Society for Immunotherapy of Cancer

ADVANCES IN Cancer IMMUNOTHERAPY™

What's Next for Cancer Immunotherapy?

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AAEM AMERICAN ACADEMY OF EMERGENCY MEDICINE CHAMPION OF THE EMERGENCY PHYSICIAN

ACCC Association of Community Cancer Centers

HOPA Hematology/Oncology Pharmacy Association

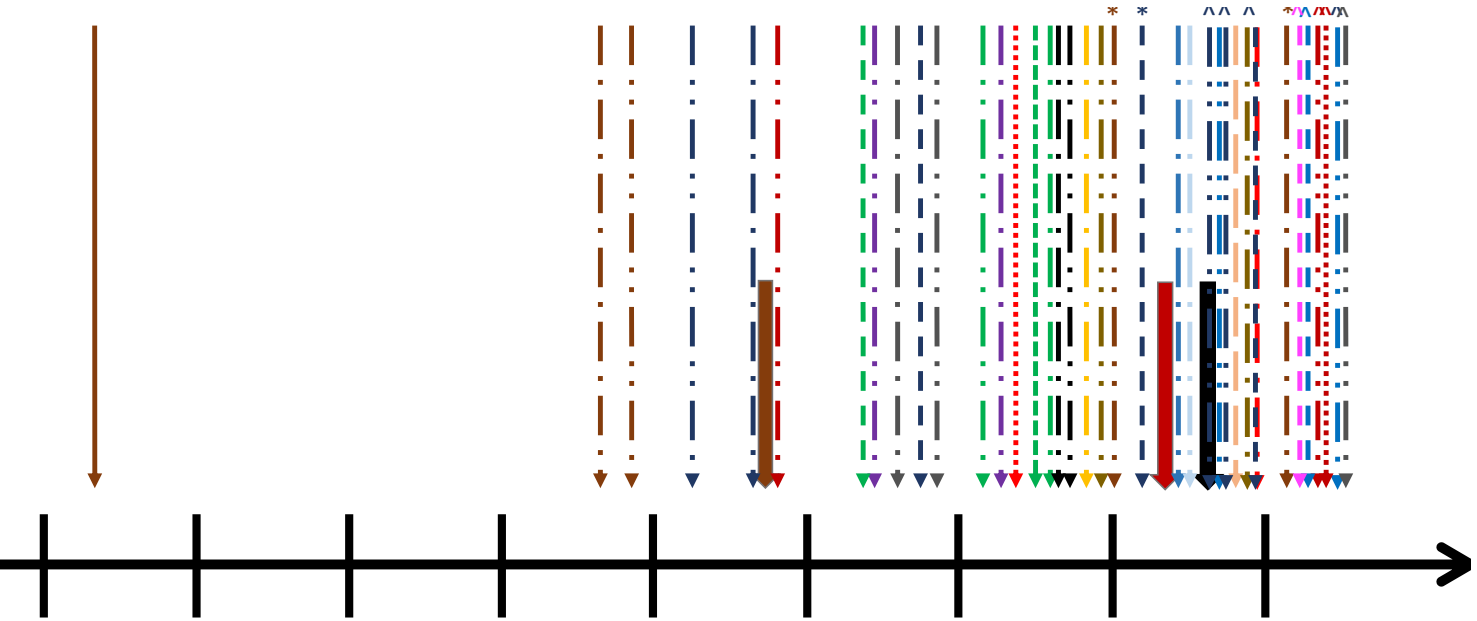
sitc Society for Immunotherapy of Cancer

Disclosures

- Consulting Fees: Asana Biosciences, Bristol Myers Squibb, Eisai, Iovance, Merck, Novartis, Pfizer, Replimune
- Contracted Research: Merck, Amgen
- I will be discussing non-FDA approved indications during my presentation.

I am biased by experience to checkpoint inhibitors, cytokines, and all things related melanoma

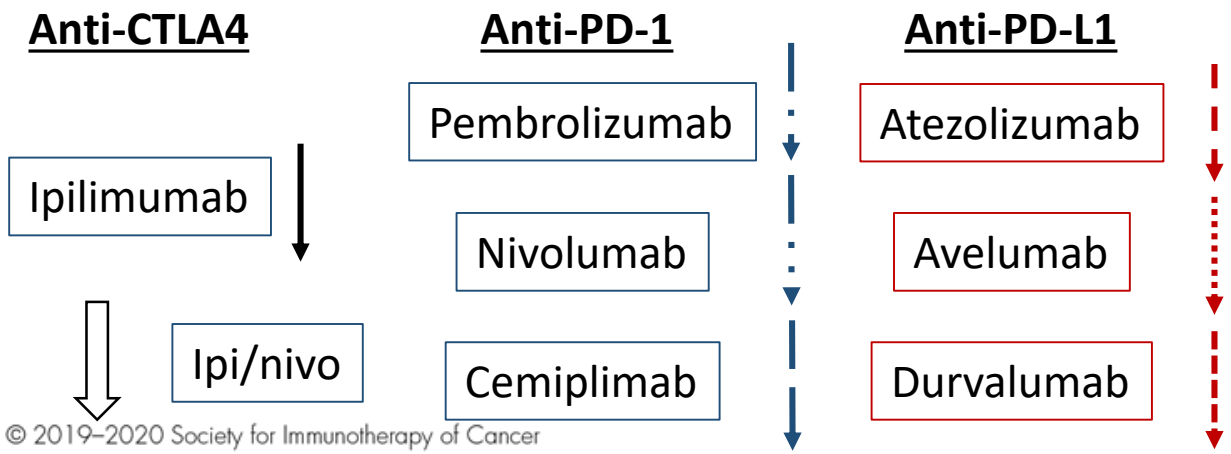
Immune checkpoint inhibitors and US FDA approvals



*Adjuvant; ^combo

Melanoma
NSCLC
Renal Cell Carcinoma
Urothelial Bladder Cancer
Hodgkin Lymphoma
Head and Neck Squamous Cell Carcinoma
Merkel Cell Carcinoma
Esophageal
Endometrial

MSI Cancers
Gastric Cancer
Hepatocellular Carcinoma
Primary mediastinal BCL
Cervical SCC
Small cell lung cancer
Cutaneous SCC (cuSCC)
Triple neg breast cancer
TMB high
Colorectal cancer



Year	Drugs	Approvals	Diseases	Combos
2011	1	1	1	
2014	2	2	1	
2015	3	4	3	1
2016	3	5	4	
2017	4	10	7	
2018	5	12	10	5
2019	4	7	5	6

Rise of combination therapies

Year	Drugs	Approvals	Diseases	Combos
2011	1	1	1	
2014	2	2	1	
2015	3	4	3	1
2016	3	5	4	
2017	4	10	7	
2018	5	12	10	5
2019	4	7	5	6
2020	6	8	8	3

PD-1/PD-L1 plus:

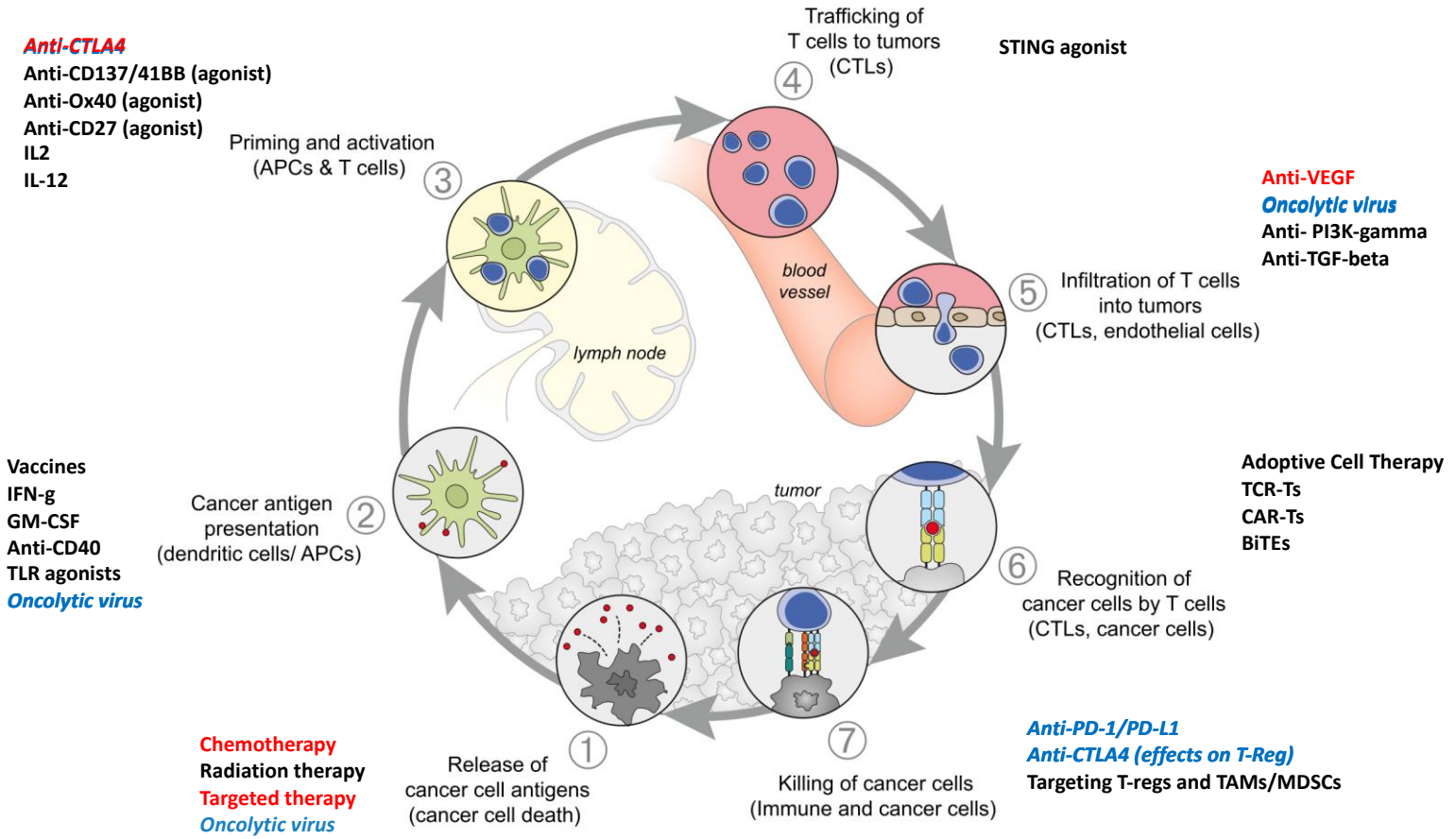
- **Ipilimumab**
  - **anti-CTLA-4 mAb**
- **Cytotoxic chemotherapy**
- **Bevacizumab**
  - **anti-VEGF mAb**
- **Axitinib**
  - **targets VEGFR 1-3**
- **Lenvatinib**
  - **targets VEGF 1-3, FGFR 1-4, PDGF alpha, KIT, RET**
- **Vemurafenib and cobimetinib**
  - **Targets BRAF and MEK**

