15th MADRID CONGRESS on Lung CANCER

23&24 November 2023

#15CongressGECP

Fundación GECP lung cancer research

Overcoming resistance to immunotherapy

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Disclosures

- Consultant or Advisory Role: Sanofi.
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- Education grants: Takeda, MSD

- Thanks to Dr. Edurne Arriola, Hospital del Mar.

Definition of resistance

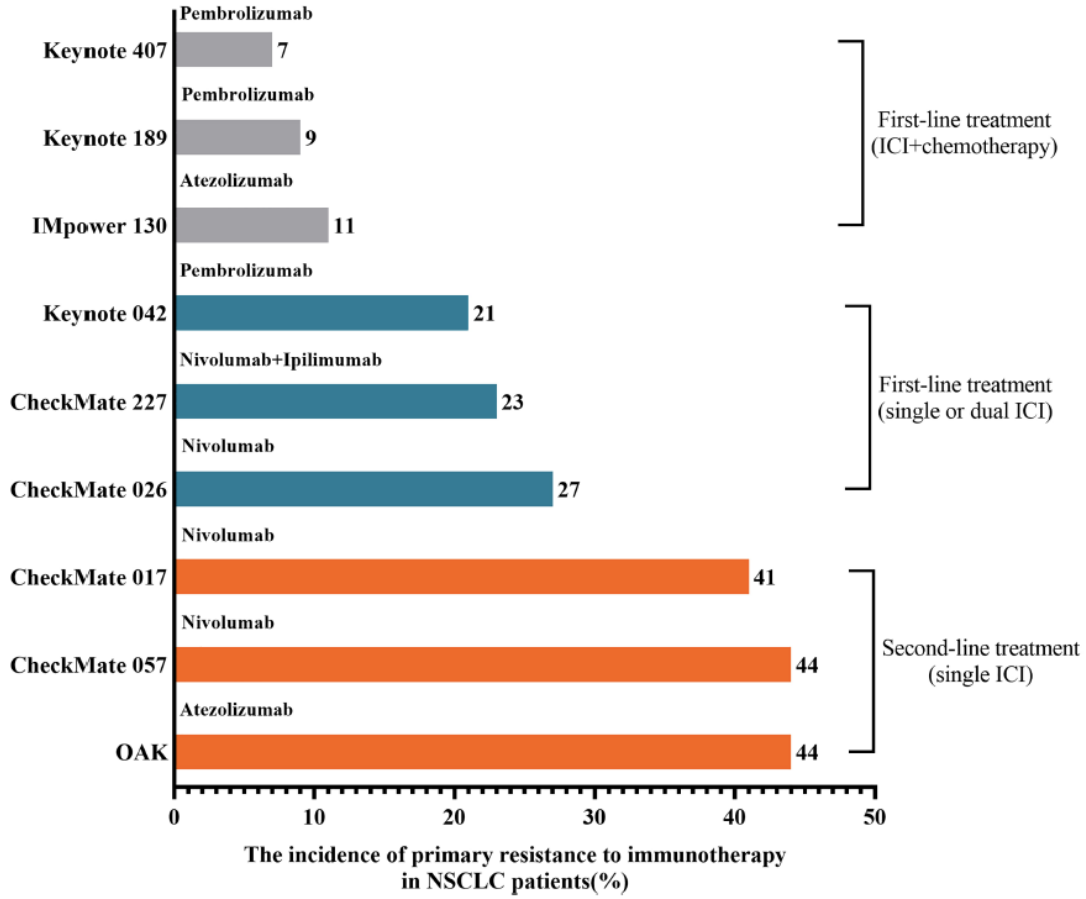
Resistencia Primaria

"the inability of immune cells to mount an antitumor response on initial drug exposure" -> el tratamiento no ha funcionado (no beneficio clínico)

PD como mejor respuesta, SD que dura <6 meses (≥ 6 semanas de tratamiento) - Society for Immunotherapy of Cancer (SITC)

Varía en función línea y fármacos:

- 1ª Línea QT-IO: 7-11%
- 1ª Línea IO (sin QT): 21-27%
- 2ª Línea IO (monoterapia): 41-44%



Kluger HM, J Immunother Cancer (2020)
Zhou et al. Front Immun 2023

Hyperprogression

- No hay un claro consenso sobre su definición (varía según estudios y criterios utilizados)
- Más visto en 2ª línea y en monoterapia.

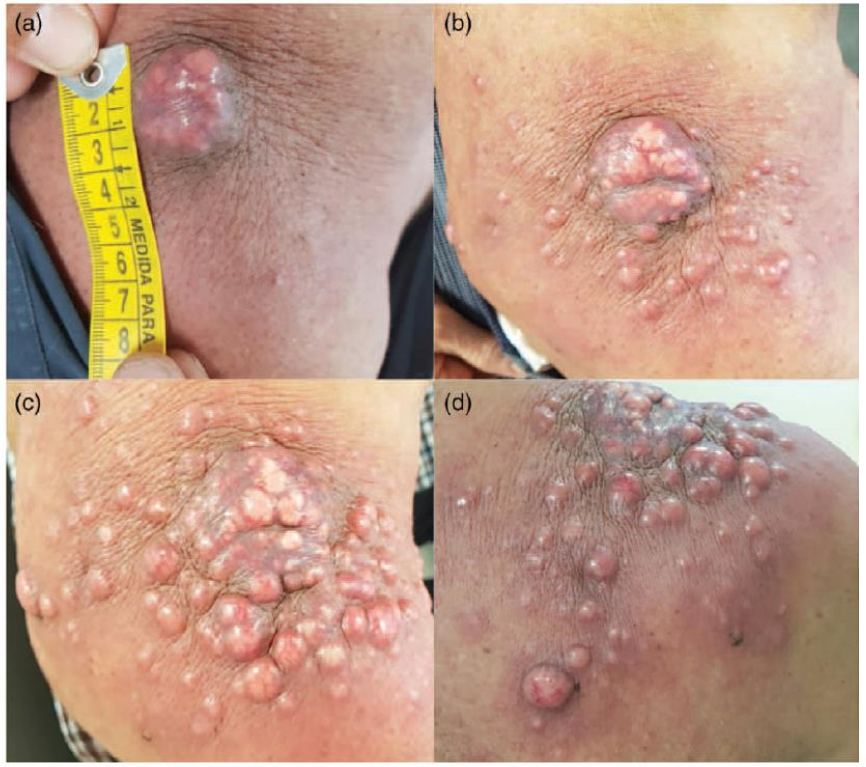


TABLE 1 The prevalence of HPD is varied based on different criteria in NSCLC.

Study	Incidence	Criteria	Conclusion	Ref
Ignacio Matos et al	12.5% (4/32)	HPD = 1.4 x baseline sum Target lesions Or HPD = 1.2 x baseline sum Target lesions + new lesions in at least two different organs	Capturing HPD by using RECIST criteria is intuitive and easy to implement.	(15)
	16.2% (1/27)	HPD = TGR experimental period/TGR reference period ≥ 2		
Youjin Kim et al	14.3% (48/135)	volumetry	volumetric measurement is more precise than the basis of one-dimensional analysis.	(16)
	13.1%(44/135)	RECIST 1.1		
Deirdre M.H.J. ten Berge et al	7%(4/58)	TGK	TGK has predictive value for OS	(17)
Roberto Ferrara et al	13.8%	ΔTGR exceeding 50%.	HPD is associated with high metastatic burden and poor prognosis	(4)
Baptiste Kas et al	18.5%(22/406)	the TGR ratio	ΔTGR>100 is close to the characteristics of HPD (increase of the tumor kinetics and poor survival).	(18)
	5.4%(75/406)	a progression pace >2-fold and TTF<2 months		
C G Kim et al	20.9%(55/263)	TGK	HPD meeting both TGK and TGR criteria is associated with worse PFS and OS	(19)
	20.5%(54/263)	TGR		
	37.3%(98/263)	TTF		
B Abbar et al	11.3%	TGRratio	TTF is the only indicator of significantly worsened OS.	(20)
	5.7%	ΔTGR		
	17.0%	TGK		
	9.6%	RECIST		
	31.7%	TTF		

PFS, progression-free survival; TGK, tumor growth kinetics; OS, overall survival; ΔTGR, The difference between TGR before and during therapy; TTF, time to treatment failure.

