XXIII JORNADA DE REVISIÓN DEL

CONGRESO AMERICANO DE ONCOLOGÍA

Miscelania II: MELANOMA y SARCOMA

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

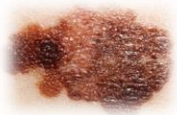
Conflictos de interés

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;

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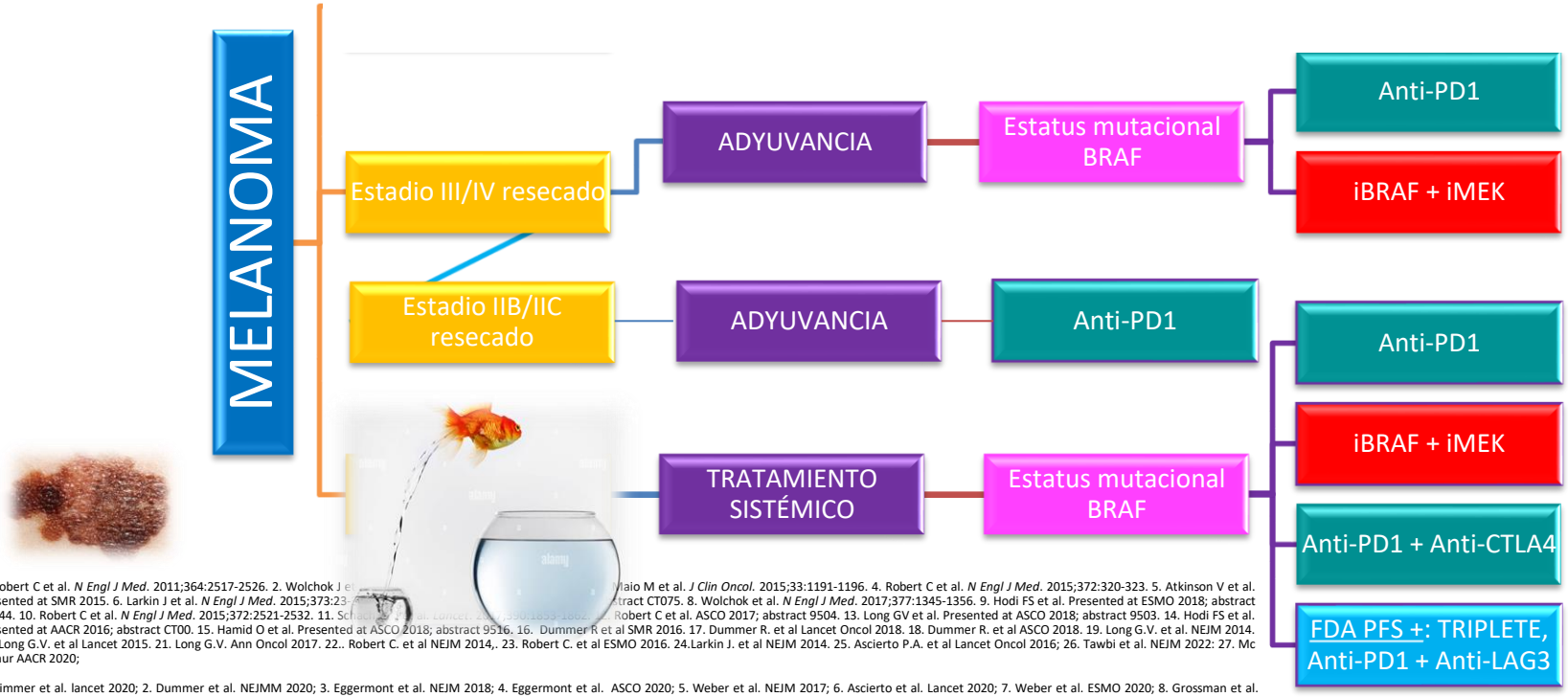

(US only)

(US & EMA

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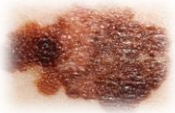

- MELANOMA
  - Estadio III clínico → NEOADYUVANCIA (ensayo clínico)
  - Es[illegible]do → ADYUVANCIA → Estatus mutacional BRAF
    - Anti-PD1
    - iBRAF + iMEK
  - ADYUVANCIA → Anti-PD1
  - TRATAMIENTO SISTÉMICO → Estatus mutacional BRAF
    - Anti-PD1
    - iBRAF + iMEK
    - Anti-PD1 + Anti-CTLA4
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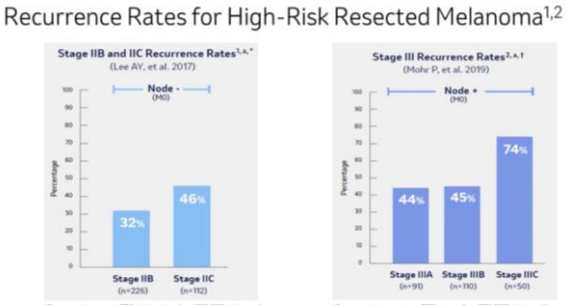
MELANOMA DE ALTO RIESGO:
¿Qué objetivos busco con la elección del tratamiento?



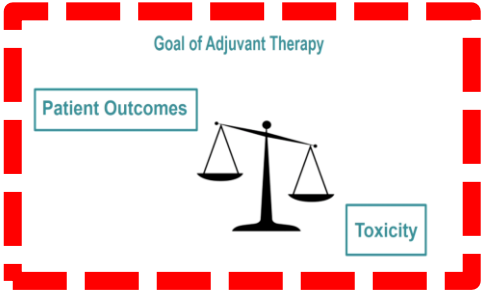
Objetivo 1º: RFS

Objetivo 2º: DMFS

Objetivo 2º: OS, PFS

Toxicidades

Calidad de vida



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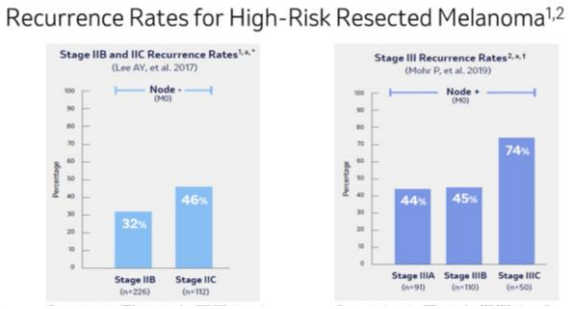

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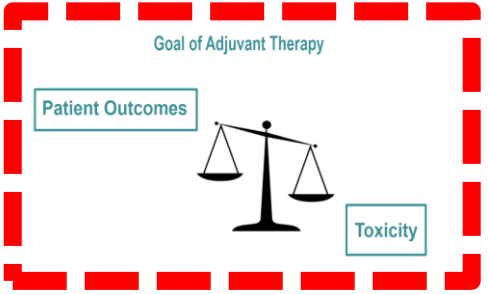
Objetivo 2º: DMFS

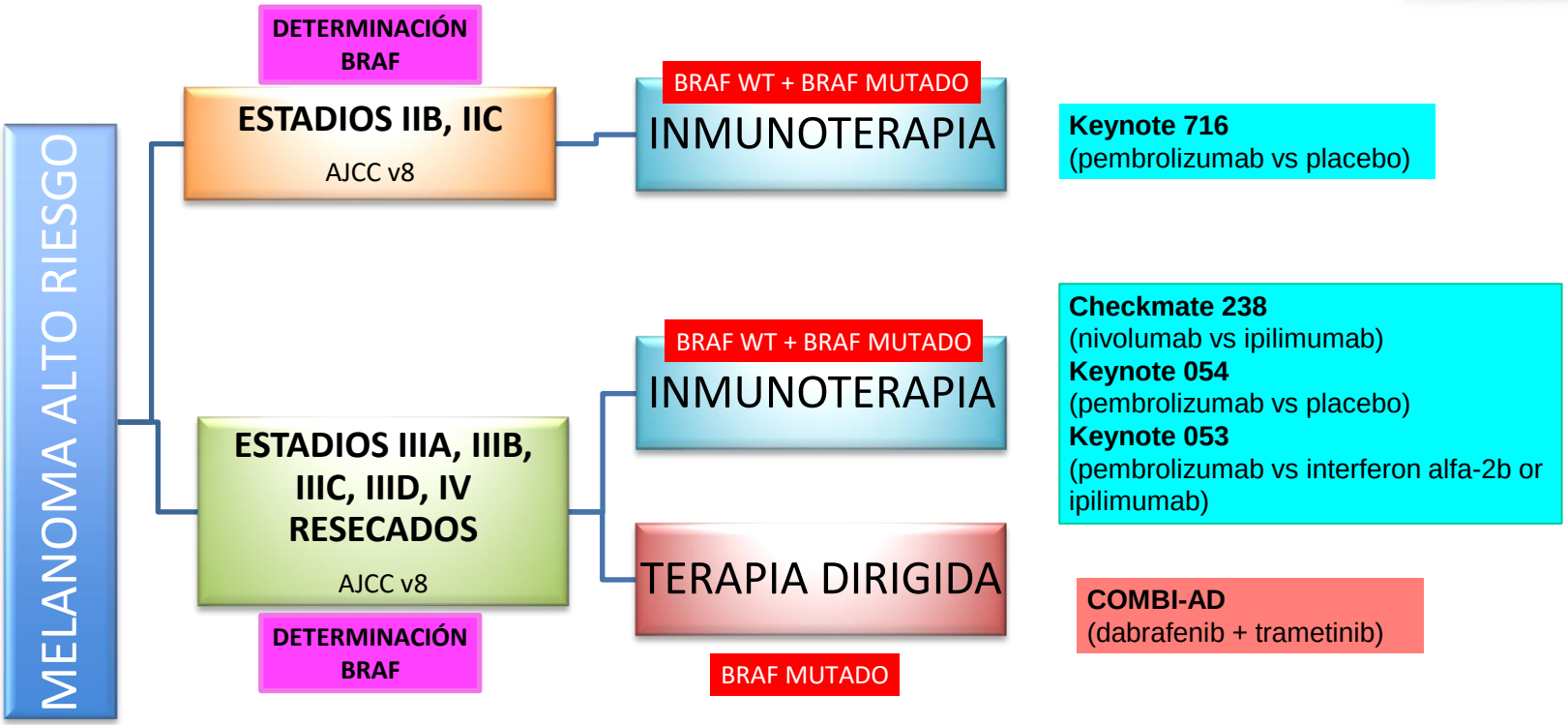
Objetivo 2º: OS, PFS

Toxicidades

Calidad de vida

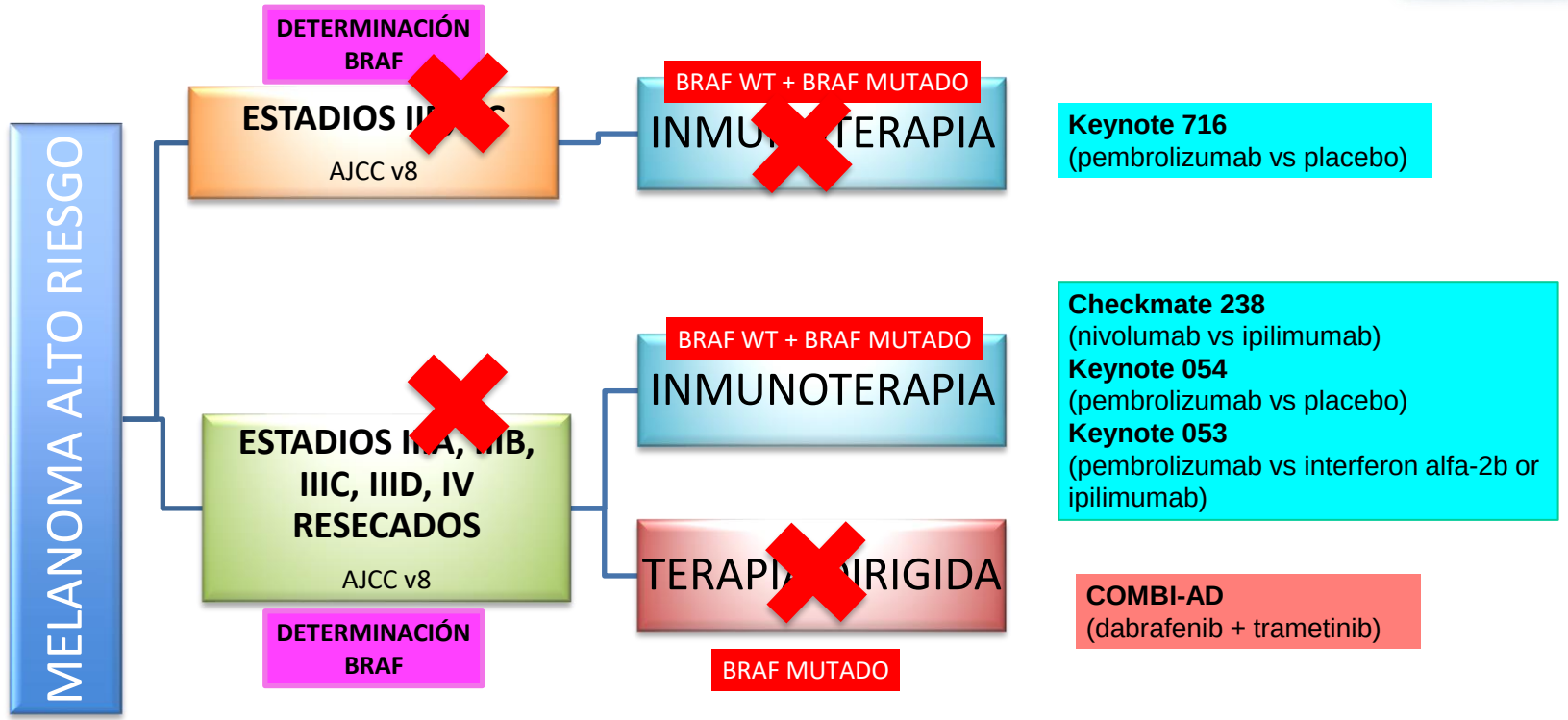


Tratamiento del MELANOMA ADYUVANTE 2023



Weber et al SMR 2021; Eggermont 2022 NEJM; Dummer NEJM 2020; Luke ESMO 2021

Tratamiento del MELANOMA ADYUVANTE 2023



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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)

Weber et al SMR 2021; Eggermont 2022 NEJM; Dummer NEJM 2020; Luke ESMO 2021

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. Luke[1]; Paolo A. Ascierto[2]; Muhammad A. Khattak[3]; Luis de la Cruz Merino[4]; Michele Del Vecchio[5]; Piotr Rutkowski[6]; Francesco Spagnolo[7]; Jacek Mackiewicz[8]; Vanna Chiarion-Sileni[9]; John M. Kirkwood[1]; Caroline Robert[10]; Jean-Jacques Grob[11]; Federica de Galitiis[12]; Dirk Schadendorf[13]; Matteo S. Carlino[14]; Xi Lawrence Wu[15]; Mizuho Fukunaga-Kalabis[15]; Clemens Krepler[15]; Alexander M. M. Eggermont[16]; Georgina V. Long[17]

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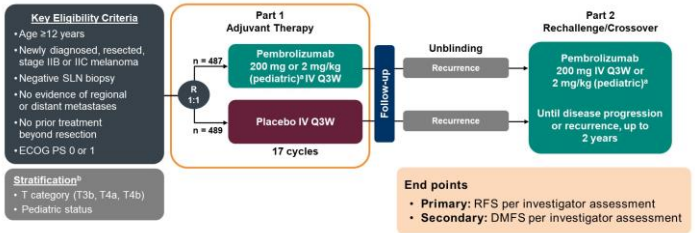
KEYNOTE-716 Study Design (NCT03553836)



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[b]BRAF mutation and PD-L1 expression status were not prespecified stratification factors because of tissue availability.