Where do we go from here?

More combinations

Phase 3 trials (melanoma)

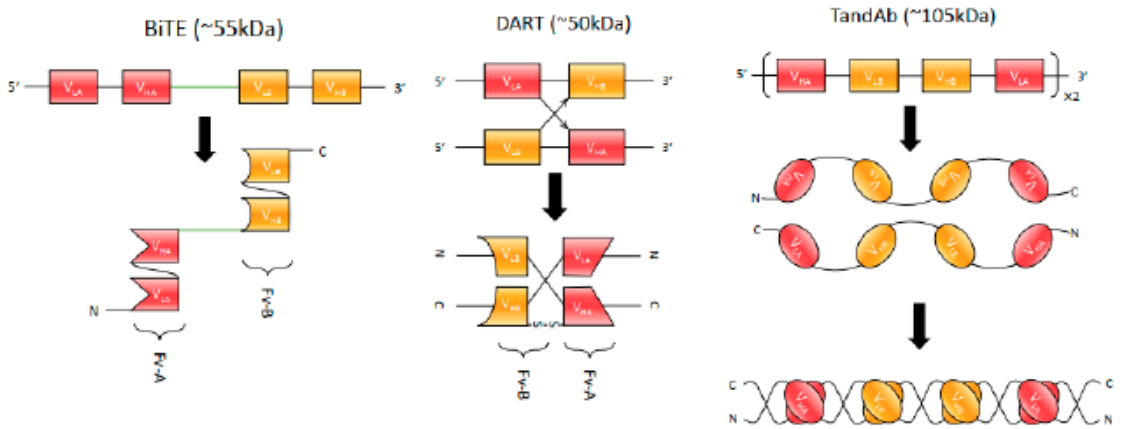
- Anti-PD-1/PD-L1 +
  - BRAFi/MEKi
  - Oncolytic virus
  - GM-CSF
  - Anti-LAG-3
  - Peg-IL-2
- Anti-CTLA-4 +
  - TLR agonist



Modified from Chen and Melman, Immunity 2015

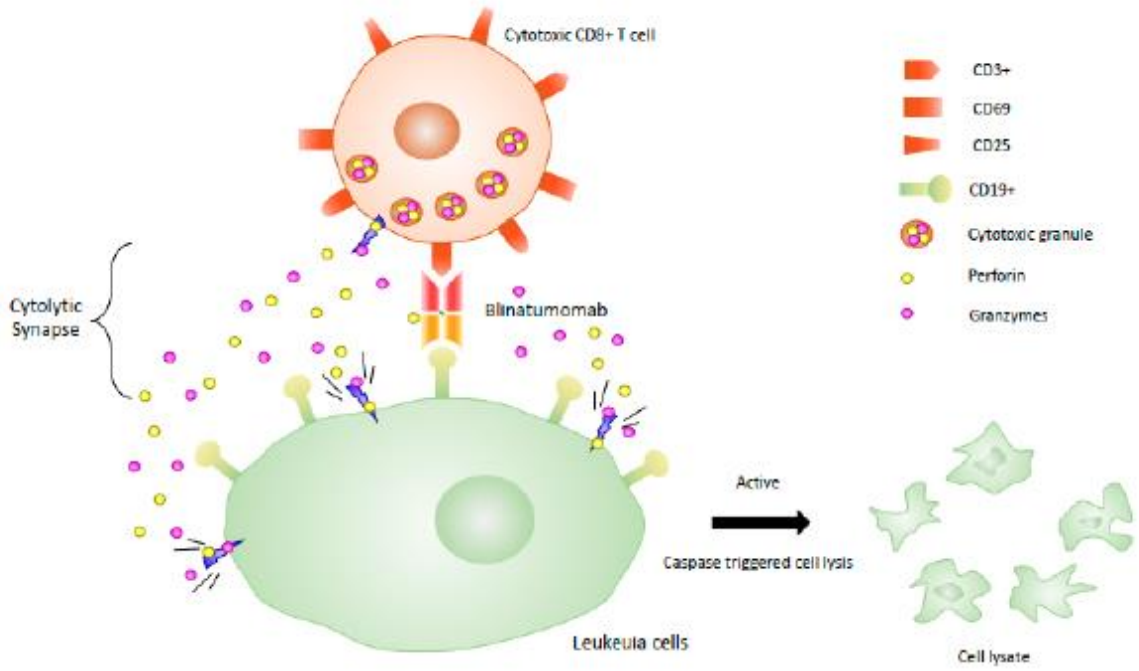
What about new targets/approaches?

- New constructs
  - Bi-specific T cell engagers (BiTE)
  - Dual affinity re-targeting proteins (DART)
  - Tandam diabodies (TandAbs)
  - ImmTAC (immune mobilizing monoclonal T-cell receptors against cancer)

