

**II Giornata Nazionale  
della Ricerca  
Oncologica**



**II Incontro Nazionale FICOG**

**I GRUPPI  
COOPERATIVI  
IN ONCOLOGIA**

**LE NUOVE SFIDE  
DELLA RICERCA INDIPENDENTE**

**Dove va l'immunoterapia?**

**Anna Maria Di Giacomo**

**Center for Immuno-Oncology**

**University of Siena and University Hospital of Siena**

**Italy**

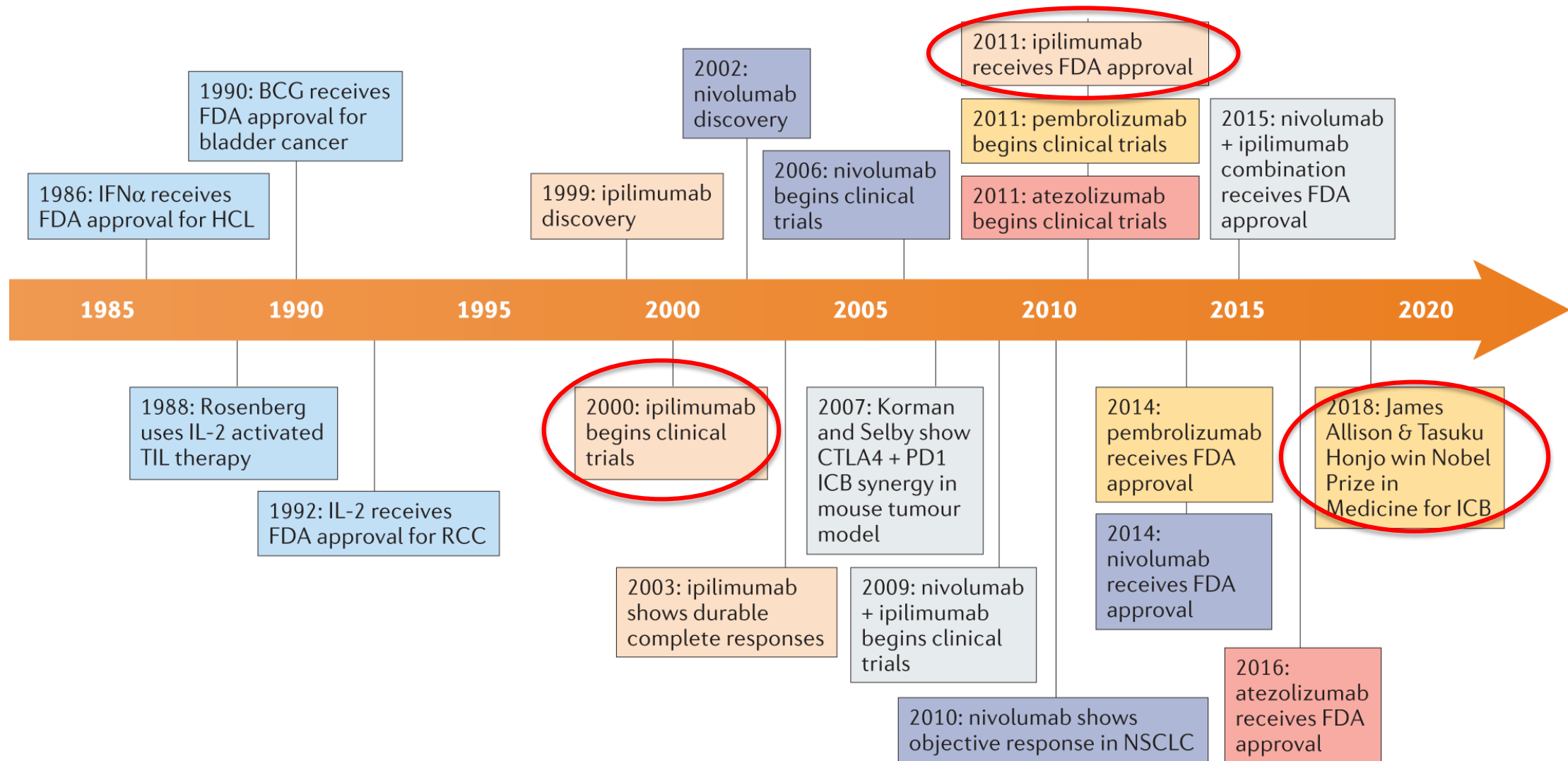


# DECLARATION OF INTERESTS

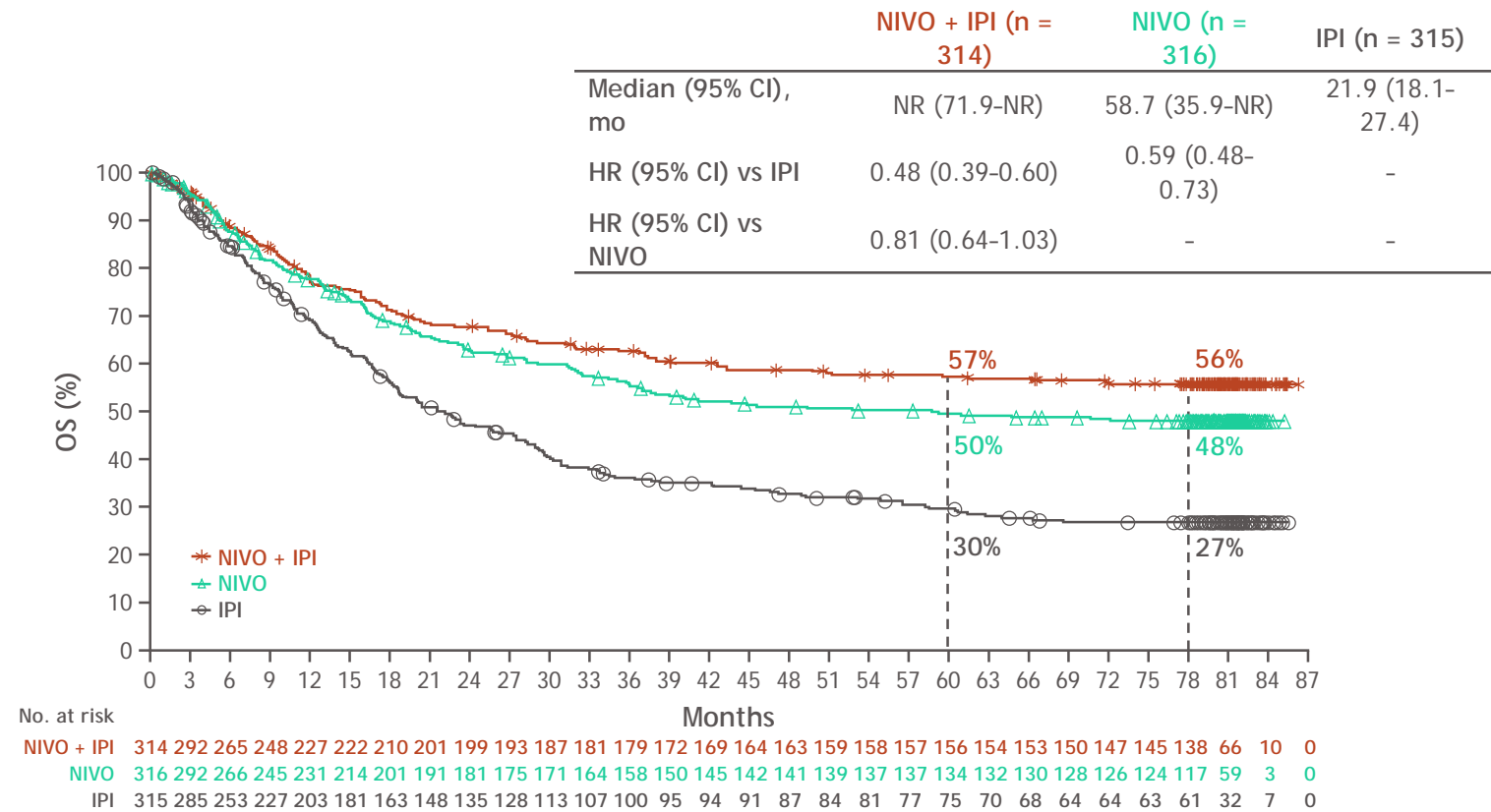
## **Prof. Anna Maria Di Giacomo, MD**

- Advisor/board member for Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA; Bristol Myers Squibb; IncytePierre Fabre; Sanofi; GlaxoSmithKline; Novartis
- Honoraria for Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA; Roche; Bristol Myers Squibb; Sanofi; Pierre Fabre; GlaxoSmithKline; Vyvamed

# The foundations of immune checkpoint blockade and the ipilimumab approval decennial



# Melanoma-specific survival (post hoc analysis)<sup>a</sup>



<sup>a</sup>In this descriptive analysis, an event was defined as death due to melanoma and deaths for any other reason were censored.

## Nivolumab plus ipilimumab in melanoma brain metastases

In their Article in *The Lancet Oncology*, Hussein Tawbi and colleagues<sup>1</sup> report a remarkable 71.9% 3-year overall survival rate for patients with melanoma and asymptomatic brain metastases treated with nivolumab plus ipilimumab in the CheckMate 204 trial. These findings strongly support the activity of the nivolumab plus ipilimumab combination, recently reported in the same clinical setting by the anti-PD-1 brain collaboration (ABC) study,<sup>2</sup> in which the 5-year survival rate was 51%, and by the Italian Network for Tumor Biotherapy-Melanoma 2 (NIBIT-M2) study,<sup>3</sup> in which the 5-year survival rate was 41%. Notably, this exciting new clinical scenario for patients with melanoma and asymptomatic brain metastases has been achieved thanks to these unique multicentre clinical trials, all conceived by non-profit organisations. Indeed, the Cytokine Working Group in the USA, the Melanoma Institute in Australia, and the NIBIT Foundation in Europe asked the question about the activity of the nivolumab plus ipilimumab combination in a population of patients with melanoma who, to date, have been hard to treat, with very poor therapeutic chances. Notably, until now, patients with melanoma and brain metastases were systematically excluded from industry-sponsored clinical trials with immune checkpoint inhibitors because of their poor prognosis and the prevailing dogma that the blood-brain barrier would prevent effector immune cells from trafficking to the brain.<sup>4</sup>

This substantial change in the therapeutic landscape for patients with melanoma and asymptomatic brain metastases highlights the crucial role of independent clinical research in specific oncology settings in which, although the clinical need is

unquestionable, industry-sponsored trials are not prioritised. Consequently, a virtuous collaboration and exchange of goals between non-profit organisations and pharmaceutical industry could eventually benefit small groups of patients in specific clinical settings. However, to fully achieve this task, independent clinical research has to ask highly relevant medical questions, thus fulfilling the mission to help patients who are excluded from industry-sponsored trials, as has happened since the advent of immune checkpoint inhibitor-based clinical trials for patients with melanoma and brain metastases.<sup>4</sup> Along this line, the striking long-term survival observed in these three independent studies identify the nivolumab plus ipilimumab combination as the standard of care for patients with melanoma and asymptomatic brain metastases. Once the dogma that the brain is an immune-privileged organ is definitively broken, the next step forwards for investigator-sponsored clinical trials could be to broaden knowledge on the efficacy of immune checkpoint inhibitor therapy on brain metastases from other tumour types, and in even more challenging clinical settings, such as symptomatic brain metastases or leptomeningeal tumour spreading.