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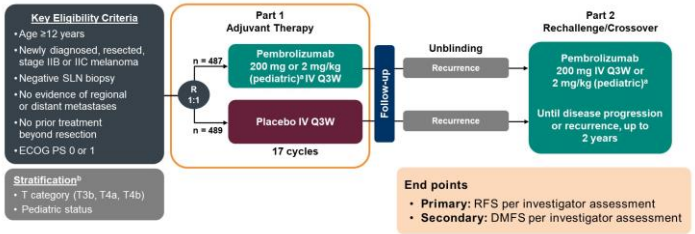

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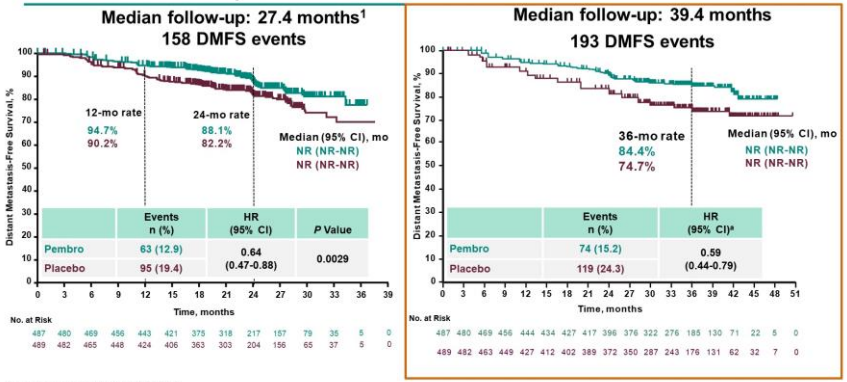
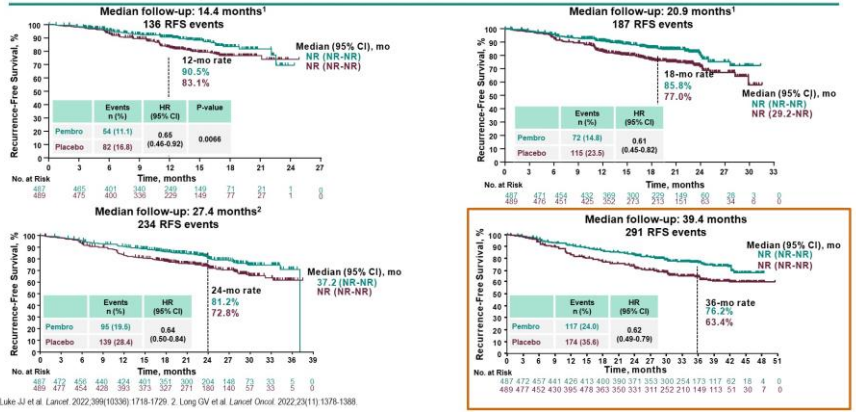
DMFS: ITT Population



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

RFS: ITT Population



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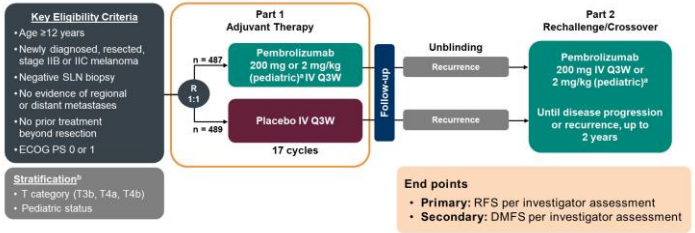

POST 2023 CAO

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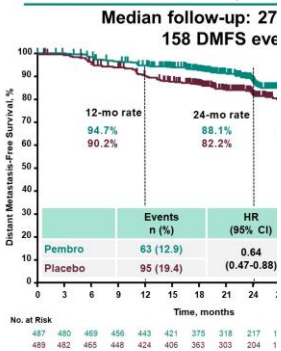

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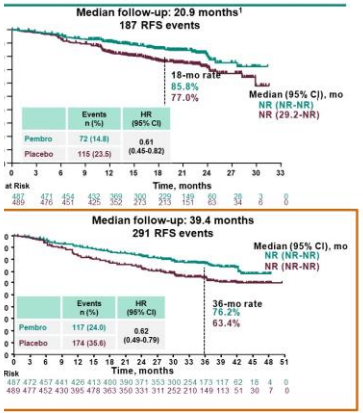
Summary and Conclusion

- 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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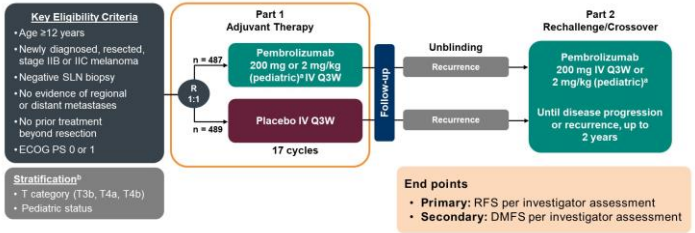

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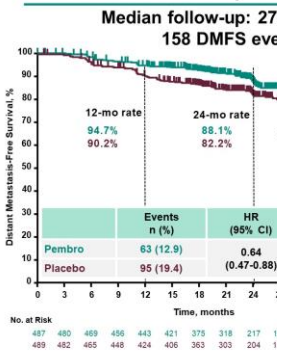

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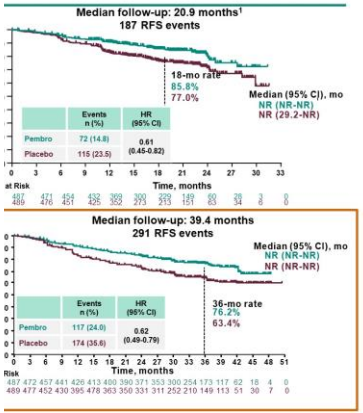
- With a median follow-up of 39.4 months, adjuvant pembrolizumab continued to demonstrate a DMFS and RFS benefit compared with placebo in patients with resected stage IIB or IIC melanoma
  - DMFS: HR, 0.59 (95% CI, 0.44-0.79)
  - RFS: HR, 0.62 (95% CI, 0.49-0.79)
- Safety was similar to that reported 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



1. Luke JJ et al. *Lancet.* 2022;399:1718-1729. 2. Long GV et al. *Lancet Oncol.* 2022;23:1378-1388.

2023 ASCO ANNUAL MEETING

Presented by Georgina V. Long

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*]

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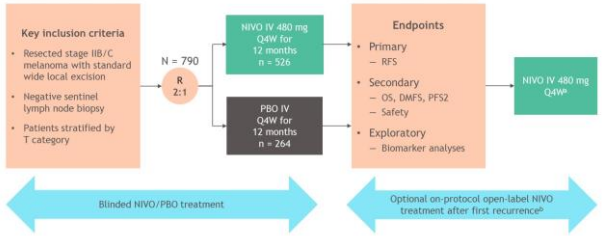
*Co-senior authors

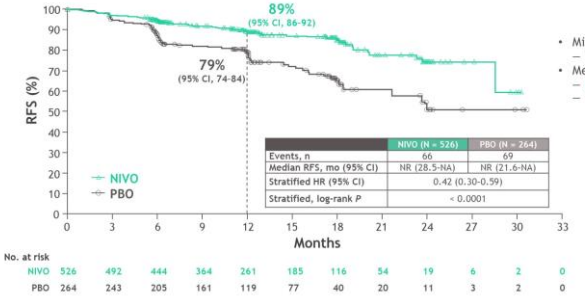
Abstract number 9504

CheckMate 76K study design[1,2]



[a]Per patient eligibility and choice. [b]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. NCT04099251. Accessed March 2023. https://clinicaltrials.gov/ct2/show/NCT04099251; 2. Long GV et al. Plenary presentation at SMR 2022. Edinburgh, Scotland, October 17-20.

CheckMate 76K primary endpoint: RFS[1,2]



	NIVO (N = 526)	PBO (N = 264)
Events, n	66	69
Median RFS, mo (95% CI)	NR (28.5-NA)	NR (21.6-NA)
Stratified HR (95% CI)	0.42 (0.30-0.59)	
Stratified, log-rank *P*	< 0.0001	

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

No. at risk

NIVO	526	492	444	364	261	185	116	54	19	6	2	0
PBO	264	243	205	161	119	77	40	20	11	3	2	0

- Adjuvant NIVO significantly prolonged RFS and had a manageable safety profile[1]

1. Long GV et al. Plenary presentation at SMR 2022. Edinburgh, Scotland, October 17-20. 2. Gastman B et al. Oral presentation at SSO 2023. Boston, MA, USA, March 22-25.

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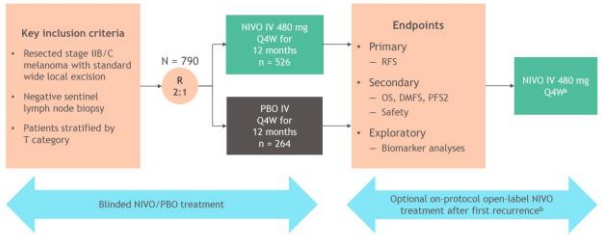

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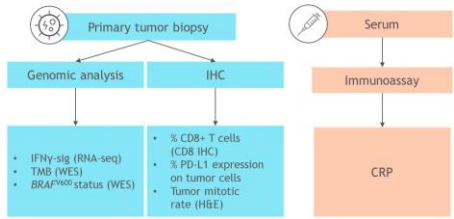
Methods

- Baseline biomarker analyses conducted on the following:



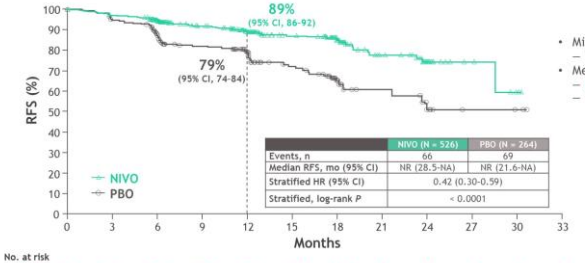
Individual biomarkers and their association with treatment outcomes using RFS were evaluated

1. As a continuous variable, by comparing higher (75th percentile) vs lower (25th percentile) groups from Cox proportional hazards model
2. Using median or other prespecified cutoffs

Analyses were performed

1. *Within* each treatment arm
2. *Comparing* NIVO vs PBO

CheckMate 76K primary endpoint: RFS[1,2]



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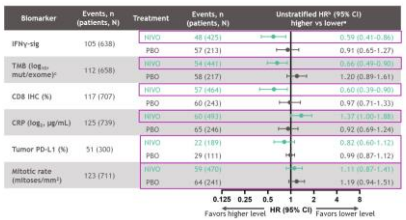
Association between biomarkers and RFS within NIVO and PBO treatment arms: higher vs lower[a] biomarker levels

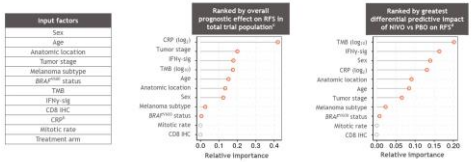


↑ IFNγ-sig
↑ TMB
↓ CRP

Are associated with improved RFS in NIVO arm

Towards a composite biomarker model[a]

- 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-sig had the largest independent effect on the relative benefit of NIVO over PBO

[a]Best final model did not include CD8 IHC and mitotic rate, likely due to redundancy between CD8 IHC and IFNγ-sig (correlation coefficient ρ = 0.7), and low independent predictive effect from mitotic rate. [b]CRP levels were independent of time from surgery (not shown). ×term = interaction term. †Interaction term only.

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

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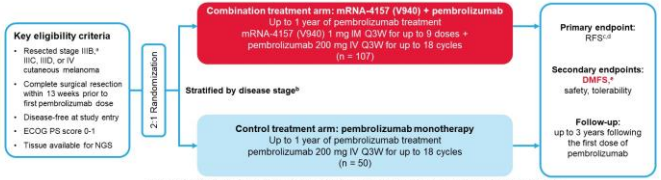
mRNA-4157 (V940) Mechanism of Action

- 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]

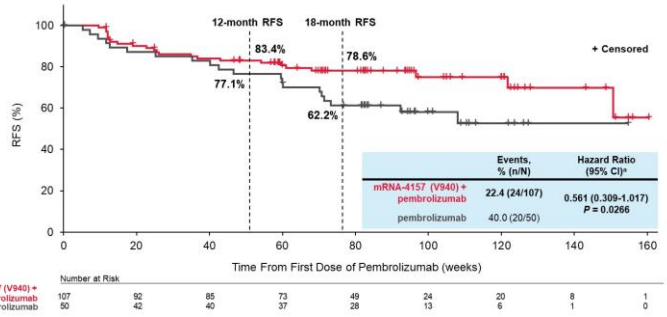
mRNA-4157-P201/KEYNOTE-942 (NCT03897881) Study Design

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[c]
Median follow-up[c]: 23 months for mRNA-4157 (V940) + pembrolizumab
24 months for pembrolizumab monotherapy

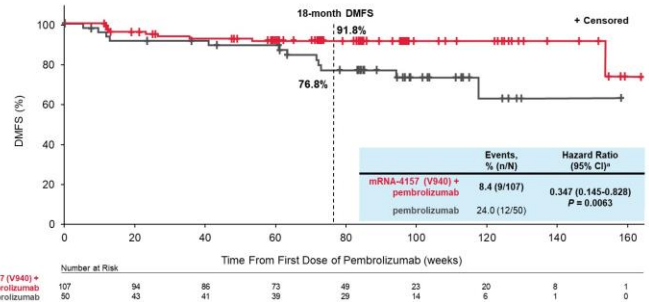
Primary Efficacy Endpoint: RFS[1]



[a]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 IIIB or IIIC 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 IIIC or IIID vs stage IV) used for randomization.