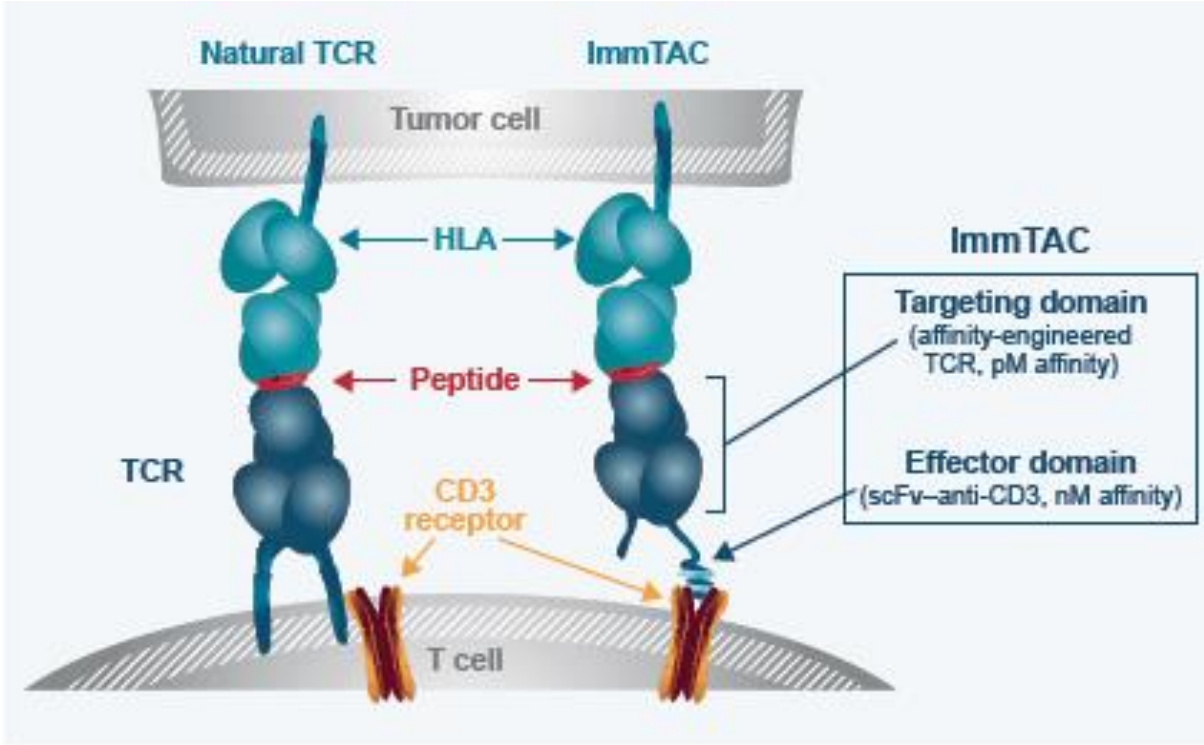


Wang et al. Antibodies 2019

New constructs



Blinatumumab – anti-CD-19, CD3 engager

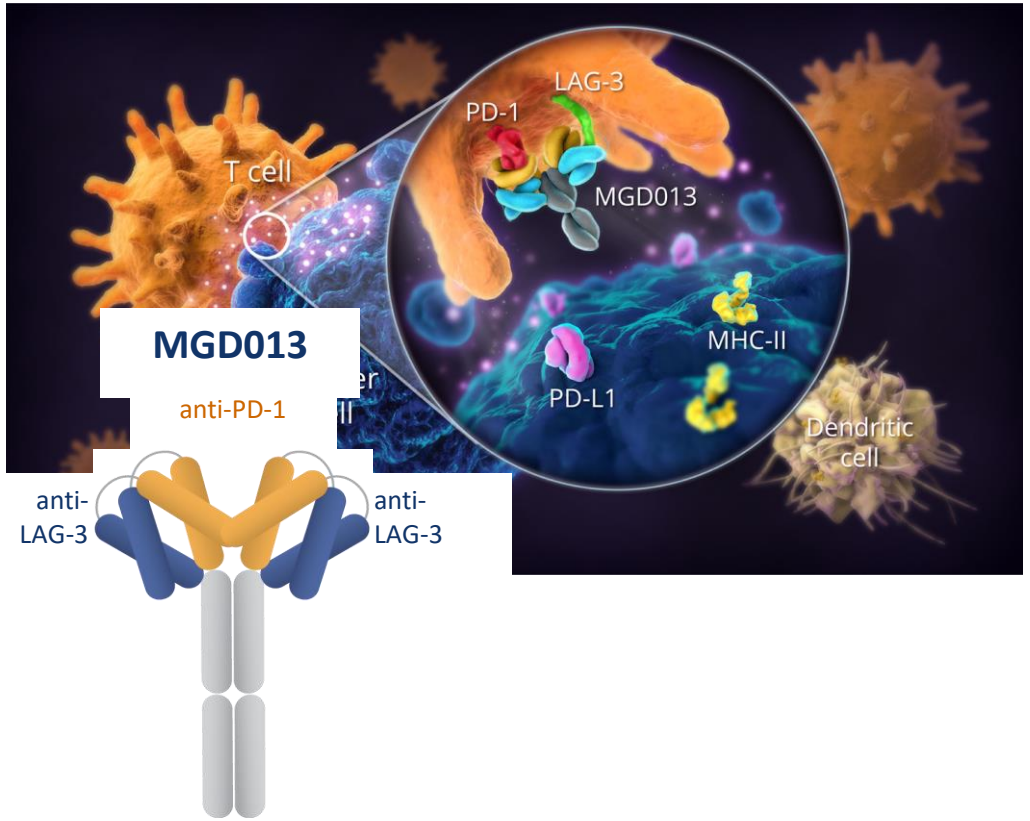


Tebentafusp – anti-gp-100, CD3 engager

Wang et al. Antibodies 2019
Middleton et al. SMR 2019

New constructs, known targets

- PD-1 and LAG-3 receptors are expressed on “exhausted” T-cells
  - Interactions with corresponding ligands negates anti-tumor T cell activity
- Synergy of anti-PD-1 + anti-LAG-3 mAbs in animal tumor models
  - Combination trials of anti-PD-1 plus anti-LAG-3 are ongoing
- MGD013, an investigational DART protein, targets PD-1 and LAG-3 with a single molecule
  - Greater synergistic T-cell activation (IFN-γ) with MGD013 compared with combination of individual constituents
- DART bispecific platform:
  - Stable diabody format
  - Multiple configurations & applications

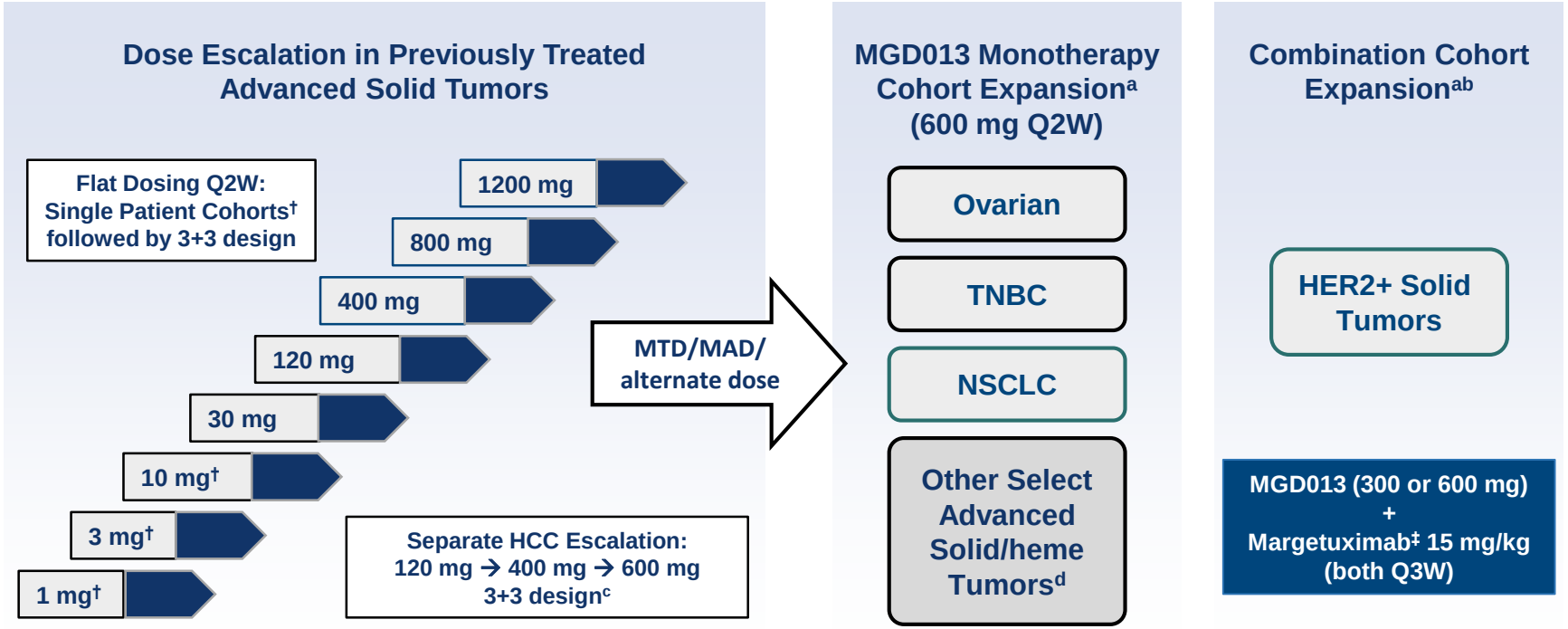


PD-1 × LAG-3
Tetravalent Bispecific DART Molecule

Luke et al. ASCO 2020

MGD013: Phase I Trial Design

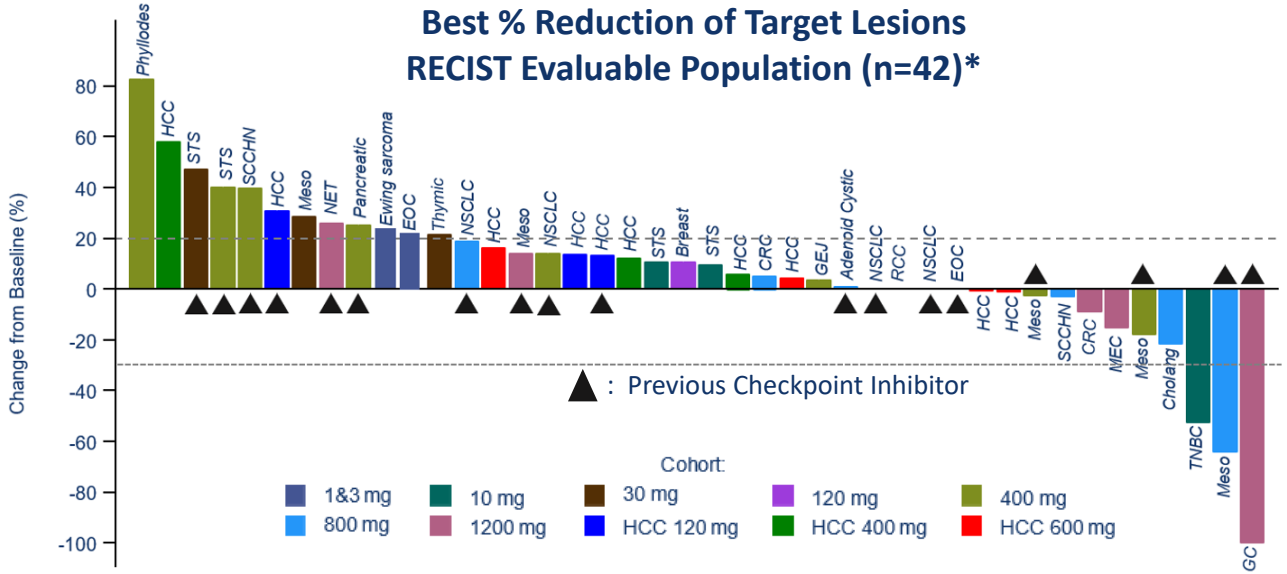
- **Primary objectives:**
  - Safety, tolerability
  - DLTs, MTD, MAD
  - Alternate dose
- **Secondary objectives:**
  - Pharmacokinetics
  - Immunogenicity
  - Preliminary activity
- **Exploratory PD objectives:**
  - Receptor/ligand expression
  - Serum biomarkers
  - Gene expression profiling



