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Ricerca clinica in Immuno-Oncologia: caratteristiche e peculiarità

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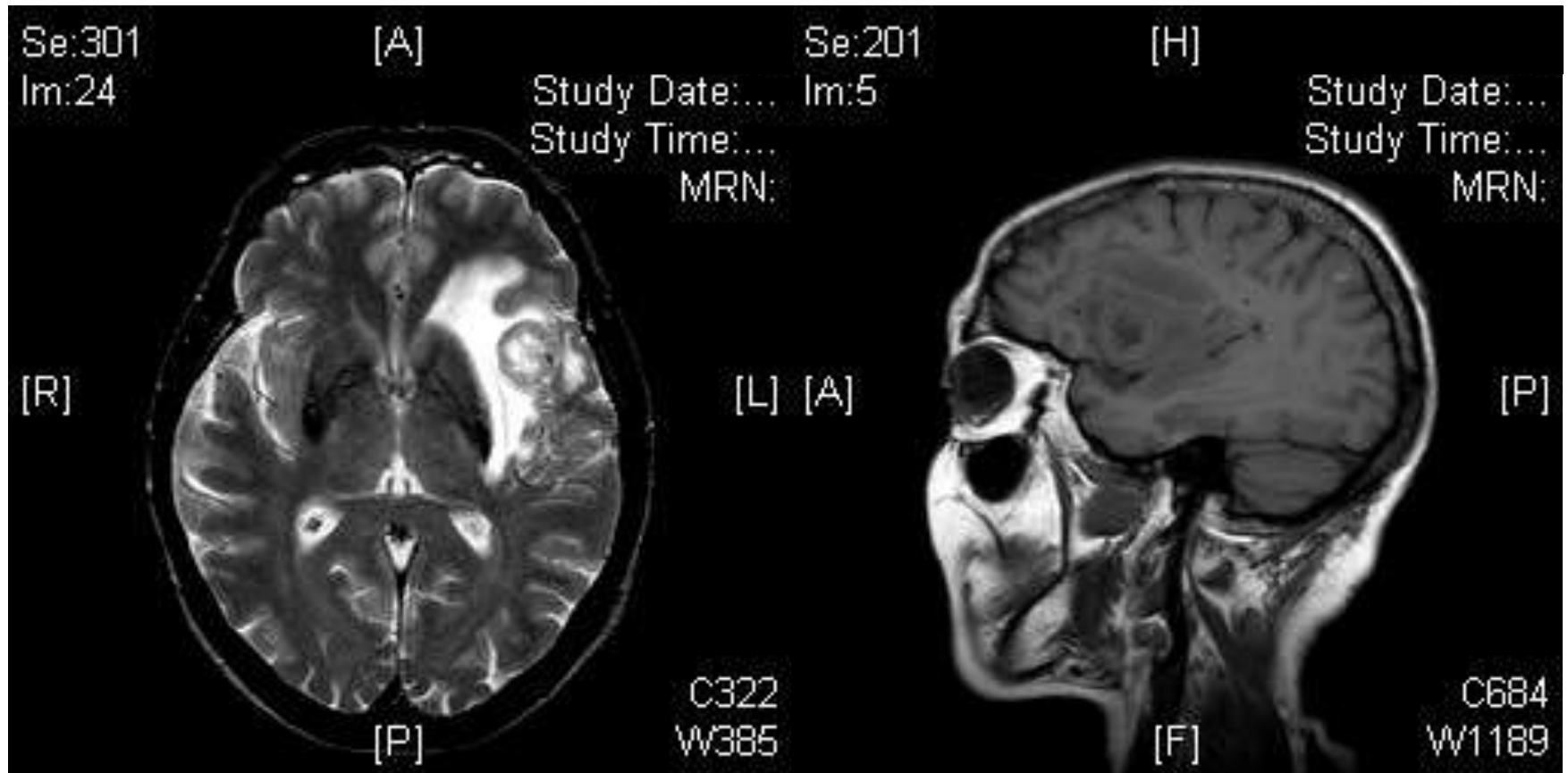
Disclosures

- Advisor/board member for Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA; Roche; Bristol Myers Squibb; Incyte; AstraZeneca; Amgen; Pierre Fabre; Eli Lilly; Sanofi; GlaxoSmithKline; Alfasigma; Merck Serono
- Honoraria for Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA; Roche; Bristol Myers Squibb; Sanofi; AstraZeneca; Amgen; Pierre Fabre; Eli Lilly; GlaxoSmithKline; Sciclone; Alfasigma; Merck Serono
- Owns stock in Epigen Therapeutics, and Theravance

Ruolo della ricerca indipendente

- **Setting clinici «specifici» e indicazioni rare**
 - *Metastasi cerebrali*
 - *Mesotelioma*
- **Dalla ricerca clinica al laboratorio di ricerca**
 - *Marcatori prognostico/predittivi di risposta/resistenza*
- **Dal laboratorio di ricerca alla ricerca clinica**
 - *es. Epigenetica*

Immunotherapy in melanoma brain metastases



Brain metastases in solid tumors

Primary Brain Tumors

- **~24,000** malignant brain tumors per year
- **~17,000** deaths per year

Brain Metastases

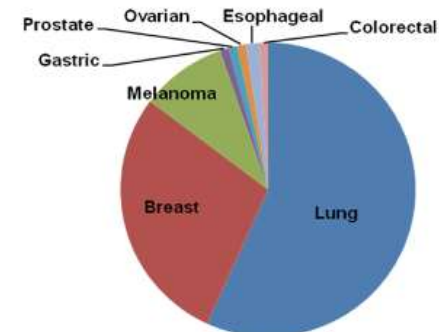
- **~98,000 – 200,000** patients diagnosed annually
 - Up to 30% of patients with stage IV cancer
- Median **survival 3 – 6 months**

*Including gastrointestinal, oesophageal, prostate and ovarian cancers

1. NCI SEER database. 2. Goyal S. et al. JAMA Onc 2015; 1: 668-676. 3. Arvold ND et al. Neuro oncology 2016; 18: 1043-1065. 4. Bollin-Fishler A. et al. OA Mol Onc 2013; 01:1:6

Sources of Brain Metastases

Tumor type	% of Brain Mets
Lung	50–60%
Breast	20–30%
Melanoma	5–10%
Various others*	5–10%



Ipilimumab and fotemustine in patients with advanced melanoma (NIBIT-M1): an open-label, single-arm phase 2 trial



Anna Maria Di Giacomo, Paolo A Ascierto, Lorenzo Pilla, Mario Santinami, Pier Francesco Ferrucci, Diana Giannarelli, Antonella Marasco, Licia Rivoltini, Ester Simeone, Stefania V L Nicoletti, Ester Fonsatti, Diego Annesi, Paola Queirolo, Alessandro Testori, Ruggero Ridolfi, Giorgio Parmiani, Michele Maio

	Study population (n=86)	Patients with brain lesions (n=20)
Immune-related disease control	40 (46.5% [35.7–57.6])	10 (50.0% [27.2–72.8])
Immune-related complete response	6 (6.9% [2.6–14.6])	2 (10.0% [1.2–31.7])
Immune-related partial response	19 (22.1% [13.8–32.3])	6 (30.0% [11.9–54.3])
Immune-related stable disease	15 (17.4% [10.1–27.1])	2 (10.0% [1.2–31.7])
Immune-related progressive disease	46* (53.4% [42.4–64.3])	10 (50.0% [27.2–72.8])
Immune-related major durable disease control†	17 (19.7% [11.9–29.7])	6 (30.0% [11.9–54.3])

Data are n (% [95% CI]). *Because of early progression, follow-up scans were not available for 15 (17%) patients who were defined as having progressive disease as per protocol. †Immune-related disease control lasting at least 24 weeks.

Table 2: Primary and secondary endpoints

Three-year follow-up of advanced melanoma patients who received ipilimumab plus fotemustine in the Italian Network for Tumor Biotherapy (NIBIT)-M1 phase II study

A. M. Di Giacomo¹, P. A. Ascierto², P. Queirolo³, L. Pilla^{4,†}, R. Ridolfi⁵, M. Santinami⁶, A. Testori⁷, E. Simeone², M. Guidoboni⁵, A. Maurichi⁶, L. Orgiano³, G. Spadola⁷, M. Del Vecchio⁸, R. Danielli¹, L. Calabrò¹, D. Annesi¹, D. Giannarelli⁹, C. Maccalli^{1,10}, E. Fonsatti¹, G. Parmiani^{4,††} & M. Maio^{1*}

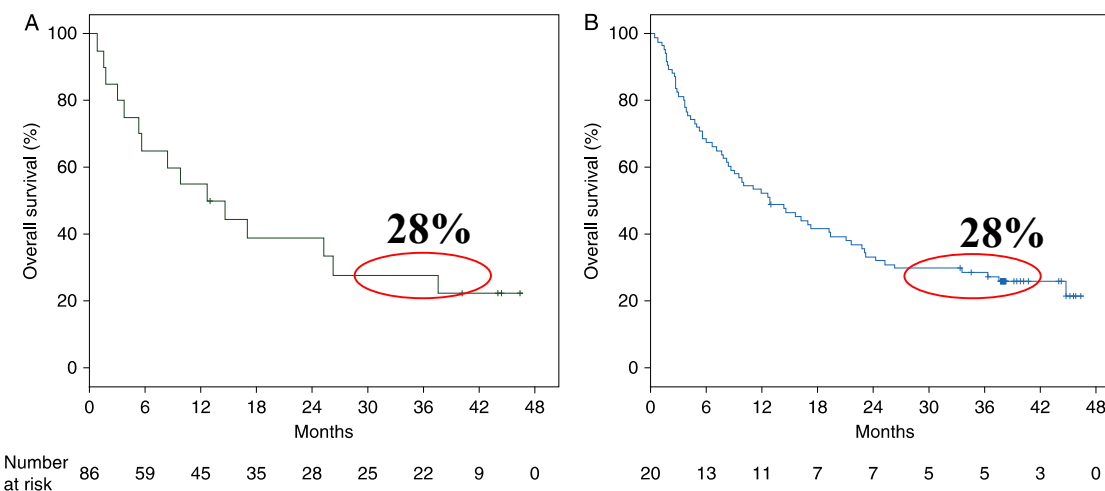
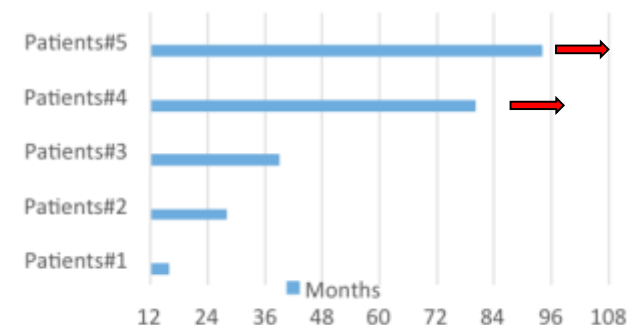


Figure 1. Kaplan-Meier plot of overall survival for all patients (A) and for patients with brain metastases (B). Vertical lines indicate censoring.

