation	19 (40.4)	1 (2.1)	0
Nausea	15 (31.9)	0	0
General			
Fatigue	21 (44.7)	1 (2.1)	1
Non-cardiac chest pain	1 (2.1)	3 (6.4)	3
Respiratory			
ALT increased	14 (29.8)	1 (2.1)	0
AST increased	13 (27.7)	1 (2.1)	0
Bilirubin increased	5 (11.0)	0	1
Infection			
Lung infection	0	1 (2.1)	1
Investigations			
Creatinine increased	6 (12.6)	1 (2.1)	1
Metabolism			
Anorexia	11 (23.4)	0	0
Nephritis			
Alanine aminotransferase increased	21 (44.7)	2 (4.3)	2
Nervous System			
Headache	15 (31.9)	0	0
Renal			
Proteinuria	19 (40.4)	2 (4.3)	0
Respiratory			
Cough	6 (12.6)	0	1
Dyspnea	4 (8.5)	3 (6.4)	3
Respiratory Failure	0	1 (2.1)	1
Vascular			
Hypertension	12 (25.5)	13 (27.7)	2
Thromboembolic event	0	2 (4.3)	2

TRAEs occurring in \geq 20% of patients or any SAE event

TAKE HOME MESSAGES MISCELANIA II: melanoma y sarcoma



- MELANOMA:

- El **tratamiento adyuvante con inmunoterapia** se presenta como la elección estándar para pacientes IIB-IV resecado -> IO COMBINATION TRIALS FOR GRANTED!
- En el **contexto metastásico**, existe una necesidad de comprender mejor la biología tumoral así como los mecanismos de resistencia 1ª y 2ª a los tratamientos aprobados de cara diseñar mejor los potenciales ensayos clínicos -> STAY TUNNED!

- SARCOMA:

- Las **combinaciones de QT/otros agentes + inmunoterapia** son seguras sin toxicidad añadida -> COMBINATION TRIALS FOR GRANTED!
- El **mejor conocimiento biológico y genómico** de los diferentes subtipos tumorales es necesario para poder ofrecer a cada paciente el mejor tratamiento -> KEEP ON MOVING!

XXIII JORNADA DE REVISIÓN DEL

CONGRESO AMERICANO DE ONCOLOGÍA

¡Muchas gracias!



emunoz@vhio.net