Luke et al. ASCO 2020

MGD013: Dose escalation results

Best % Reduction of Target Lesions
RECIST Evaluable Population (n=42)*



* Based on patients with baseline and post-treatment tumor measurements. Data cutoff: April, 25, 2020

Immune-Related Adverse Events of Special Interest (AESIs)

	No. (%) of Patients	
	All Grades (N=53)	≥ Grade 3 (N=53)
Rash	7 (13.2)	1 (1.9)
Hypothyroidism	6 (11.3)	0
Immune-mediated hepatitis	2 (3.8)	2 (3.8)
Pancreatitis	1 (1.9)	1 (1.9)
Colitis	1 (1.9)	1 (1.9)
Adrenal insufficiency	1 (1.9)	1 (1.9)
Hyperthyroidism	1 (1.9)	0

Confirmed Partial Responses (n=1, each):

- TNBC (10 mg)
- Mesothelioma (800 mg)
- Gastric Cancer (1200 mg)

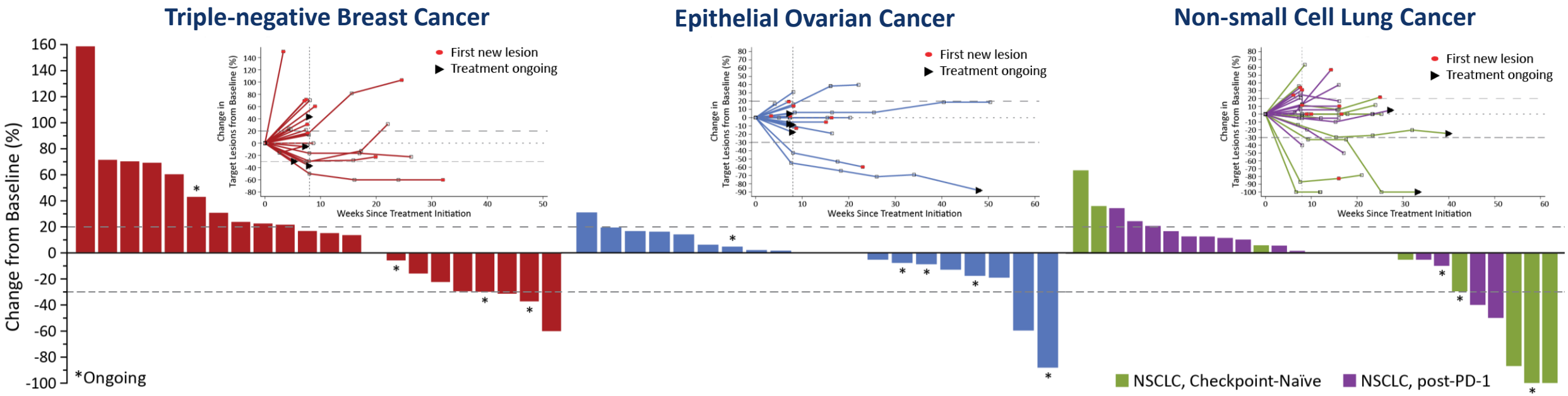
Refractory to anti-PD-1 treatment

- 18 patients with SD as best overall response (DCR = 48.8%)

- Well-tolerated with manageable irAEs
- Safety consistent with anti-PD-(L)1 toxicity profile
- MTD not exceeded or defined at up to 1200 mg Q2W
- Dose limiting toxicities:
  - Immune-mediated hepatitis (1200 mg – primary dose escalation); resolved without sequelae
  - Lipase increase with radiographic evidence of pancreatitis (600 mg – HCC escalation); dose level subsequently cleared

Luke et al. ASCO 2020

MGD013: Dose expansion results



	TNBC	EOC	NSCLC, CPI-Naïve	NSCLC, post-PD-1
Evaluable Patients	23	23	14	15
ORR (Confirmed)	4.3% (1/23)	8.7% (2/23)	14.3% (2/14)	0% (0/15)
ORR (Confirmed + Unconfirmed)	17.4% (4/23)	8.7% (2/23)	21.4% (3/14)	13.3% (2/15)
SD	34.8% (8/23)	43.5% (10/23)	50.0% (7/14)	53.3% (8/15)
DCR	39.1% (9/23)	52.2% (12/23)	64.3% (9/14)	53.3% (8/15)

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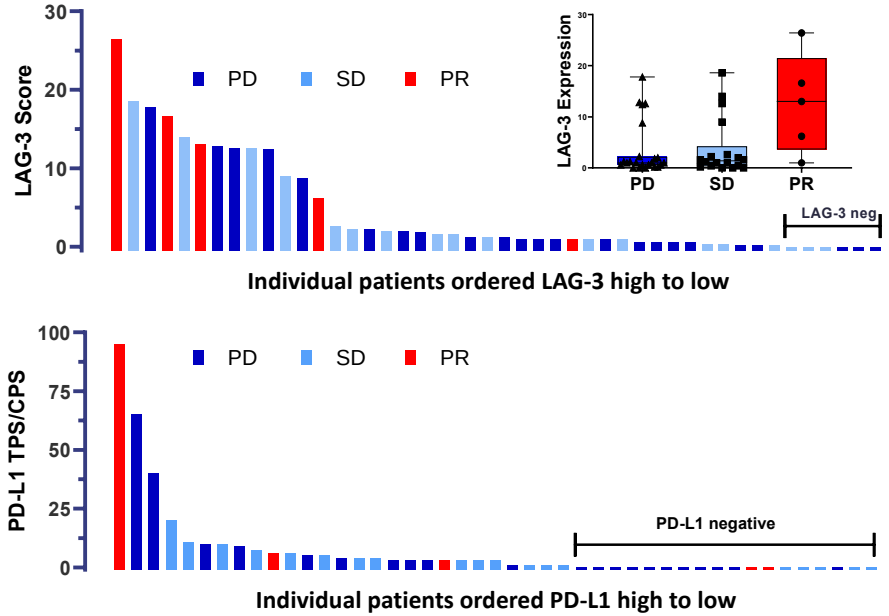
MGD013: Biomarker analysis

Objective Responses Associated with LAG-3 Expression

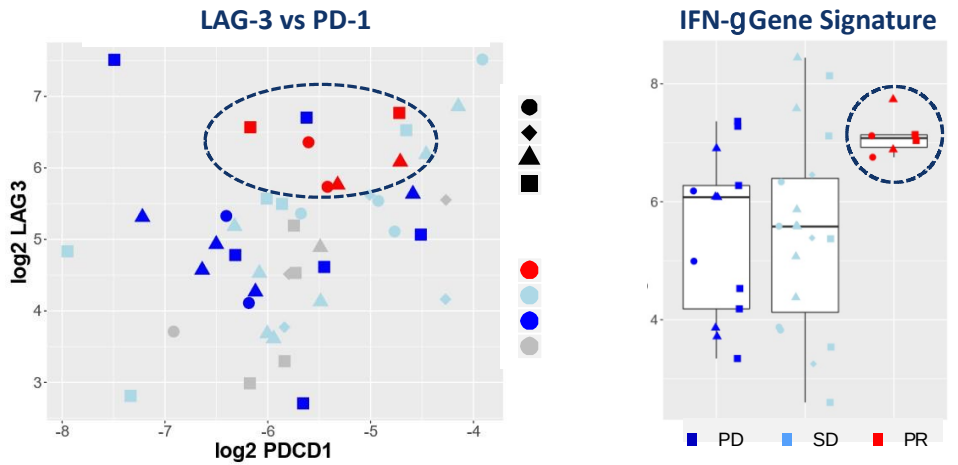
Inflammatory interferon-γ signature elevated in patients with clinical response

Retrospective IHC Analyses



Archival biopsies from TNBC, EOC, and NSCLC expansion cohorts analyzed for LAG-3 (N=46) or PD-L1 (N = 45) by IHC. LAG-3 score was determined by calculating mean value of LAG-3+ cells per 40x field across 5 LAG-3+ hot spots (Chen et al., e15086 ASCO 2020). PD-L1 expression was determined per Agilent PD-L1 (22C3) pharmDx kit; TPS (NSCLC) was calculated as per interpretation manual and CPS (EOC, TNBC) calculated as follows: number of PD-L1 + cells (tumor and immune)/total number of viable tumor cells x 100. CPS <1 or TPS <1% was considered negative.