Durable CR



Immunotherapy of brain metastases: breaking a “dogma”

Anna Maria Di Giacomo¹, Monica Valente¹, Alfonso Cerase², Maria Fortunata Lofiego¹, Francesca Piazzini¹
Luana Calabrò¹, Elisabetta Gambale¹, Alessia Covre¹ and Michele Maio^{1*} 

Table 1 Efficacy of immune checkpoint inhibitors in melanoma brain metastases

Author	Phase	Agent	No. Patients	Intracranial ORR (%)
<i>Margolin (2012)</i>	II	Ipi		
Cohort A			51	16
Cohort B			21	5
<i>Di Giacomo (2012)</i>	II	Ipi + Fotemustine	20	50
<i>Parakh (2017)</i>	Real-world (retrospective)	Nivo or Pembro	66	21
<i>Kluger (2019)</i>	II	Pembro	23	26
<i>Long (2017)</i>	II			
Cohort A		Ipi + Nivo	26	46
Cohort B		Nivo	25	20
Cohort C		Nivo	16	6
<i>Tawbi (2018)</i>	II	Ipi + Nivo	94	55

Ipi Ipilimumab, *Nivo* Nivolumab, *Pembro* Pembrolizumab, *ORR* Object Response Rate

The NIBIT-M2 trial

Study Design and Treatment

Data cut-off: June 1st, 2020 [median follow-up 45 months (IQR 34-59)]

Main inclusion criteria:

- Metastatic Melanoma (MM) patients (pts) with active and untreated asymptomatic brain metastases (2 cm max) at contrast MRI
- No prior systemic therapy for advanced disease

Main exclusion criteria:

- MM pts with symptomatic brain metastases requiring immediate local intervention (RT and/or surgery)
 - Leptomeningeal disease
 - Ocular melanoma
 - Autoimmune diseases

Screening/
Randomization*

Arm A N=23
FOTEMUSTINE

Arm B N=26
IPILIMUMAB + FOTEMUSTINE

Arm C N=27
IPILIMUMAB + NIVOLUMAB

Primary endpoint: Overall Survival (OS) as median and survival rate.

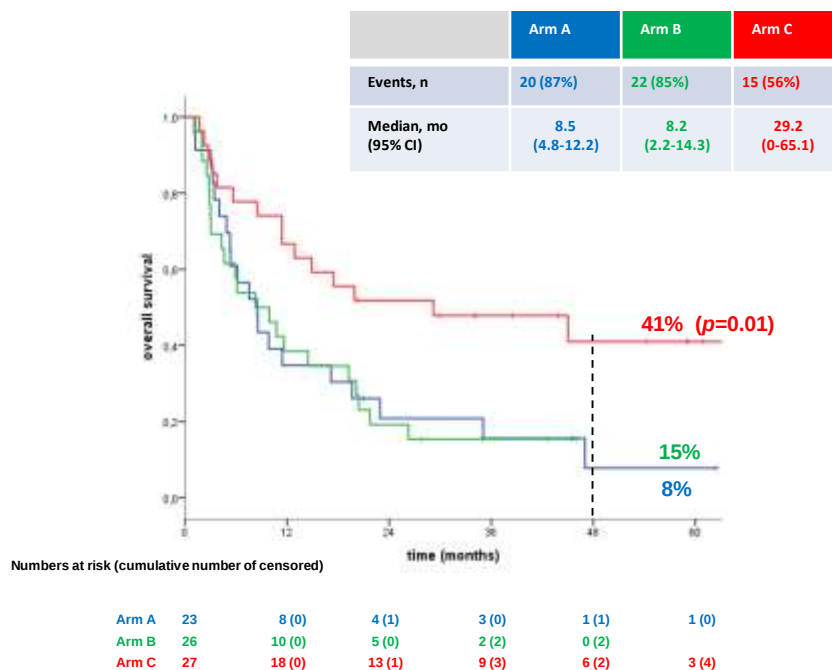
Secondary endpoints: Intracranial and global immune related (ir) Objective Response Rate (ir-ORR), ir-Disease Control Rate (ir-DCR), ir-Time To Response, ir-Duration Of Response, according to ir-Response Criteria, Progression Free Survival (PFS), and safety.

Exploratory endpoints: Immuno-biological correlates

* 96 MM pts were enrolled, 80 were randomized, and 76 were treated: 23 in arm A, 26 in arm B, and 27 in arm C. Four pts in arm A withdraw the informed consent and were removed from the study.

The NIBIT-M2 trial

Primary Endpoint – Overall Survival



Clinical outcome of *BRAF* mutant or WT melanoma

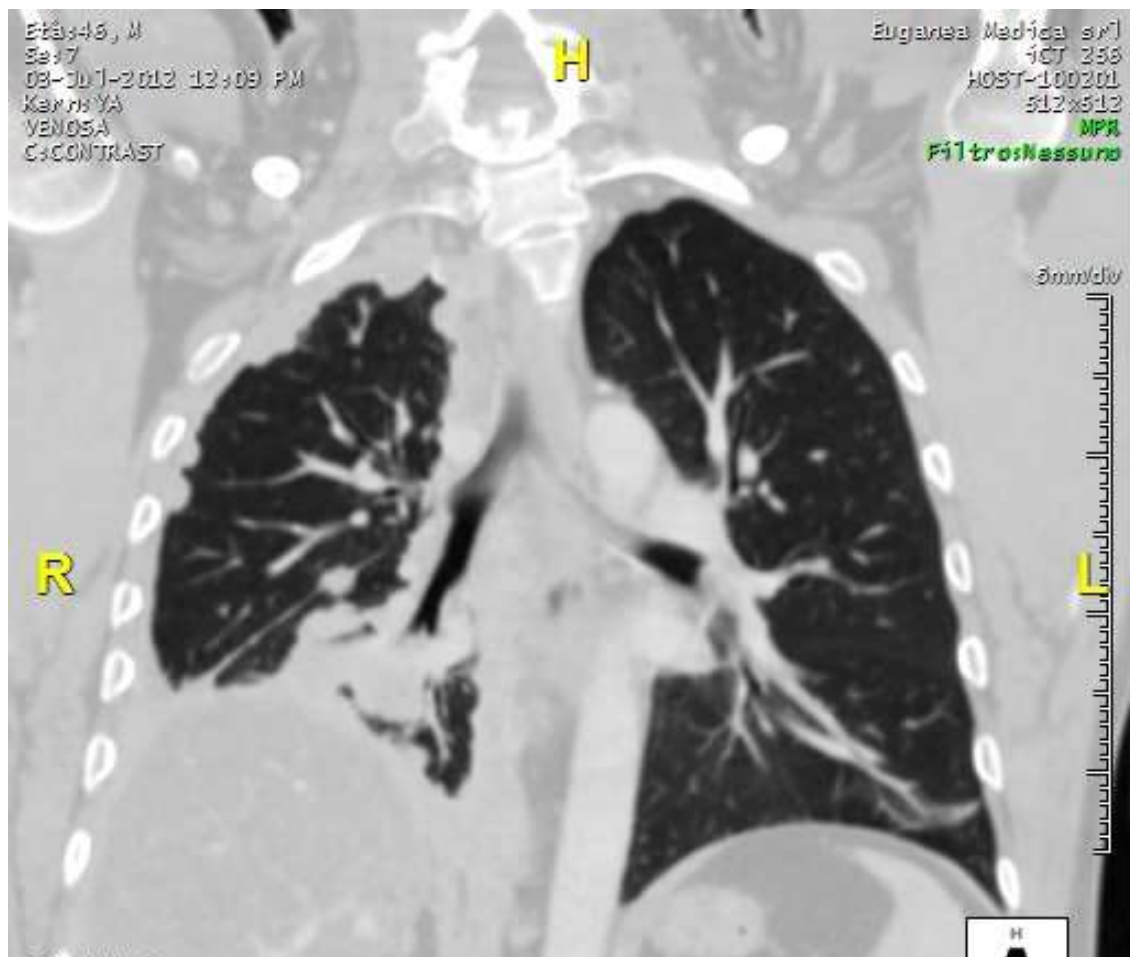
	Fotemustine (n=21)	Ipilimumab plus fotemustine (n=26)	Ipilimumab plus nivolumab (n=26)
Median OS, months (95% CI)			
BRAF mutant	19.6 (3.7–35.6)	11.6 (4.9–18.4)	45.0 (0–100.3)
BRAF wild type	5.3 (1.2–9.4)	4.3 (0.3–8.3)	19.9 (0–42.4)

The NIBIT-M2 trial

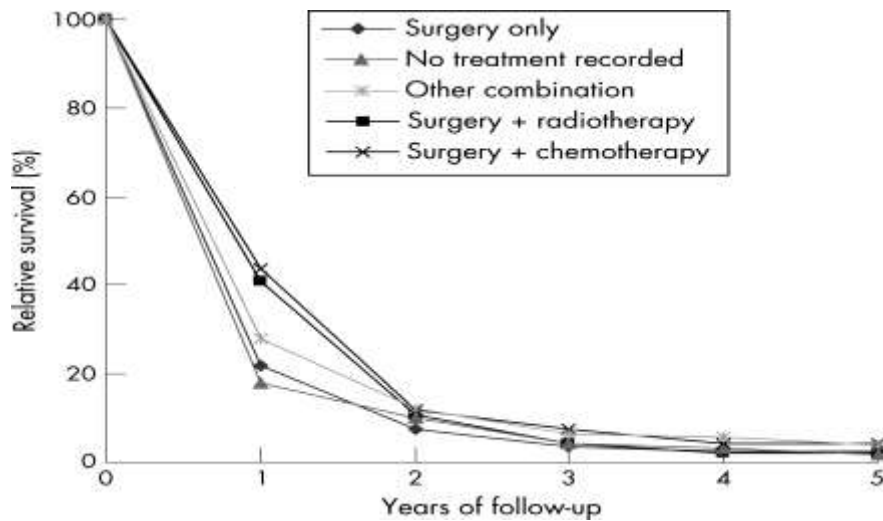
Safety profile

	Arm A N=23		Arm B N=26		Arm C N=27	
	Any Grade	G3-G4	Any Grade	G3-G4	Any Grade	G3-G4
Any AEs	23 (100%)	16 (70%)	23 (88%)	22 (85%)	23 (85%)	14 (52%)
Treatment-related AEs	19 (83%)	11 (48%)	21 (81%)	18 (69%)	21 (78%)	8 (30%)
Myelotoxicity						
Anemia	5 (22%)	0	3 (12%)	1 (4%)	0	0
Thrombocytopenia	11 (48%)	4 (17%)	14 (54%)	10 (38%)	0	0
Neutropenia	10 (43%)	7 (30%)	10 (38%)	6 (23%)	0	0
Leukopenia	10 (43%)	3 (13%)	2 (8%)	2 (8%)	0	0
Neurological events	2 (9%)	0	1 (4%)	0	1 (4%)	0
Immune-related AEs	NA	NA	15 (58%)	10 (38%)	19 (70%)	8 (30%)

No treatment-related deaths were observed; 11 patients (0 Arm A, 3 Arm B and 8 in Arm C) discontinued treatment due to drug-related AEs.