1. Khattak A, et al. Presented at the American Association for Cancer Research® (AACR) Annual Meeting; April 14-19, 2023; Orlando, FL, USA. Oral presentation CT001.

Secondary Efficacy Endpoint: DMFS



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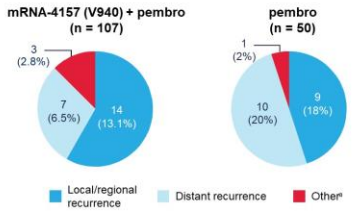
Recurrence Type and Distant Recurrence Location

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 (%)		
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)[b]	0

[a]Other: new primary cutaneous melanoma or death (n = 1). [b]Death from sepsis, unrelated to mRNA-4157 (V940) or pembro.

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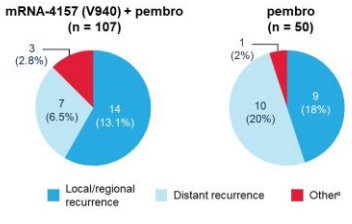

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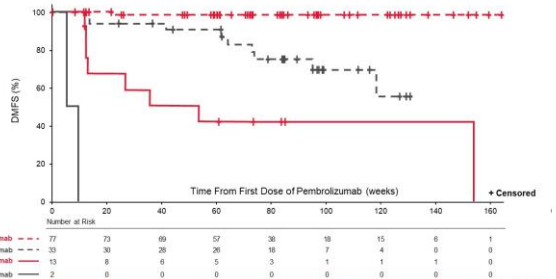
DMFS by ctDNA Status at Baseline



	mRNA-4157 (V940) + pembro vs pembro HR (95% CI)[a]	mRNA-4157 (V940) + pembro Events, % (n/N)	pembro Events, % (n/N)
ctDNA-neg	0.048 (0.006, 0.380)	1.3 (1/77)	27.3 (9/33)
ctDNA-pos	NE	61.5 (8/13)	100 (2/2)

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 = 15; pembrolizumab monotherapy, n = 14) or insufficient number of RaCaRE variants identified by WES (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.

See LBA9515 presented by Matteo S. Carlino on 03Jun

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), a personalized cancer vaccine, and pembrolizumab.

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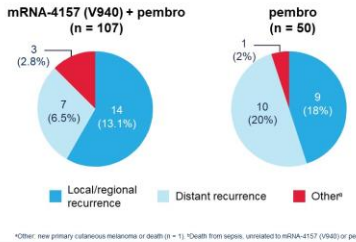
[1]Hollywood Private Hospital, Nedlands, Australia; [2]Edith Cowan University, Perth, Australia; [3]NYU Langone Medical Center, New York, NY; [4]Saint John of God Subiaco Hospital, Subiaco, Australia; [5]Earle A. Chiles Research Institute, Portland, OR, USA; [6]Washington University School of Medicine,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

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

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

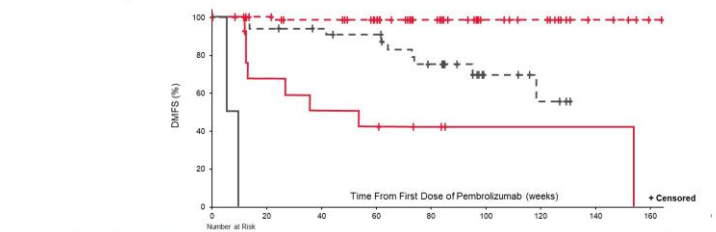
Type of RFS Event



	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 (%)		
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)[b]	0

[a]Other: new primary cutaneous melanoma or death (n = 1). [b]Death from sepsis, unrelated to mRNA-4157 (V940) or pembro.

DMFS by ctDNA Status at Baseline



	mRNA-4157 (V940) + pembro vs pembro HR (95% CI)[a]	mRNA-4157 (V940) + pembro Events, % (n/N)	pembro Events, % (n/N)
ctDNA-neg	0.048 (0.006, 0.380)	1.3 (1/77)	27.3 (9/33)
ctDNA-pos	NE	61.5 (8/13)	100 (2/2)

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 = 15; pembrolizumab monotherapy: n = 14) or insufficient number of RaCaR® variants identified by WES (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.

See LBA9515 presented by Matteo S. Carlino on 03Jun

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), a personalized cancer vaccine, and pembrolizumab.

mRNA-4157-P201/KEYNOTE-942 Safety and Tolerability[1]

	mRNA-4157 (V940) + pembro (n = 104)		pembro (n = 50)	
Event, n (%)	**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[b] occurring in >20% of patients				
Any	98 (94.2)	**12 (11.5)**	-	-
Fatigue	63 (60.6)	5 (4.8)	-	-
Injection site pain	58 (55.8)	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[c] occurring in >20% of patients				
Any	101 (97.1)	24 (23.1)	41 (82.0)	9 (18.0)
Fatigue	72 (69.2)	6 (5.8)	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. [a]Serious AEs included grade 1 fever, attributed to mRNA-4157 (V940), and grade 3 muscular weakness and grade 3 autoimmune nephritis, attributed to both mRNA-4157 (V940) and pembrolizumab. [b]mRNA-4157 (V940) treatment-related AEs included events attributed by the investigator to mRNA-4157 (V940) alone as well as events attributed to both mRNA-4157 (V940) and pembrolizumab. [c]AEs related to pembrolizumab include events attributed by the investigator to pembrolizumab alone and events attributed to both pembrolizumab and mRNA-4157 (V940).

1. Khattak A, et al. Presented at the American Association for Cancer Research® (AACR) Annual Meeting; April 14–19, 2023; Orlando, FL, USA. Oral presentation CT001.

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DMFS by c

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

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Type of RFS Event

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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 (%)		

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

	Grade ≥3
	18 (36.0)
	9 (18.0)
	4 (8.0%)
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	9 (18.0)
	0
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erms version 5.0. †Serious AEs included grade 1 attributed by the investigator to mRNA-4157 (V940) and mRNA-4157 (V940).

PRESENTED BY: Adnan Khattak, MBBS, FRACP, PhD

2023 ASCO ANNUAL MEETING

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2023 ASCO ANNUAL MEETING #ASCO23 PRESENTED BY: Adn

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Site of distant recurrence, n (%)		

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

h-risk
65%
ow-up

DMFS by c

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2023

	Grade ≥3
	18 (36.0)
	9 (18.0)
	4 (8.0%)
	-
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	-
	-
	-
	-
	-
	-
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	0
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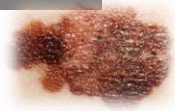
MELANOMA METASTÁSICO:
¿Qué objetivos busco con la elección del tratamiento?

Objetivo 1º:
Alta tasa de respuestas ORR

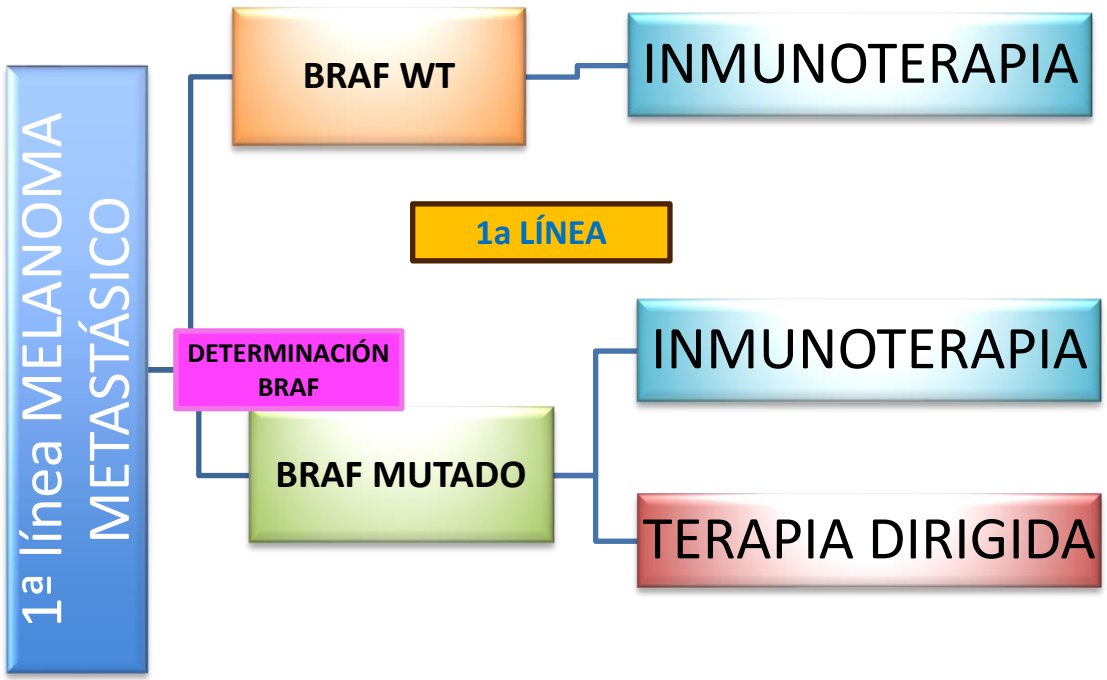
Objetivo 2º:
Respuestas duraderas, PFS y OS

Toxicidades
Calidad de vida

LARGOS RESPONDEDORES,
LARGOS SUPERVIVIENTES



Tratamiento del MELANOMA METASTÁSICO



Keynote 006 (pembro vs Ipi 1ª/2ª 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

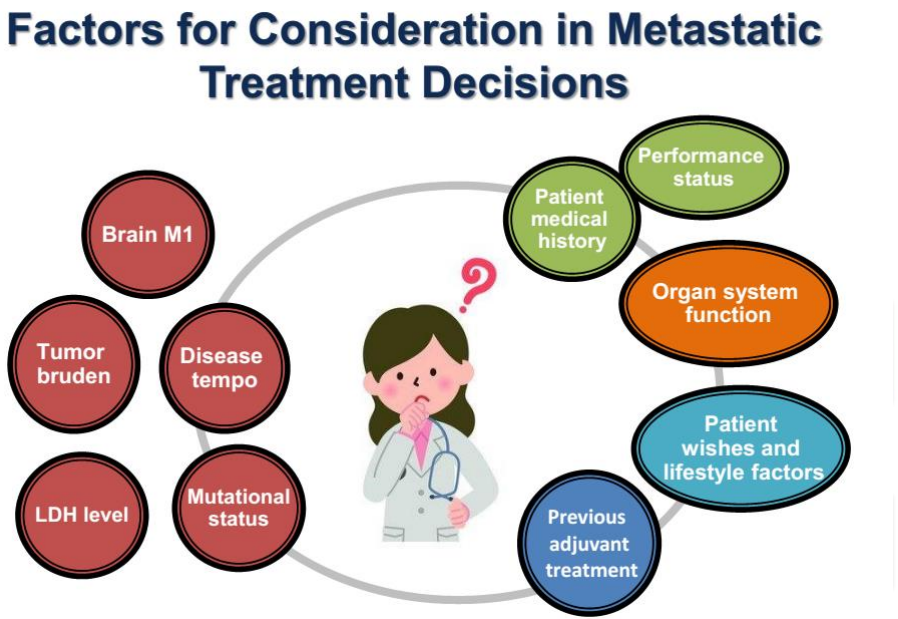
coBRIM (vemu/cobi vs vemu)
COMBI-D (dabra(trame vs dabra)
COMBI –V (dabra/trame vs vemu)
COLUMBUS (encorafenib/binimetinib vs encorafenib vs vemu)

IMSPIRE 150 (vemu + cobi vs vemu+cobi+atezo)

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

Tratamiento del MELANOMA METASTÁSICO

1ª línea MELANOMA METASTÁSICO



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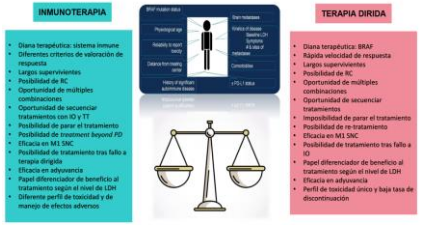
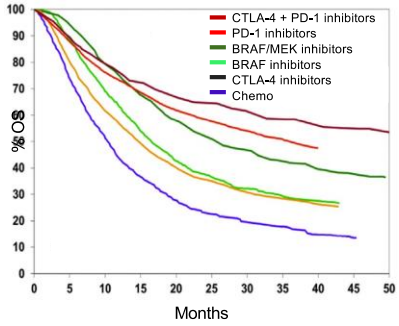
STEP 1



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



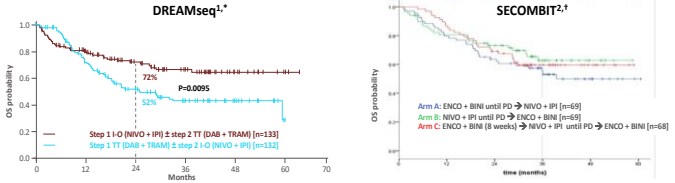
OS rates, %	PD1 + CTLA4 inhibitors	PD-1 inhibitors	BRAF+MEK inhibitors		
Year	Nivo + ipi CM-067	Nivo CM-067	Enco/bini COLUMBUS	Dab/tram COMBI-v, COMBI-d	coBRIM[9,10]
1	-	-	76%[7]	-	75%[9]
2	64%[1]	59%[1]	58%[7]	52%[8]	49%[9]
3	58%[2]	52%[2]	47%[7]	44%[8]	39%[9]
4	53%[3]	44%[3]	39%[7]	37%[8]	35%[9]
5	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.