Transcript Profiling (Baseline Tumor Biopsy)



Objective responses associated with high baseline LAG-3/PD-1 expression and IFN-γ gene signature (CXCL9, CXCL10, CXC11, STAT1)

The NanoString PanCancer IO 360™ assay was used to interrogate gene expression, including the abundance of 14 immune cell types and 32 immuno-oncology signatures from archival biopsies from EOC (N= 14) NSCLC (N= 25) and TNBC (N=13) expansion cohorts

Luke et al. ASCO 2020

MGD013: Summary

First-in-class bispecific checkpoint inhibitor

- Designed to independently or coordinately block PD-1 and LAG-3
- Well tolerated at doses up to 1200 mg Q2W
- RP2D: 600 mg Q2W or Q3W
- Safety profile consistent with anti-PD-1 monotherapy

Encouraging monotherapy activity in multiple tumor types

- Baseline LAG-3 expression & IFN-γ signature associated with objective response

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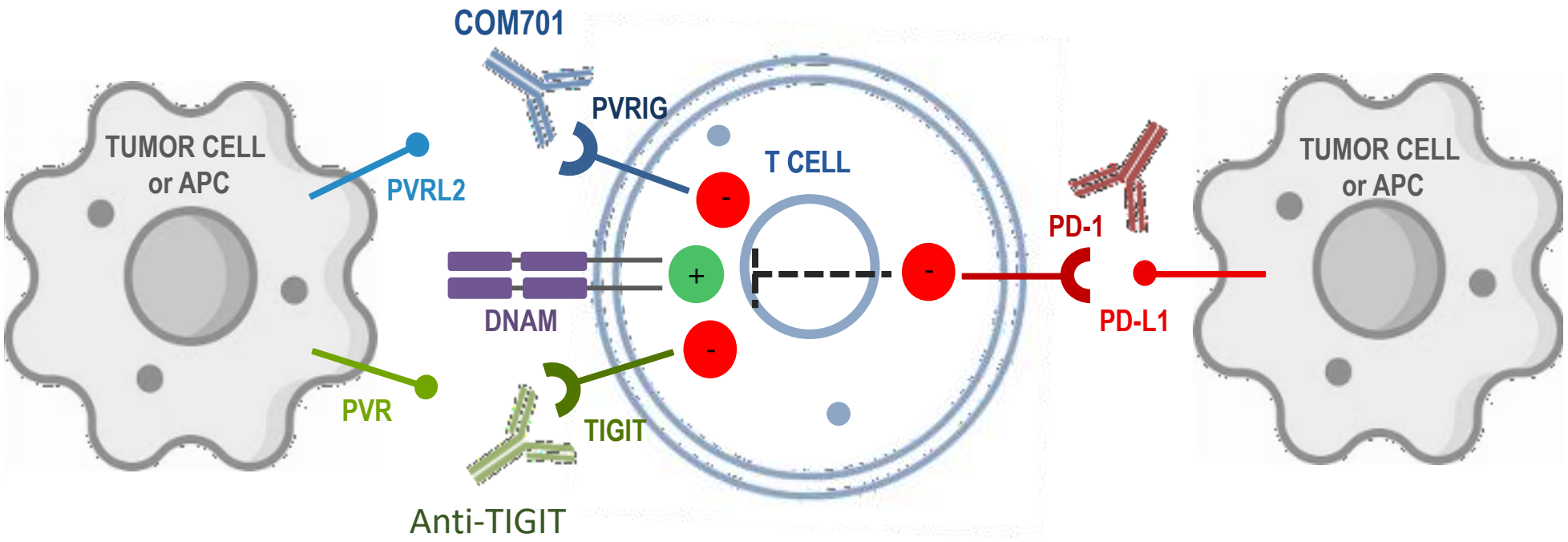
New Targets

PVRIG PATHWAY IN THE DNAM AXIS



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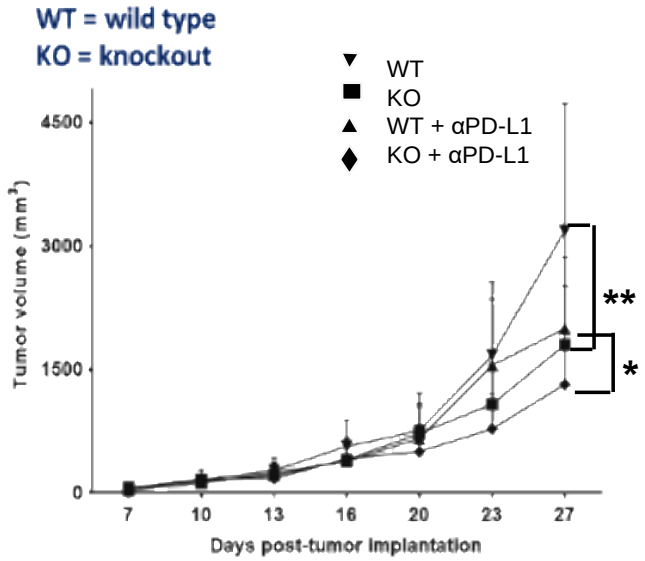
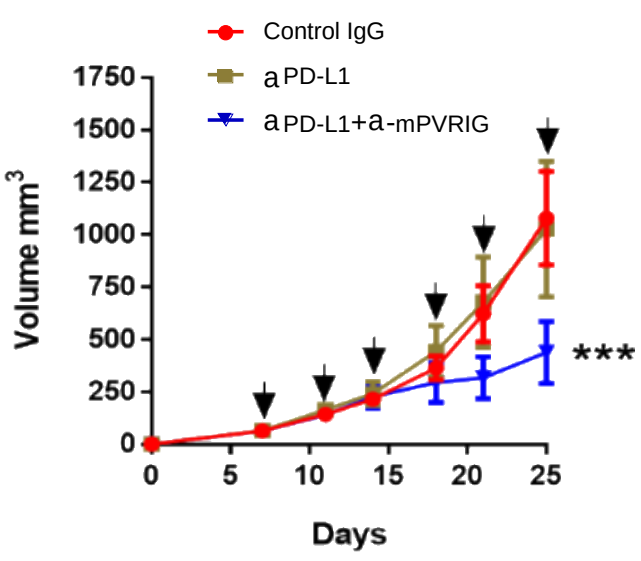
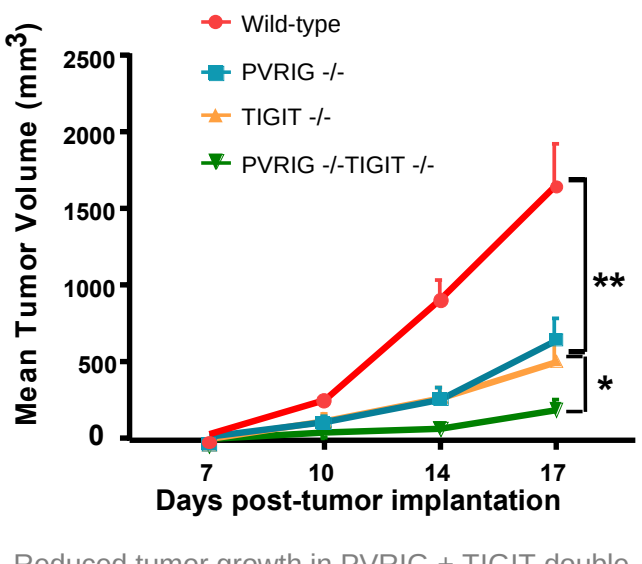
PVRIG KO/inhibition is associated with reduced tumor growth



Reduced tumor growth in KO mice



Synergistic tumor growth inhibition with anti-PD-L1



Reduced tumor growth in PVRIG + TIGIT double KO mice

Ganguly and Pardoll, Johns Hopkins Univ. MC38 model

SITC, November 2016, Hunter, *et al.*, oral presentation
SITC, November 2019, Logronio, *et al.*, poster presentation

PD-1/PD-L1 resistant models

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COM701 (anti-PVRIG): Phase 1 design

PHASE 1 (Identifier: NCT03667716)

Arm A

Monotherapy Dose Escalation	Monotherapy Cohort Expansion (20 patients; progressed on SOC)
All-comers (progressed on SOC)	NSCLC, Ovarian, Breast, Endometrial, Colorectal

Arm B

Dual Combination
Escalating doses of COM701 with fixed dose of nivolumab (Up to 20 patients)

All-comers (progressed on SOC)

Study Objectives

- Safety & Tolerability
- PK/PD
- Clinical activity – COM701 monotherapy and in combination

Response Assessment

CT Imaging Q6 or Q8 wks as per schedule of study drugs

Responses per Investigator assessment – RECIST v1.1

PHASE 1/2 (in development)

Triple Combination Dose Escalation
Escalating doses of COM701 with fixed doses of nivolumab + BMS-986207