The Unmet Need in Mesothelioma



- Highly aggressive tumor usually diagnosed in late stage disease
- Median survival 9-12 mos, 5-yrs survival <5%
- Surgical generally is not curative
- First line chemotherapy:
 - Platinum/Pemetrexed¹ +/- Beva² or +/- TTF-1³ with modest benefit (mOS=12-18 months)
- Second line chemotherapy: not yet defined

1. Vogelzang *et al*, J Clin Oncol 2003; 21:2636-44
2. NCCN, ESMO Clinical Guidelines 2015, 3rd Consensus conference of mesothelioma, Guidelines V1 2015
3. Ceresoli G, IASLC-MESO, 2019 New York

Immunotherapy in mesothelioma

Tremelimumab for patients with chemotherapy-resistant advanced malignant mesothelioma: an open-label, single-arm, phase 2 trial



Luana Calabrò, Aldo Morra, Ester Fonsatti, Ornella Cutaia, Giovanni Amato, Diana Giannarelli, Anna Maria Di Giacomo, Riccardo Danielli, Maresa Altomonte, Luciano Murri, Michele Maio

Summary

Background Monoclonal antibodies to cytotoxic T-lymphocyte antigen 4 (CTLA4) have therapeutic activity in different tumour types. We aimed to investigate the efficacy, safety, and immunological activity of the anti-CTLA4 monoclonal antibody, tremelimumab, in advanced malignant mesothelioma.

Published Online
September 11, 2015
[http://dx.doi.org/10.1016/S1473-2600\(15\)00092-2](http://dx.doi.org/10.1016/S1473-2600(15)00092-2)

Efficacy and safety of an intensified schedule of tremelimumab for chemotherapy-resistant malignant mesothelioma: an open-label, single-arm, phase 2 study



Luana Calabrò, Aldo Morra, Ester Fonsatti, Ornella Cutaia, Carolina Fazio, Diego Annesi, Marica Lenoci, Giovanni Amato, Riccardo Danielli, Maresa Altomonte, Diana Giannarelli, Anna Maria Di Giacomo, Michele Maio

Summary

Background CTLA4 blockade by tremelimumab 15 mg/kg every 90 days provided preliminary evidence of activity in patients with pretreated malignant mesothelioma; however, retrospective exposure–response analysis of data from patients with melanoma suggested that this schedule could result in underexposure to tremelimumab. We therefore investigated the efficacy and safety of an intensified schedule of tremelimumab in patients with advanced malignant mesothelioma.

Lancet Respir Med 2015
Published Online
March 26, 2015
[http://dx.doi.org/10.1016/S2213-2600\(15\)00092-2](http://dx.doi.org/10.1016/S2213-2600(15)00092-2)

CTLA-4 blockade in mesothelioma: ineffective or reason for optimism?

Malignant pleural mesothelioma is an aggressive disease with a poor prognosis and few treatment options. The combination of pemetrexed and cisplatin is the only approved therapy for patients with unresectable disease.¹ No therapies have been approved for mesothelioma that has progressed after this initial systemic therapy. The regulatory approval of antibodies blocking immune checkpoints that function as negative regulators of T-cell function—cytotoxic-T-lymphocyte-associated antigen 4 (CTLA-4), programmed death-1 (PD-1), and programmed death ligand 1 (PD-L1)—in several different cancers² has prompted substantial interest in the clinical investigation of these agents for mesothelioma.

Luana Calabro and colleagues were the first to test immune checkpoint inhibition in clinical trials of mesothelioma. In two small non-randomised studies, the anti-CTLA-4 antibody tremelimumab showed preliminary evidence of activity in patients with previously treated mesothelioma.^{3,4} This work led to the DETERMINE trial, reported by Michele Maio and colleagues in *The Lancet Oncology*,⁵ a phase 2b, randomised, double-blind, placebo-controlled study of tremelimumab in patients with mesothelioma.

Maio and colleagues randomly assigned patients (2:1) with advanced unresectable pleural or peritoneal mesothelioma and disease progression after first-

placebo, including grade 3 or worse diarrhoea (58 [15%] patients receiving tremelimumab vs one [$<1\%$] receiving placebo) and colitis (26 [7%] vs none).

The results of the DETERMINE trial showed no benefit for CTLA-4 blockade with tremelimumab in patients with mesothelioma that progressed after the first or second line of therapy. Could CTLA-4 blockade still have a role in the treatment of mesothelioma? This question is being addressed in several ongoing studies. One approach is the combined blockade of both CTLA-4 and PD-L1 checkpoints, with the premise that this combined blockade could result in higher efficacy, as has been recorded in patients with melanoma and non-small-cell lung cancer. A randomised phase 3 clinical trial is investigating ipilimumab plus nivolumab versus pemetrexed and cisplatin or carboplatin as front-line therapy in patients with unresectable pleural mesothelioma (CheckMate743), with primary endpoints of overall survival and progression-free survival (NCT02899299). The results of a randomised clinical trial of nivolumab versus nivolumab plus ipilimumab as second-line or third-line therapy in mesothelioma have also been reported.⁶ In this clinical trial, 108 eligible patients were randomly assigned 1:1 to receive either nivolumab 3 mg/kg every 2 weeks or nivolumab 3 mg/kg every 2 weeks plus ipilimumab 1 mg/kg every 6 weeks until disease progression or unacceptable



Zephyr/Science Photo Library

Lancet Oncol 2017

Published Online

July 17, 2017

[http://dx.doi.org/10.1016/](http://dx.doi.org/10.1016/S1470-2045(17)30511-9)

[S1470-2045\(17\)30511-9](http://dx.doi.org/10.1016/S1470-2045(17)30511-9)

See [Online/Articles](#)

[http://dx.doi.org/10.1016/](http://dx.doi.org/10.1016/S1470-2045(17)30446-1)

[S1470-2045\(17\)30446-1](http://dx.doi.org/10.1016/S1470-2045(17)30446-1)

Immunotherapy of mesothelioma

Tremelimumab combined with durvalumab in patients with mesothelioma (NIBIT-MESO-1): an open-label, non-randomised, phase 2 study



Luana Calabrò, Aldo Morra, Diana Giannarelli, Giovanni Amato, Armida D'Incecco, Alessia Covre, Arthur Lewis, Marlon C Rebelatto, Riccardo Danielli, Maresa Altomonte, Anna Maria Di Giacomo, Michele Maio

Summary

Background Tremelimumab, an anti-CTLA4 monoclonal antibody, initially showed good activity when used alone in patients with mesothelioma, but did not improve the overall survival of patients who failed on first-line or second-line chemotherapy compared with placebo in the DETERMINE study. We aimed to investigate the efficacy and safety of first-line or second-line tremelimumab combined with durvalumab, an anti-PD-L1 monoclonal antibody, in patients with malignant mesothelioma.

Lancet Respir Med 2018;
6: 451–60

Published Online
May 14, 2018
[http://dx.doi.org/10.1016/S2213-2600\(18\)30151-6](http://dx.doi.org/10.1016/S2213-2600(18)30151-6)

The future of mesothelioma treatment: time to shift gear



As of May 2019, the standard treatment regimen for unresectable pleural mesothelioma still consists of a platinum-based drug plus pemetrexed, first described by Vogelzang and colleagues¹ in 2003. The median overall survival of patients with unresectable pleural mesothelioma remains around 1 year, which is far from satisfactory. Thus, new and more effective treatments for patients who have this highly aggressive and lethal malignancy with very few treatment options are eagerly awaited.

Over the past decade, the dismal therapeutic

(6·8 months in the nintedanib group vs 7·0 months in the placebo group) and median overall survival (14·4 months vs 16·1 months) were similar between the groups.⁴

This latest failure of an anti-angiogenetic drug in patients with mesothelioma fosters consistent doubts and scepticism and raises the questions of whether we should drop the anti-angiogenetic approach after so many trial failures; whether angiogenesis should still be considered an adequate therapeutic target in this disease and whether it should still be investigated



Lancet Respir Med 2019
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May 15, 2019
[http://dx.doi.org/10.1016/S2213-2600\(19\)30171-7](http://dx.doi.org/10.1016/S2213-2600(19)30171-7)
See Online/Article
[http://dx.doi.org/10.1016/S2213-2600\(19\)30139-0](http://dx.doi.org/10.1016/S2213-2600(19)30139-0)

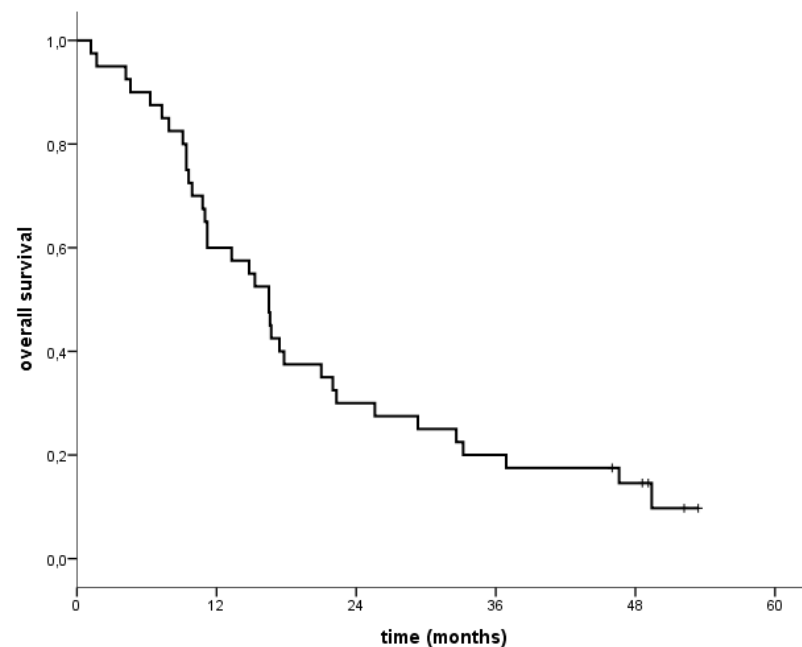
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53100, Italy