Bosch-Barrera, Anticancer Drugs. 2019 Nov;30(10):1067-1070.
Yanping Li, Front. Immunol. 2023

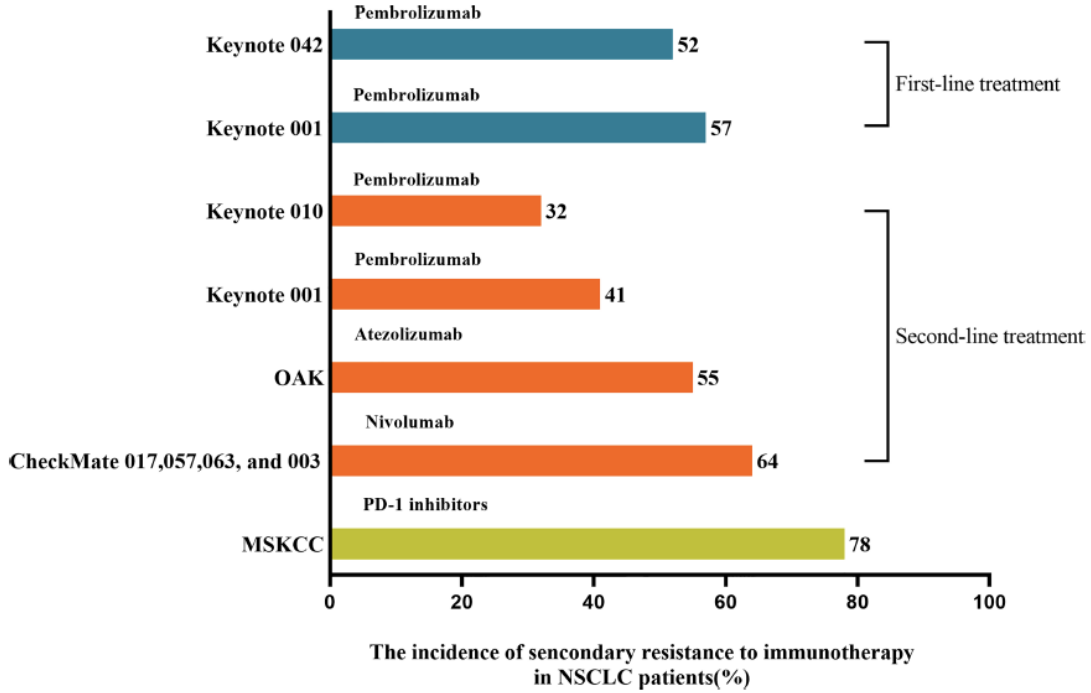
Definition of resistance

Resistencia secundaria

"which arises when a patient is treated with antineoplastic therapy, has a documented, confirmed objective response or prolonged SD (>6 months), and then has disease progression in the setting of ongoing treatment" -> el tratamiento deja de funcionar

Varía en función línea:

- 1ª Línea IO: 52-57%
- 2ª Línea IO: 32-64%



Kluger HM, J Immunother Cancer (2020)
Zhou et al. Front Immun 2023

Different patterns of PD

Estudio con 208 pacientes que progresaron >3 meses de inicio de tratamiento con IO.

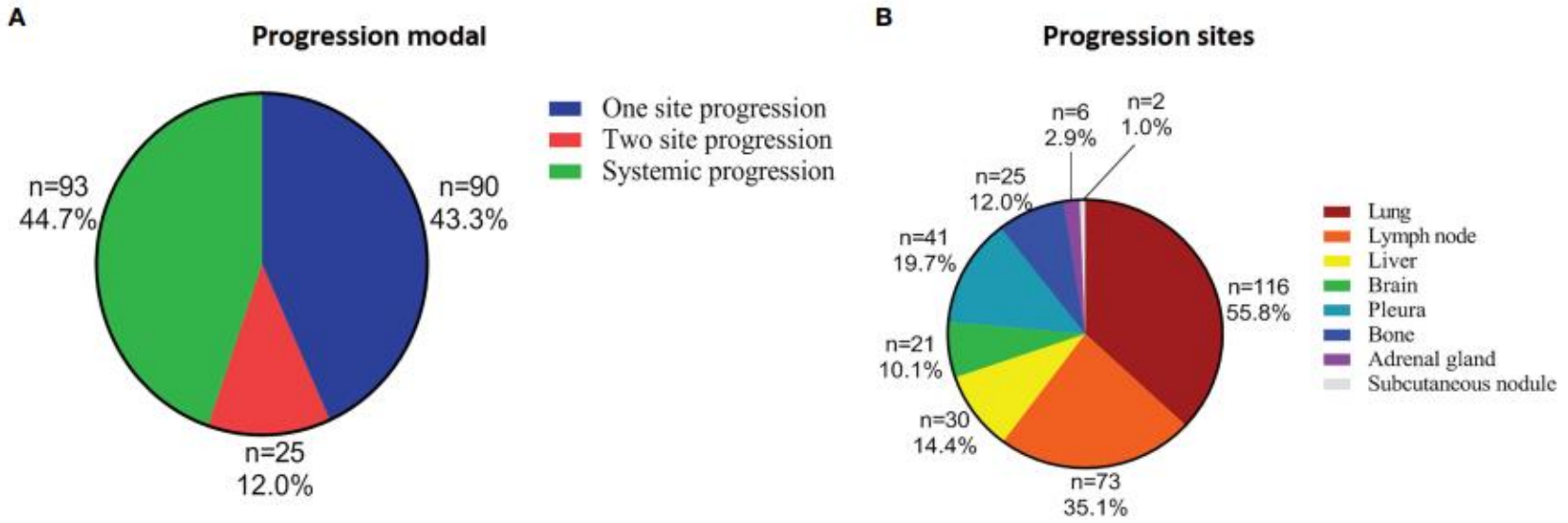


FIGURE 2 | Progression patterns and sites beyond immunotherapy resistance. **(A)** 115 (55.3%) patients developed oligoprogression, and 93 (44.7%) developed systemic progression. Ninety (90/208, 43.3%) patients developed progressive disease at one site. **(B)** The progression sites included the lung (N = 116, 55.8%), lymph node (N = 73, 35.1%), liver (N = 30, 14.4%), brain (N = 21, 10.1%), pleura (N = 41.19.7%), bone (N = 25, 12%), adrenal gland (N = 6, 2.9%), and subcutaneous nodule (N = 2, 1.0%).

Different patterns of PD

Oligoprogresión

Empeoramiento de la enfermedad entre 1-5 lesiones (según estudios) nuevas o que crecen

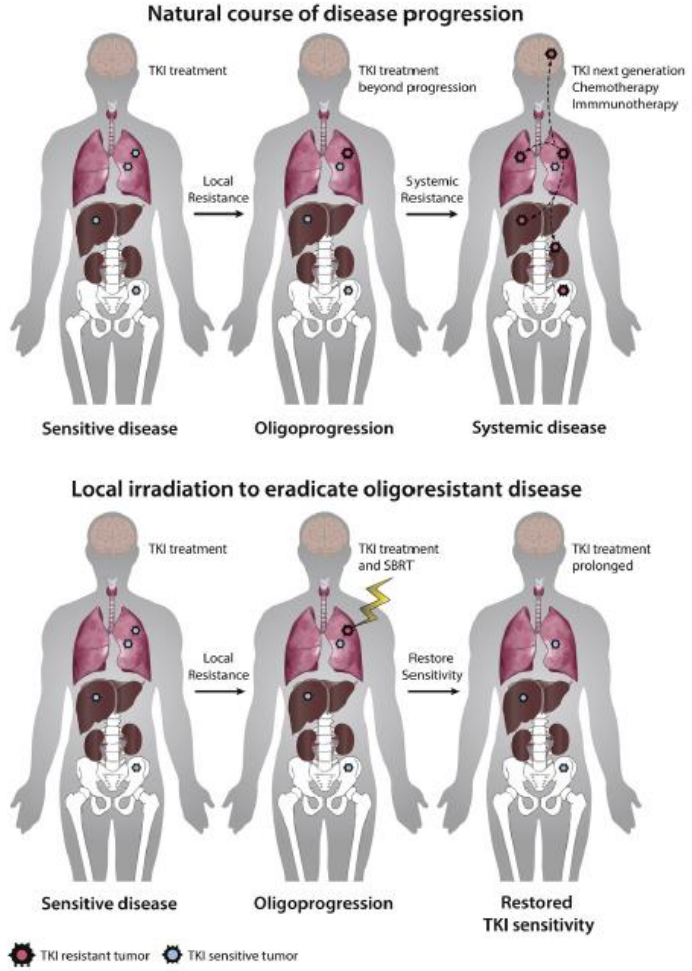
However, for patients with oligoprogression, the question regarding the optimal therapeutic approach remains valid, despite the availability of new drugs.