Figure adapted from: Ugurel S, et al. *Eur J Cancer.* 2020;130:126–138. OS, overall survival.
1. Larkin J et al. Abstract CT075. AACR Annual Meeting. 1-5 April 2017; 2. Wolchok JD et al. *N Engl J Med.* 2017;377:1345–1356; 3. Hodi FS et al. Abstract LBA44. ESMO 2018; 4. Larkin J, et al. *N Engl J Med.* 2019;381(16):1535-1546; 5. Wolchock JD, et al. Abstract 9506. ASCO Annual Meeting. 20 May 2021; 6. Hodi FS, et al. Poster 9522. ASCO Annual Meeting. 3-7 June 2022; 7. Dummer R, et al. Oral 9507. ASCO Annual Meeting. 20 May 2021; 8. Robert C, et al. *N Engl J Med.* 2019;381:626–636; 9. Dréno B, et al. *J Clin Oncol.* 2018;36(suppl 15):9522. 10. McArthur GA, et al. Oral presentation. SMR. 20-23 November 2019.

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

STEP 2



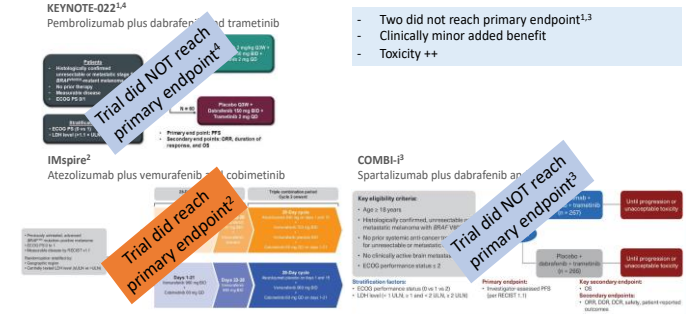
- Exploratory analyses from IMspire150 showed that adding ATEZO to 1L VEM + COBI resulted in a numerically lower rate for the development of CNS metastases among patients with advanced *BRAF*-mutant melanoma who had no CNS metastases at baseline[3]

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.
1L, first-line; ATEZO, atezolizumab; BINI, binimetinib; COBI, cobimetinib; DAB, dabrafenib; ENCO, encorafenib; I-O, immuno-oncology; IPI, ipilimumab; NIVO, nivolumab; OS, overall survival; PD, progressive disease; TRAM, trametinib; TT, targeted therapy; VEM, vemurafenib.
1. Atkins MB et al. Abstract 356154. ASCO Monthly Plenary 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.

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

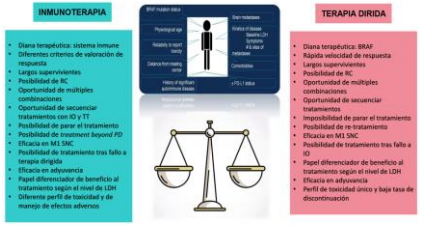
STEP 2



1. Ribas A, et al. Poster 9516. ASCO Annual Meeting 3–7 June 2022; 2. McArthur GA, et al. Poster 9547. ASCO Annual Meeting 3–7 June 2022; 3. Dummer R, et al. Poster 9527. ASCO Annual Meeting 3–7 June 2022; 4. Ferrucci PF, et al. *J Immunother Cancer.* 2020;8(2):e001806.

STEP 1

IO vs TT



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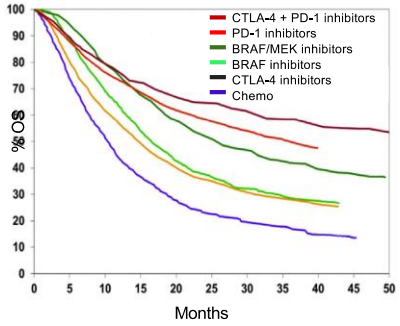

OS rates, %	PD1 + CTLA4 inhibitors	PD-1 inhibitors	BRAF+MEK inhibitors		
Year	Nivo + ipi CM-067	Nivo CM-067	Enco/bini COLUMBUS	Dab/tram COMBI-v, COMBI-d	coBRIM[9,10]
1	-	-	76%[7]	-	75%[9]
2	64%[1]	59%[1]	58%[7]	52%[8]	49%[9]
3	58%[2]	52%[2]	47%[7]	44%[8]	39%[9]
4	53%[3]	44%[3]	39%[7]	37%[8]	35%[9]
5	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.

Figure adapted from: Ugurel S, et al. *Eur J Cancer.* 2020;130:126–138. OS, overall survival.

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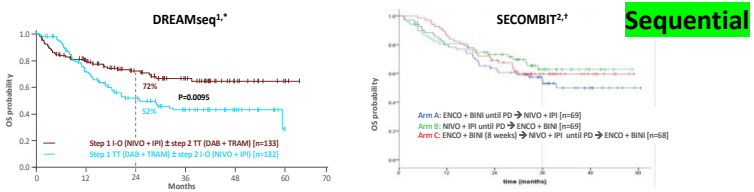
STEP 2

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

STEP 2

Sequential



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

STEP 2

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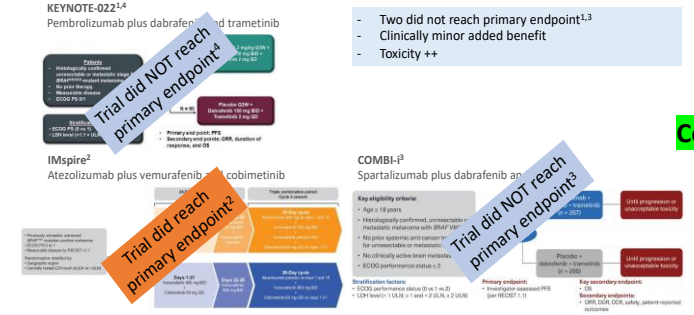

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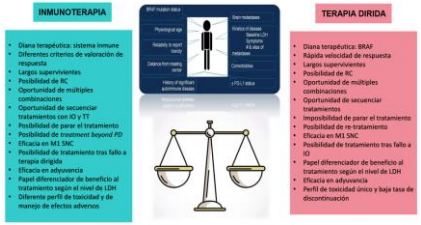
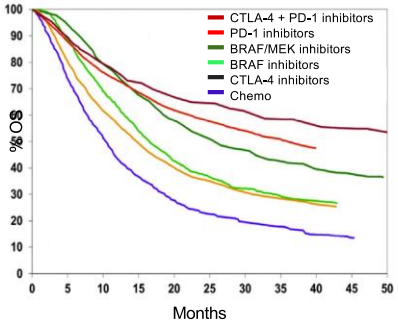
STEP 1

IO vs TT



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



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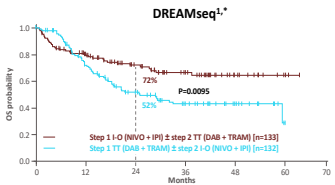
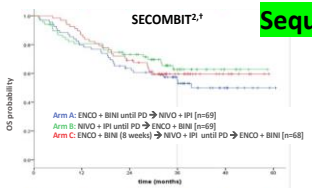
STEP 2

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

Sequential





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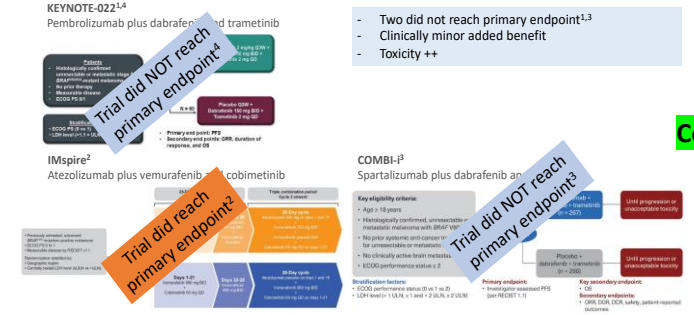

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2023 ASCO ANNUAL MEETING

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] Saima Rodriguez,[15] Yuanfang Xu,[15] Peter Wang,[15] Sonia Dolfi,[15] Georgina V. Long[16]

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Abstract number 9502

Study design

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

Key eligibility criteria
- Previously untreated, unresectable, or metastatic melanoma
- ECOG PS 0-1

R 1:1
- NIVO 480 mg + RELA 160 mg FDC IV Q4W
- NIVO 480 mg IV Q4W

Primary endpoint
- PFS by BICR[a]

Secondary endpoints
- OS[b]
- ORR by BICR[c]

Stratified by: LAG-3,[d] PD-L1,[e] *BRAF*, and AJCC v8 M stage
Endpoints were tested in hierarchy: PFS → OS → ORR

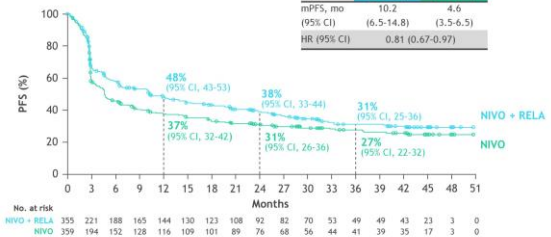
Database lock	March 9, 2021	October 28, 2021	October 27, 2022
Min. follow-up[f]	1.3 months	8.7 months	21.0 months
Median follow-up	13.2 months	19.3 months	25.3 months
Endpoint(s)	PFS per BICR	OS, ORR per BICR, and updated PFS per BICR	Updated PFS per BICR, OS, and ORR per BICR

RELATIVITY-047 (NCT03470922).
[a]First tumor assessment (RECIST v1.1) was performed 12 weeks after randomization, every 8 weeks up to 52 weeks, and then every 12 weeks. [b]OS boundary for statistical significance was $P < 0.0400$ (2-sided) analyzed at 69% power; target HR, 0.75. [c]ORR could not be formally tested and was descriptively analyzed. [d]LAG-3 expression on immune cells (1%) was determined by an analytically validated IHC assay (Labcorp, Burlington, NC, USA). [e]PD-L1 expression on tumor cells (1%) was determined by a validated Agilent Dako PD-L1 IHC 28-8 pharmDx test (Agilent, Santa Clara, CA, USA). [f]Minimum potential follow-up was defined as the time from last patient randomized to last patient, last visit.

PFS by BICR

Updated primary endpoint

	NIVO + RELA (n = 355)	NIVO (n = 359)
mPFS, mo	10.2	4.6
(95% CI)	(6.5-14.8)	(3.5-6.5)
HR (95% CI)	0.81 (0.67-0.97)	



RELATIVITY-047 (NCT03470922). 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 M stage. PD-L1 was removed from stratification because it led to subgroups with < 10 patients.

OS

Updated secondary endpoint

	NIVO + RELA (n = 355)	NIVO (n = 359)
mOS, mo	NR	33.2
(95% CI)	(31.5-NA)	(25.2-45.8)
HR (95% CI)	0.82 (0.67-1.02)	

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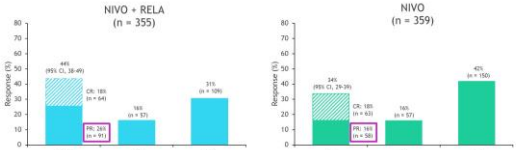
Best overall response per BICR

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.
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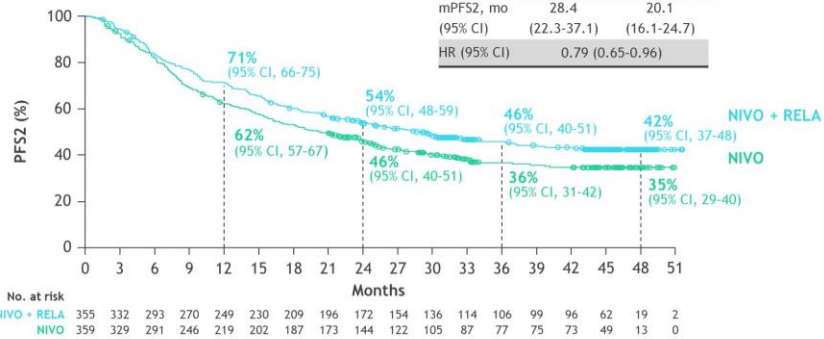
Progression-free survival 2 (PFS2)

Investigator assessed

	NIVO + RELA (n = 355)	NIVO (n = 359)
mPFS2, mo	28.4	20.1
(95% CI)	(22.3-37.1)	(16.1-24.7)
HR (95% CI)	0.79 (0.65-0.96)	



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.

Subsequent therapy

Characteristic	NIVO + RELA (n = 355)	NIVO (n = 359)
Any subsequent therapy,[a] 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)

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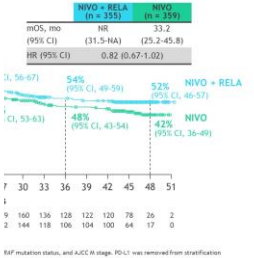
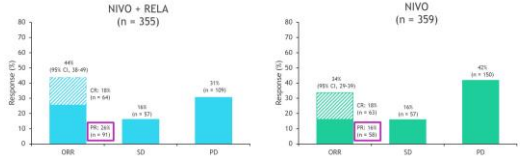
mOS, mo	NR	33.2
(95% CI)	(31.5-NA)	(25.2-45.8)
HR (95% CI)	0.82 (0.67-1.02)	



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

Best overall response per BICR

Updated secondary endpoint



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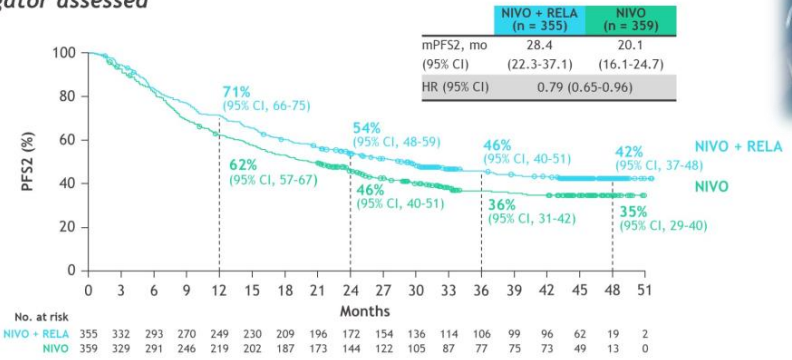

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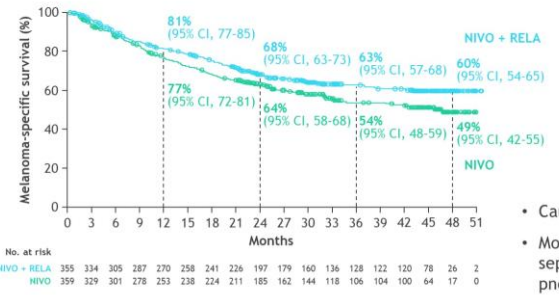
Efficacy on 2L systemic therapy following progression

Investigator reported

	NIVO + RELA arm			NIVO arm		
Subsequent 2L therapy	NIVO + IPI (n = 16)	IPI (n = 9)	BRAFi/MEKi (n = 43)	NIVO + IPI (n = 16)	IPI (n = 14)	BRAFi/MEKi (n = 45)
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 follo
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.