AMDG has served as a consultant or advisor to Incyte, Pierre Fabre, GlaxoSmithKline, Bristol-Myers Squibb, Merck Sharp Dohme, and Sanofi and has received compensated educational activities from Bristol-Myers Squibb, Merck Sharp Dohme, Pierre Fabre, and Sanofi. MM has served as a consultant or advisor to Roche, Bristol-Myers Squibb, Merck Sharp Dohme, Incyte, AstraZeneca, Amgen, Pierre Fabre, Eli Lilly, GlaxoSmithKline, Sciclon, Sanofi, Alfasigma, and Merck Serono and own shares in Epigen Therapeutics.

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1 Tawbi HA, Forsyth PA, Hodi FS, et al. Long-term outcomes of patients with active melanoma brain metastases treated with combination nivolumab plus ipilimumab (CheckMate 204): final results of an open-label, multicentre, phase 2 study. *Lancet Oncol* 2021; 22: 1692-704.

- 2 Long GV, Atkinson V, Lo S, et al. Five-year overall survival from anti-PD-1 brain collaboration (ABC study): randomized phase 2 study of nivolumab (nivo) or nivo+ipilimumab (ipi) in patients (pts) with melanoma brain metastases (mets). *Proc Am Soc Clin Oncol* 2021; 39 (suppl 15): 9508 (abstr).
- 3 Di Giacomo AM, Chiarion-Sileni V, Del Vecchio M, et al. Primary analysis and 4-year follow-up of the phase III NIBIT-M2 trial in melanoma patients with brain metastases. *Clin Cancer Res* 2021; 27: 4737-45.
- 4 Di Giacomo AM, Valente M, Cerase A, et al. Immunotherapy of brain metastases: breaking a "dogma". *J Exp Clin Cancer Res* 2019; 38: 419.



## Combined Nivolumab and Ipilimumab in Melanoma Metastatic to the Brain

Hussein A. Tawbi, M.D., Ph.D., Peter A. Forsyth, M.D., Alain Algazi, M.D., Omid Hamid, M.D., F. Stephen Hodi, M.D., Stergios J. Moschos, M.D., Nikhil I. Khushalani, M.D., Karl Lewis, M.D., Christopher D. Lao, M.D., M.P.H., Michael A. Postow, M.D., Michael B. Atkins, M.D., Marc S. Ernstoff, M.D., David A. Reardon, M.D., Igor Puzanov, M.D., Ragini R. Kudchadkar, M.D., Reena P. Thomas, M.D., Ph.D., Ahmad Tarhini, M.D., Ph.D., Anna C. Pavlick, D.O., Joel Jiang, Ph.D., Alexandre Avila, M.D., Ph.D., Sheena Demelo, M.D., and Kim Margolin, M.D.



## Combination nivolumab and ipilimumab or nivolumab alone in melanoma brain metastases: a multicentre randomised phase 2 study

Georgina V Long, Victoria Atkinson, Serigne Lo, Shahneen Sandhu, Alexander D Guminiski, Michael P Brown, James S Wilmott, Jarem Edwards, Maria Gonzalez, Richard A Scolyer, Alexander M Menzies\*, Grant A McArthur\*

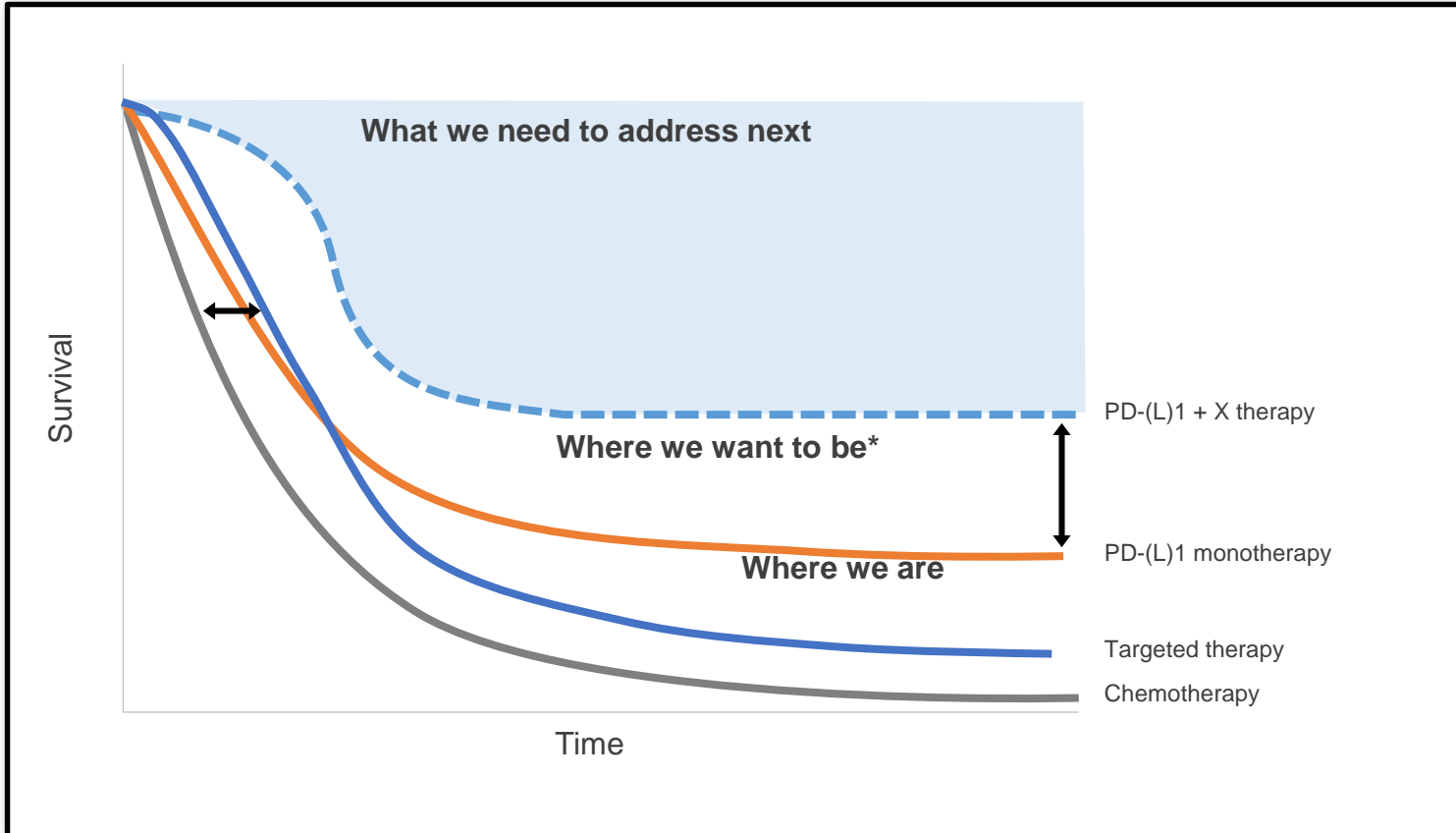
CLINICAL CANCER RESEARCH | CLINICAL TRIALS: IMMUNOTHERAPY

## Primary Analysis and Four-Year Follow-Up of the Phase III NIBIT-M2 Trial in Melanoma Patients With Brain Metastases

Anna Maria Di Giacomo<sup>1</sup>, Vanna Chiarion-Sileni<sup>2</sup>, Michele Del Vecchio<sup>3</sup>, Pier Francesco Ferrucci<sup>4</sup>, Michele Guida<sup>5</sup>, Pietro Quaglino<sup>6</sup>, Massimo Guidoboni<sup>7</sup>, Paolo Marchetti<sup>8</sup>, Ornella Cutaia<sup>1</sup>, Giovanni Amato<sup>1</sup>, Alessia Covre<sup>1</sup>, Roberto Camerini<sup>9</sup>, Luana Calabrò<sup>1</sup>, Monica Valente<sup>1</sup>, Diana Giannarelli<sup>10</sup>, Mario Mandalà<sup>11</sup>, and Michele Maio<sup>1,9,12</sup>