There are essentially three treatment options:

(1) change systemic therapy,

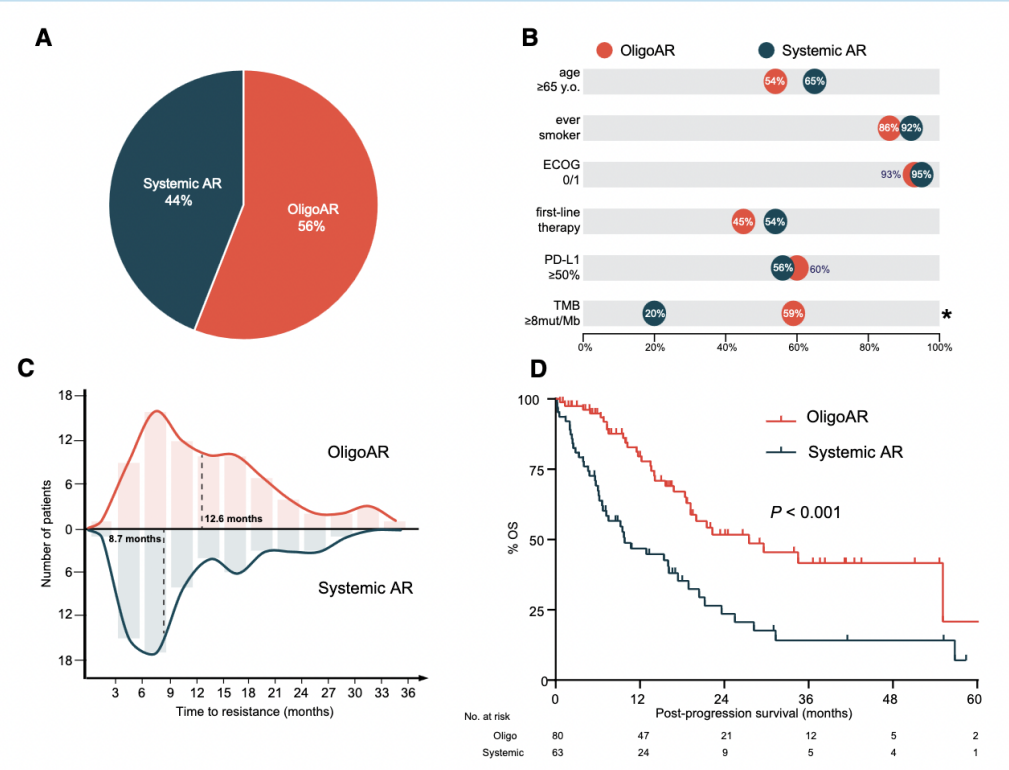
(2) continue the same systemic therapy strategy beyond progression

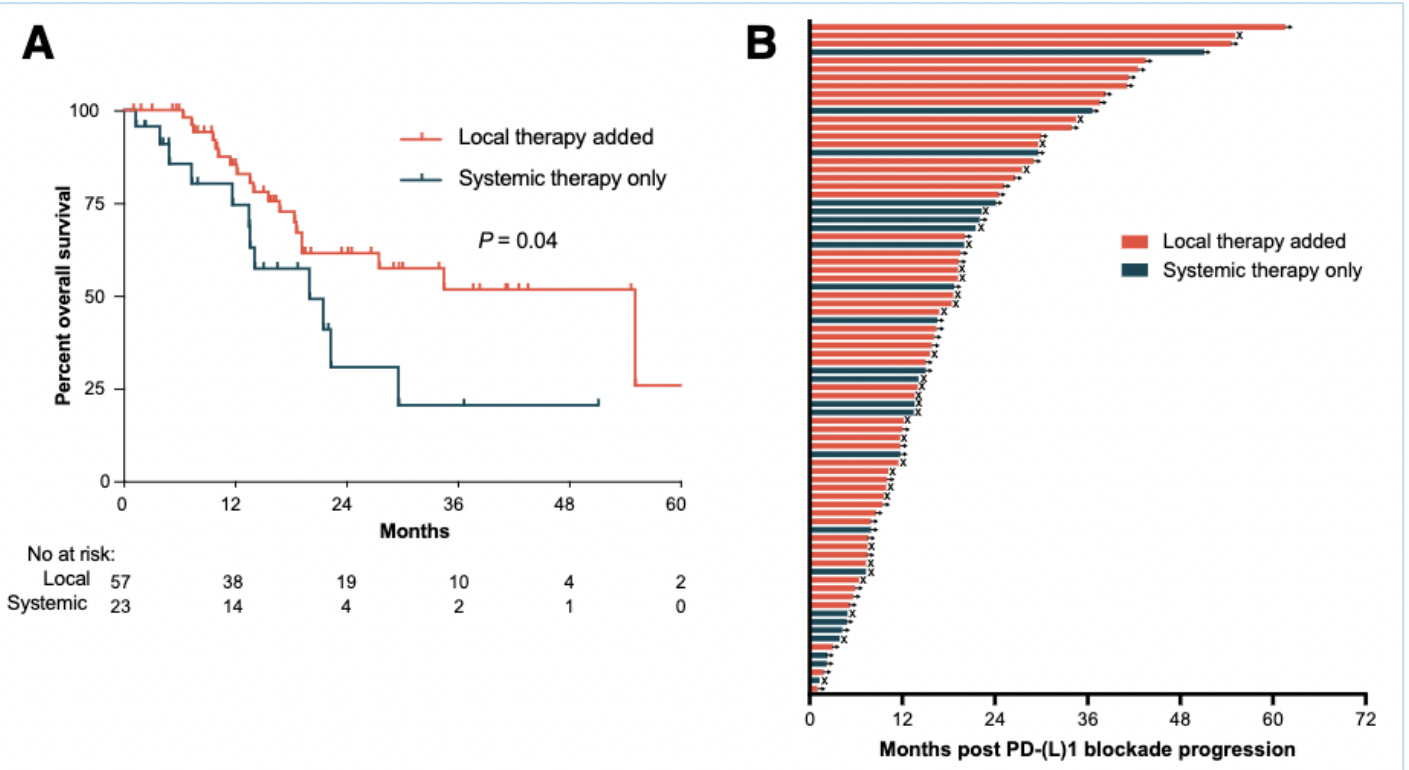
(3) use local therapy, such as SBRT, to eradicate the resistant clones while remaining on the same systemic therapy strategy (Cheung, 2016; Planchard et al., 2019).