Melanoma-specific survival



	NIVO + RELA (n = 355)	NIVO (n = 359)
Median melanoma-specific survival, months	NR	46.7
(95% CI)	(NA-NA)	(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 (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. [a]Reasons for death were determined by the investigator. [b]Death due to toxicity was considered non-melanoma death.

2023 ASCO ANNUAL MEETING

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PD-1 experienced cohort MM3# (n=18)
1L advanced melanoma patients with prior (neo)adjuvant systemic therapy†, 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-uveal melanoma
- ≥18 years of age
- ECOG PS of 0 or 1
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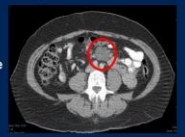
Tumor response by cohort

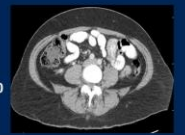
Response endpoints	Initial cohort MM1# (n=40)	Confirmatory cohort MM2# (n=40)	PD-1 experienced cohort MM3# (n=18)*
Median follow-up (IQR), months	**20.8 (11.2–30.8)**	**11.5 (8.9–13.9)**	**9.7 (4.8–14.1)**
Treatment exposure, median (IQR), weeks	**37 (20–81)**	**35 (15–51)**	**23 (12–37)**
ORR, (n)	**63% (25)**	**63% (25)**	**56% (10)**
95% CI for ORR	(46–77)	(46–77)	(31–79)
DoR, median (95% CI), months	**NR (12–NE)**	**NR (NE–NE)**	**NR (6–NE)**
DCR, (n)	**80% (32)**	**80% (32)**	**67% (12)**
95% CI for DCR	(64–91)	(64–91)	(41–87)
Best overall response, (n)			
CR	15% (6)	13% (5)	6% (1)
PR	48% (19)	50% (20)	50% (9)
SD	18% (7)	18% (7)	11% (2)
PD	15% (6)	15% (6)	28% (5)
NE	5% (2)	5% (2)	6% (1)
KM-estimated PFS, median (95% CI), months	**24 (4–NE)**	**15 (7–NE)**	**12 (1–NE)**

MM#, Cohort 6; MM2#, Cohort 15; MM3#, Cohort 16; *17 patients in cohort MM3 received prior adjuvant therapy and 1 patient in cohort MM3 received prior neoadjuvant and adjuvant therapy.
CI, confidence interval; CR, complete response; DCR, disease control rate; DoR, duration of response; IQR, interquartile range; KM, Kaplan-Meier; MM, metastatic melanoma; n, number; NE, not estimated; NR, not reached; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

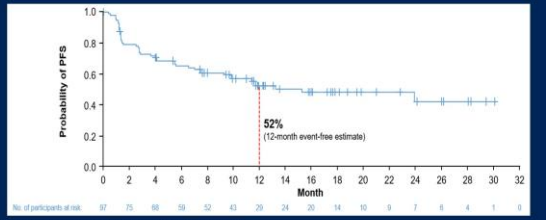
Progression-free survival

Prior adjuvant PD-1 treatment*





	Cohorts MM1# + MM2# + MM3# Advanced melanoma (N=98)
KM-estimated PFS, median (95% CI), months	**15 (9–NE)**
Estimated event-free probability at 12 months, (95% CI)	**52% (41–62)**



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Tumor responses compared with historical controls

Response endpoints	Cohorts MM1# + MM2# + MM3# Advanced melanoma (N=98)	Nivo Relativity-047[1] (N=359)	Nivo + Rela Relativity-047[1] (N=355)	Ipi + Nivo CheckMate-067[2,3] (N=314)
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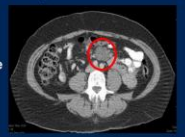

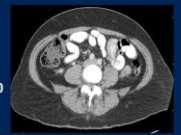

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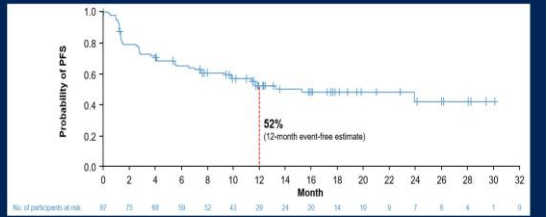

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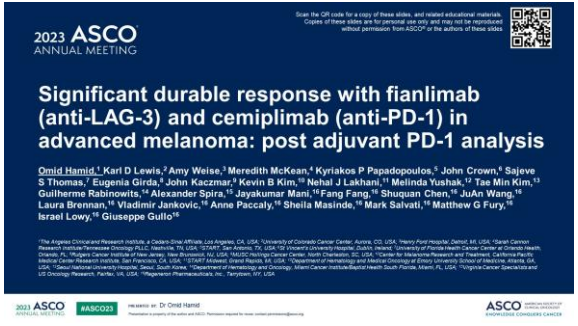
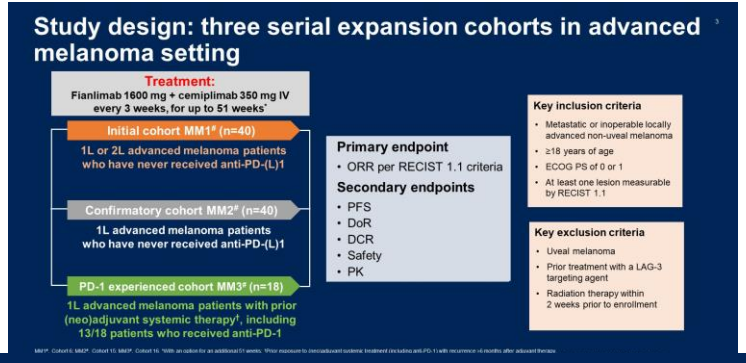
Safety overview in combined cohorts

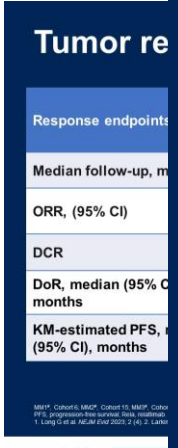
	Cohorts MM1# + MM2# + MM3# Advanced melanoma (N=98)	
Treatment exposure, median (IQR), weeks	33 (15–54)	
TEAEs, regardless of attribution, (n)	**Any grade**	**Grade 3–5**
Overall	94% (92)	44% (43)
Serious	33% (32)	30% (29)
TRAEs, (n)		
Overall	79% (77)	22% (22)
Serious	16% (16)	15% (15)
Treatment-emergent immune-related adverse events, (n)		
Any	65% (64)	12% (12)
Occurred in ≥10% of patients in either group		
Rash	20% (20)	0
Pruritis	16% (16)	0
Diarrhea	15% (15)	0
Arthralgia	13% (13)	0
Hypothyroidism	12% (12)	0
Adrenal insufficiency	11% (11)	4% (4)
Myalgia	10% (10)	0
Any TEAE leading to treatment discontinuation, (n)	16% (16)	

- Overall, 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 rate (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

MM1#, Cohort 6; MM2#, Cohort 15; MM3#, Cohort 16. IQR, interquartile range; MM, metastatic melanoma; n, number; PD-1, programmed cell death-1; TEAE, treatment-emergent adverse event; TRAEs, treatment-related adverse event.

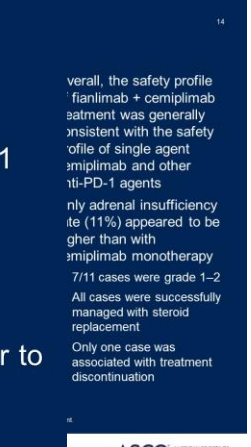






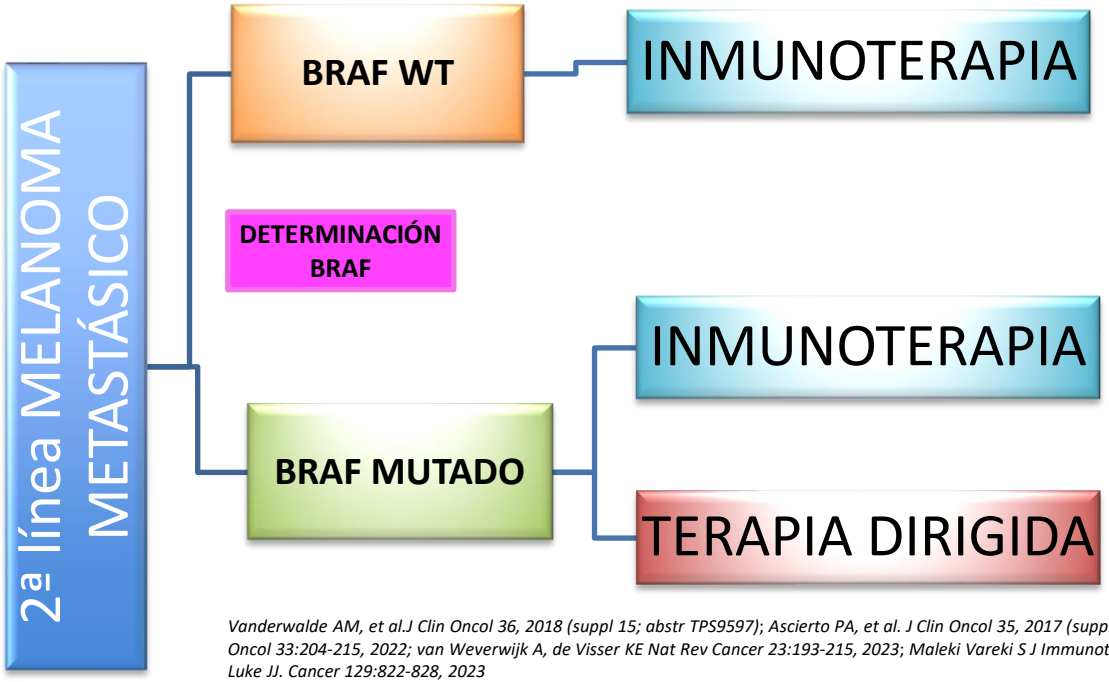
Conclusions

- 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



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

Vanderwalde AM, et al.J Clin Oncol 36, 2018 (suppl 15; abstr TPS9597); Ascierto PA, 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 23:193-215, 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

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

KEYNOTE-D36 EVX-01 + anti-PD1

Vanderwalde AM, et A, 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 23:193-215, 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

2023 ASCO ANNUAL MEETING

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	26 (28.6)	0	0	0	26 (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

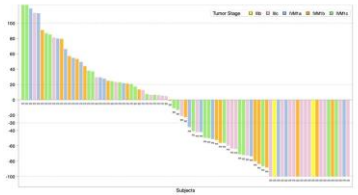
Objective response rates

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%**

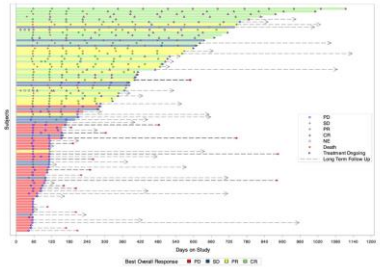
- The overall objective response rate (ORR) was 37.4%
- ORR of at least 28.3% in all subgroups analyzed, including in patients:
  - Having failed anti-CTLA-4 therapy as well as anti-PD1 therapy (34.4% ORR)
  - With Stage IVM1b/c disease (28.3% ORR)
  - Who progressed *while on* prior adjuvant anti-PD1 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

Depth of response



Duration 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

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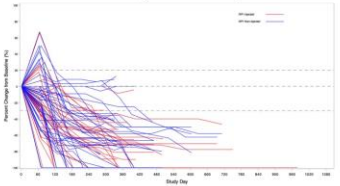
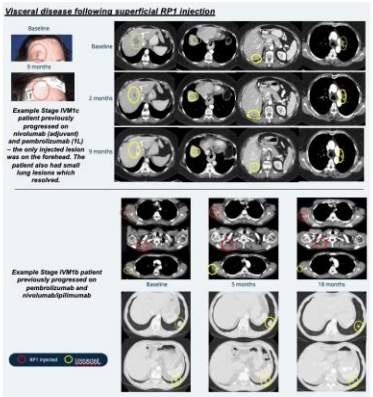
  - Activity seen in both BRAF wild-type & mutant patients, and patients with PD-L1 positive & negative disease (see poster)

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

SARCOMA PARTES BLANDAS

Estadio III irresecable/IV

TRATAMIENTO SISTÉMICO

Doxorrubicina

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.

1. Derbel O, Heudel PE, Cropet C, Meeus P, Vaz G, et al. (2017). Muss HB, *Cancer* 1985; 2. Edmonson JH, *J Clin Oncol* 1993; **3.** Antman L, *J Clin Oncol* 1993; 4. Santoro A, *J Clin Oncol* 1995; 5. Le Cesne A, *J Clin Oncol* 2005; 6. Lorigan P, *J Clin Oncol* 2007; 7. Fayette J, *Invest New Drugs* 2009; 8. Judson I, *Lancet Oncol* 2014; 9. Seddon BM, *Lancet Oncol* 2017; 10. Ryan CW, *J Clin Oncol* 2016; 11. Tap W, *Lancet Oncol* 2017; 12. Juan de Ferré A, Álvarez R, Casado A. et al. Clin and Translat Oncol 2021; 23: 922-930; 13. Pautier P, Italiano S, A, Piper no-Neumann C, et al Annals of Oncology (2021) 32 (suppl_5): S1283-S1346; 14.