NIBIT-MESO-1: A single arm, phase II clinical study of tremelimumab combined with durvalumab in pleural or peritoneal mesothelioma patients

Antitumor Activity (ITT Population)

Tumor response*	Patients (N=40)
Ir-ORR, % (95% CI)	28 (15-44)
ir-CR, %	0
ir-PR, %	28
ir-SD, %	38
Ir-PD, %	35.0
Ir-DCR, % (95% CI)	65 (48-79)
median duration ir-OR, months (95% CI)	16.1 (11.5-20.5)
median duration DC, months (95% CI)	10.6 (8.2-16.5)

Calabrò L *et al*, Lancet Resp Med 2018



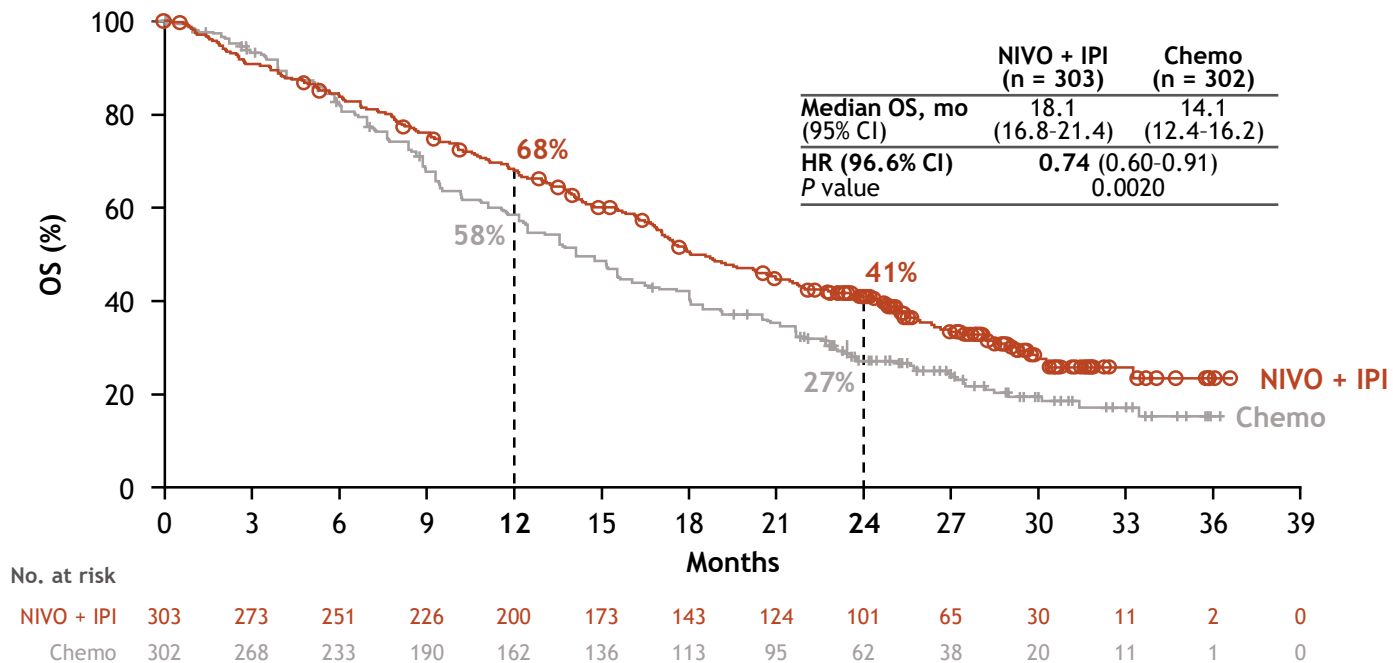
Calabrò L *et al*, Lancet Resp Med, 2021



2020 Presidential Symposium

AUGUST 8, 2020 | WORLDWIDE

Primary endpoint: Overall survival



Minimum follow-up: 22.1 months; median follow-up: 29.7 months.

Subsequent systemic therapy was received by 44% of patients in the NIVO + IPI arm and 41% in the chemo arm; subsequent immunotherapy was received by 3% and 20%, and subsequent chemotherapy by 43% and 32%, respectively.



Tremelimumab plus durvalumab retreatment and 4-year outcomes in patients with mesothelioma: a follow-up of the open label, non-randomised, phase 2 NIBIT-MESO-1 study

Luana Calabrò, Giulia Rossi, Aldo Morra, Claudio Rosati, Ornella Cutaia, Maria Grazia Daffinà, Maresa Altomonte, Anna Maria Di Giacomo, Milena Casula, Carolina Fazio, Giuseppe Palmieri, Diana Giannarelli, Alessia Covre, Michele Maio

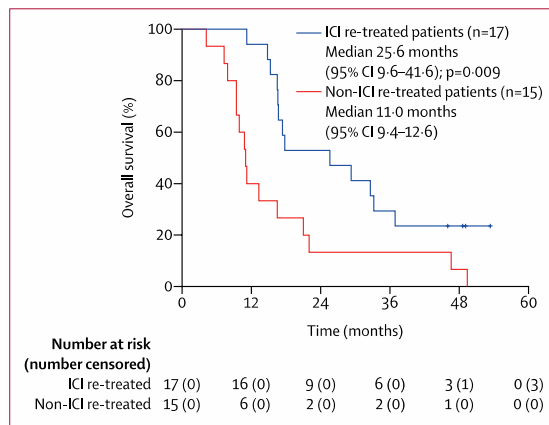


Figure 3: Kaplan–Meier curve of overall survival of patients retreated with tremelimumab and durvalumab (ICI retreated) versus non-ICI retreated patients who received additional chemotherapy (post-hoc analysis)
Vertical lines indicate censored observations. ICI=immune checkpoint inhibitor.

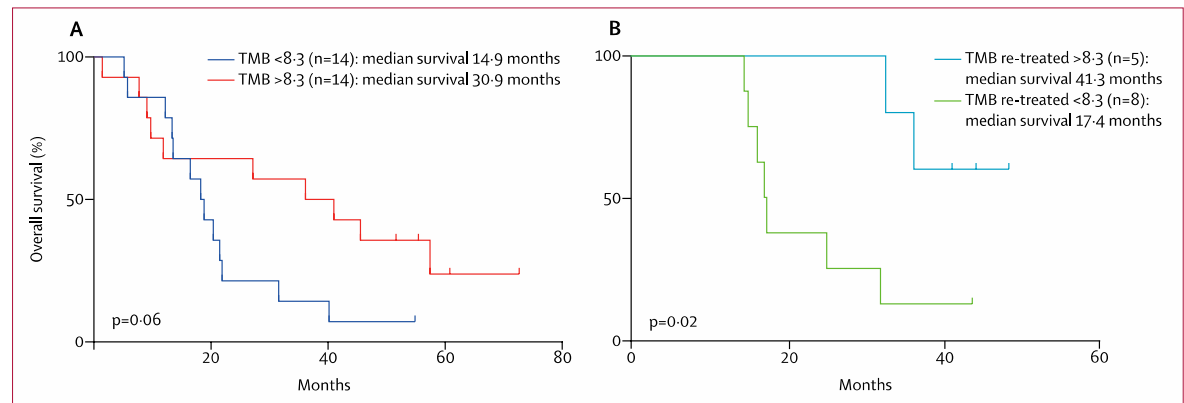
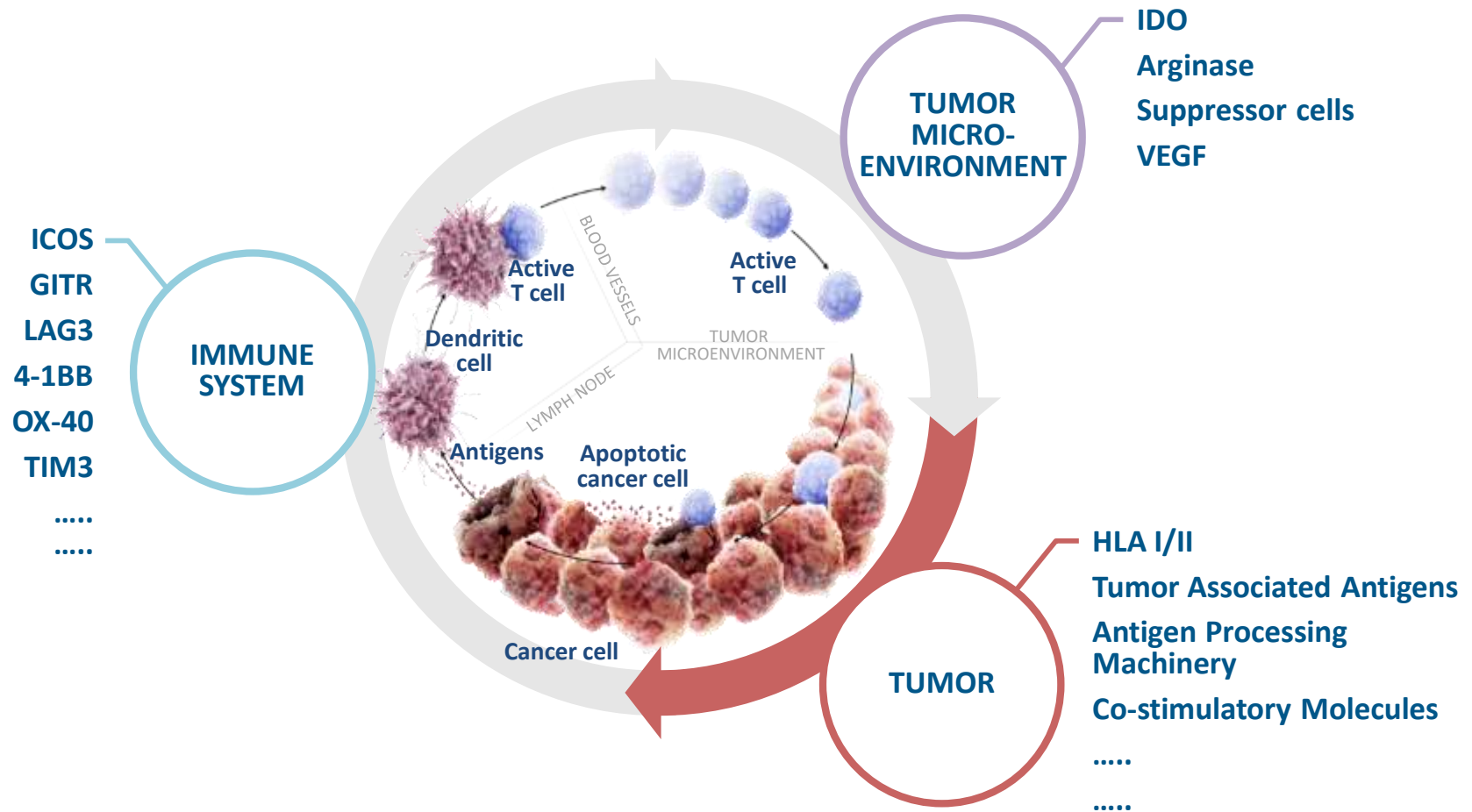