Basler et al. Lung Cancer 2017;106:50−57
Franceschini et al. Crit Rev in Oncol/Hematol 2020;148:102894

Local treatment for Oligo PD



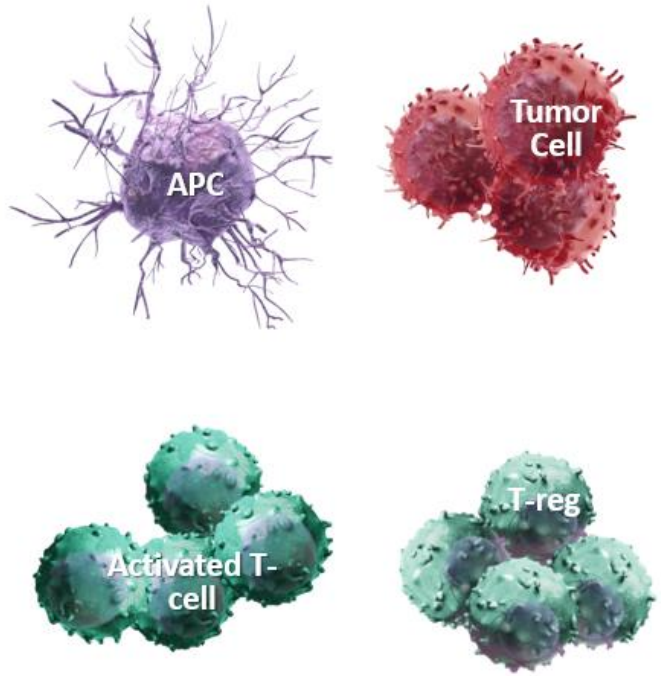


Máximo 3 lesiones para OligoPD

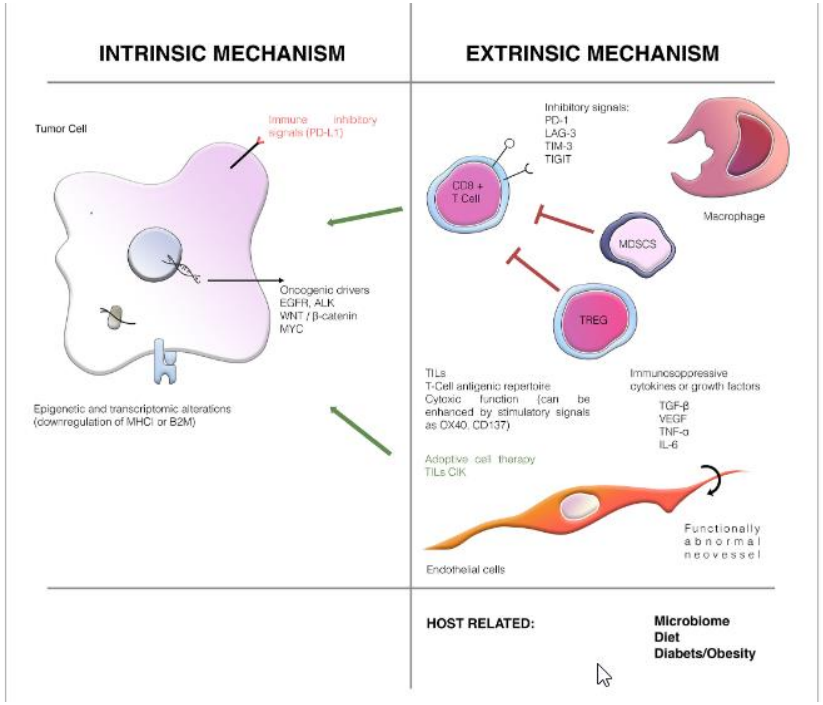
Shoenfeld CCR 2022
Zhou et al. Front Immun 2023

Mechanism of resistance to IO

- Acción de la inmunoterapia implica diversas células y procesos, lo que hace mucho más complejo los potenciales mecanismos de resistencia.

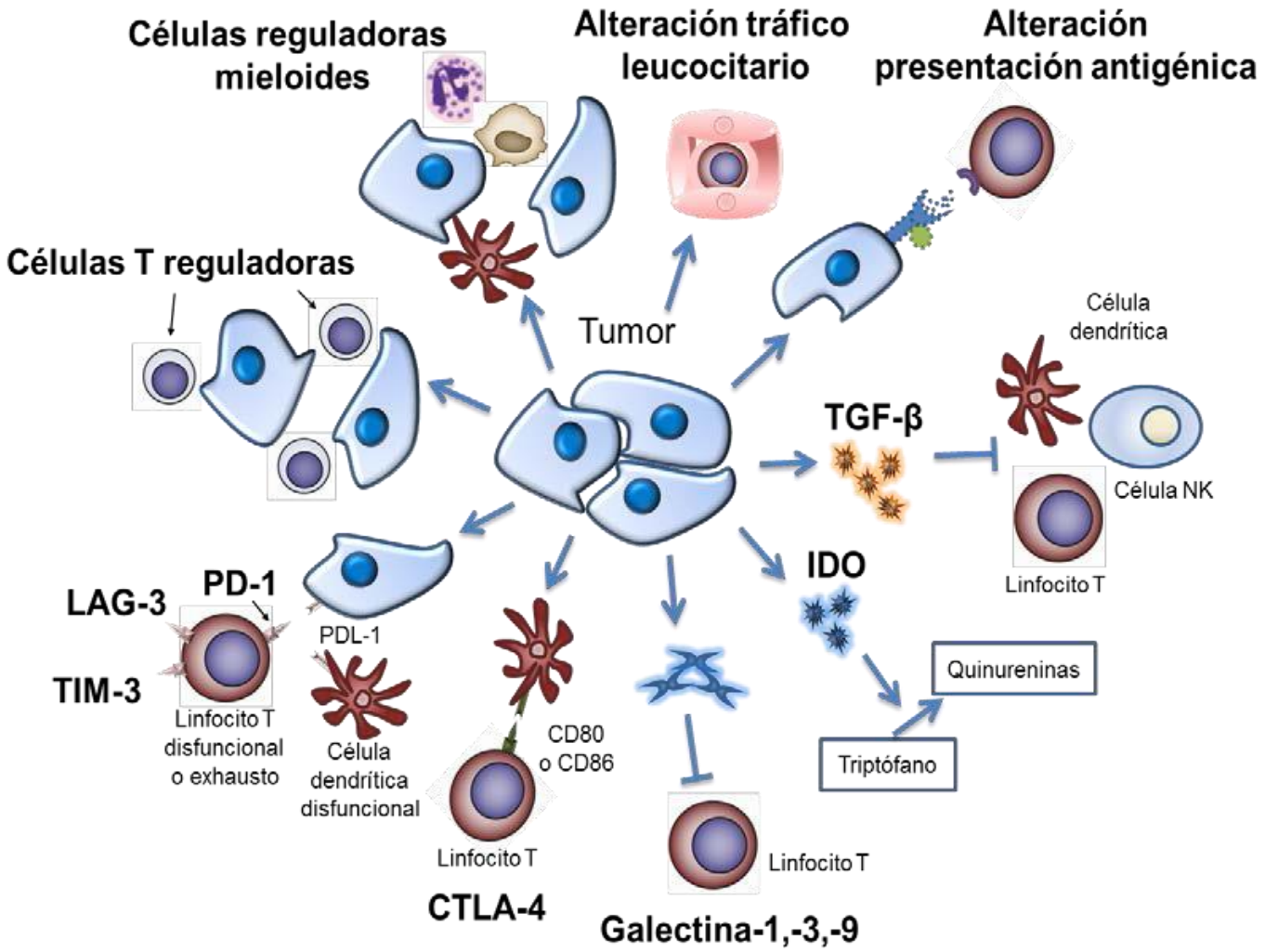


•Resistència intrínseca (célula tumoral) o extrínseca (microambiente tumoral)