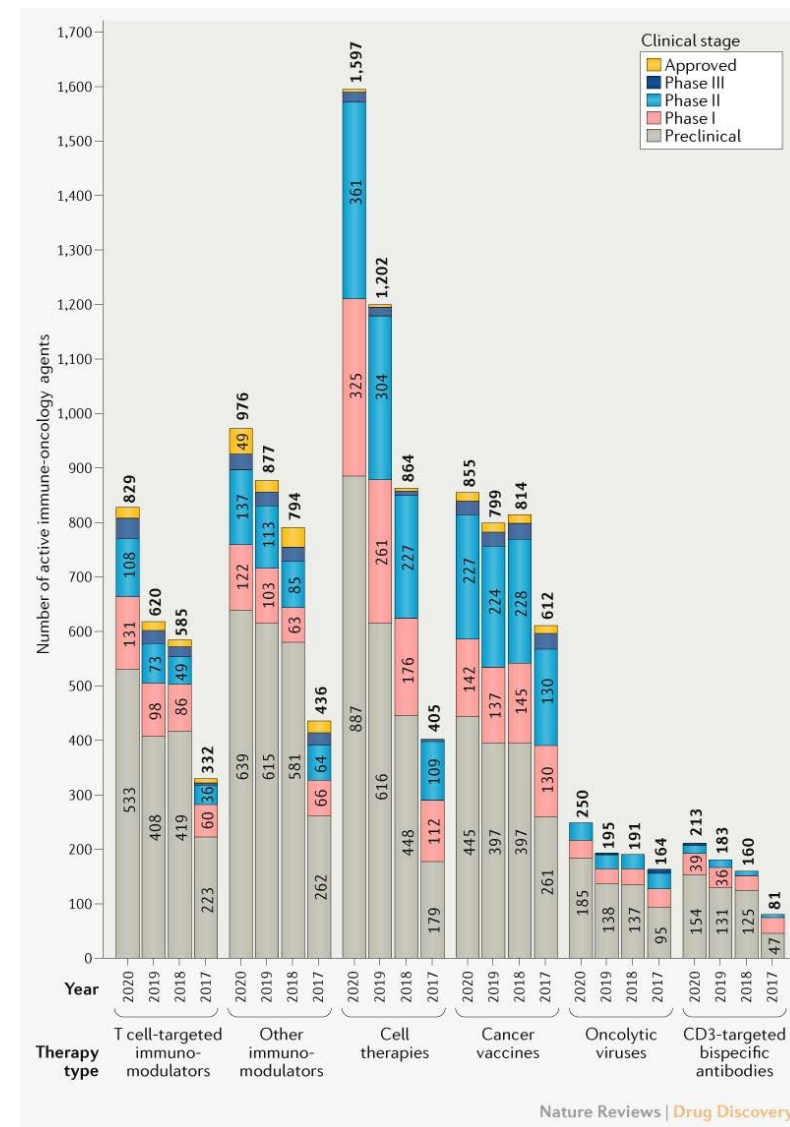
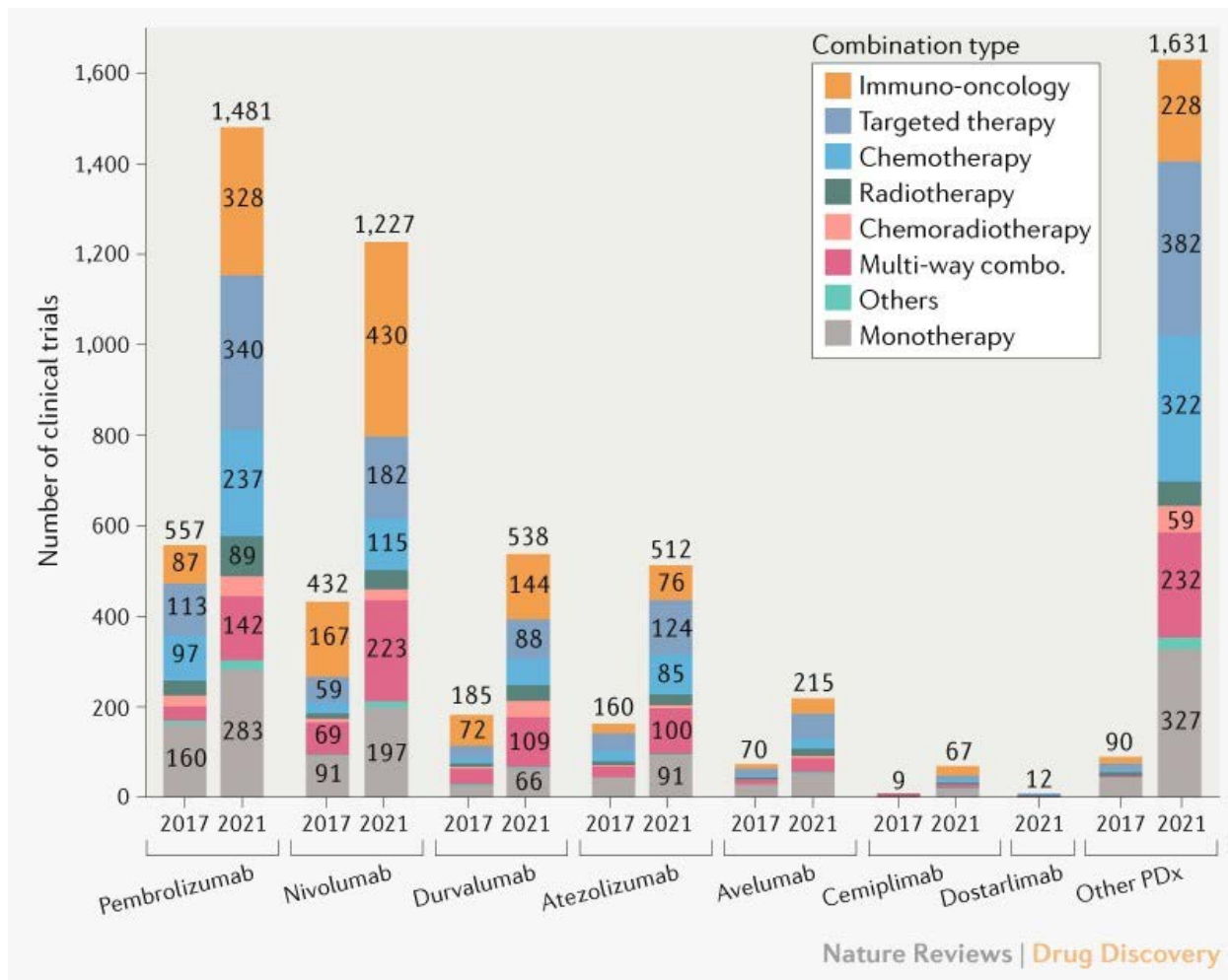
# The evolving scenario(s) of cancer immunotherapy



- Some tumors have **primary resistance mechanisms** and escape the immune response
- **Several tumor types** with low frequency of response (e.g. breast, prostate, colon, or pancreatic)
- Tumors may develop novel **escape mechanisms** leading to **secondary resistance**<sup>2</sup>
- **Secondary resistance** has been documented across a variety of tumor types



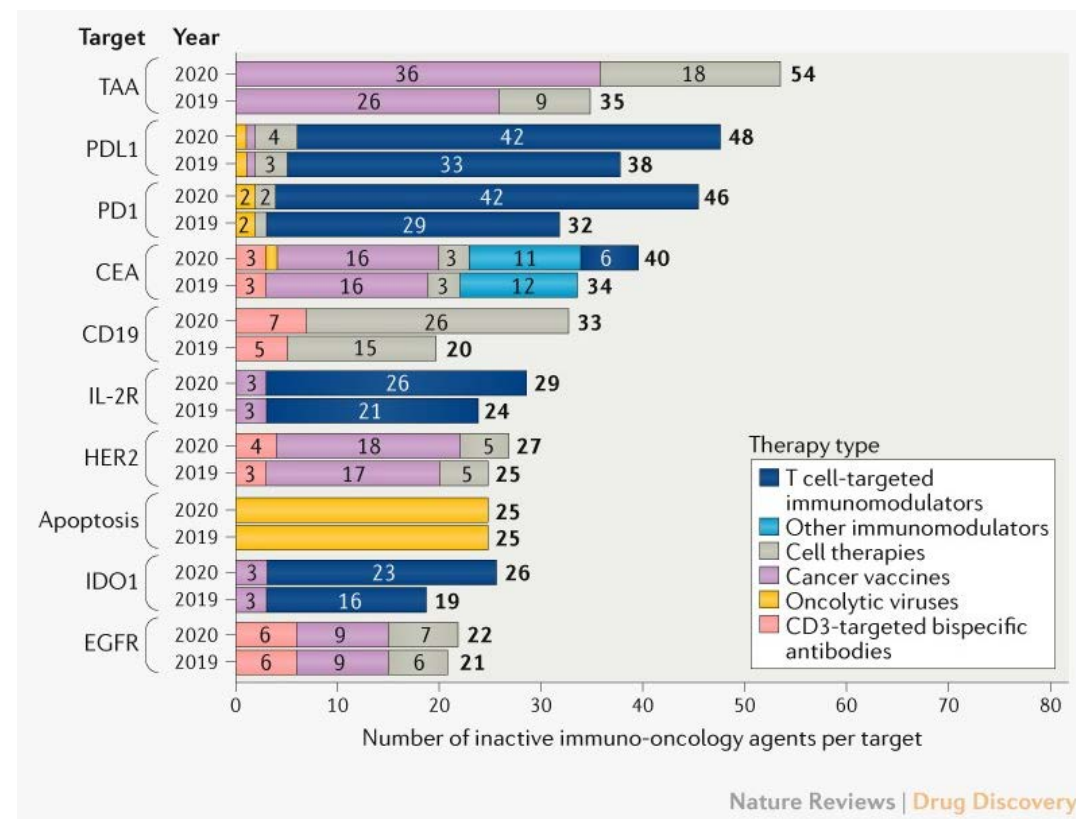
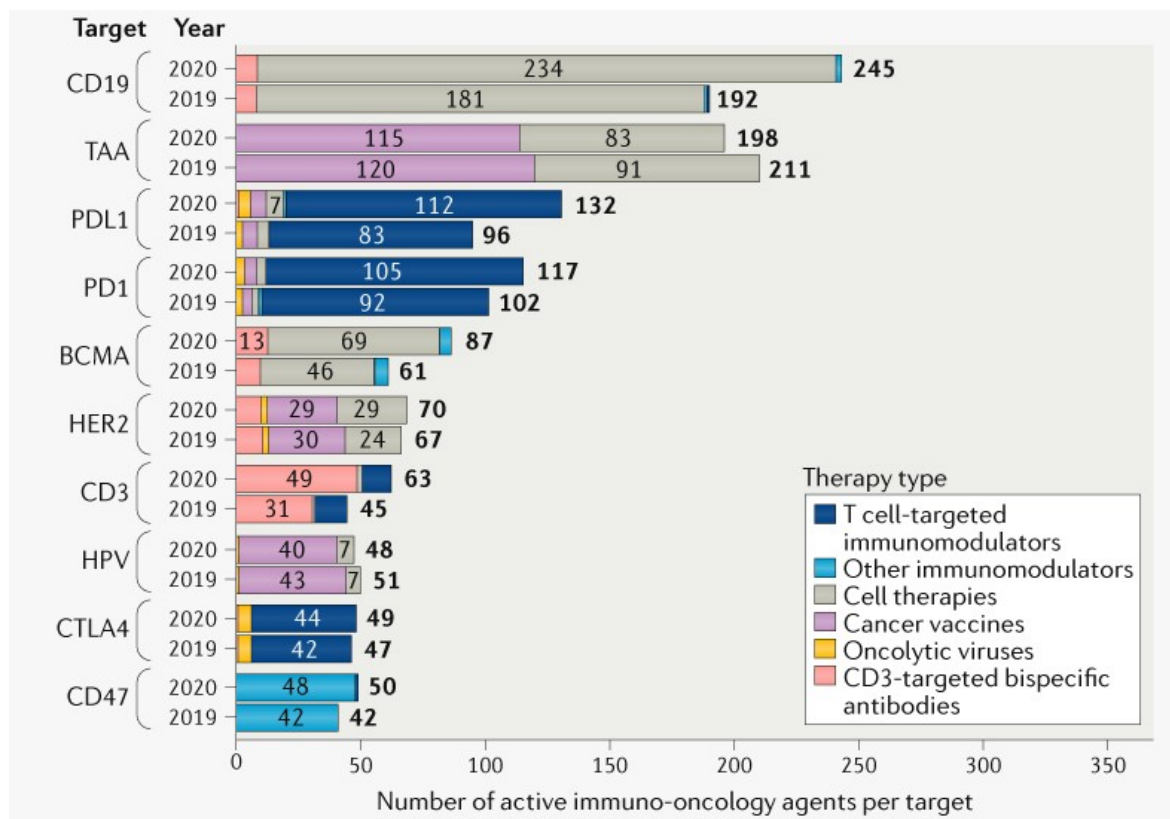
# Challenges and opportunities in the PD1/PDL1 inhibitor clinical trial landscape