Figure 4: Kaplan–Meier cumulative survival analyses according to TMB (post-hoc analysis)

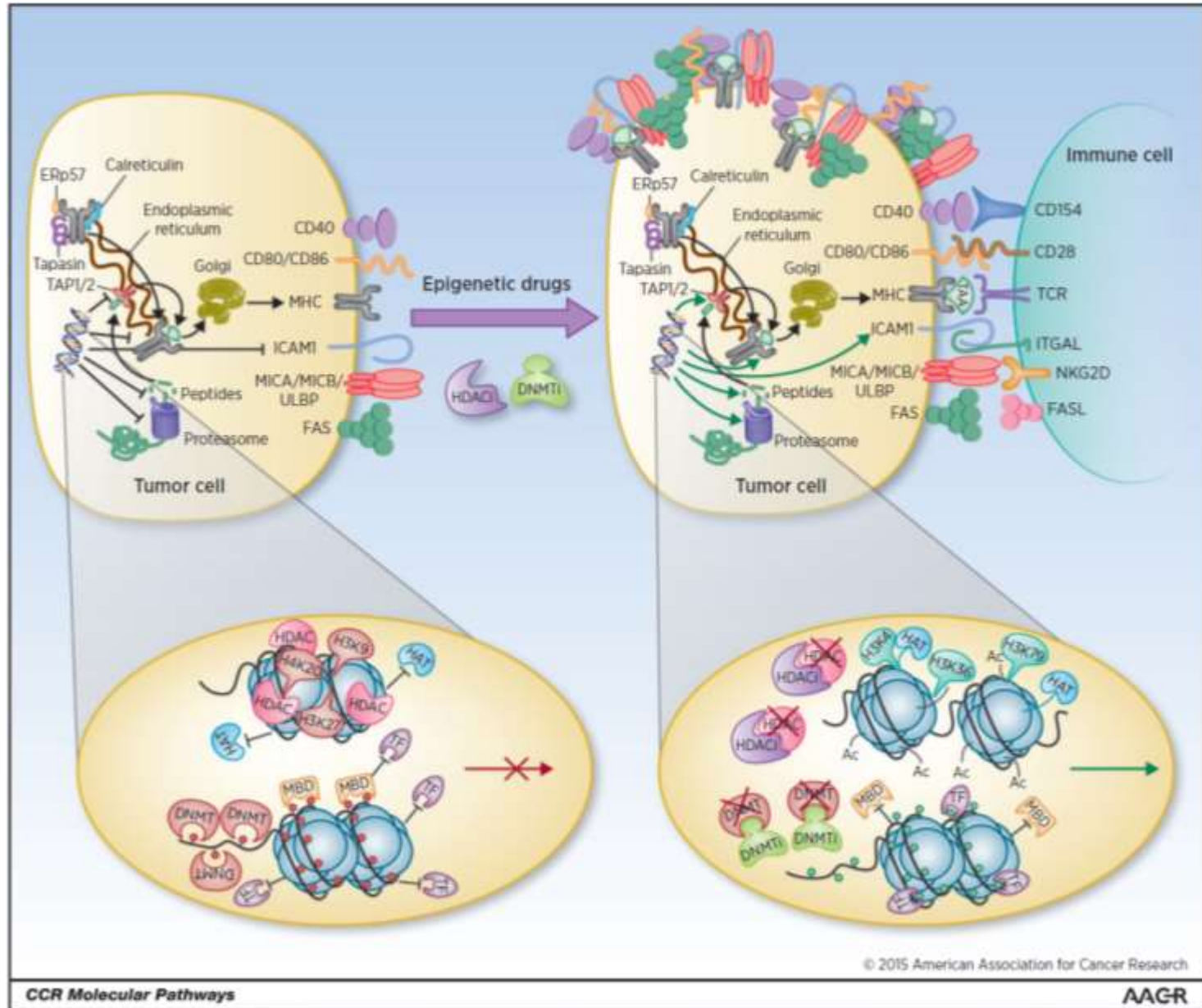
Kaplan–Meier overall survival for all patients in the NIBIT-MESO-1 study with samples available for TMB analysis. Vertical lines indicate censored observations. (A) Overall survival of patients stratified by median TMB of less than 8.3 and more than 8.3 mutations per Mb (n=28). (B) Overall survival of patients stratified by median TMB of less than 8.3 and more than 8.3 mutations per Mb in patients retreated with tremelimumab and durvalumab (n=13). TMB=tumour mutational burden.

The future of Cancer Immunotherapy

Targeting and modulating multiple compartments



Epigenetic Immunomodulation of Cancer cell





Take two:

Combining immunotherapy with epigenetic drugs to tackle cancer

By Karen Weintraub

npj

In 2010, six individuals with advanced lung cancer all received bad news. Early preclinical studies in mice had suggested that a drug called azacitidine might work in combination with an experimental medication called entinostat to treat their non-small cell lung cancer (NSCLC). But none of these six people enrolled in the subsequent clinical trial saw any significant tumor shrinkage. Hoping to buy the patients a little more time, Julie Brahmer, the group's oncologist at Johns Hopkins' Sidney Kimmel Cancer Center, gave them an immunotherapy drug called nivolumab. When it works, this drug unchecks the immune system to fight cancer.

Among people with NSCLC participating in other studies, fewer than half of those on nivolumab—a checkpoint inhibitor that targets a cell surface protein known as PD-1—survived six months without cancer progression. Brahmer and her colleagues expected similar results in her trial: perhaps three of the six would survive for at least six

months, and maybe one for longer than a year (*N. Engl. J. Med.* 366, 2443–2454, 2012). Yet five survived past the initial six months—and four years later, two are still alive. A third person, who died of complications from previous treatment, showed no evidence of cancer recurrence at the time of death, according to Brahmer (*Cancer Discov.* 1, OF1–OF10, 2011).

Given the small size of the group, the possibility that the success could be due simply to chance cannot be ruled out. But azacitidine and entinostat, which alter the epigenome, may have primed the patients' immune systems to respond to the checkpoint inhibitor. The experiment was the first to suggest that pairing these drugs could radically improve patient outcomes.

The idea of combining different therapeutic agents to fight cancer is not new. Immunotherapeutic agents such as checkpoint inhibitors are being tested and used in combination with other treatment

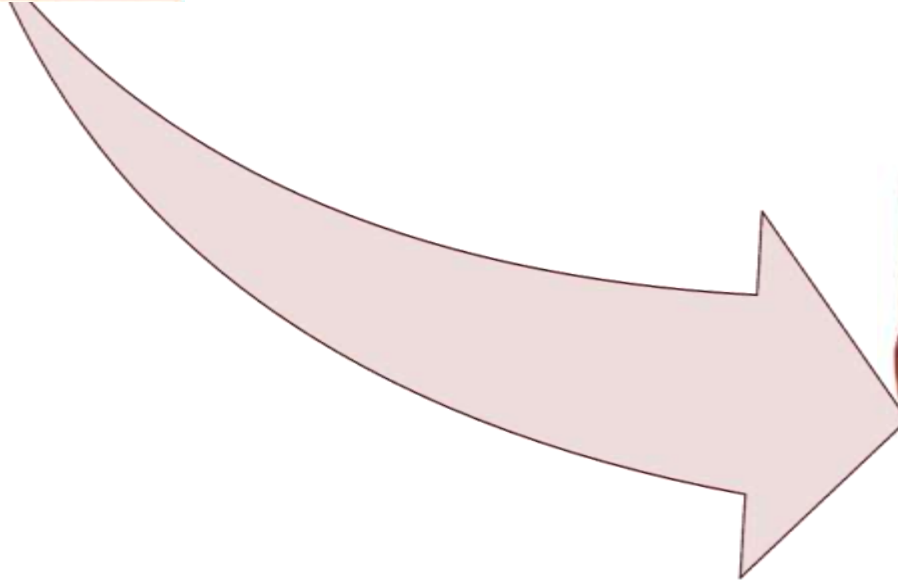
methods, such as chemotherapy and radiation, and in October 2015, the US Food and Drug Administration (FDA) approved for the first time a combination immunotherapy—nivolumab and another checkpoint inhibitor known as ipilimumab—for the treatment of melanoma. These combinations have proved more effective than using one drug alone, which supports the idea that cancer is more likely to yield if hit from multiple directions at once (*N. Engl. J. Med.* 373, 23–34, 2015).

Epigenetic therapies such as azacitidine and entinostat might offer another approach to rendering combinations more effective, and the next few years will see this idea put to the test. Shored up by a growing body of translational research that hints at tremendous potential, at least seven trials in the US, and more in Canada and Europe, are underway to test combinations of immune checkpoints and epigenetic therapies in solid tumors. A trial in people with melanoma started in October 2015 in Siena, Italy. At Johns

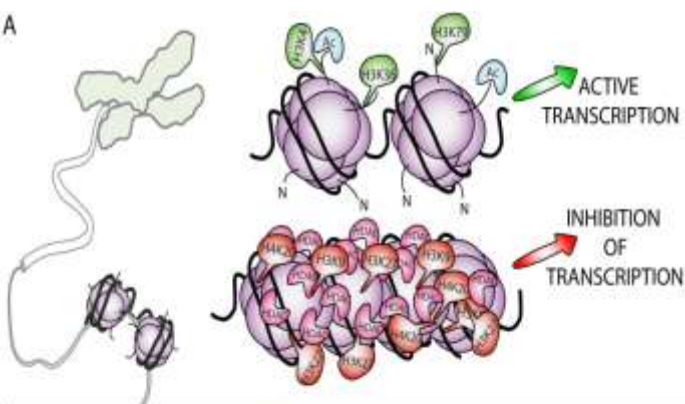
EPIGENETICS



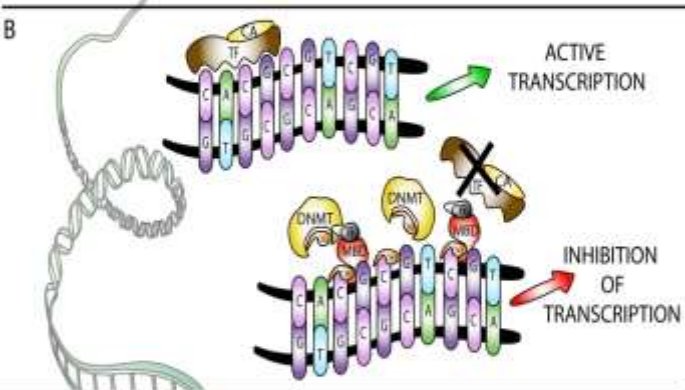
Heritable changes in gene expression
not based
on modifications of the DNA sequence