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

Estadio III irresecable/IV → TRATAMIENTO SISTÉMICO → Doxorrubicina

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Algoritmo tratamiento de los SARCOMAS 2023

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Estadio III irresecable/IV

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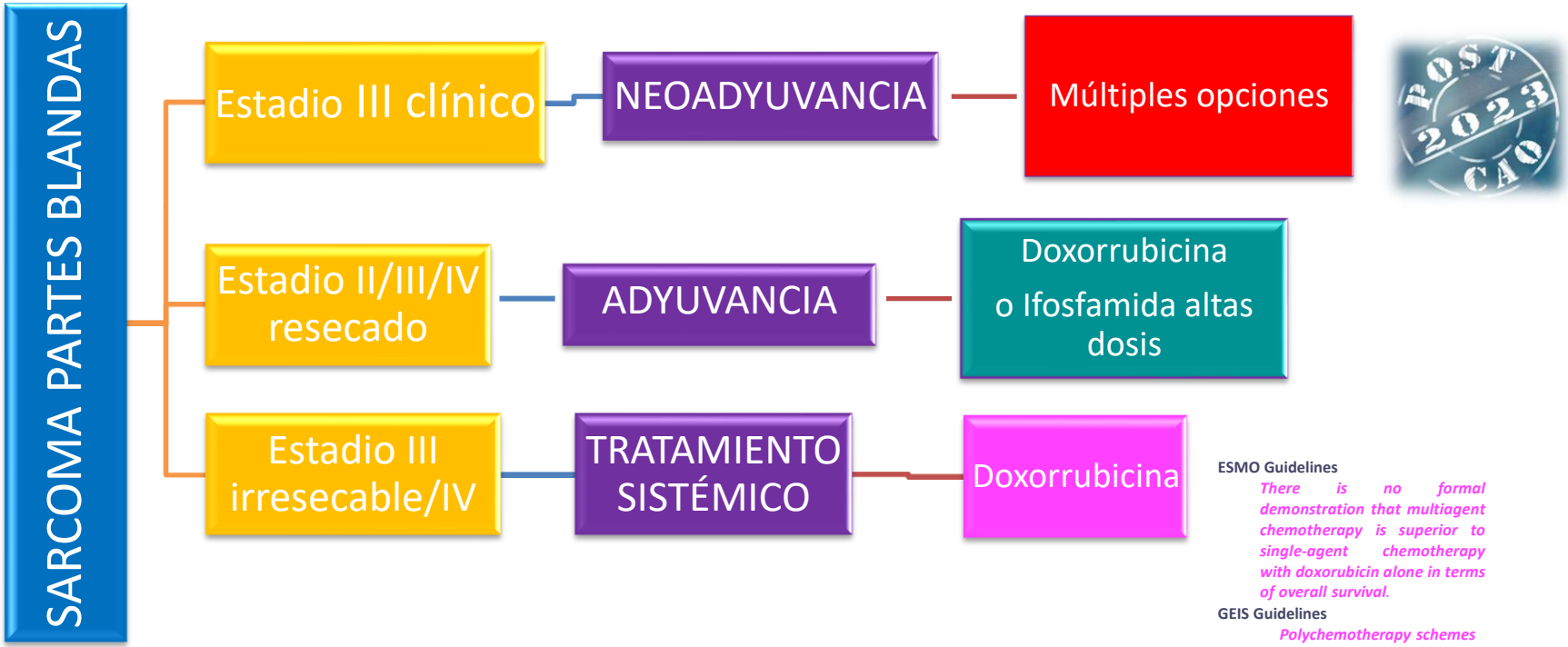
Algoritmo tratamiento de los SARCOMAS 2023



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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 tunned!)
- ✓ **TRABECTEDINA** → tratamiento especifico para LIPOSARCOMA MIXOIDE / DE CÉLULAS REDONDAS
- ✓ **DOXORRUBICINA + IFOSFAMIDA-HD** → tratmiento neoadyuvante "estándar" si se pretende reducir el volumen
- ✓ **DOXORRUBICINA 75** → en el caso de pacientes inapropiados para IFOSFAMIDA HD

- ✓ **QUIMIO-RADIOTERAPIA** → parece que es major que DOXORRUBICINA/DOXORRUBICINA-IFOSFAMIDA HD en grado alto quimiosensibles
  - ✓ → "sandwich" con DOXORRUBICINA + IFOSFAMIDA HD
  - ✓ → concomitante con GEMCITABINA
  - ✓ → concomitante con IFOSFAMIDA HD
  - ✓ → concomitante con TRABECTEDINA

1. Derbel O, Heudel PE, Cropet C, Meeus P, Va
New Drugs 2009; 8. Judson I, *Lancet Oncol* 201
no-Neumann C, et al Annals of Oncology (2021

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

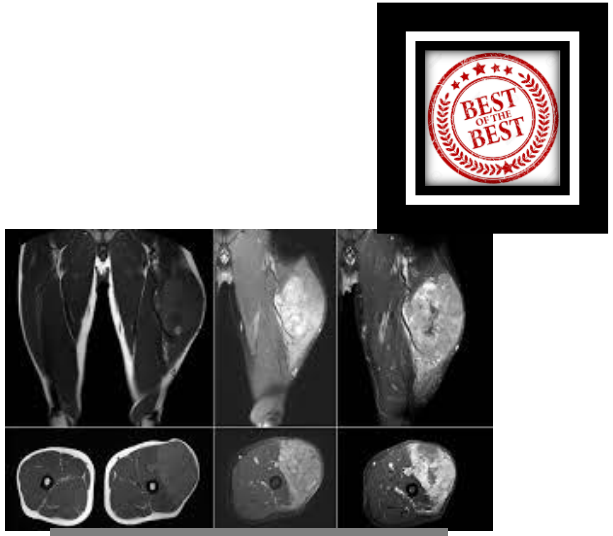
Objetivo 1º: resecabilidad, evitar amputación, márgenes correctos, menor morbilidad

Objetivo 1º pCR

Objetivo 2º PFS: evitar/retrasar M1

Objetivo 2º OS: evitar/retrasar muerte

Toxicidades
Calidad de vida

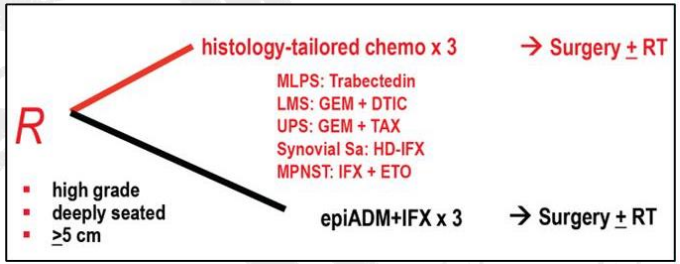


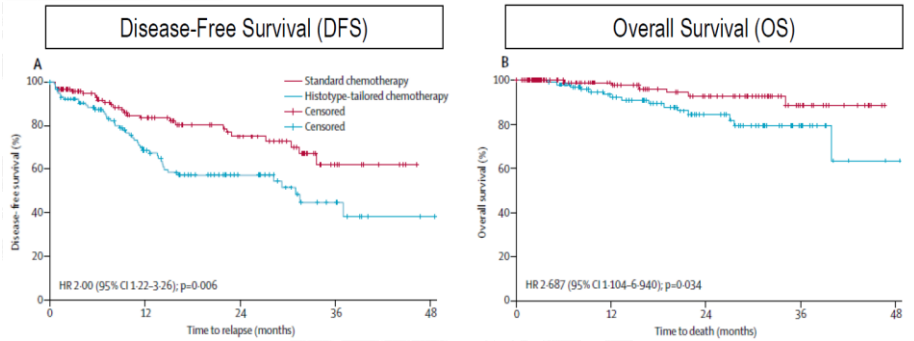
RESECABILIDAD

Tratamiento del SARCOMA NEOADYUVANTE

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

Alessandro Gronchi, Stefano Ferrari, Vittorio Quagliuolo, Javier Martin Broto, Antonio Lopez Pousa, Giovanni Grignani, Umberto Basso, Jean-Yves Blay, Oscar Tendero, Robert Diaz Beveridge, Virginia Ferraresi, Iwona Lugowska, Domenico Franco Merlo, Valeria Fontana, Emanuela Marchesi, Davide Maria Donati, Elena Palassini, Emanuela Palmerini, Rita De Sanctis, Carlo Morosi, Silvia Stacchiotti, Silvia Bagué, Jean Michelle Coindre, Angelo Paolo Dei Tos, Piero 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 epirrubicina-ifosfamida
- RT concomitante en casos seleccionados

Gronchi A et al. Lancet Oncol 2017

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 tunned!
- ✓ **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 doxorrubicina o incluso que doxorrubicina e ifosfamida-HD en tumores de alto grado quimiosensibles
  - ✓ opción de 'sándwich' con doxorrubicina e ifosfamida_HD
  - ✓ concomitante con gemcitabina, ifosfamida-HD o trabectedina

Sanfilippo R, et al. Ann Surg Oncol 2011; EurJCancer; 2001; 37:1096-103; Ann Oncol 2016. Cancer 2012

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 Lugowska; Valeria Fontana; Giuseppe Bianchi; Silvia Stacchiotti; Angelo Paolo Dei Tos; Paolo Verderio; Paolo Giovanni Casali and Alessandro Gronchi

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%
demolitive	7	2.4%	4	2.7%	3	2.1%
NA	2	0.7%	2	1.4%	0	0.0%
Margins						
R0	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 completation						
yes	275	95.8%	141	96.6%	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)		60 (54-64.8)	

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

RECIST radiological responses

	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: ChT

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ChT completation						
ChT completed per protocol	260	90.6%	127	87%	133	94.3%
ChT completed with >3 cycles	8	2.8%	7	4.8%	1	0.7%
ChT discontinued	19	6.6%	12	8.2%	7	5%
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	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

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missing or NA	3	1.0%	3	2.1%	0	0.0%
RT completation						
yes	275	95.8%	141	96.6%	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)		60 (54-64.8)	

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

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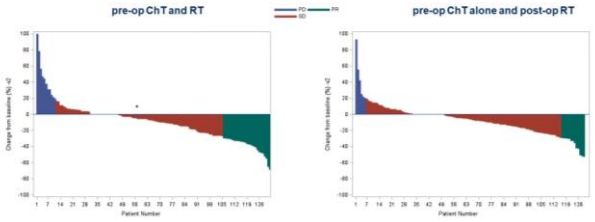
RECIST radiological responses

	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%	

Dimensional change on maximum diameter



Treatment received: ChT

	ALL (N=287)		pre-op ChT and RT (N=146)		pre-op ChT alone and post-op RT (N=141)	
ChT completation						
ChT completed per protocol	260	90.6%	127	87%	133	94.3%
ChT completed with >3 cycles	8	2.8%	7	4.8%	1	0.7%
ChT discontinued	19	6.6%	12	8.2%	7	5%
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	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

2023 ASCO ANNUAL MEETING #ASCO23 PRESENTED BY: Elena Palassini, MD
ASCO KNOWLEDGE CONQUERS CANCER

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 Lugowska; Valeria Fontana; Giuseppe Bianchi; Silvia Stacchiotti; Angelo Paolo Dei Tos; Paolo Verderio; Paolo Giovanni Casali and Alessandro Gronchi

RECIST radiological responses

	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%	

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

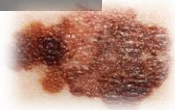
SARCOMA METASTÁSICO:
¿Qué objetivos busco con la elección del tratamiento?

Objetivo 1º:
Alta tasa de respuestas
ORR, PFS

Objetivo 2º:
Respuestas duraderas, OS

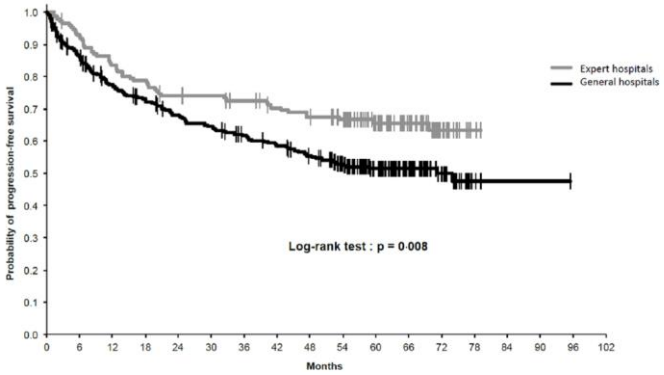
Toxicidades
Calidad de vida

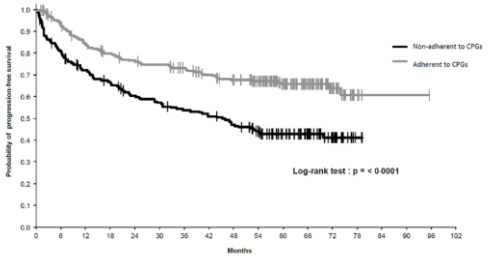
LARGOS RESPONDEDORES,
LARGOS SUPERVIVIENTES

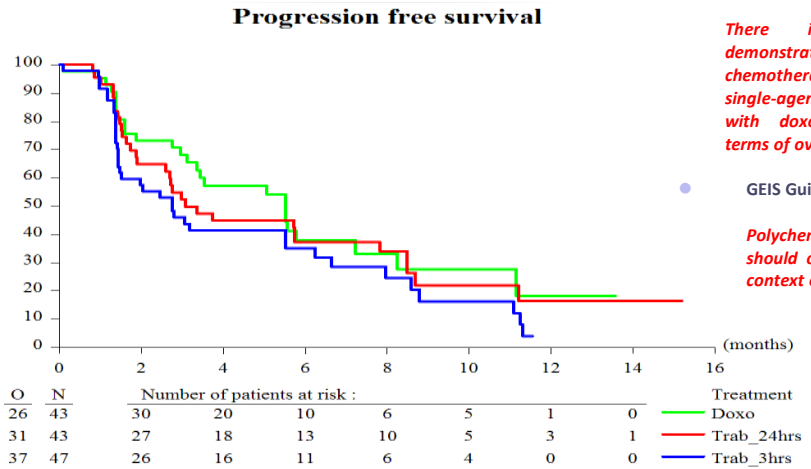


Tratamiento del SARCOMA METASTÁSICO

CENTROS DE REFERENCIA CON EXPERIENCIA







- **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).