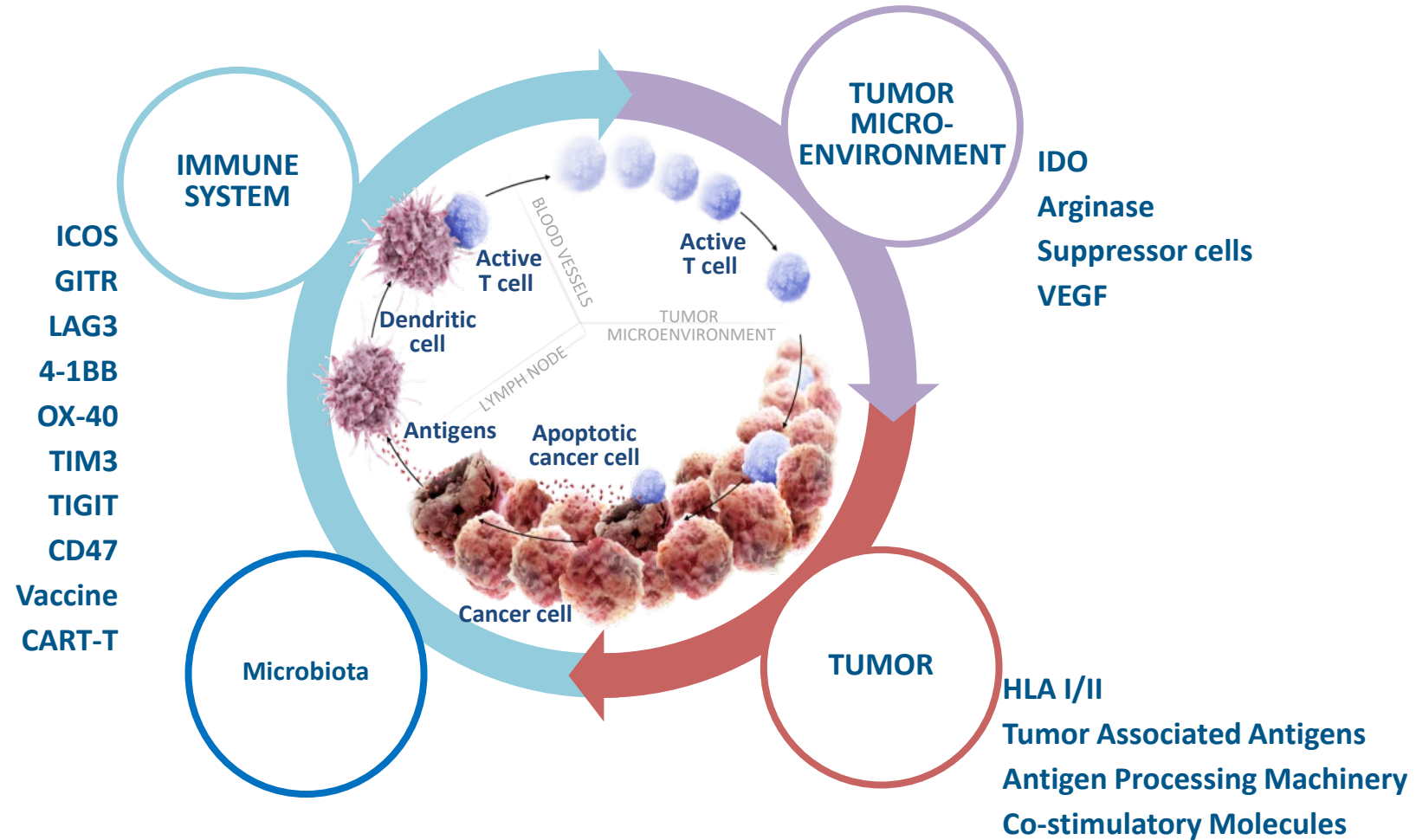


# Immuno-oncology drug development forges on despite COVID-19

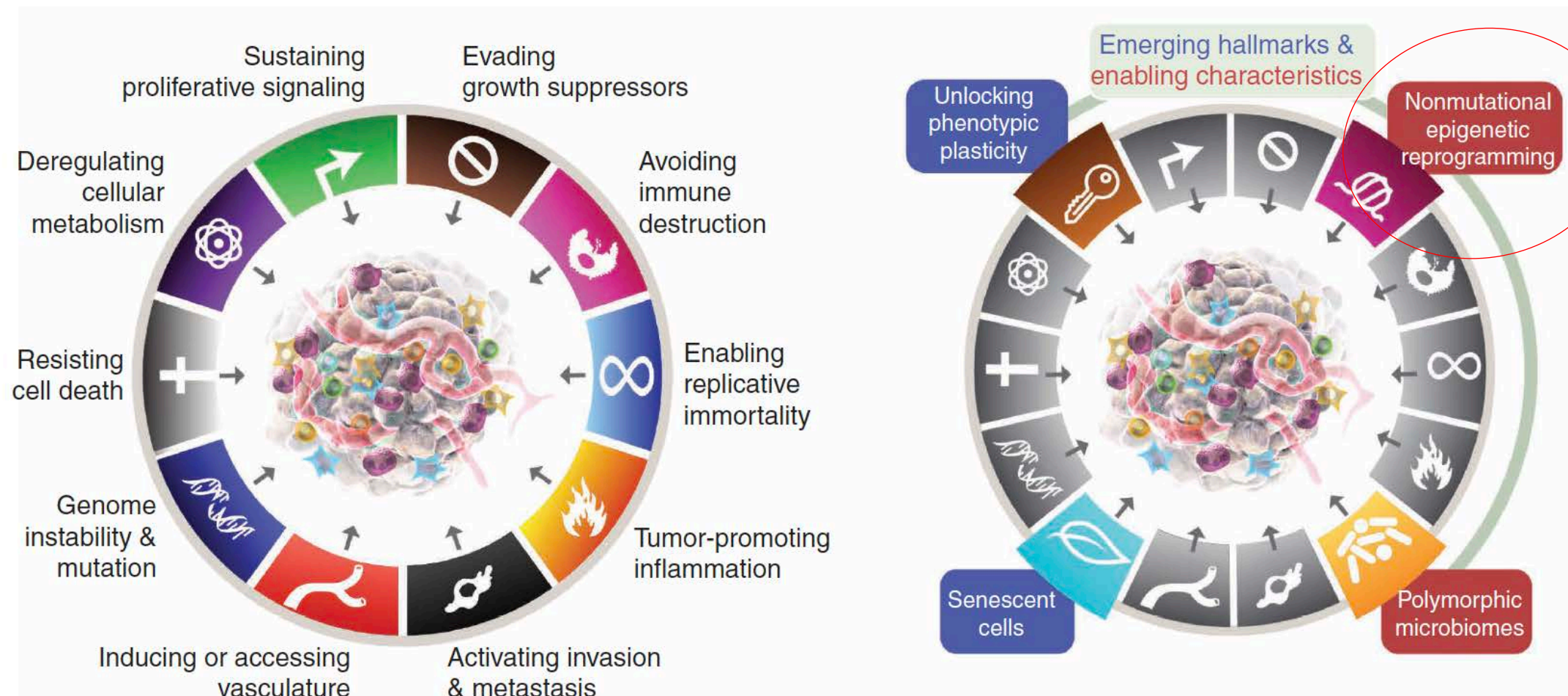


# The future of Immunotherapy

## Targeting and modulating multiple compartments



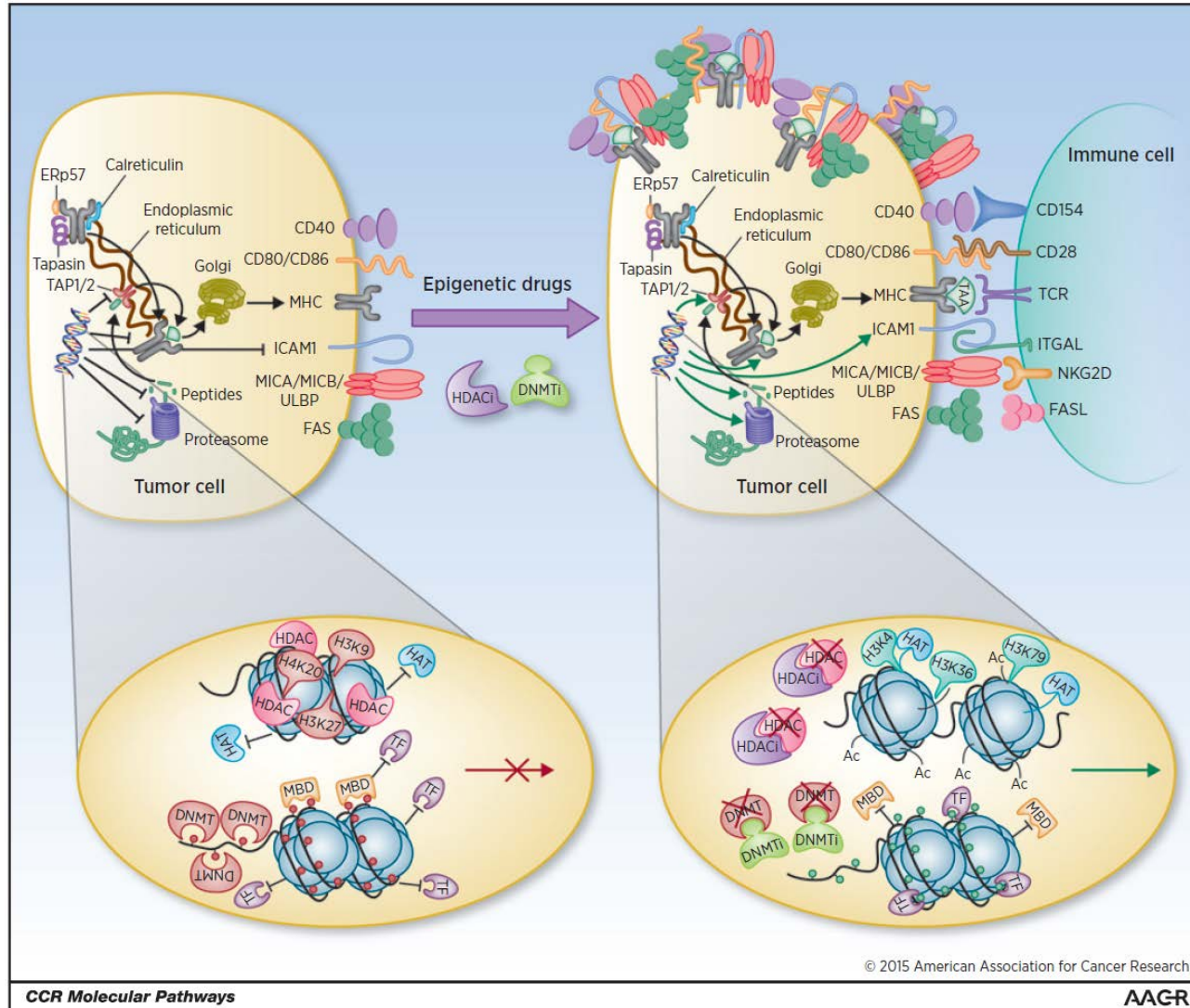
## REVIEW



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



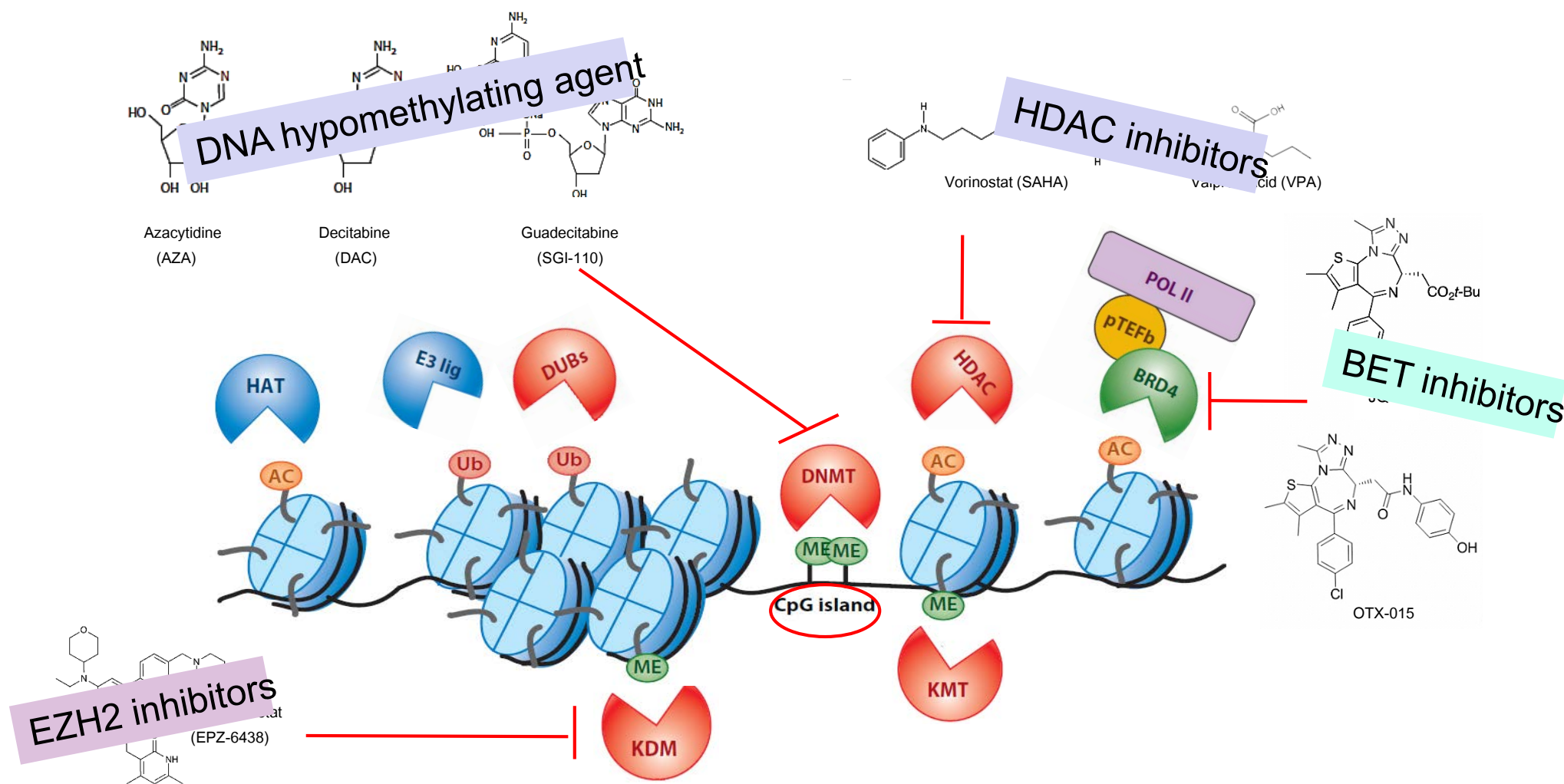