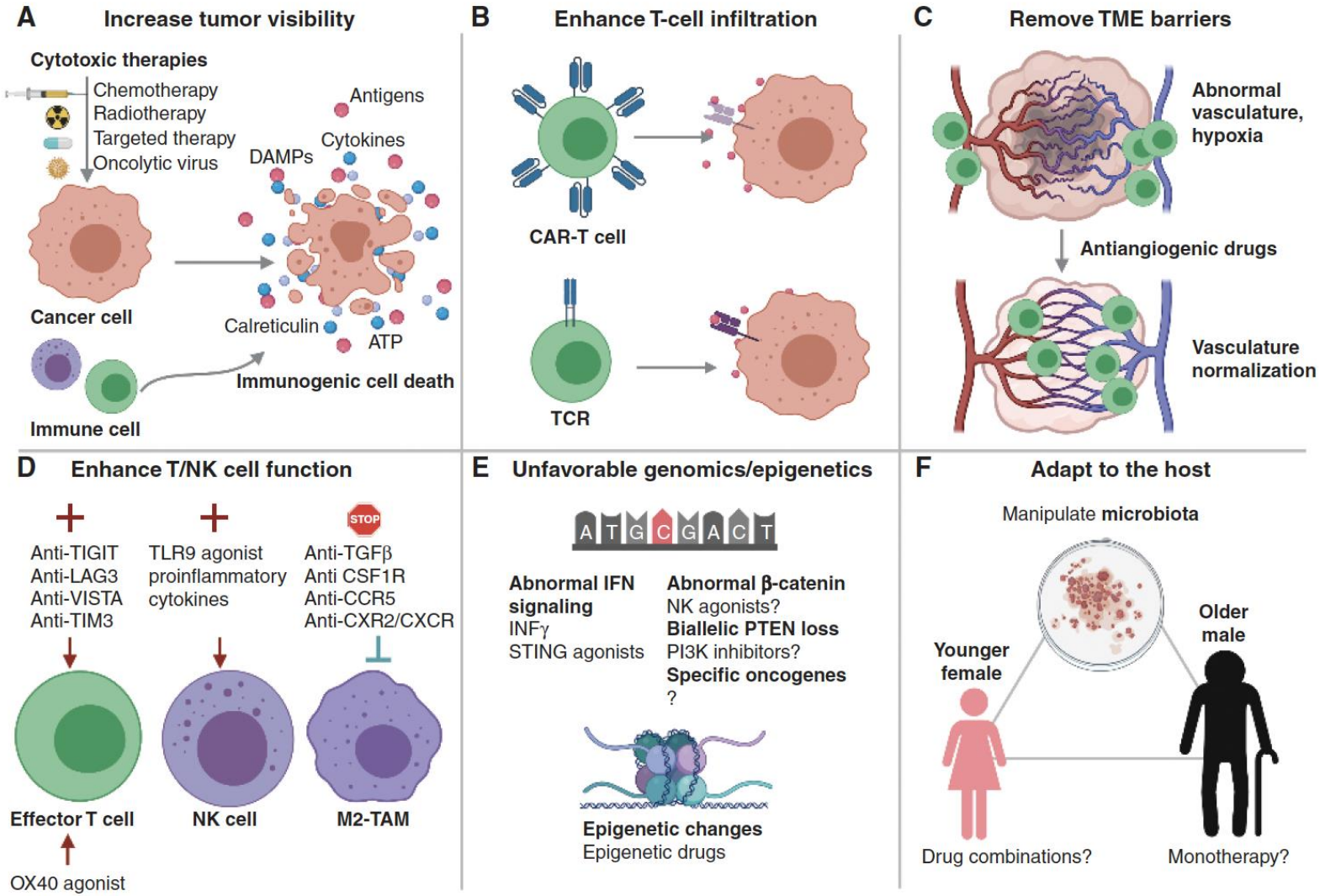


Frisone D, Friedlaender A, Addeo A and Tsantoulis P (2022) The Landscape of Immunotherapy Resistance in NSCLC. Front. Oncol. 12:817548

Mechanism of resistance to IO



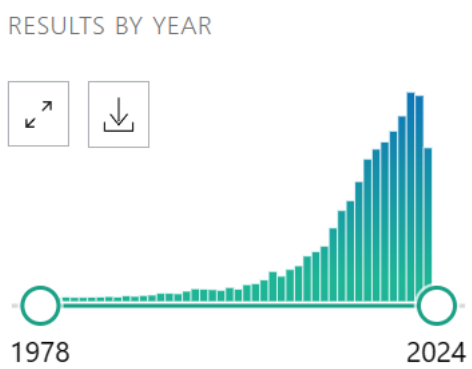
Potential strategies to overcome resistance

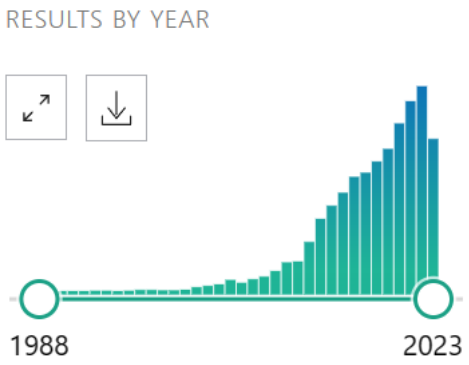


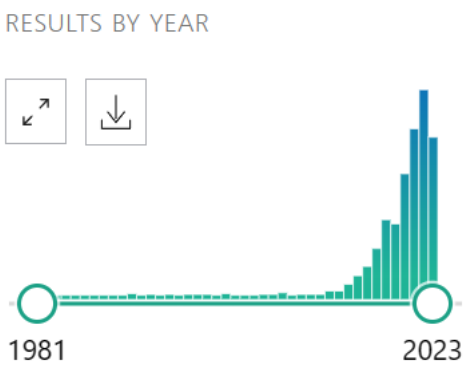
Aldea et al. Can Disc 2021

Un campo en expansión en NSCLC

Resistencia a QT	Resistencia a Terapia dirigida	Resistencia a IO
8631 publicaciones (2002)	4708 publicaciones (2008)	1004 publicaciones (2013)







Potential strategies to overcome resistance

IO-Combos

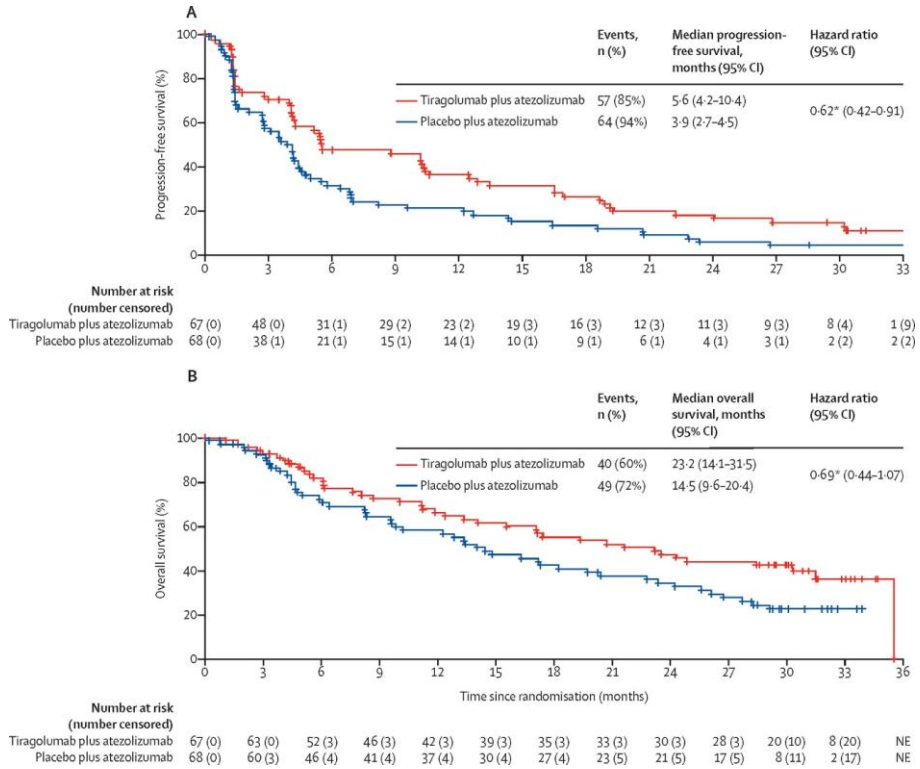
- Actuar sobre más ICIs más allá vía PD1/PDL1:

- CTLA4 -> estrategia ya utilizada
- LAG-3 (Lymphocyte-Activation Gene-3): MHC clase 2 -> agotamiento Linfocitos T
- TIM-3 (T-cell immunoglobulin and mucin domain 3): glicoproteína tipo 1 -> peor pronóstico + resistencia
- TIGIT (T cell immunoglobulin and ITIM domain): receptor transmembrana inhibidor -> NK y linfocitos T
- VISTA (V-domain immunoglobulin suppressor of T –cell activation): receptor transmembrana -> suprime activación Linfocitos T.
- ...