Derbel O, Heudel PE, Cropet C, Meeus P, Vaz G, et al. (2017) PLOS ONE 12(2): e0158406; Muss HB, *Cancer* 1985; Edmonson JH, *J Clin Oncol* 1993; Antman L, *J Clin Oncol* 1993; Santoro A, *J Clin Oncol* 1995; Le Cesne A, *J Clin Oncol* 2005; Lorigan P, *J Clin Oncol* 2007; Fayette J, *Invest New Drugs* 2009; Judson I, *Lancet Oncol* 2014; Seddon BM, *Lancet Oncol* 2017; Ryan CW, *J Clin Oncol* 2016; Tap W, *Lancet Oncol* 2017;

Tratamiento del SARCOMA METASTÁSICO

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

Is the patient symptomatic?

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

Is surgery potentially feasible?

Surgery of residual disease

Asymptomatic patient
No surgical rescue options

Doxorubicin monotherapy

Close follow-up

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

ESMO Guidelines

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

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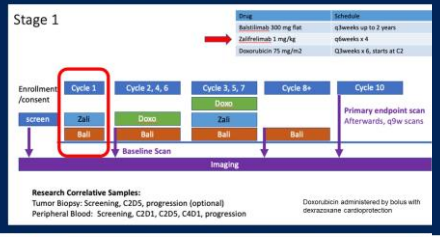
2023 ASCO ANNUAL MEETING

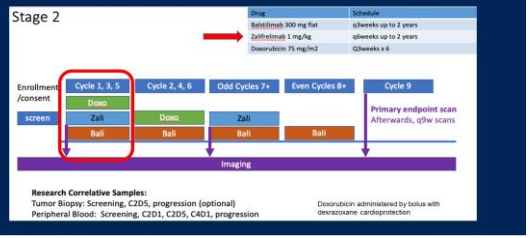
A single-arm, open-label phase 2 trial of doxorubicin plus zalifrelimab, a CTLA-4 inhibitor, with balstilimab, a PD-1 inhibitor in patients with advanced/metastatic soft tissue sarcomas

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

Treatment Schema – Stage 1

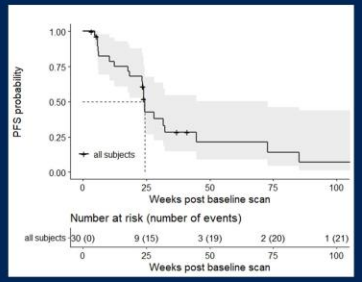


Treatment Schema – Stage 2



POST 2023 CAO

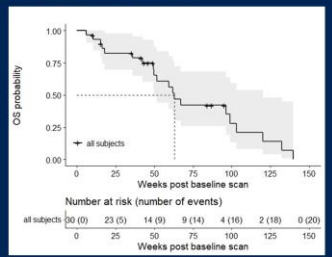
Results – Primary Endpoint



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]

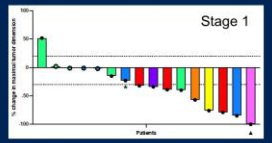
Results – Overall Survival



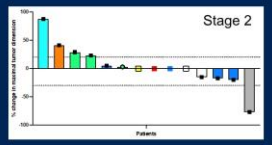
Median OS:
63 weeks [50-120]

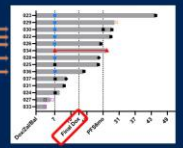
Median follow up time:
95 weeks [84.3 – NA]

Impact of Treatment Schema (Stage 1 vs 2)

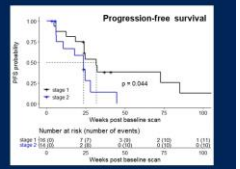


uLMS
sLMS
dLPS
angiosarcoma
endometrial stromal sarcoma
MPNST
UPS/MFS
Clear cell sarcoma
Sclerosing epith fibrosarcoma
intimal sarcoma





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
Immune related AEs requiring steroids/anti-TNFα	ALL Colitis Thyroiditis CNS/CNA Hypertriglyceridemia Pancreatitis	4 (12) 2 (6) 1 (3) 2 (6) 1 (3) 2 (6)	4 (12) 2 (6) 1 (3) 1 (3) 1 (3) 2 (6)	Pt #12 – colitis Pt #17 – colitis/pancreatitis Pt. #27 – pancreatitis/DKA/thyroiditis Pt. #29 – hypothyroid, hypertriglyceridemia, DM
GI	ALL Colitis Diarrhea Nausea/Vomiting/Dyspepsia	26 (79) 3 (9) 11 (33) 17 (51)	4 (12) 2 (6) 1 (3) 1 (3)	Primarily Dox-related including1 colitis, 1 diarrhea
Fatigue		22 (67)	0 (0)	Attributed to Dox and IO
Dermatologic	(Rashes, hand-foot syndrome)	17 (52)	0 (0)	Attributed to Dox and IO
Heme		15 (45)	9 (27)	Primarily Dox-related
Mucositis		12 (36)	0 (0)	Dox-related
Transaminitis		4 (12)	0 (0)	Attributed to Dox and IO
Arthralgias/Myalgias		4 (12)	0 (0)	Attributed to Dox and IO
Decreased ejection fraction		2 (6)	0 (0)	Dox-related, no myocarditis

2023 ASCO ANNUAL MEETING

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

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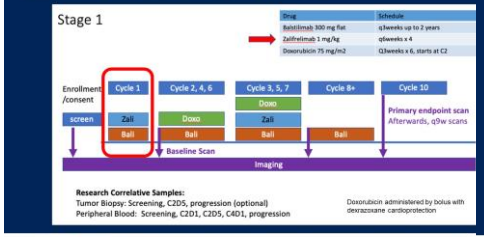
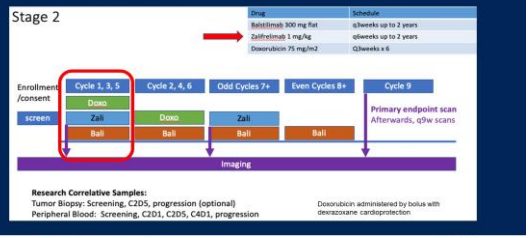
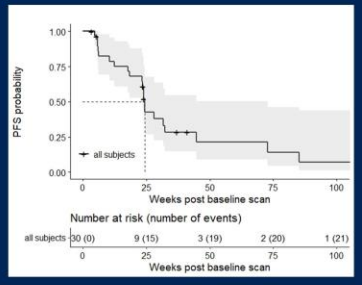


Treatment Schema – Stage 2



POST 2023 CAO

Results – Primary Endpoint



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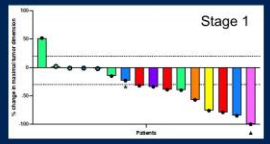
Median PFS:
24.4 weeks [23.4 – 72.9]

Impact of Treatment Schema (Stage 1 vs 2)



uLMS
sLMS
dLPS
angiosarcoma
endometrial stromal sarcoma
MPNST
UPS/MFS
Clear cell sarcoma
Sclerosing epith fibrosarcoma
intimal sarcoma

Variable	Stage 1	Stage 2
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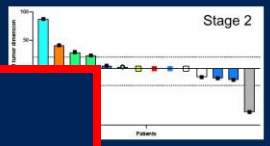

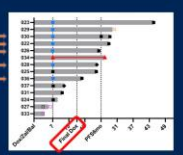

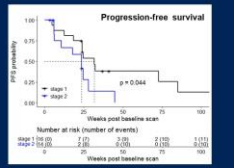

Conclusions

- 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

Treatment-Related Adverse Events

Category	Adverse Events	All grades	Grade 3+	Notes
Immune related AEs requiring steroids/anti-TNFα	ALL	4 (12)	4 (12)	Pt #12 – colitis
	Colitis	2 (6)	2 (6)	Pt #17 – colitis/pancreatitis
	Thyroiditis	1 (3)	1 (3)	Pt. #27 – pancreatitis/DKA/thyroiditis
	DM/DKA	2 (6)	1 (3)	Pt. #29 – hypothyroid,
	Hypertriglyceridemia	1 (3)	1 (3)	hypertriglyceridemia, DM
	Pancreatitis	2 (6)	2 (6)	
GI	ALL	26 (79)	4 (12)	Primarily Dox-related including1 colitis, 1 diarrhea
	Colitis	3 (9)	2 (6)	
	Diarrhea	11 (33)	1 (3)	
	Nausea/Vomiting/Dyspepsia	17 (51)	1 (3)	
Fatigue		22 (67)	0 (0)	Attributed to Dox and IO
Dermatologic	(Rashes, hand-foot syndrome)	17 (52)	0 (0)	Attributed to Dox and IO
Heme		15 (45)	9 (27)	Primarily Dox-related
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Transaminitis		4 (12)	0 (0)	Attributed to Dox and IO
Arthralgias/Myalgias		4 (12)	0 (0)	Attributed to Dox and IO
Decreased ejection fraction		2 (6)	0 (0)	Dox-related, no myocarditis

2023 ASCO ANNUAL MEETING

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

Javier Martin-Broto[1], Roberto Diaz-Beveridge[2], David Moura[1], Rafael Ramos[3], Javier Martinez-Trufero[4], Irene Carrasco[5], Antonio Lopez-Pousa[6], Enrique González[7], Antonio Gutierrez[3], Claudia Valverde[8], Josefina Cruz[9], Nadia Hindi[1]

1 Hospital Universitario Fundación Jiménez Díaz; 2 Hospital Universitari i Politècnic la Fe; 3 Hospital Universitari Son Espases; 4 Hospital Universitario Miguel Servet; 5 Hospital Universitario Virgen del Rocío; 6 Hospital de la Santa Creu i Sant Pau; 7 Hospital Universitario 12 de Octubre; 8 Hospital Universitari Vall d'Hebron; 9 Hospital Universitario de Canarias

METHODS

IMMUNOSARC TRIAL cohort 7b

.- Phase Ib trial with 2 dose-levels: (3+3 design[1] with a minimum of 20 evaluable patients in RP2D)

- **Level 0**: Doxorubicin 75 mg/m^2/d d1+ DTIC 400 mg/m^2/d d1-2 + Nivolumab 360 mg on day 2/ 21d + GCSF
- **Level -1**: Doxorubicin 75 mg/m^2/d d1+ DTIC 400 mg/m^2/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	10 (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%)	1 (5.0%)	0	0
Lymphocytosis	1 (5.0%)	1 (5.0%)	0	0	0
Febrile 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/nail alterations	4 (20.0%)	4 (20.0%)	0	0	0
ALT increased	4 (20.0%)	4 (20.0%)	0	0	0
Dysgeusia	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%)	1 (5.0%)	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.

RESULTS-3

Efficacy Variables

.- Median follow-up: 8 months (2-12)

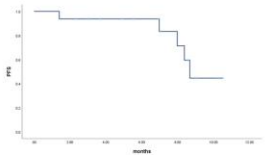
.- #Cycles (combo): 94. Median: 6 (1-6)

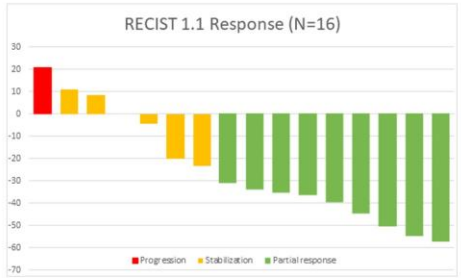
.- ORR from 16 evaluable patients:

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% CI1.1-9)

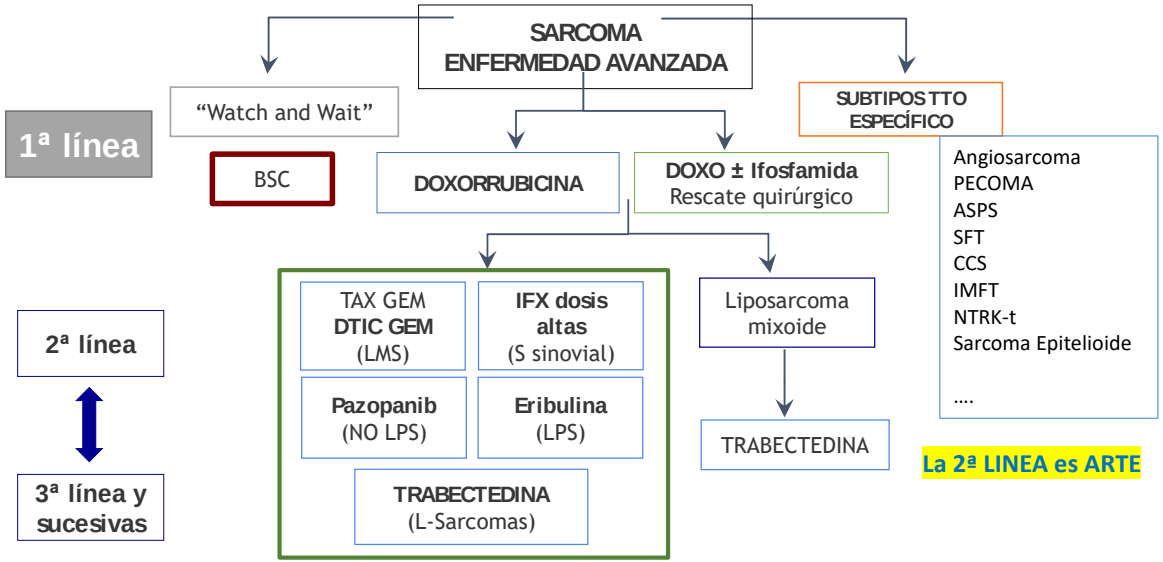




Conclusions

- The combination of Doxorubicin 75 mg/m^2/d d1+ DTIC 400 mg/m^2/d 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.