# Epigenetic (DHAs) immunomodulation of cancer cell



- Up-regulate/induce TAA (e.g., CTA, melanoma associated antigens)
- Up-regulate APM components
- Up-regulate co-stimulatory molecules
- Up-regulate IFN pathway
- Up-regulate/induce cytotoxic T cell recognition of tumors



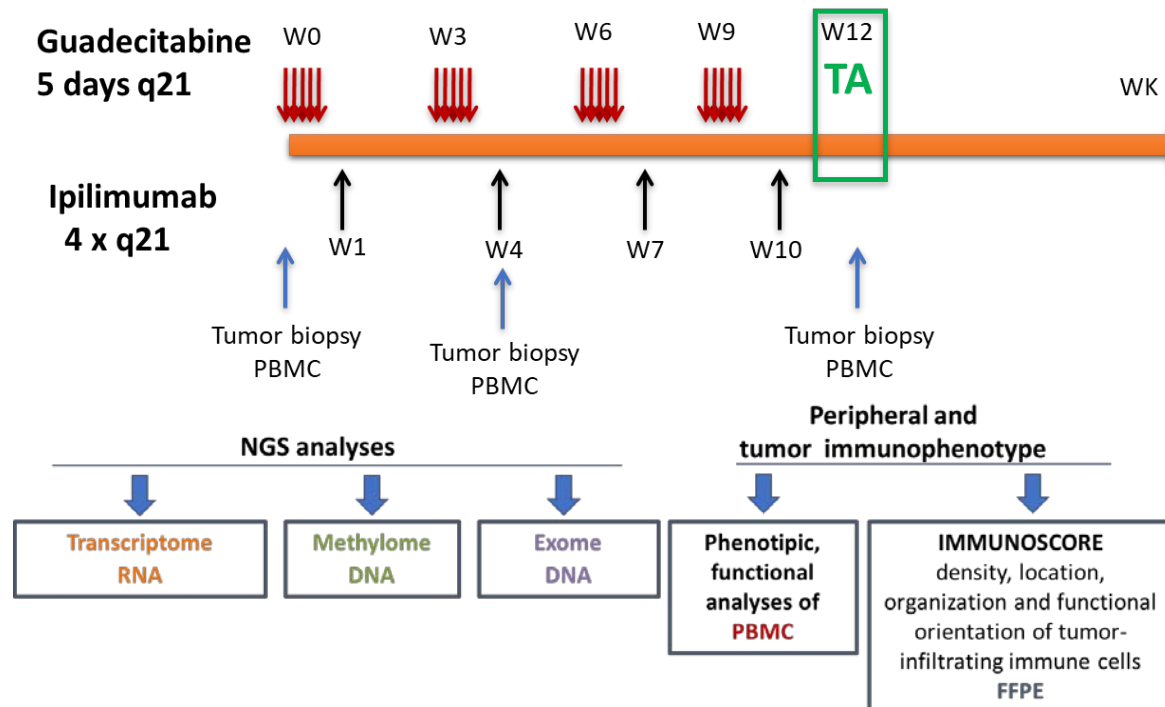
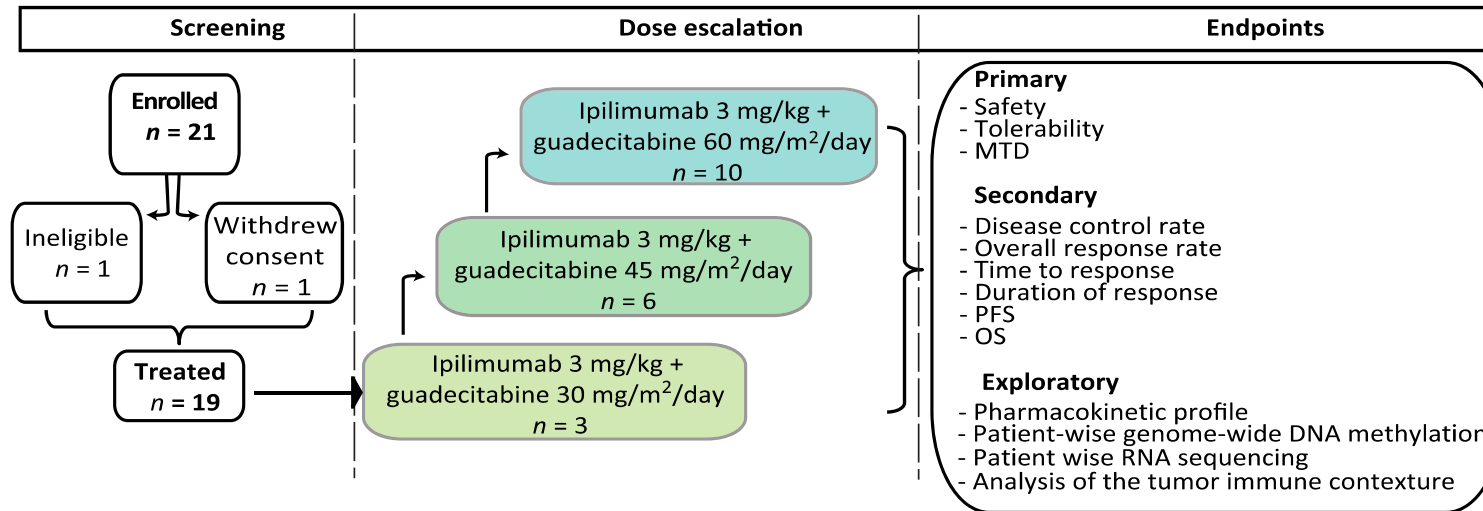
# EPIGENETIC MODIFICATIONS