Potential strategies to overcome resistance

ANTI-TIGIT (otros checkpoints) - Resistencia primaria

Estudio Fase 2, Cityscape



ADVANTIG 302

Key Inclusion Criteria
- **NSCLC**
  - Locally advanced or recurrent unresectable or not amenable to CRT or chemotherapy
  - Metastatic
- **SQ and NSQ histology**
- **PD-L1 ≥ 50% (SP263)**

Key Exclusion Criteria
- **Known EGFR sensitizing mutations or ALK re-arrangements**
  (Patients with non squamous NSCLC must be tested for EGFR sensitizing mutations)
- **Prior Check Point Inhibitor**

Stratification:
- **Region (Asia vs Non-Asia)**
- **Histology (SQ vs NSQ)**

R 5:5:1

- **Arm A: Tislelizumab (200 mg) + BGB-A1217 (900 mg) IV Q3W** (275 pts)
- **Arm B: Pembrolizumab (200 mg) + Placebo IV Q3W** (275 pts)
- **Arm C: Tislelizumab (200 mg) + Placebo IV Q3W** (55 pts)

No crossover allowed

Treatment until Disease progression, or loss of clinical benefit, intolerable toxicity, or withdrawal of consent

Figure 2. STAR-121 study design

Population
- mNSCLC with no actionable gene alterations
- No prior systemic treatment for mNSCLC
- ECOG PS 0-1

Stratification
- Histology: nonsquamous vs squamous
- Baseline PD-L1 TC:[a] < 50% vs ≥ 50%
- Region: East Asia vs non–East Asia

R 4:4:1 N = 720

- **Group A (n = 320)**: DOM IV Q3W[b] ZIM IV Q3W[b] Platinum doublet[c]
- **Group B (n = 320)**: PEMBRO IV Q3W[b] Platinum doublet[c]
- **Group C (n = 80)**: ZIM IV Q3W[b] Platinum doublet[c]

Potential strategies to overcome resistance

ANTI-LAG 3 (otros checkpoints) -Resistencia secundaria

elcc European Lung Cancer Congress 2023

Final data from a phase II study (TACTI-002) of eftilagimod alpha (soluble LAG-3) & pembrolizumab in 2nd line metastatic NSCLC patients resistant to PD-1/PD-L1 inhibitors

Majem M[1]; Forster M[2]; Krebs M[3]; Peguero J[4]; Clay T[5]; Felip E[6]; Iams W[7]; Roxburgh P[8]; Dodger B[9]; Bajaj P[10]; Mueller C[11]; Triebel F[12]

[1]Majem: Hospital de la Santa Creu i Sant Pau, Barcelona, Spain; [2]Forster: UCL Cancer Institute / University College London Hospitals Foundation, London, UK; [3]Krebs: Division of Cancer Sciences, The University of Manchester and The Christie NHS Foundation Trust, Manchester, UK; [4]Peguero: Oncology Consultants, P.A., Houston, USA; [5]Clay: St John of God Subiaco Hospital, Perth, Australia; [6]Felip: d'Hebron University Hospital, Barcelona, Spain; [7]Iams: Vanderbilt Ingram Cancer Center Division of Hematology/Oncology, Tennessee; [8]Roxburgh: Wolfson Wohl Cancer Research Centre, Institute of Cancer Sciences, University of Glasgow and Beatson West of Scotland Cancer Centre, Scotland, UK; [9]Doger: Fundación Jiménez Diaz, Madrid, Spain; [10]Bajaj: Tasman Oncology, Queensland, Australia; [11]Mueller: Clinical Development, Immutep GmbH, Berlin, Germany; [12]Triebel: Research & Development, Immutep S.A.S., Saint Aubin, France

Organisers: ESMO, IASLC

Partners: ESTRO, etop

Efficacy – Primary & Secondary Objectives

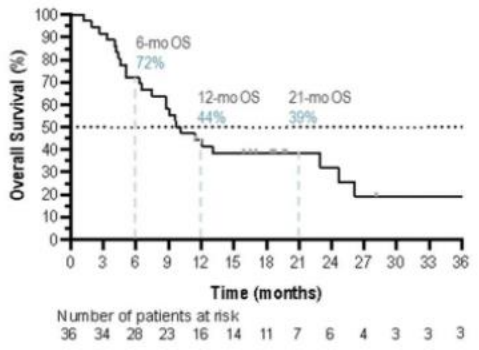
Efficacy Overview[1]

Response parameter (N=36)	
Partial Response, n (%)	3 (8.3)
Stable Disease, n (%)	9 (25.0)
Progression, n (%)	23 (63.9)
Not Evaluable[2], n (%)	1 (2.8)
ORR[3], n (%) [95% CI][4]	3 (8.3) [1.8-22.5]
DCR, n (%) [95% CI][4]	12 (33.3) [18.6-51.0]

DCR: disease control rate; ITT: intent to treat population; ORR: overall response rate.
[1] by iRECIST.
[2] Pts with no on-study post-baseline radiological assessment for any reason.
[3] Confirmed ORR.
[4] 95% CIs calculated using Clopper-Pearson method.
[5] 95% CIs calculated using Kaplan Meier survival analysis method.
Note: ORR of evaluable population (N=35) of 8.6%.
Figures have been cropped for visualisation purposes.

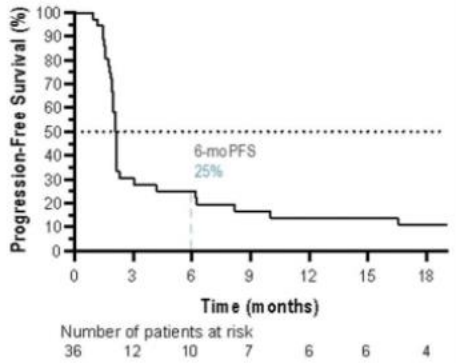
Overall Survival ITT

OS (N=36)	
Events, n (%)	25 (69.4)
Median, months [95% CI][5]	9.9 [6.5-23.0]



Progression Free Survival[1] ITT

PFS (N=36)	
Events, n (%)	34 (94.4)
Median, months [95% CI][5]	2.1 [1.9-2.1]



- 6-mo PFS rate of 25% and OS rates at 12-mo and 21-mo of 44% and 39%, respectively.

elcc European Lung Cancer Congress 2023

PRESENTED BY: Margarita Majem, MD, PhD

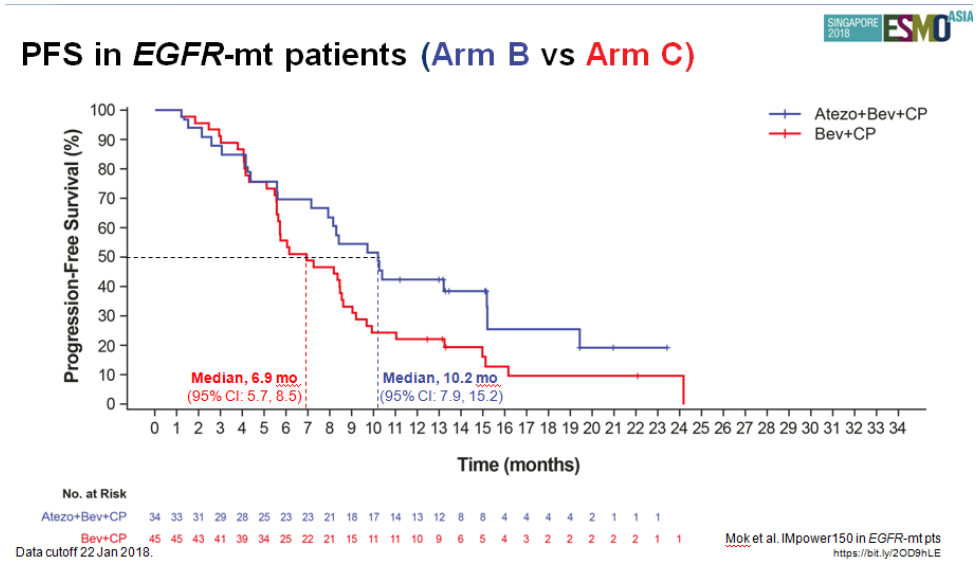
Data cut-off: December 31, 2022

Potential strategies to overcome resistance

Antiangiogénicos

Facilitar normalización vasos sanguíneos que permita mayor penetración células inmunes en el tumor