All-comers (progressed on SOC); expected initiation in 2H 2020

Triple Combination
Cohort Expansion

Ovarian, Endometrial, additional tumor types with high PVRL2 expression

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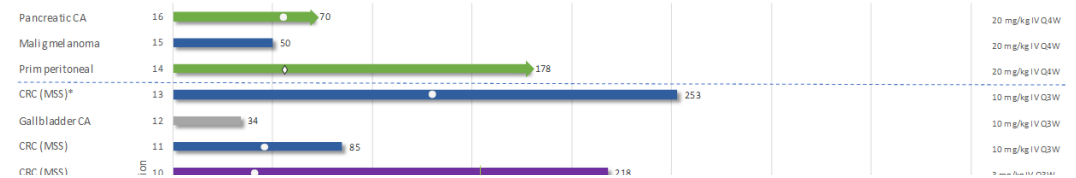
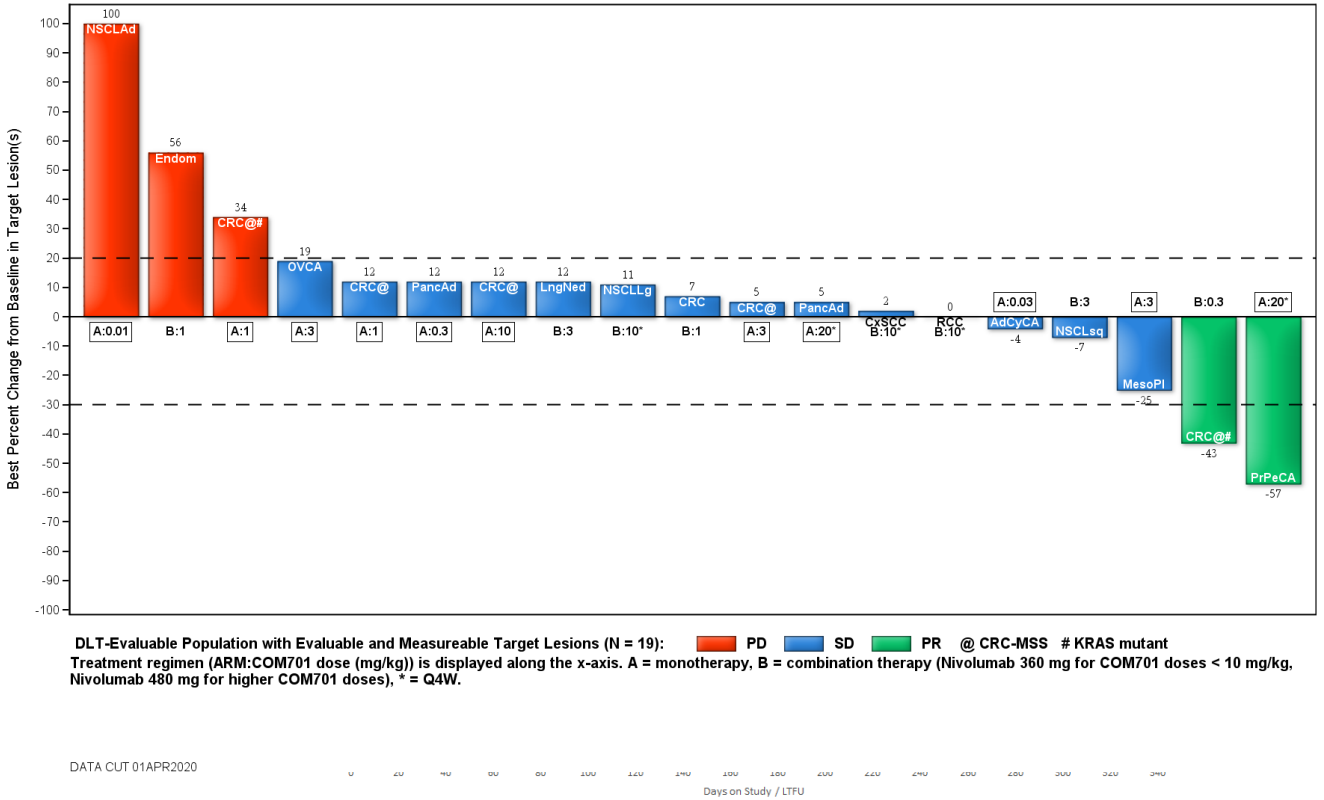
COM701: Results

	Arm A (N = 16) N (%)	Arm B (N = 12) N (%)
ORR (CR+PR)	1 (6)	1 (8)
Disease control rate (CR+PR+SD)	11 (69)	9 (75)
Durable SD (SD ≥ 6 months)	2 (13)	4 (33)
Best response		
CR	0	0
PR	1 (6)*	1 (8)#
SD	10 (63	8 (67)
PD	4 (25)	2 (17)
NA	1 (6)	1 (8)





*63 yo F with MSS platinum-resistant PPSC
66 yo M with MSS CRC

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COM701: Summary

- COM701 well tolerated and with a manageable safety profile as monotherapy and in combination with nivolumab
  - No increase in toxicity in combination with nivolumab
  - No subjects discontinued study treatment due to toxicity of any study drug

- Confirmed partial responses in 2 pts
  - COM701 monotherapy 20 mg/kg IV Q4 wks - primary peritoneal cancer (ongoing on study treatment 25 wks)
  - COM701 (COM701 0.3 mg/kg IV Q3 wks) + Nivolumab (480 mg IV Q3 wks) - MSS-CRC (ongoing on study treatment 44 wks)

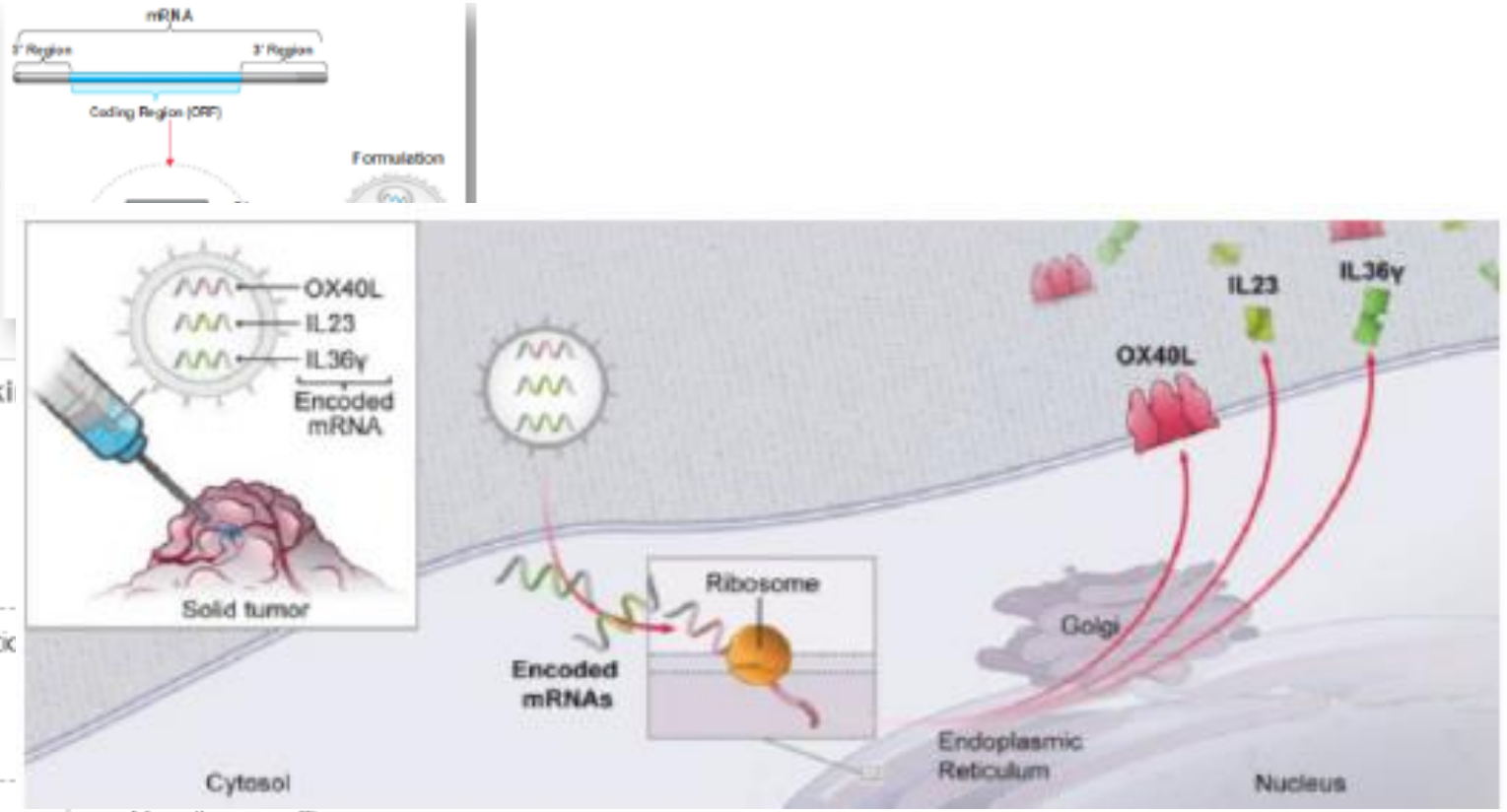
- Disease control rate (COM701 monotherapy 11/16 [69%]; COM701+nivolumab 9/12 [75%]) in diverse tumor types
  - Durable stable disease (SD ≥ 6 months) in 6/28 pts [Arm A: 2 pts, Arm B: 4 pts]
    - Arm A: Adenoid cystic CA, CRC-MSS
    - Arm B: Anal SCC, CRC-MSS, Endometrial, NSCLC (squamous)