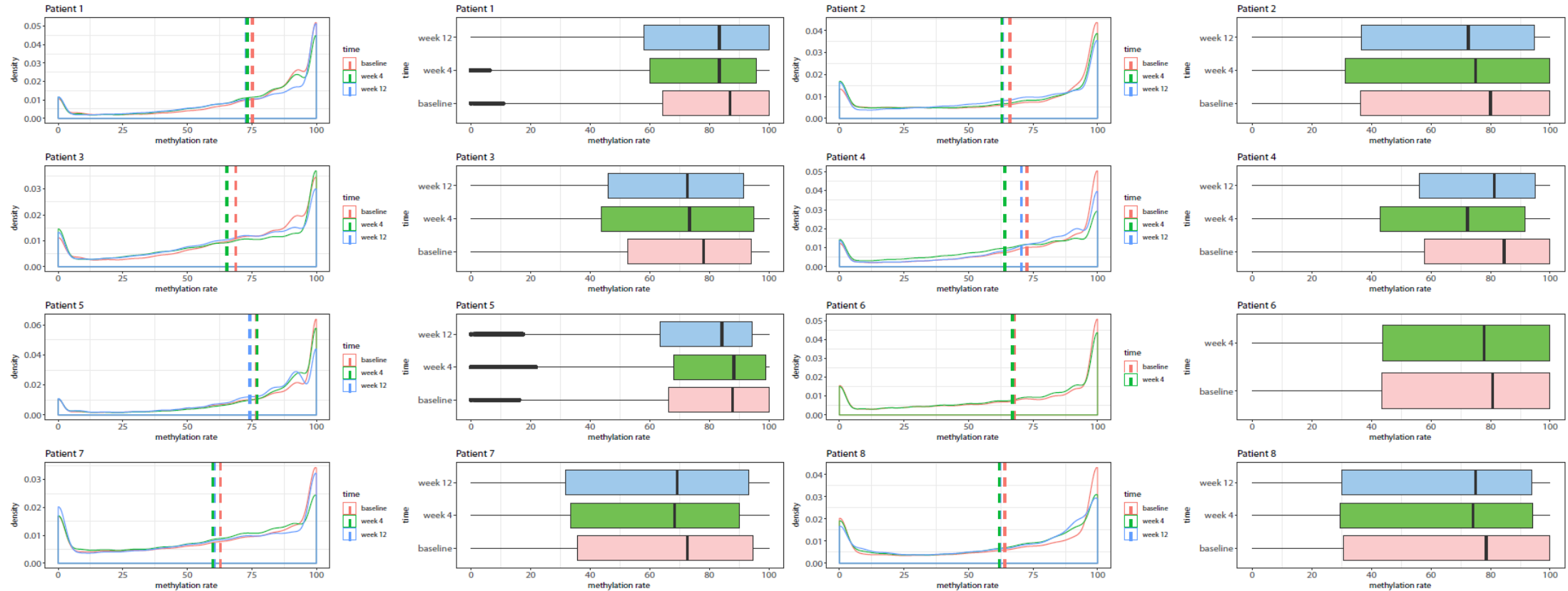
**ARE PHARMACOLOGICALLY REVERSIBLE**

# Epigenetic immuno-sequencing: the NIBIT-M4 Study

## NCT02608437



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



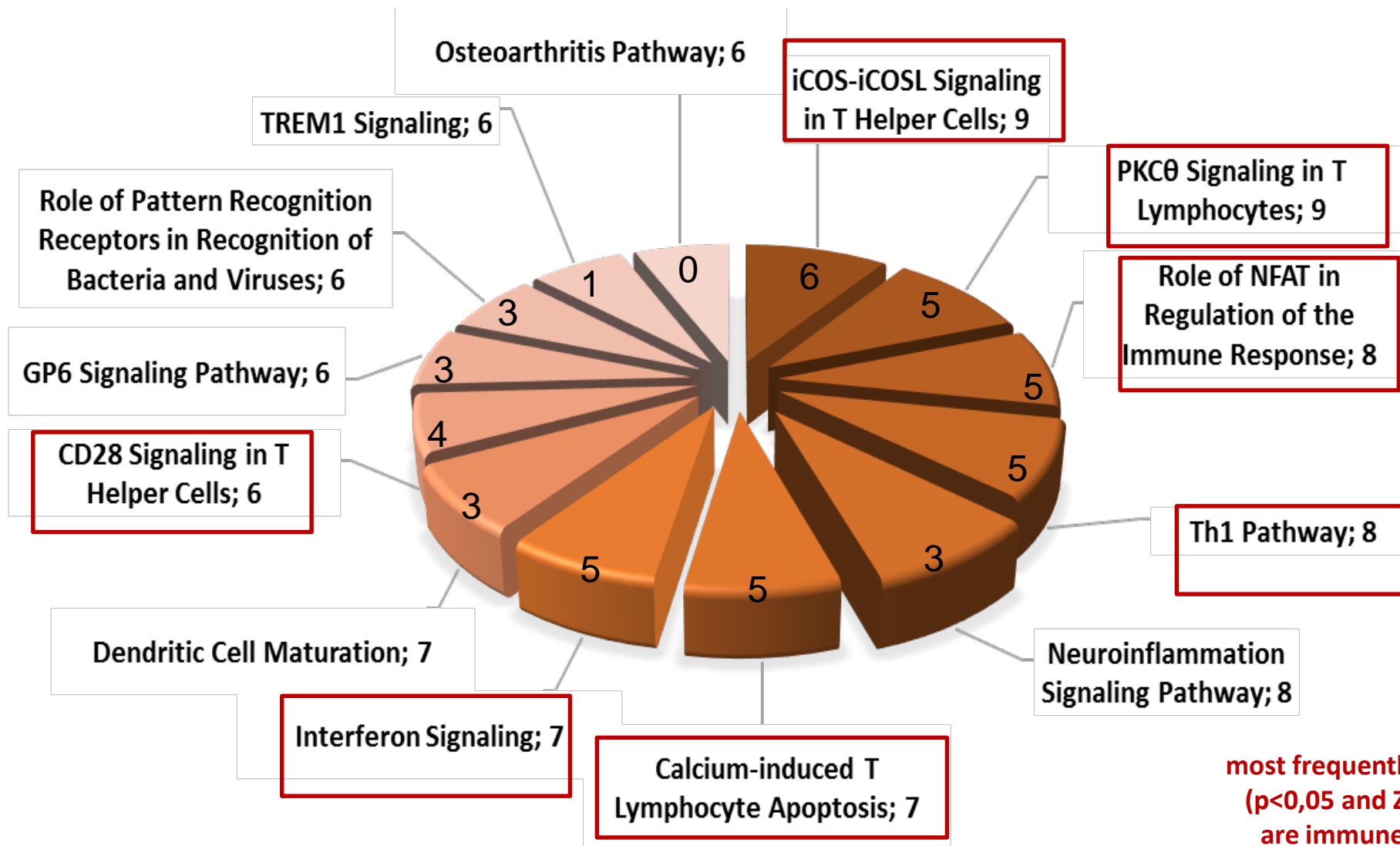
# Differentially expressed pathways most frequently modulated at W4 and/or W12 vs. baseline

DEG  
W4 vs baseline  
W12 vs baseline

baseline  
Median 2454  
(49,4% up)