QT + atezolizumab + bevacizumab en pacientes EGFRmutado - Impower 150 (N=79 pacientes con mutación EGFR)



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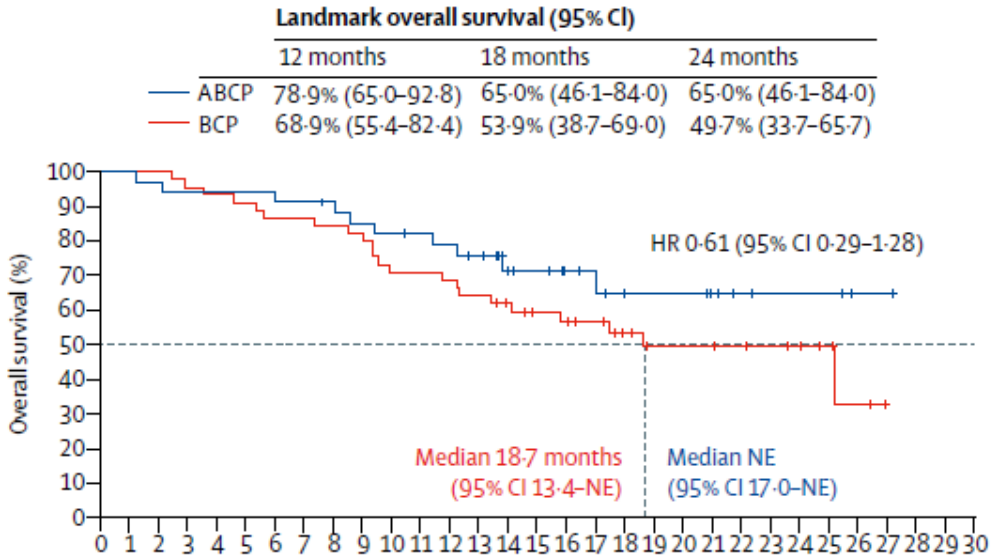
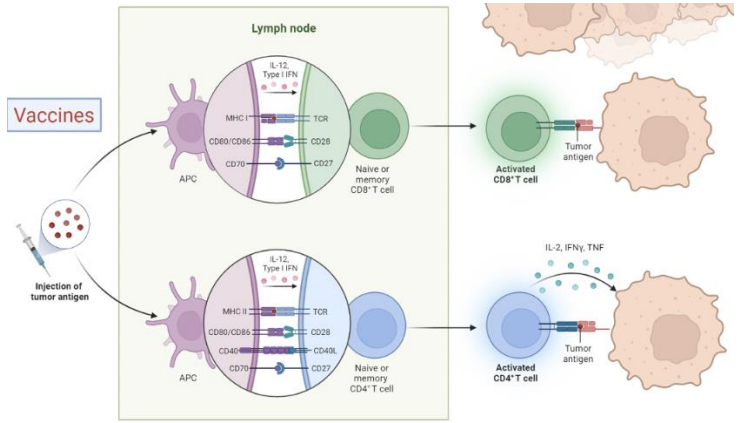


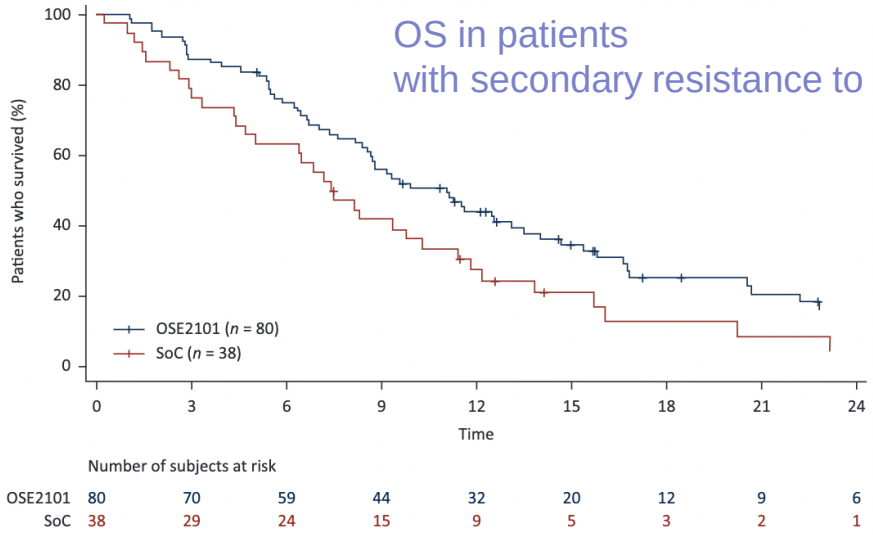
Vacunas

ATALANTE-1: OSE2101

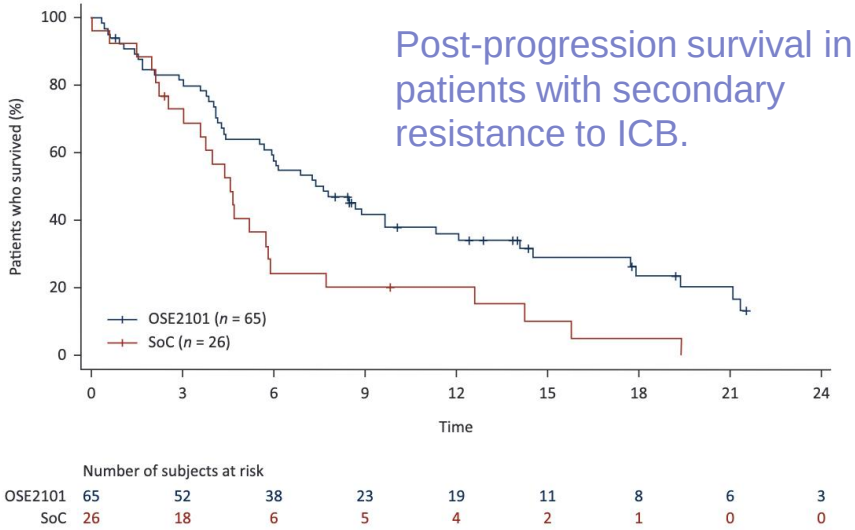


- HLA-A2-positive (45%) advanced NSCLC without actionable alterations, failing sequential or concurrent CT and IC
- OSE2101- Induce cytotoxic T lymphocytes (CTLs) against five tumorassociated antigens (TAAs) frequently overexpressed in NSCLC (HER-2/neu, CEA, MAGE 2, MAGE 3 and p53)

OS in patients with secondary resistance to ICB



Post-progression survival in patients with secondary resistance to ICB.