Sullivan et al. AACR 2020

New Targets, old approach: mRNA-2752

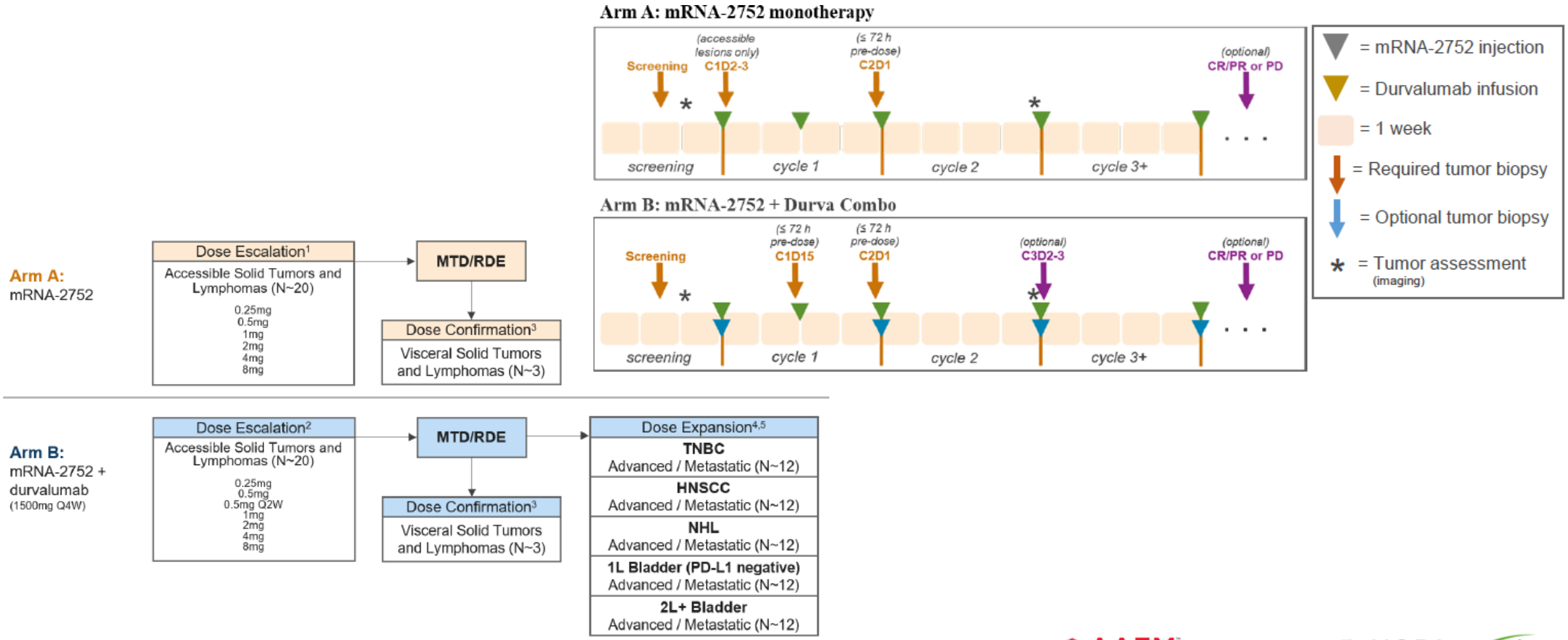
Immune modulation with OX40L/IL-23/IL-36γ

	IL-23	IL-36γ
	Proinflammatory cytokine of the IL-12 family	Proinflammatory cytoki of the IL-1 family
	• Reported to prime DC • Activates other cells that bridge innate to adaptive immunity (NKT, ILCs, γδ T cells)	• Acts on DCs to promote maturation and ↑ cytokine/chemokines
	• Expands and maintains Th17 • Acts on antigen experienced T cells	• Enhances T cell proliferatic Th1, Th9 differentiation
Rationale as IO therapeutic?	• Monotherapy efficacy established and reported (pre-clin) • Clear role in human barrier immunity and inflammatory disease	• Reported to enhance anti-cancer immunity (pre-clin) • Clear role in human barrier immunity and inflammatory disease • Monotherapy efficacy established and reported (pre-clin)



Patel et al. ASCO 2020

mRNA-2752: Phase 1/1b trial



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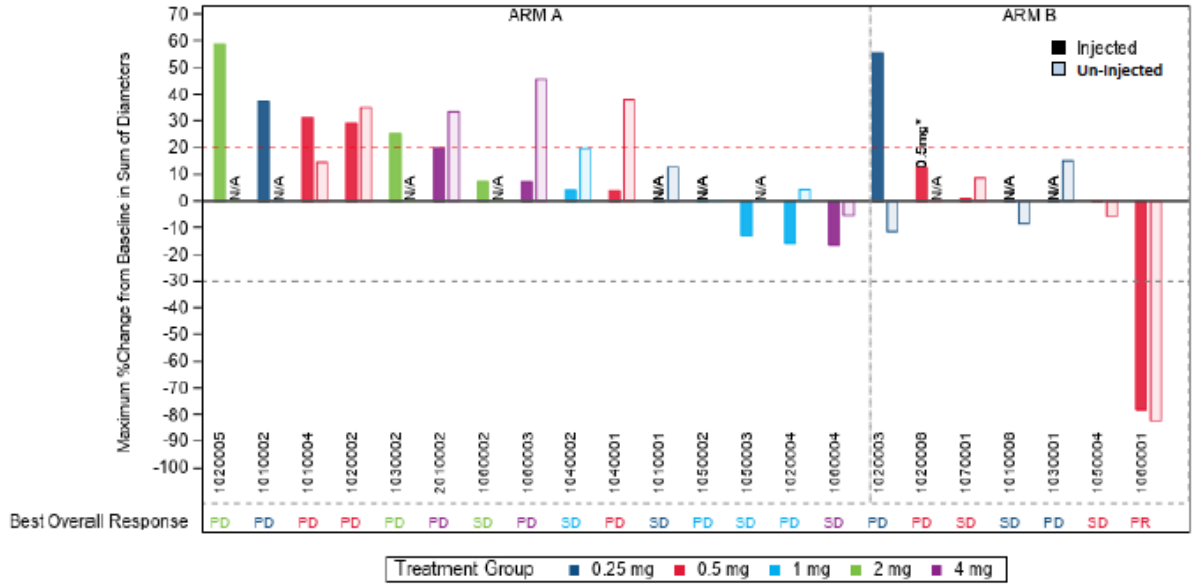
mRNA-2752: Phase 1/1b trial results

Best Response	Total
Arm A: monotherapy	N = 15
Stable Disease (SD)	5
Progression of disease (PD)	10
Arm B: combination	N = 8
Partial response (PR)	1
SD	4
PD	3



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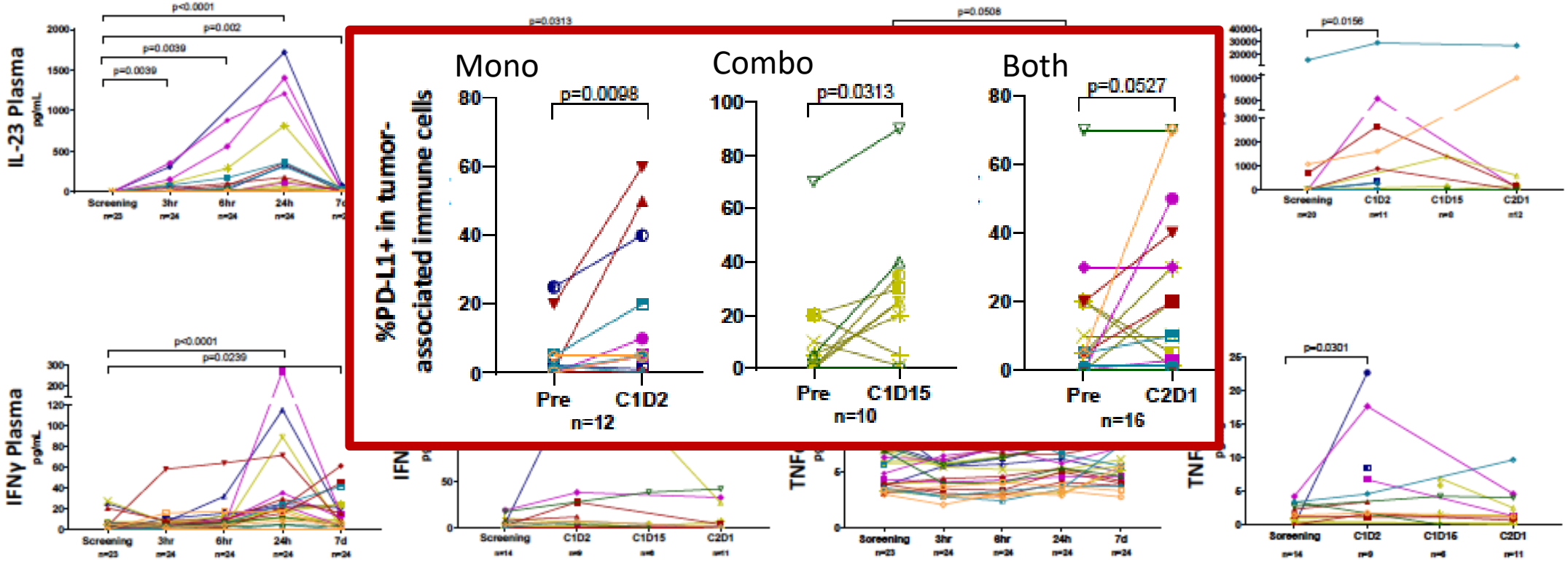
mRNA-2752 leads to increased levels of IL-23 and IL-36γ but also IFNγ, TNFa, and PD-L1



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mRNA-2752: Summary

- IT (intertumoral) mRNA-2752 is safe and well tolerated
  - Associated with injection site reactions as single-agent
  - No increase in toxicity in combination with durvalumab
- Confirmed partial responses in 1 pt on Part B (combo)
  - Patient with squamous cell carcinoma of the bladder
- IT injection is associated with increase in IL-23 and IL-23y levels, as well as activation of markers of inflammation (IFN-gamma, TNF-alpha) and PD-L1
- Dose escalation continues with combination therapy, dose expansion planned for TNBC, HNSCC, NHL, 1L and 2L Bladder cancer