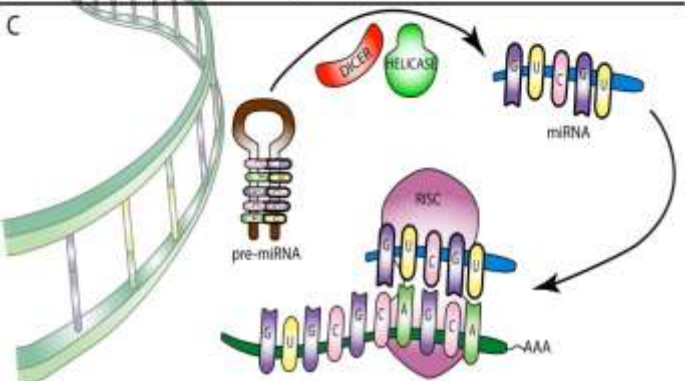
EPIGENETIC MODIFICATIONS



**Histone
modifications**



**DNA
methylation**



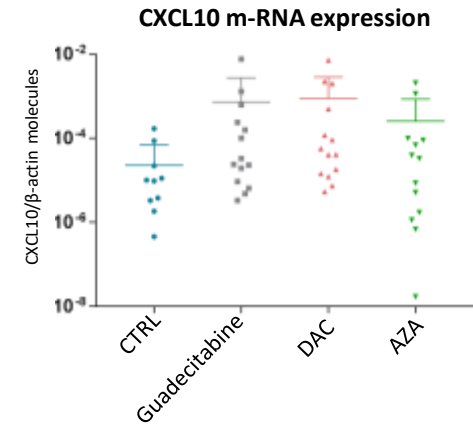
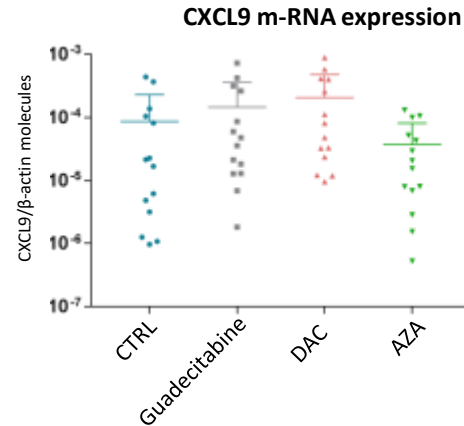
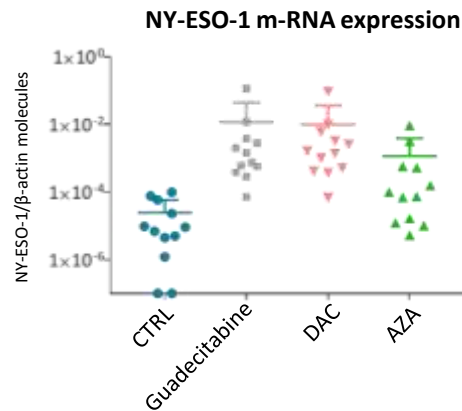
**MicroRNA
gene silencing**

**PHARMACOLOGICALLY
REVERSIBLE**

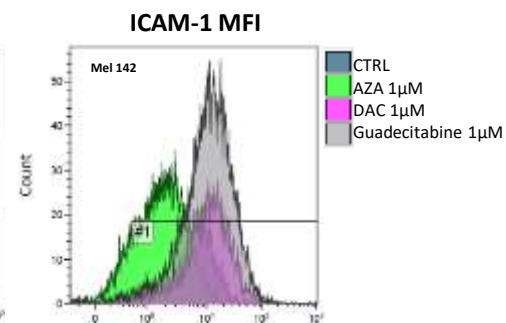
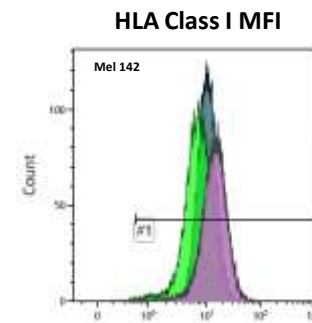
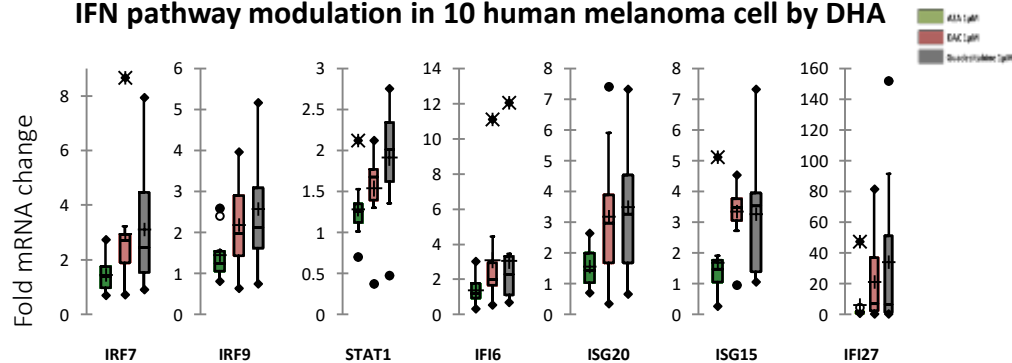
↓
HDAC inhibitors
(HDACi)

↓
DNMTs inhibitors
(DNMTi)

Immunomodulatory Properties of different DHAs

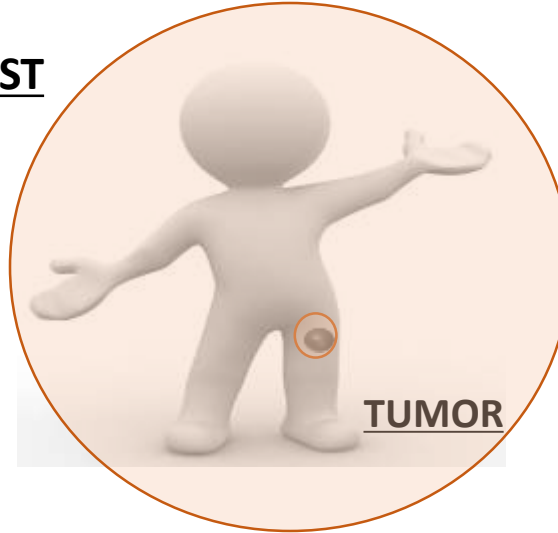


IFN pathway modulation in 10 human melanoma cell by DHA



Epigenetic immuno-sequencing

HOST



TUMOR

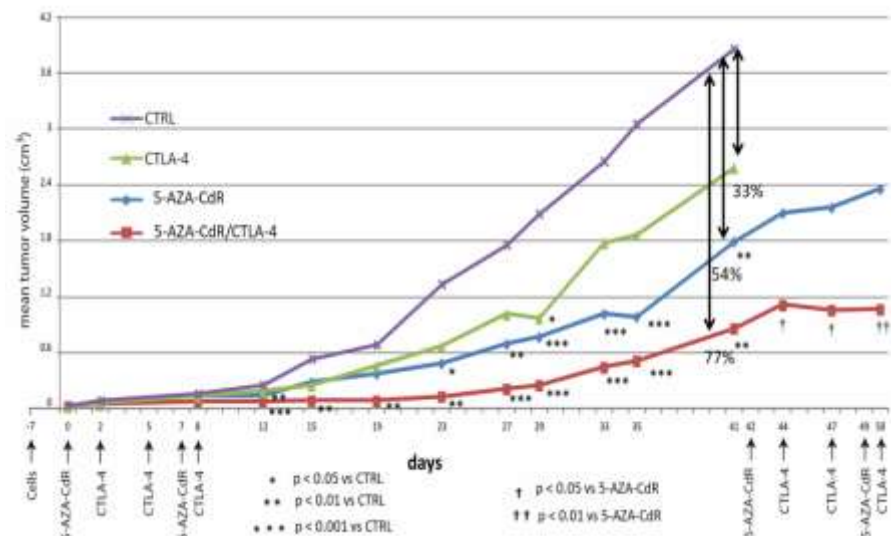
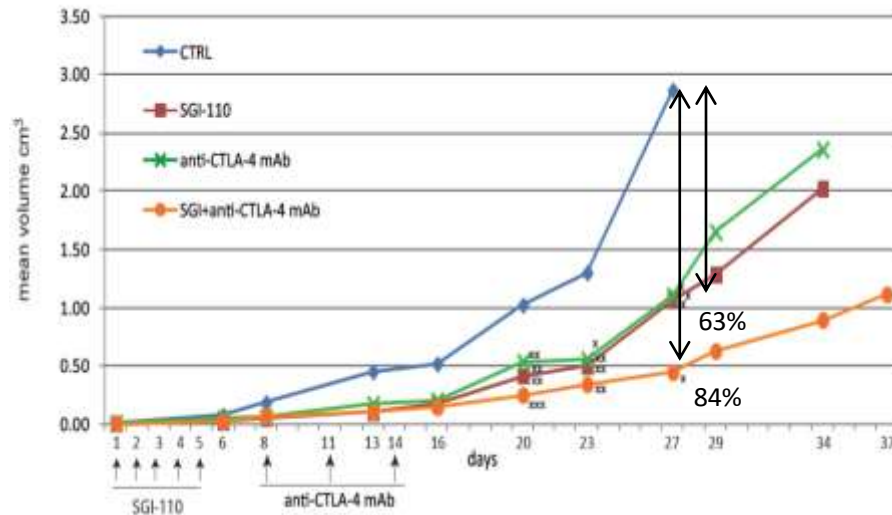
Improve the anti-tumor activity
of host's immune system