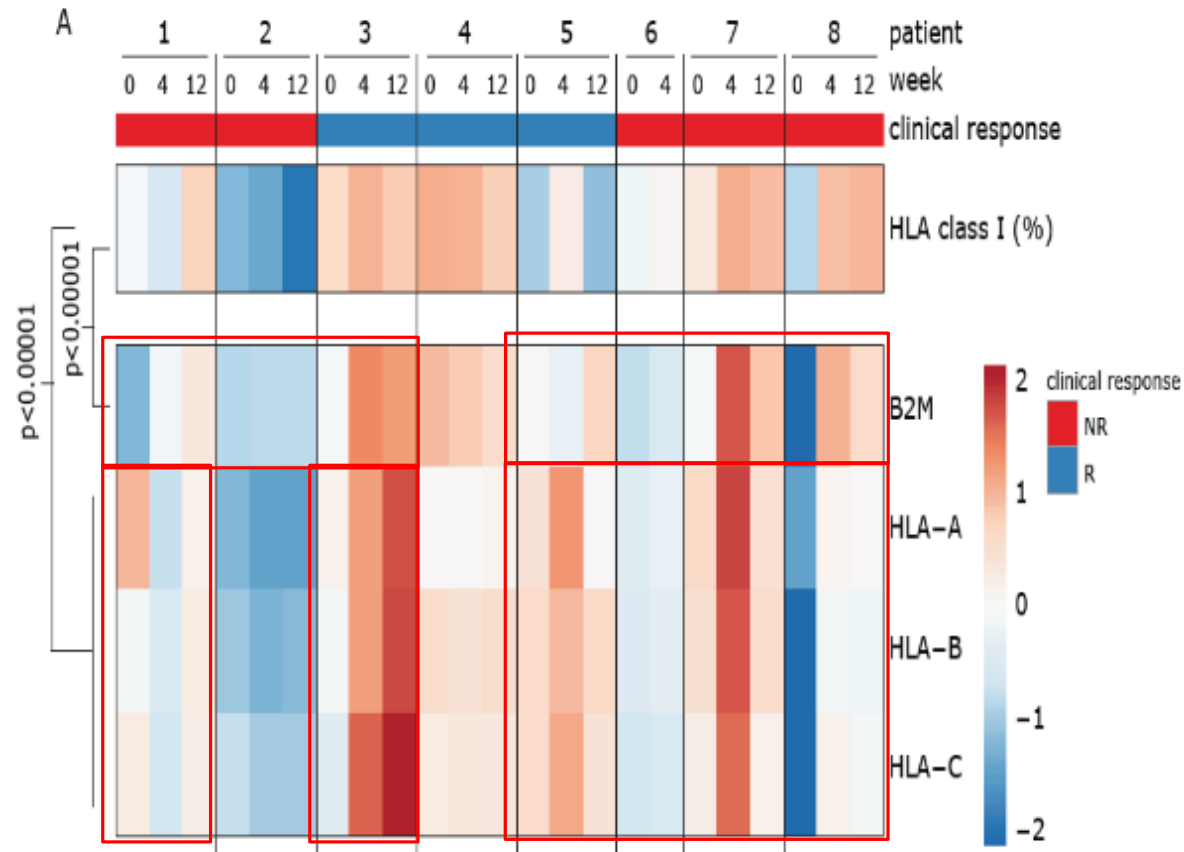
W4  
Median 4131  
(53,9% up)

W12



most frequently activated  
( $p < 0,05$  and  $Z \text{ score} \geq 2$ )  
are immune-related

# HLA class I expression in NIBIT-M4 tumor samples



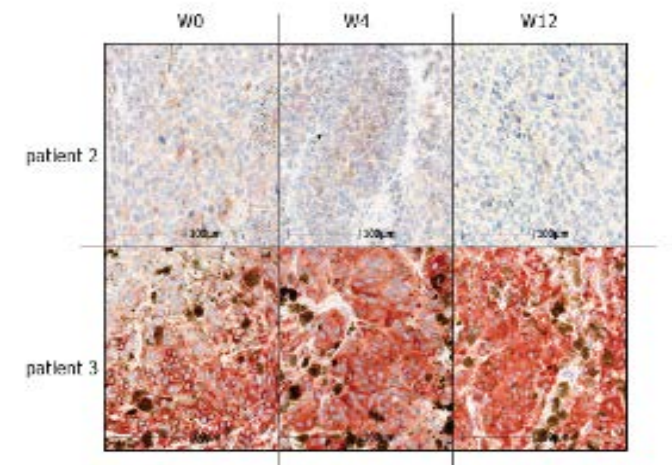
up-regulation of HLA-A, HLA-B and HLA-C in 6/8 (75%) patients

up-regulation of B2M in 7/8 (87,5 %) patients

HLA expression (IHC, %)

patient #	baseline	W4	W12
1	16	7	55
2	2	1	0
3	45	86	62
4	94	90	61
5	4	28	3
6	13	21	
7	31	93	77
8	4	73	82
10	8	2	21
11	17	45	11
12	41	57	NA

low (<10%) expression in 4/11 (36,4%) patients  
up-regulation in 3 out of these 4 tumors (75%)





# Modulation of tumor immune (T cells) contextures in NIBIT-M4 patients

■ No DCR  
■ DCR

■ No DCR  
■ DCR

# 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%

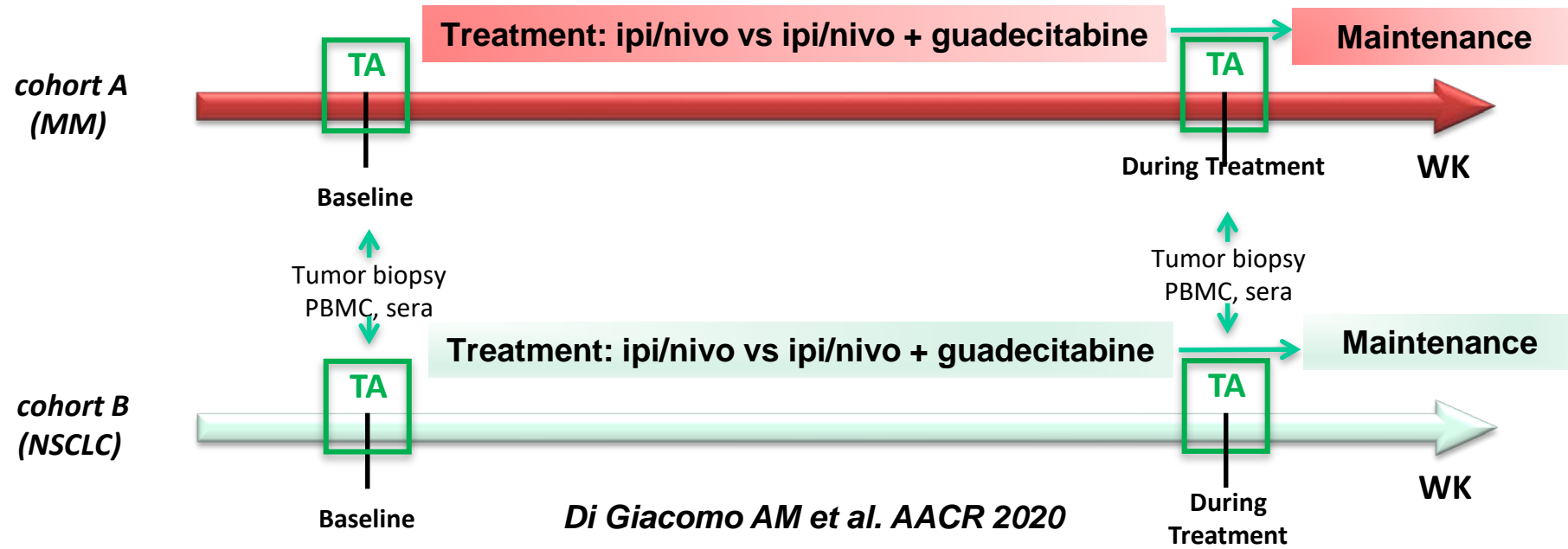
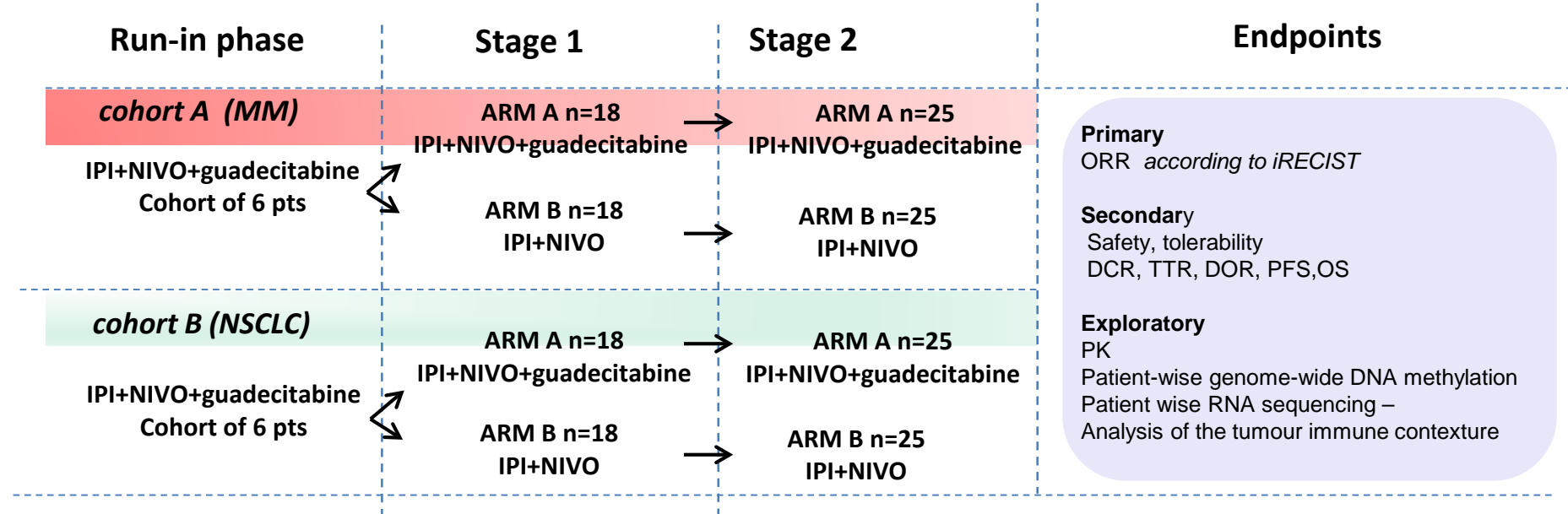
*Di Giacomo AM et al, Unpublished*