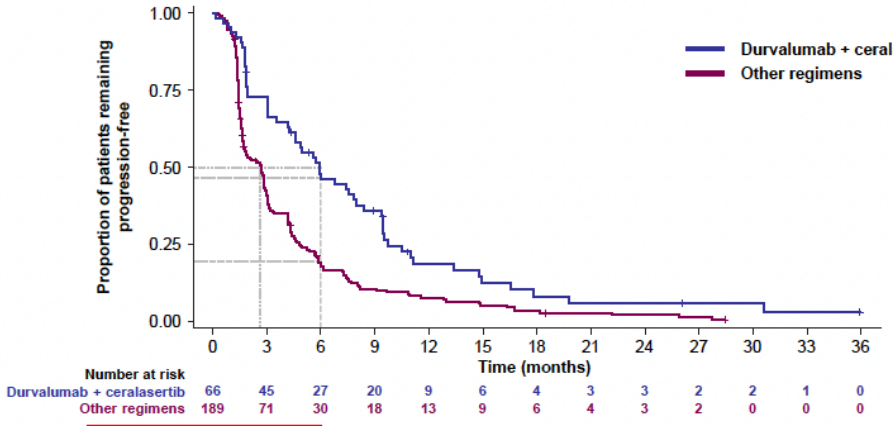
Besse et al. Ann Oncol 2023; Li et al. Ann Transl Med 2023

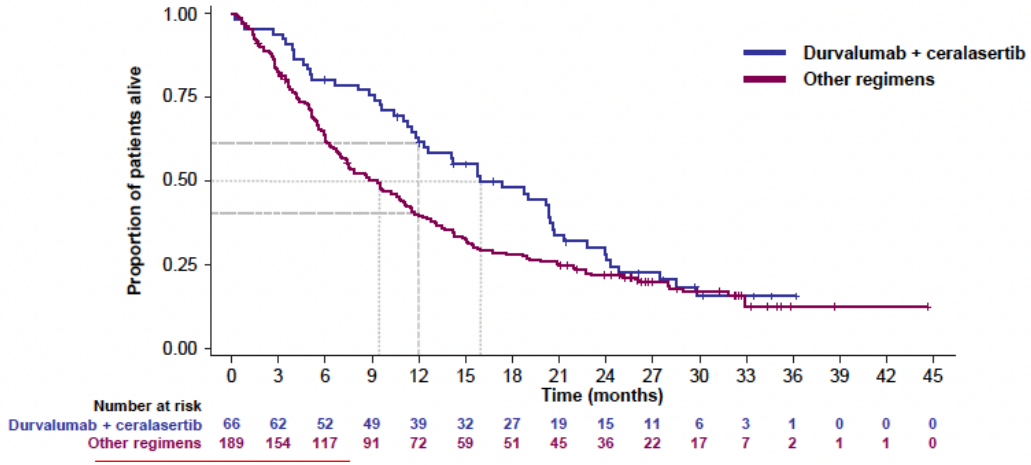
Potential strategies to overcome resistance

Otras estrategias

- BITES: bi-specific antibodies
- Antibody Drug Conjugates (ADC)
- Adoptive cell therapy: TILs, CAR T cells
- Moduladores del TME:
  - Citoquinas: IL10, IL2, IL15, anti-TGF-b
  - Inhibidores PARP/ATR
  - Inhibidores STAT3

Ceralsertib - iATR





Iyer et al. AACR 2023

Potential strategies to overcome resistance

Sistema immune del huésped: Microbiota

Fecal microbiota transplantation plus anti-PD-1 immunotherapy in advanced melanoma: a phase I trial

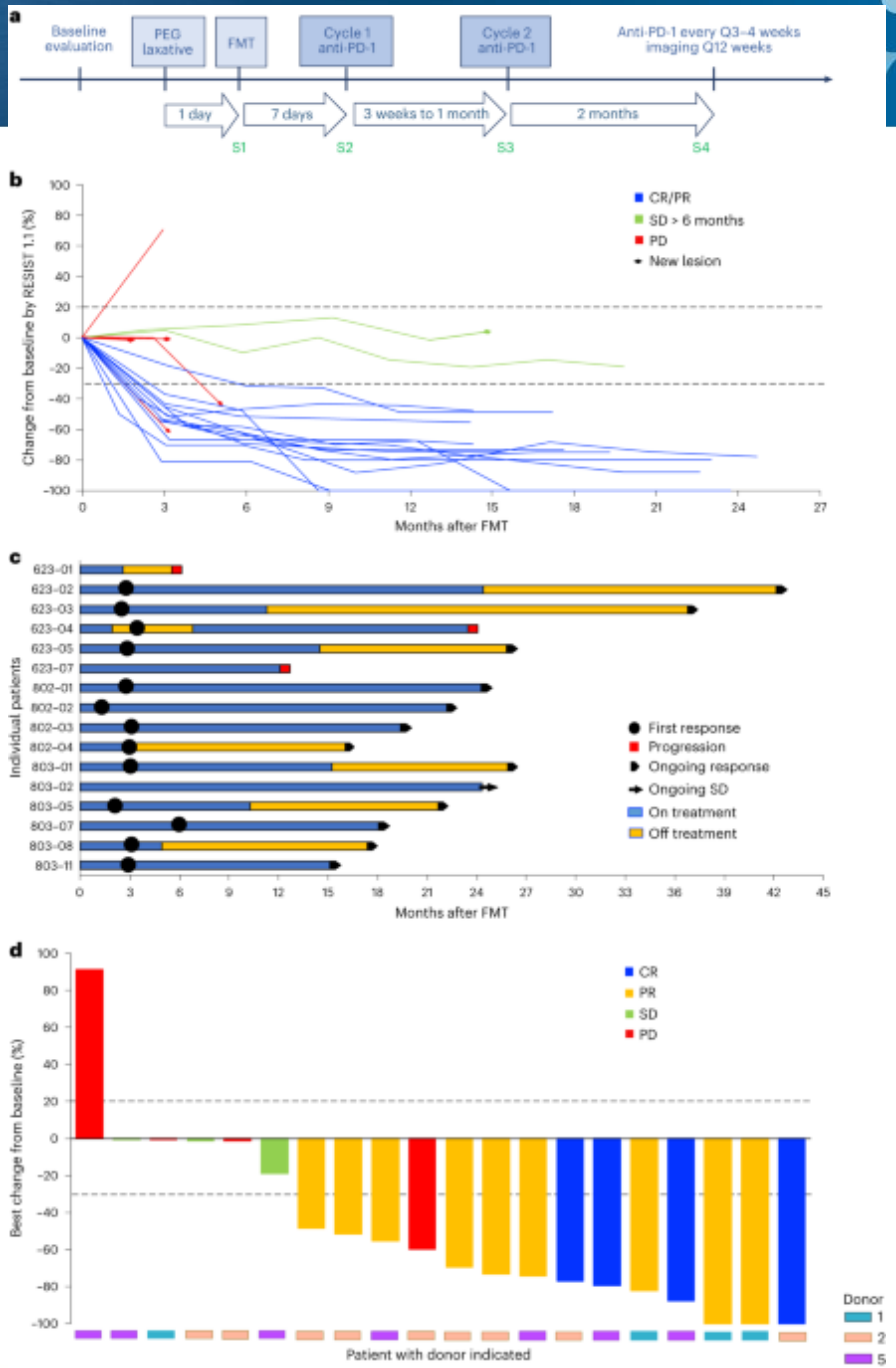
Bertrand Routy, John G. Lenehan, Wilson H. Miller Jr, Rahima Jamal, Meriem Messaoudene, Brendan A. Daisley, Cecilia Hes, Kait F. Al, Laura Martinez-Gili, Michal Punčochář, Scott Ernst, Diane Logan, Karl Belanger, Khashayar Esfahani, Corentin Richard, Marina Ninkov, Gianmarco Piccinno, Federica Armanini, Federica Pinto, Mithunah Krishnamoorthy, Rene Figueredo, Pamela Thebault, Panteleimon Takis, Jamie Magrill, ... Saman Maleki Vareki + Show authors

Nature Medicine **29**, 2121–2132 (2023) | Cite this article

Microbiota Transplant in Advanced Lung Cancer Treated With Immunotherapy NCT04924374
Sponsor: Fundacion para la Investigacion Biomedica del Hospital Universitario Ramon y Cajal

Fecal microbiota transplantation to improve efficacy of immune checkpoint inhibitors in metastatic lung cancer NCT05502913
Sponsor: Israel

Clinicaltrials.gov



Conclusiones

- Hay mucha investigación en el campo de la resistencia a la IO
- La resistencia primaria (e hiperprogresión) ha disminuido con los combos de quimio-IO y uso en primeras líneas / selección pacientes.
- La resistencia secundaria sigue siendo un gran reto.
- Oligoprogresión es un escenario particular no infrecuente en esta población.
- Múltiples mecanismos implicados -> difícil encontrar una única solución -> medicina personalizada y de precisión
- Existen numerosos ensayos clínicos y estrategias en desarrollo, aunque todavía faltan datos fase III positivos.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23&24
November 2023
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research
Muchas Gracias