Immunomodulating mAb

Modulate
tumor immunogenicity
and immune recognition

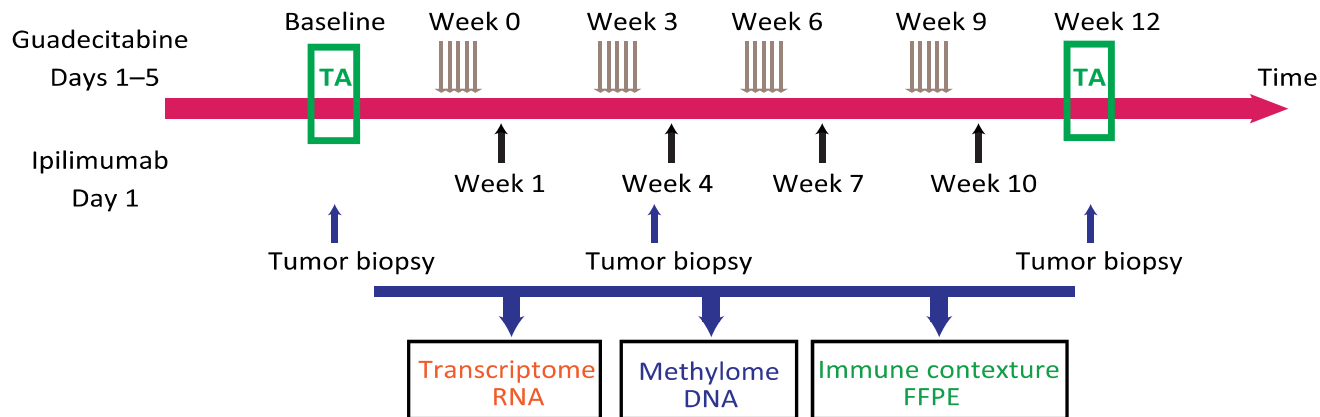
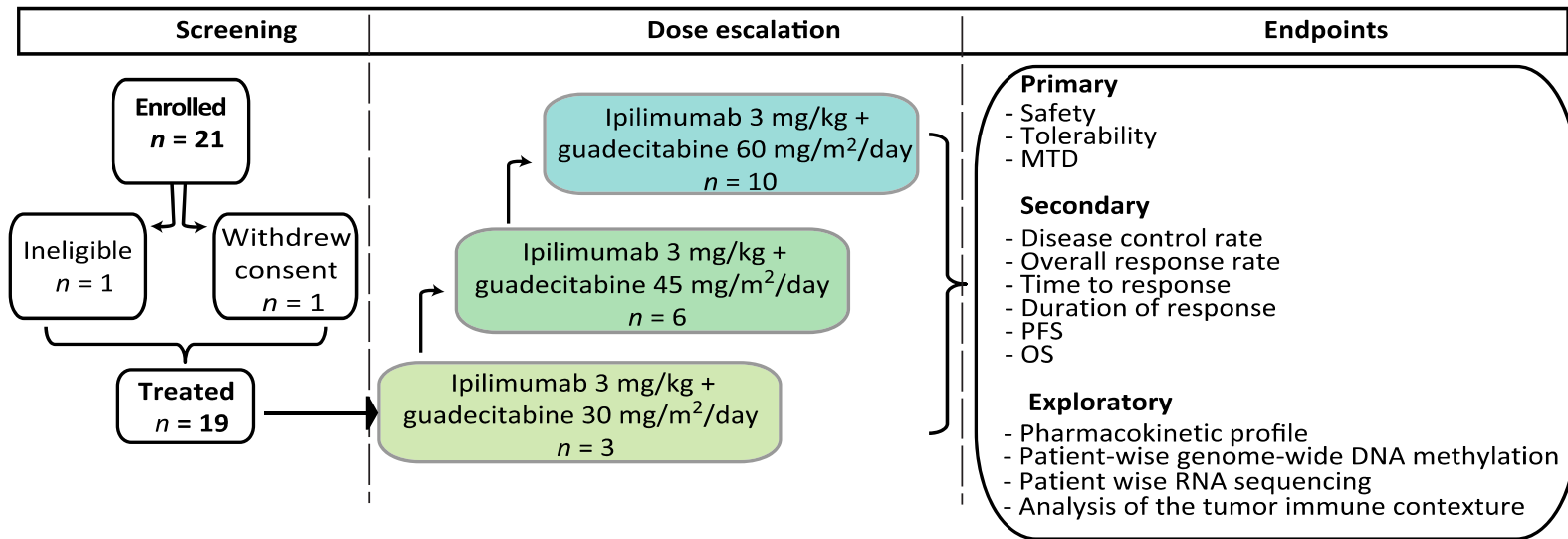
Epigenetic drugs

Anti-tumor activity of epigenetic immuno-sequencing in the TS/A syngeneic mouse model

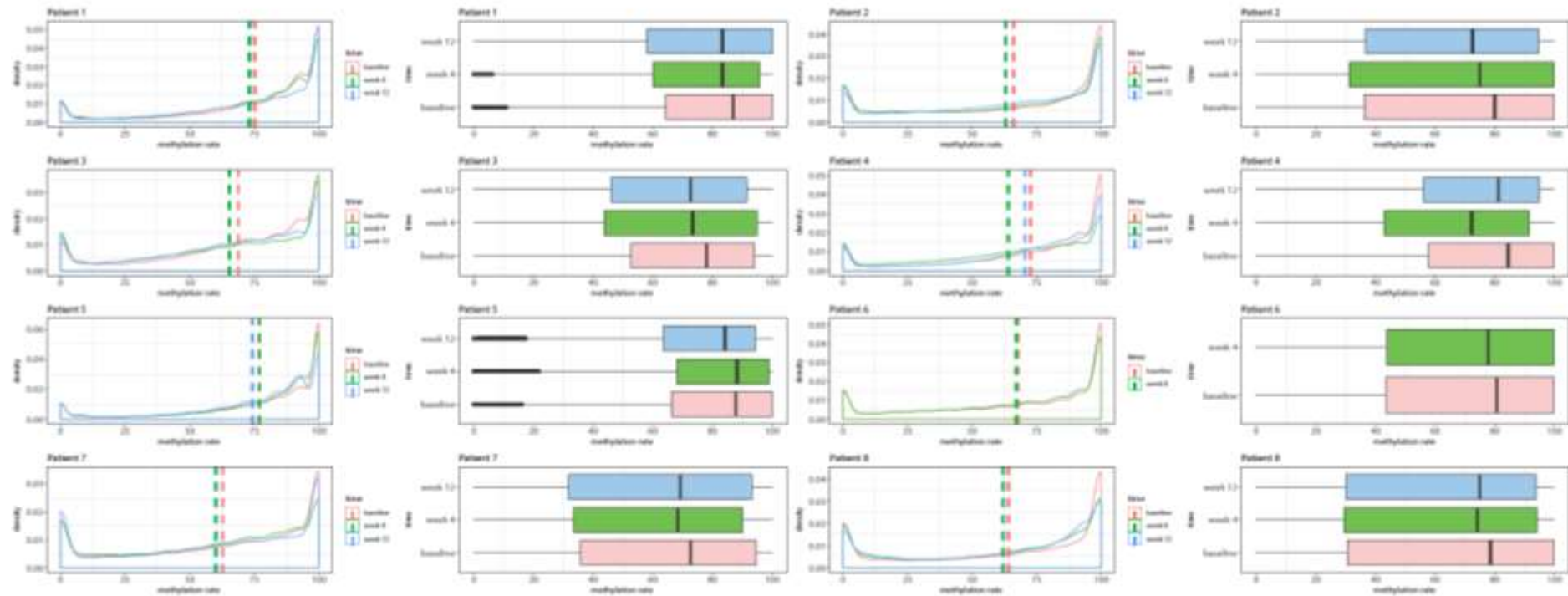


Can epigenetic immune remodeling of neoplastic cells be used to design novel immunotherapeutic approaches in cancer?

Epigenetic immuno-sequencing: the NIBIT-M4 Study NCT02608437



Global methylation analyses of tumors from NIBIT-M4 patients (RRBS CpG sites)



Differentially expressed pathways most frequently modulated at W4 and/or W12 vs. baseline

DEG

W4 vs baseline
W12 vs baseline

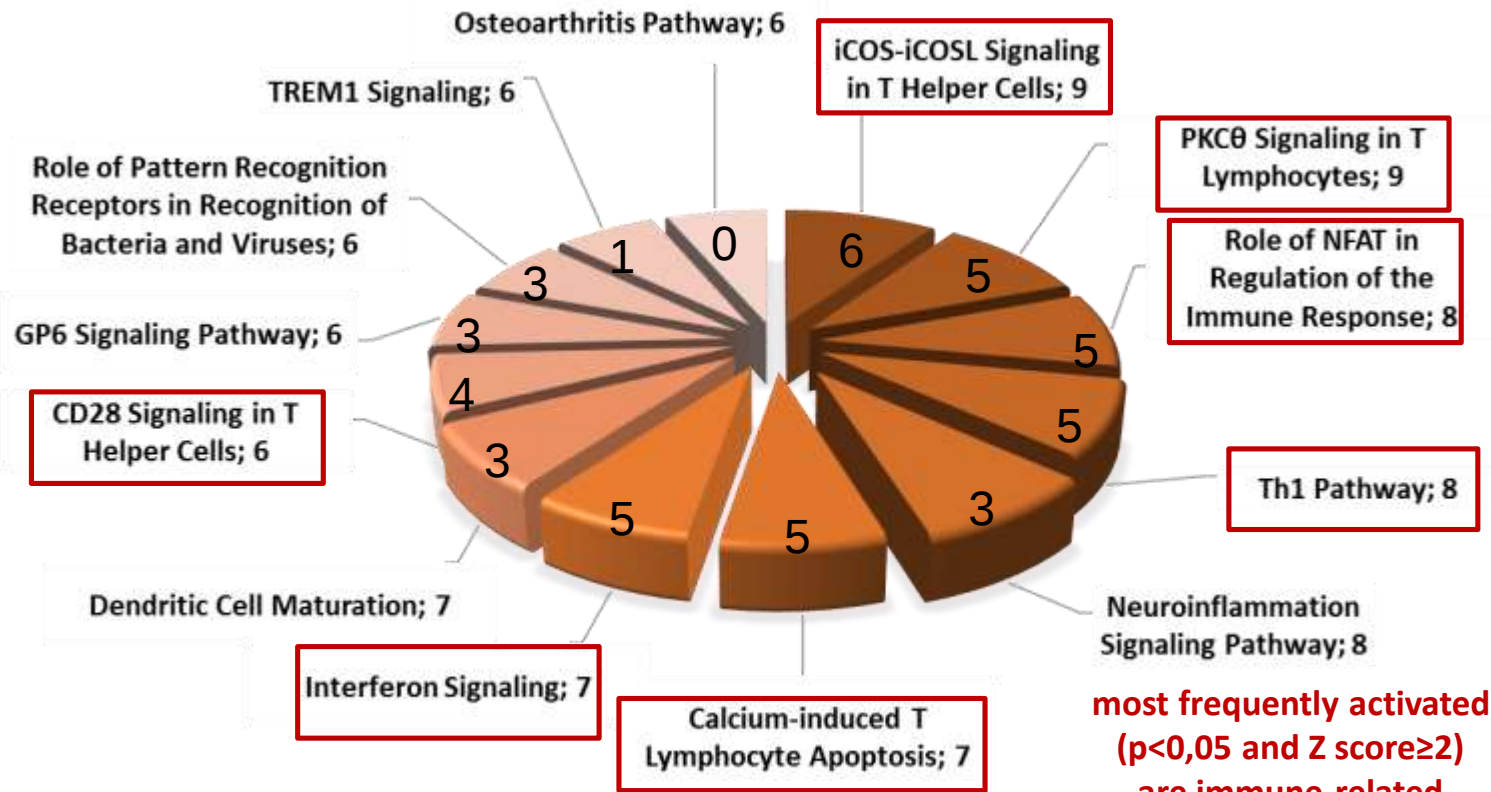
baseline

Median 2454
(49,4% up)