Tratamiento del SARCOMA METASTÁSICO



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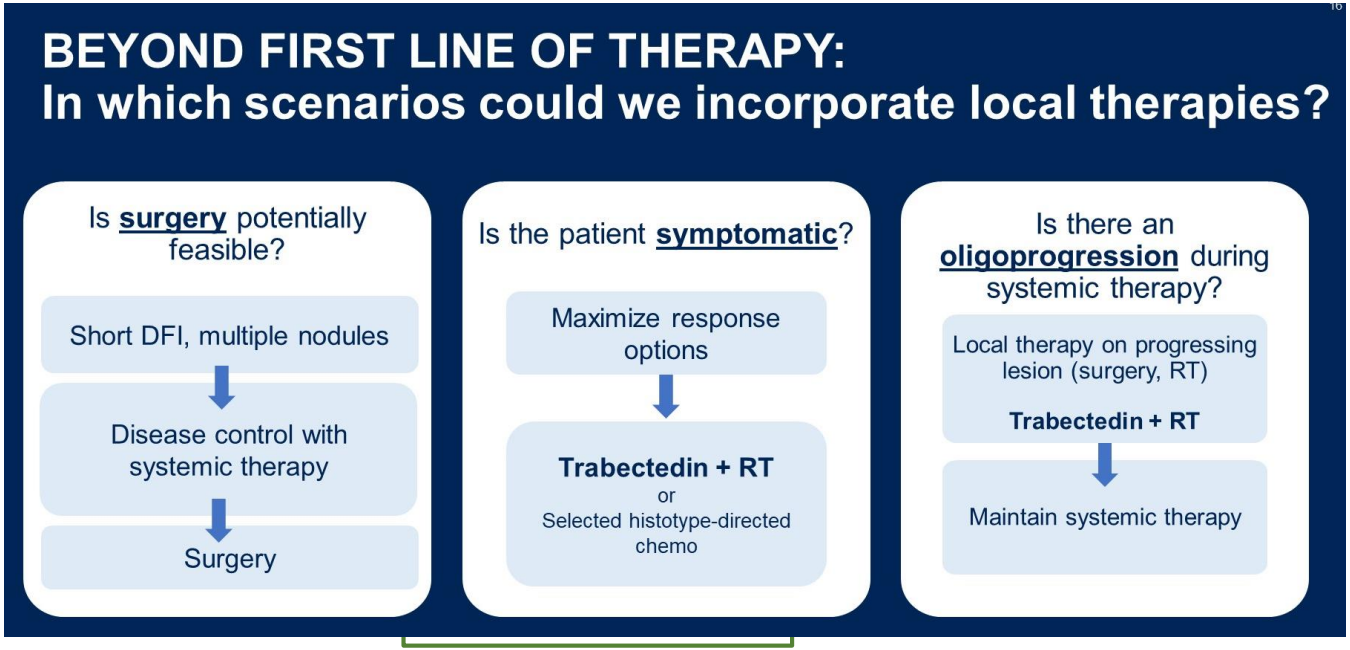
- COSTE
- DISPONIBILIDAD
- ESTABILIZACIÓN
- NECESIDAD DE RESPUESTA
- TRATAMIENTO DE MANTENIMIENTO
- PREFERENCIAS DEL PACIENTE

Tratamiento del SARCOMA METASTÁSICO



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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

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- 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

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%

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PRESENTED BY: Nam Bui, MD

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2023 ASCO ANNUAL MEETING

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

Alliance A091902

Juneko Grilley-Olson, MD

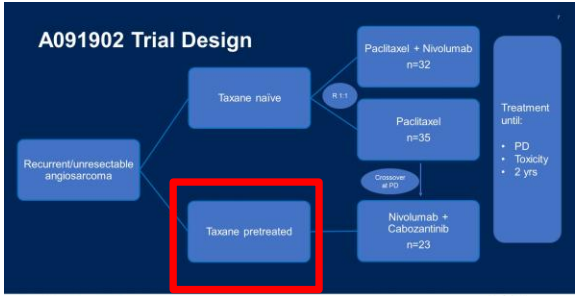
Duke University

Authors: Juneko E. Grilley-Olson, Jacob B. Allred, Scott Schuetze, Elizabeth J. Davis, Michael J Wagner, Andrew Stewart Poklepovic, 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 Health System, 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



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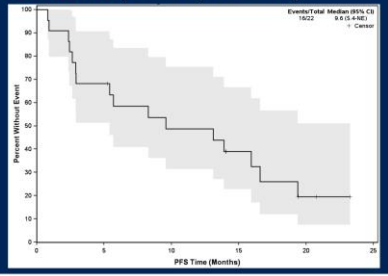
Cabozantinib/Nivolumab in Angiosarcoma

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

Median PFS: 9.6 mo (95% CI, 5.4 – NR)



Cabozantinib/Nivolumab in Angiosarcoma

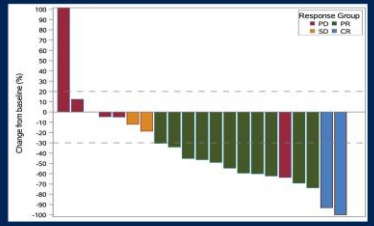
Best Overall Response: RECIST v1.1

Significant responses including 2 CRs

ORR 13/22 = 59%
(95% CI, 36 – 79%)

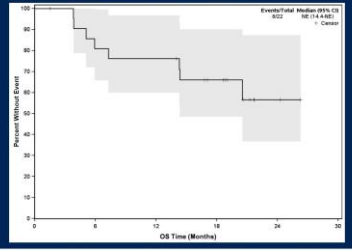
1st stage 8/9 (89%)

Overall CBR 16/22 (73%)



Cabozantinib/Nivolumab in Angiosarcoma

Median OS: NR (95% CI, 14.4 – NR)



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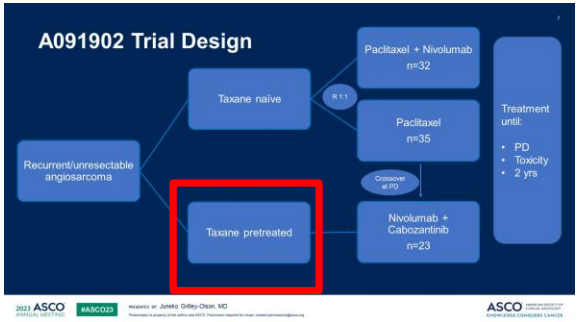

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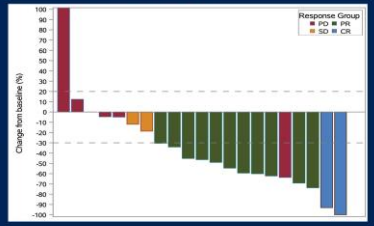


Conclusions

- 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 mo[1])
- 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

[1]Jones JAMA Onc 2022

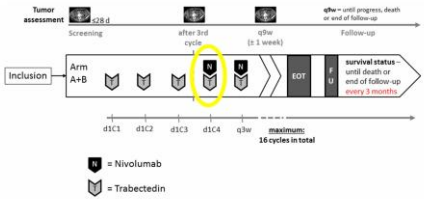
2023 ASCO ANNUAL MEETING

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 Reichardt[1], Dimosthenis Andreou[2], Anne Flörcken[3], Thorben Groß[4], Stephan Richter[5], Torsten Kessler[6], Martin Kortüm[7], Christian A Schmidt[8], Bernd Kasper[9], Eva Wardelmann[6], Benedict Atzler[10], Disorn Sookthai[10], Daniel W Mueller[10], Daniel Pink[8, 11]

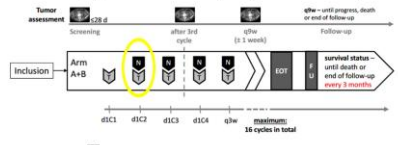
[1] Helios Klinikum Berlin-Buch, Medical School Berlin, Berlin, Germany. [2] Medizinische Universität Graz, Austria. [3] Charité–Universitätsmedizin Berlin, Berlin, Germany. [4] Universitätsklinikum Tübingen, Tübingen, Germany. [5] Universitätsklinikum Carl „Gustav Carus", Dresden, Germany. [6] Universitätsklinikum Münster, Münster, Germany. [7] Universitätsmedizin Greifswald, Greifswald, Germany. [8] 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*



*Chawla SP, Samhaia KH, Ravivz JR, Kang OE, Liu S, Asaulani N, et al. Clinical Experience with Combination Chemo-Immunotherapy using Trabectedin and Nivolumab for Advanced Soft Tissue Sarcoma. J Sarcoma Res. 2018; 2(1): 1009.

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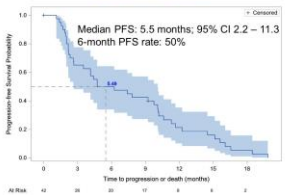
L-Sarcoma (Group A): progression-free survival

Group A: overall



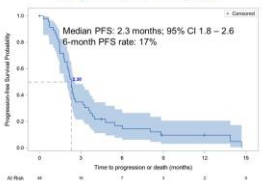
Statistical Design

combination insufficient, if PFSR6 ≤ 35%

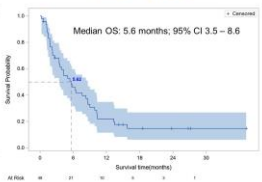
combination highly promising, if PFSR6 ≥ 55%

Non-L-Sarcoma (Group B): Survival

progression-free survival

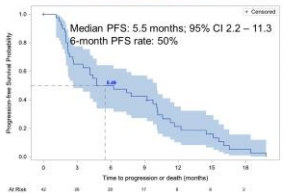


overall survival

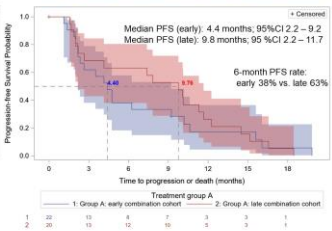


L-Sarcoma (Group A): progression-free survival

Group A: overall

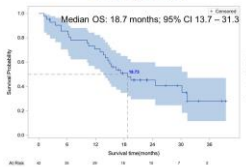


early combination vs. late combination



L-Sarcoma (Group A): overall survival

Group A: overall



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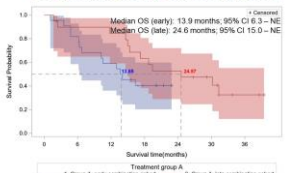

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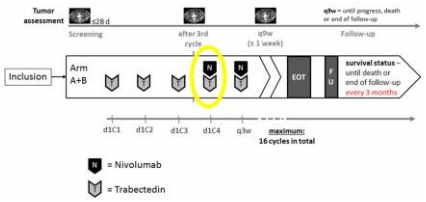

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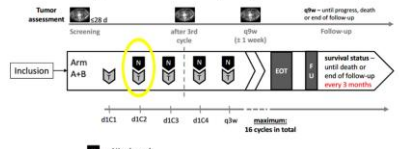

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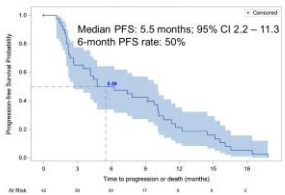
Group A: overall



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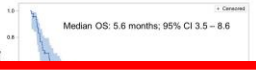
Non-L-Sarcoma (Group B): Survival

progression-free survival

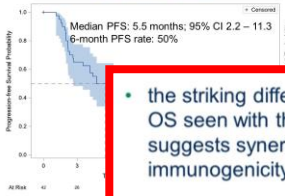
overall survival



- 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

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

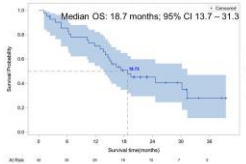
Group A: overall



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

Group A: overall



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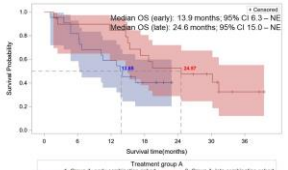
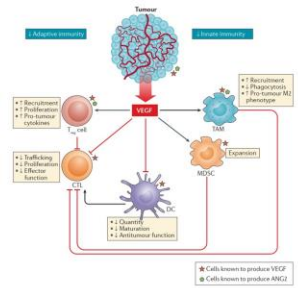
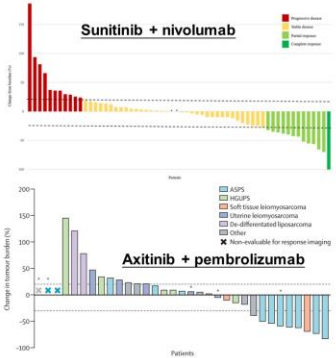


2023 ASCO ANNUAL MEETING

Lenvatinib plus pembrolizumab in patients with advanced sarcoma

Sujana Movva, Viswetej Avutu, Ping Chi, Mark Andrew Dickson, Mrinal M. Gounder, Ciara Marie Kelly, Mary Louise Keohan, Paul A. Meyers, Seth M. Cohen, Mattee L. Hensley, Jason A. Konner, Alison M. Schram, Robert A Lefkowitz, Joseph Patrick Erinjeri, Li-Xuan Qin, Tiffany Salcito, Kenneth Seier, William D. Tap, Sandra P. D'Angelo





Martin-Broto et al. JITC 2020

Wilky et al. Lancet Oncol 2016

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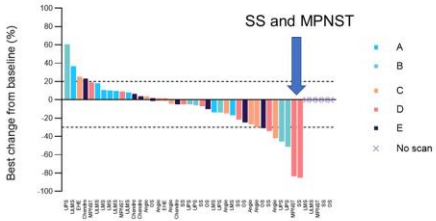
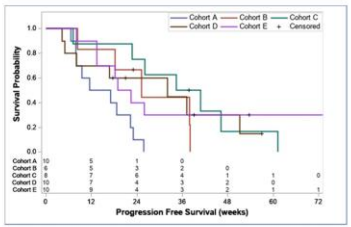
ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY KNOWLEDGE CONQUERS CANCER

Efficacy results





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

- Median PFS ≥ 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 ≥ 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

	Number of Patients, (%) n= 47		
Adverse Event	**Grade 1/2**	**Grade 3/4**	**SAE (#)**
Blood and Lymphatic			
Anemia	9 (19.1)	2 (4.3)	0
Leukopenia	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
Diarrhea	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
Hepatobiliary			
ALT increased	14 (29.8)	1 (2.1)	0
AST increased	13 (27.7)	1 (2.1)	0
Bilirubin increased	8 (17.0)	0	1
Infection			
Lung infection	0	1 (2.1)	1
Investigations			
Creatinine increased	6 (12.8)	1 (2.1)	1
Metabolism			
Anorexia	11 (23.4)	0	0
Neoplasm			
Pain	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 (12.8)	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 (2.1)	2

TRAEs occurring in ≥ 20% of patients or any SAE event

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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