## Next question

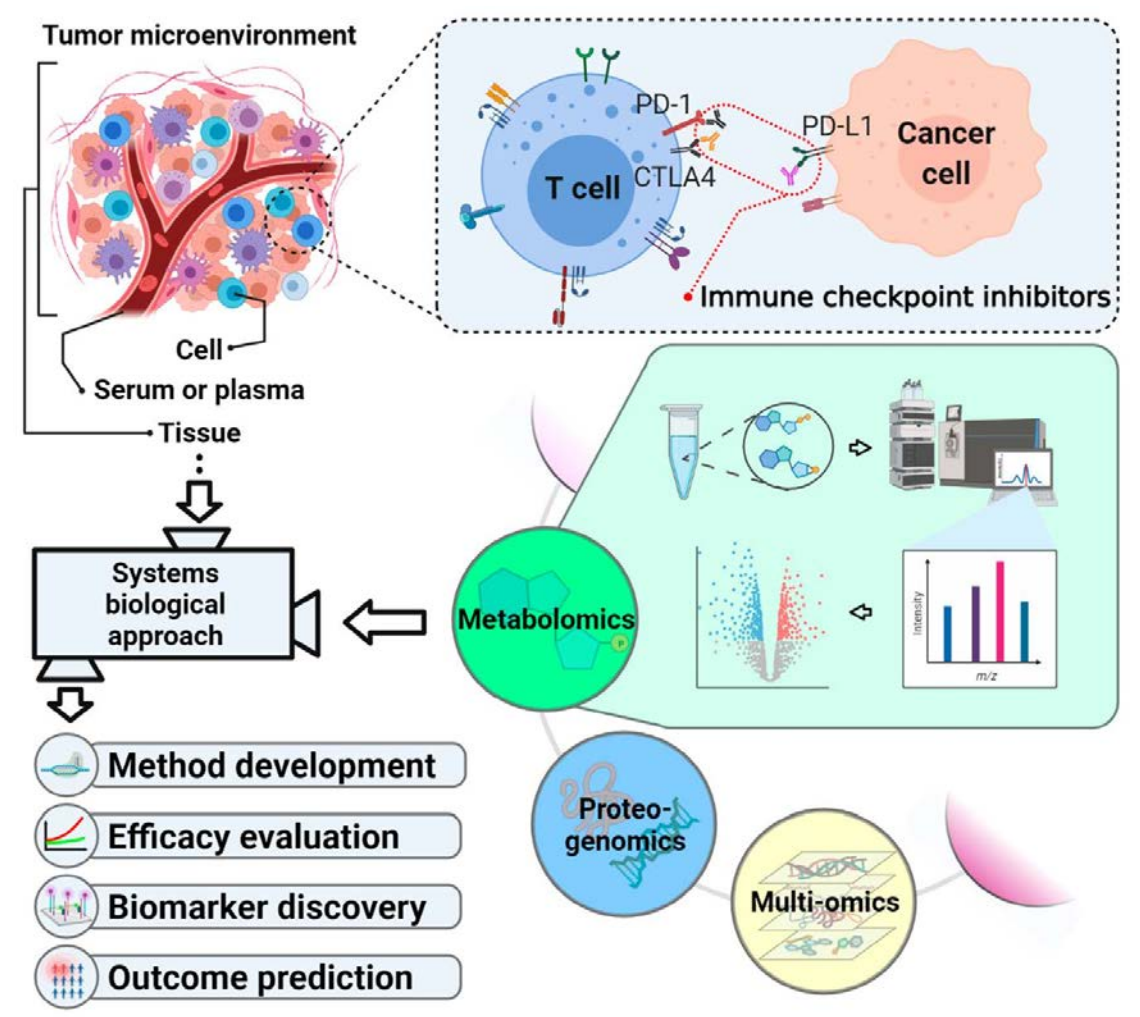
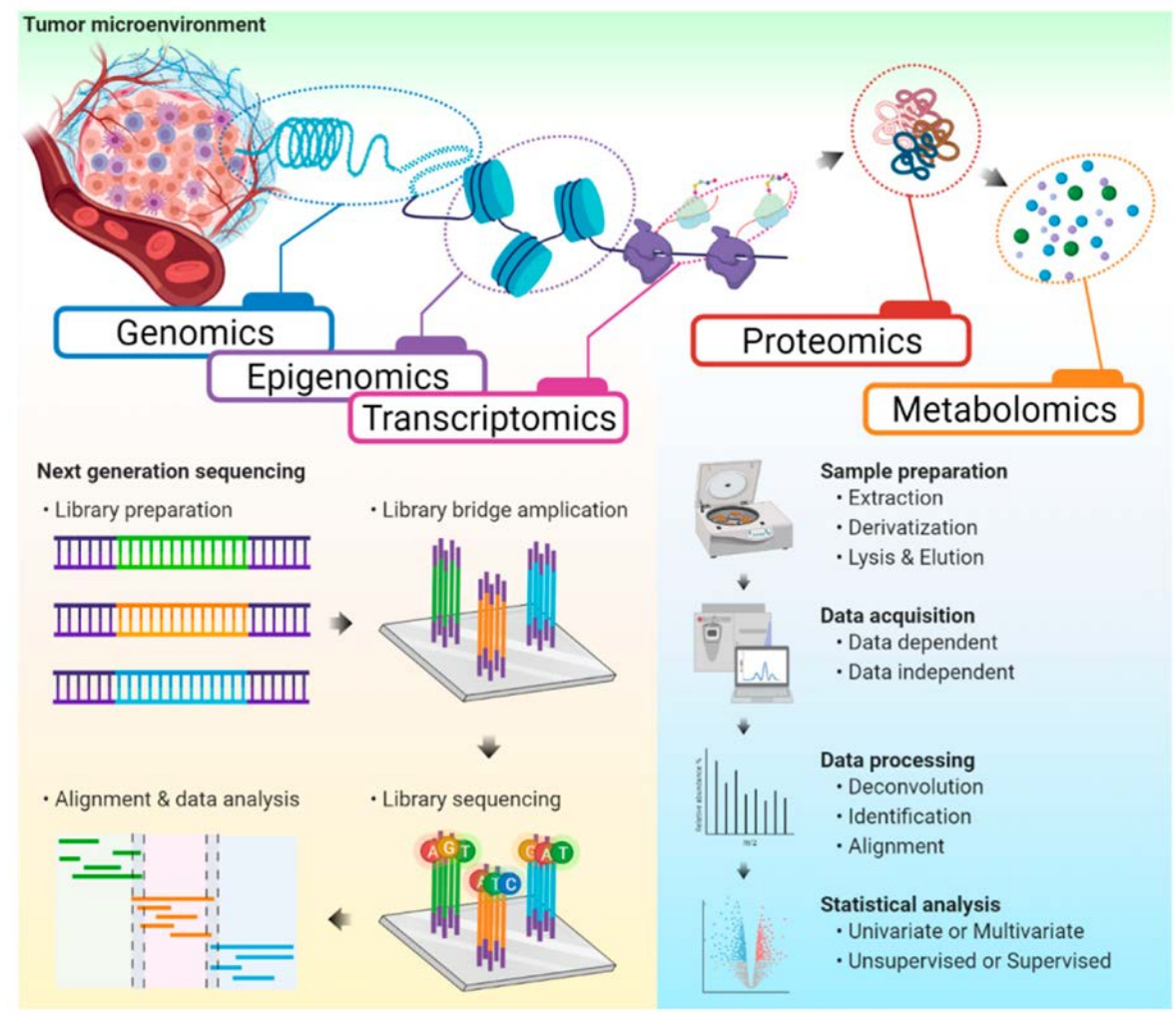
**Can epigenetic immune remodeling  
of neoplastic cells be used to  
overcome resistance to  
immunotherapy?**

# NIBIT-ML1 clinical trial: study design

EUDRACT Number:2019-002986-36



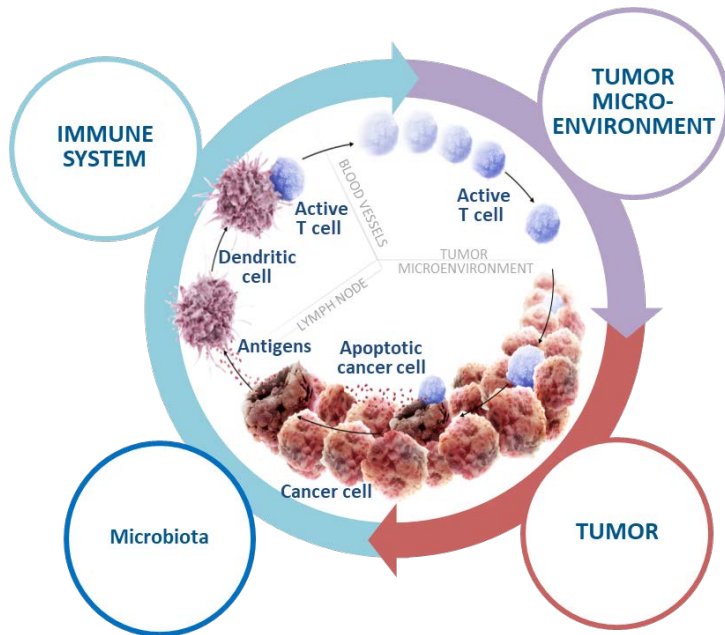
# Onco-Multi-OMICS Approach: A New Frontier in Cancer Research



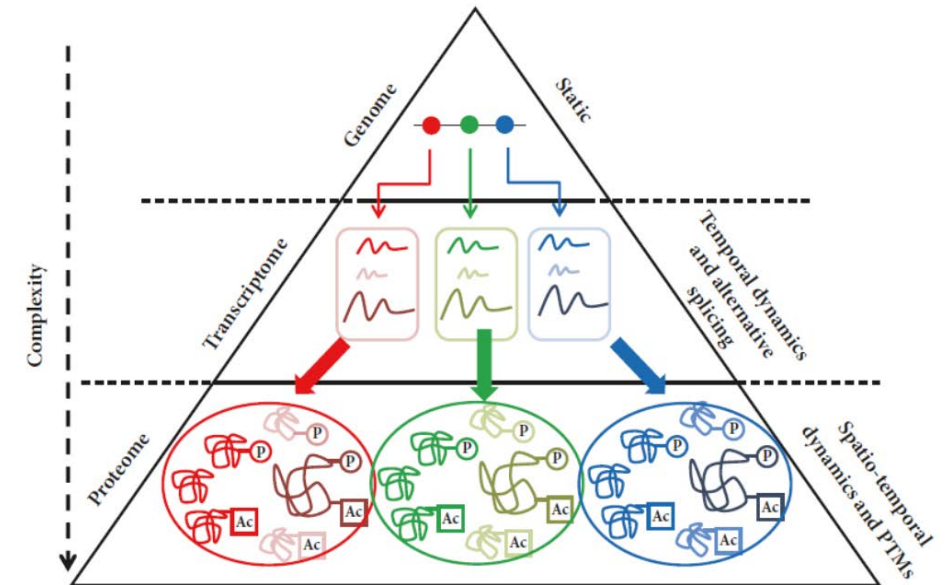


# Untangling the threads of Immunotherapy research

- Targeting and modulating multiple compartments to identify novel therapeutic strategies



- Identify biomarkers predictive of response and toxicity to improve efficacy of IO strategies





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