W4

Median 4131
(53,9% up)

W12



**most frequently activated
($p < 0,05$ and Z score ≥ 2)
are immune-related**

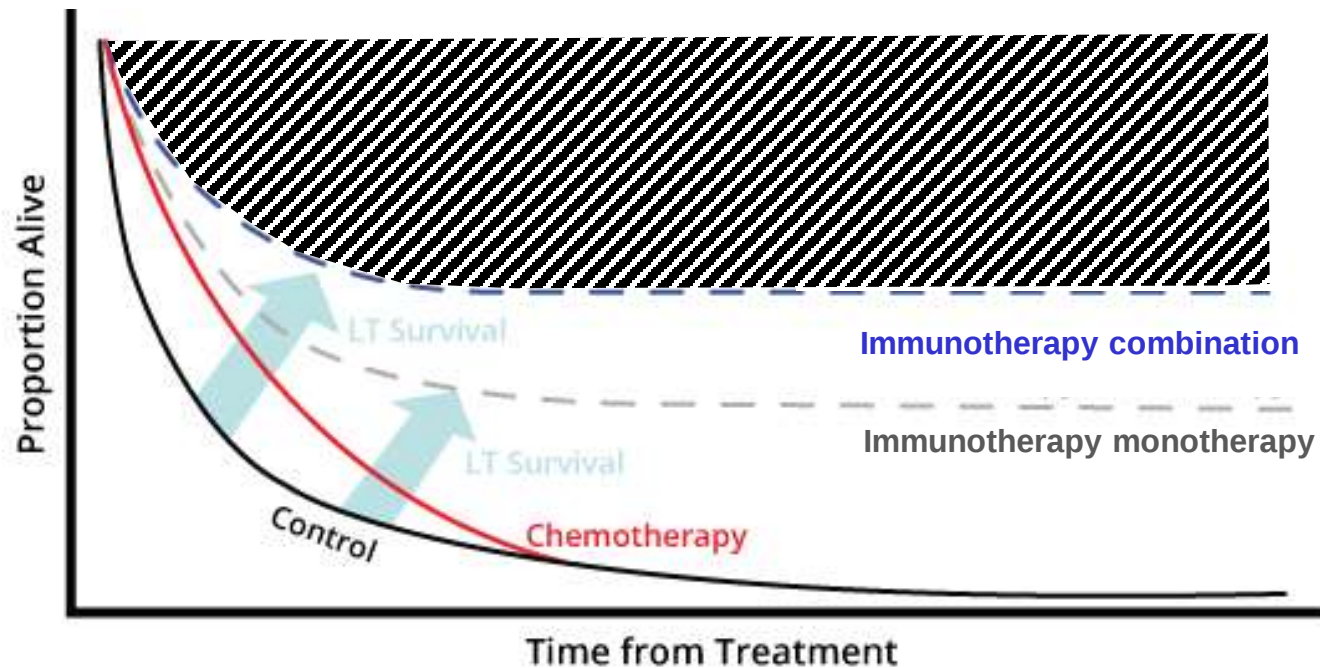
Clinical activity of NIBIT-M4 sequencing

Clinical activity	
N=19	
Ir-Objective response	
Ir-Complete Response	2/19 (10.5%)
Ir-Partial Response	3/19(15.8%)
Ir-Stable Disease	3/19(15.8%)
Ir-Disease progression	11/19 (57.9%)
Ir-ORR	5/19 [26%; 95% CI: 10.1–51.4]
Ir-DCR	8/19 (42%; 95% CI: 21.1–66.0)

Di Giacomo AM, et al. Clin Can Res 2019

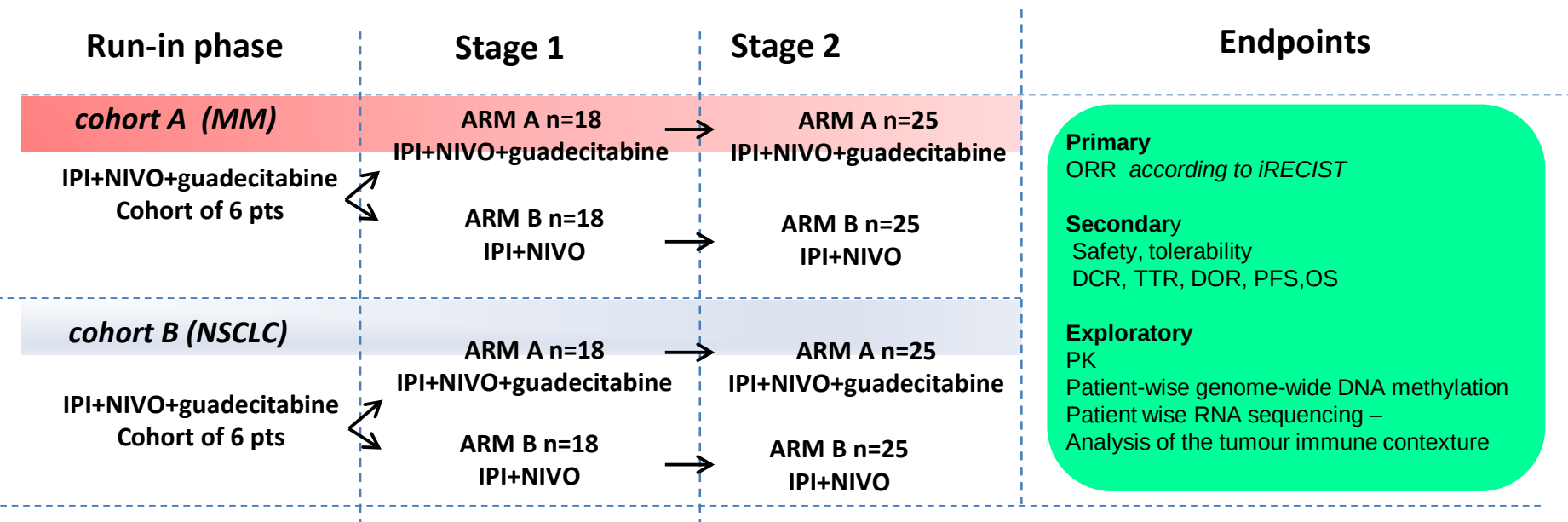
mOS	26.2 months (95% CI: 3.8-48.6)]
1-year OS	73.3%
2-year OS	50.1%
3-year OS	38.5%

The evolving scenario(s) of cancer immunotherapy

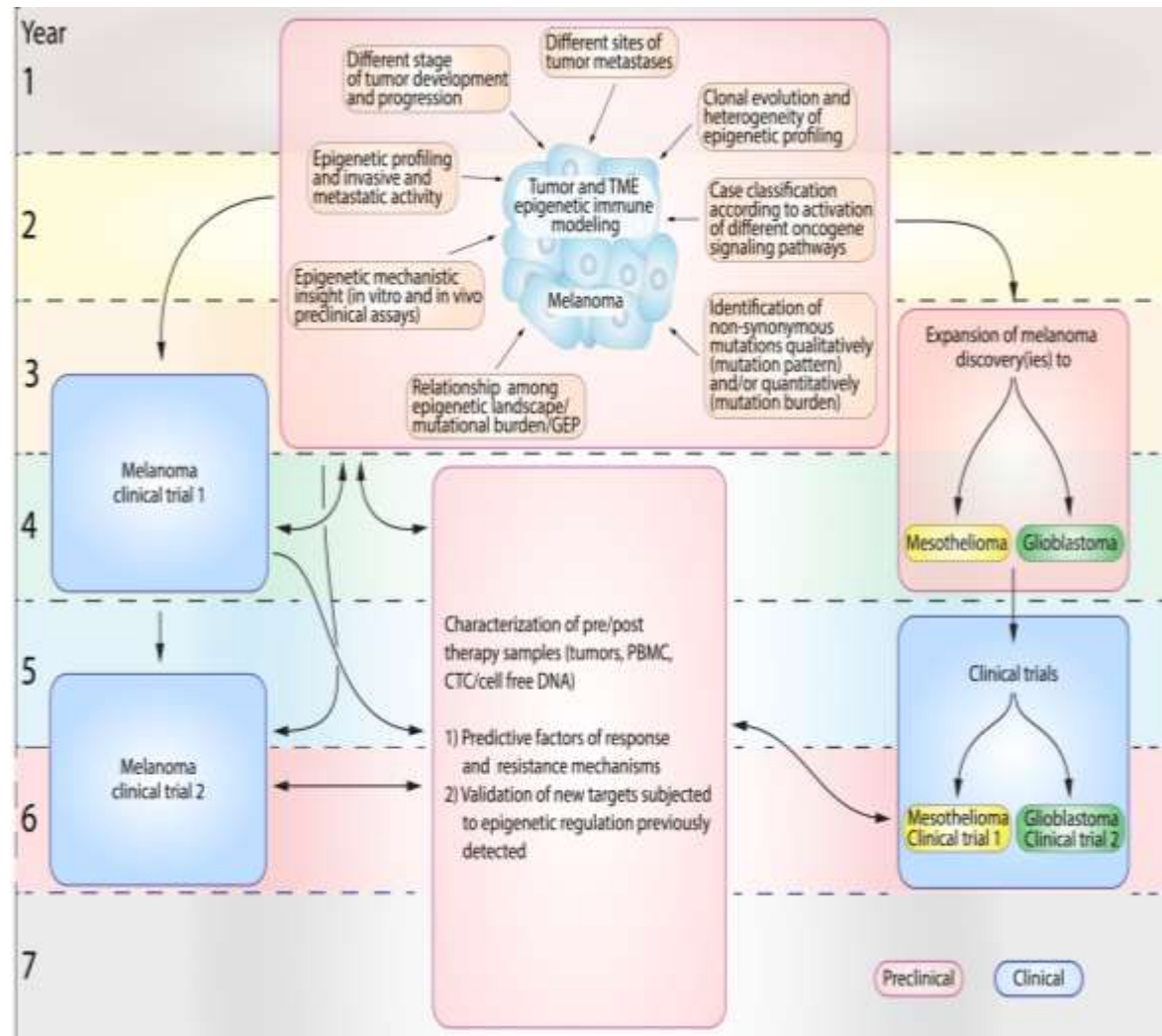


Next question

**Can epigenetic immune remodeling
of neoplastic cells be used to
overcome resistance to
immunotherapy?**



Epigenetic modeling/remodeling of cancer metastases and tumor immune contexture to improve efficacy of immunotherapy





Medical Oncology and Immunotherapy

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