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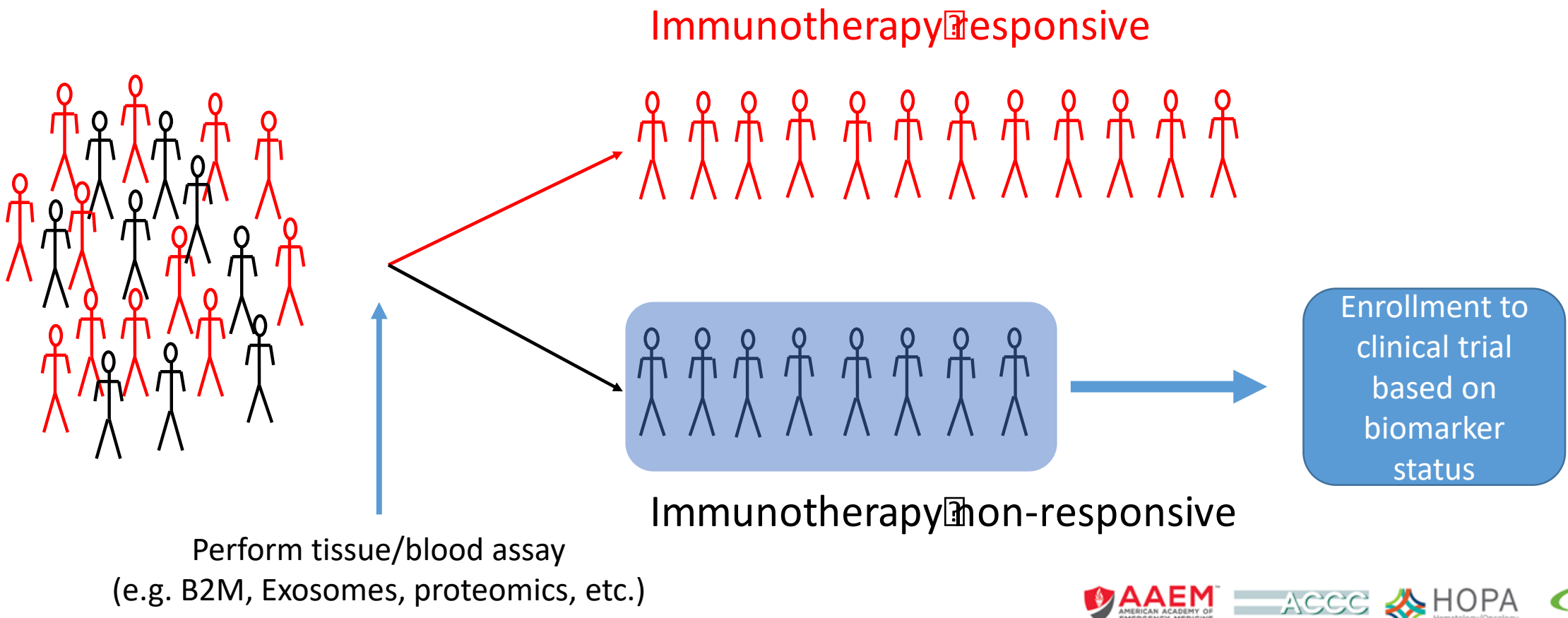
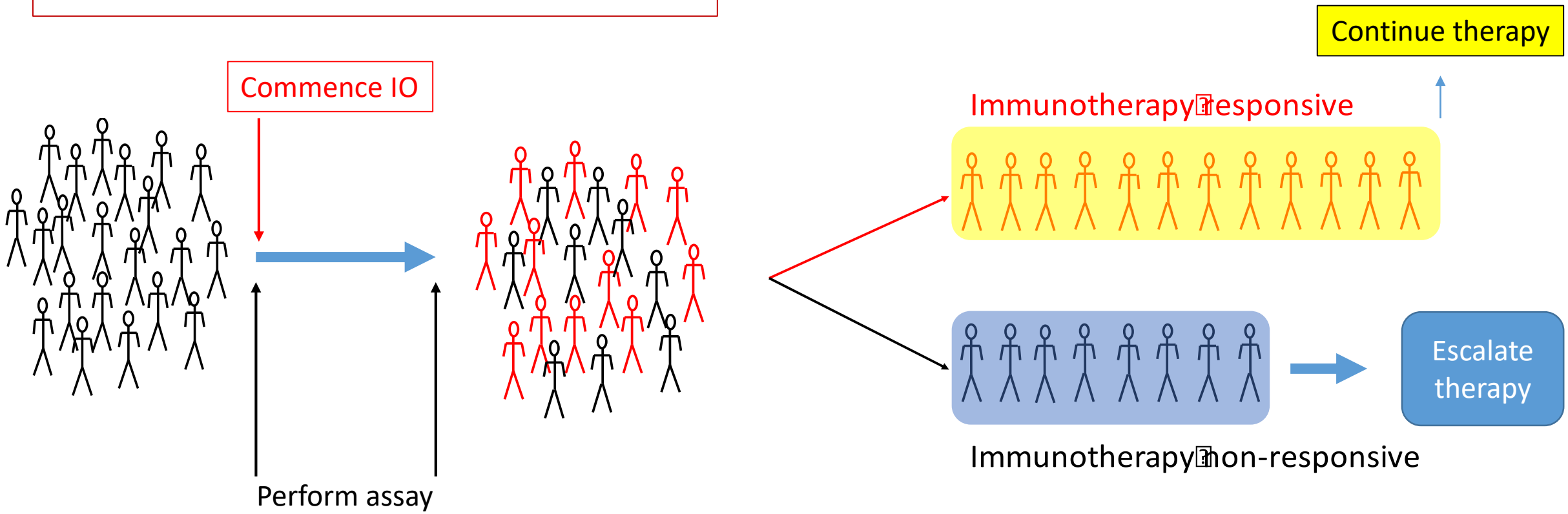
What about using biomarkers?

1. Biomarker enrichment (current strategy – PD-L1 in NSCLC)



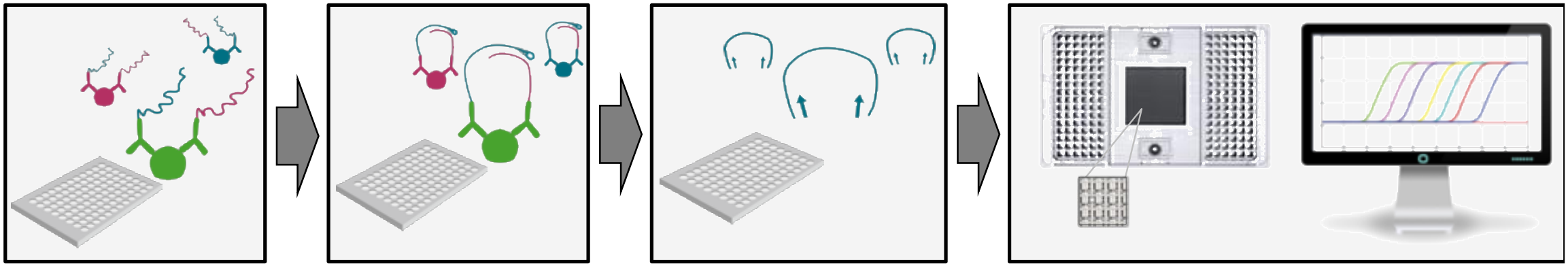
What about using biomarkers?

2. Biomarker directed escalation



Proteomic Profiling

Proximity extension assay (PEA)*



Protein detection with pairs of antibodies

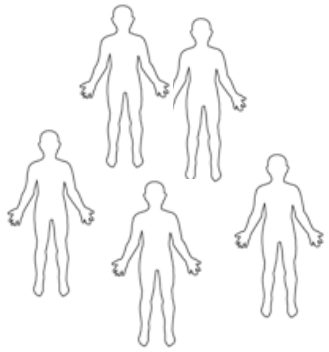
Extension reaction

Amplification

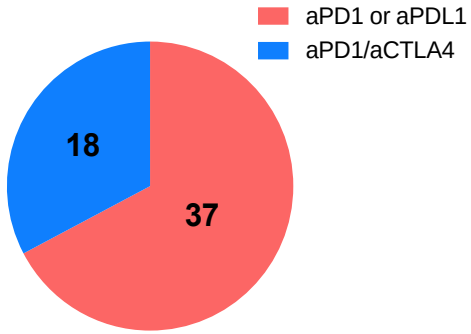
Detection and analysis

*Olink Proteomics

Mehta et al. ASCO 2020

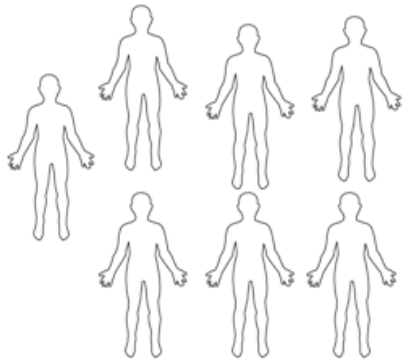


Cohort 1: 58 patients
44 responders
14 non-responders
1104 proteins detected

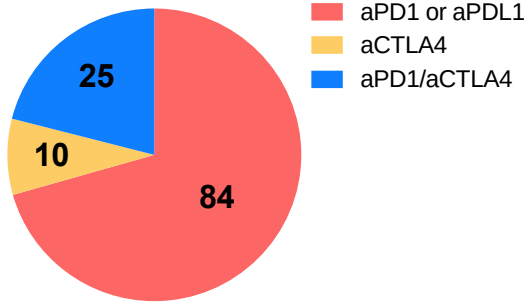


Sample time points in this study

Baseline → 6 weeks → 6 months



Cohort 2: 116 patients
66 responders
50 non-responders
707 proteins detected

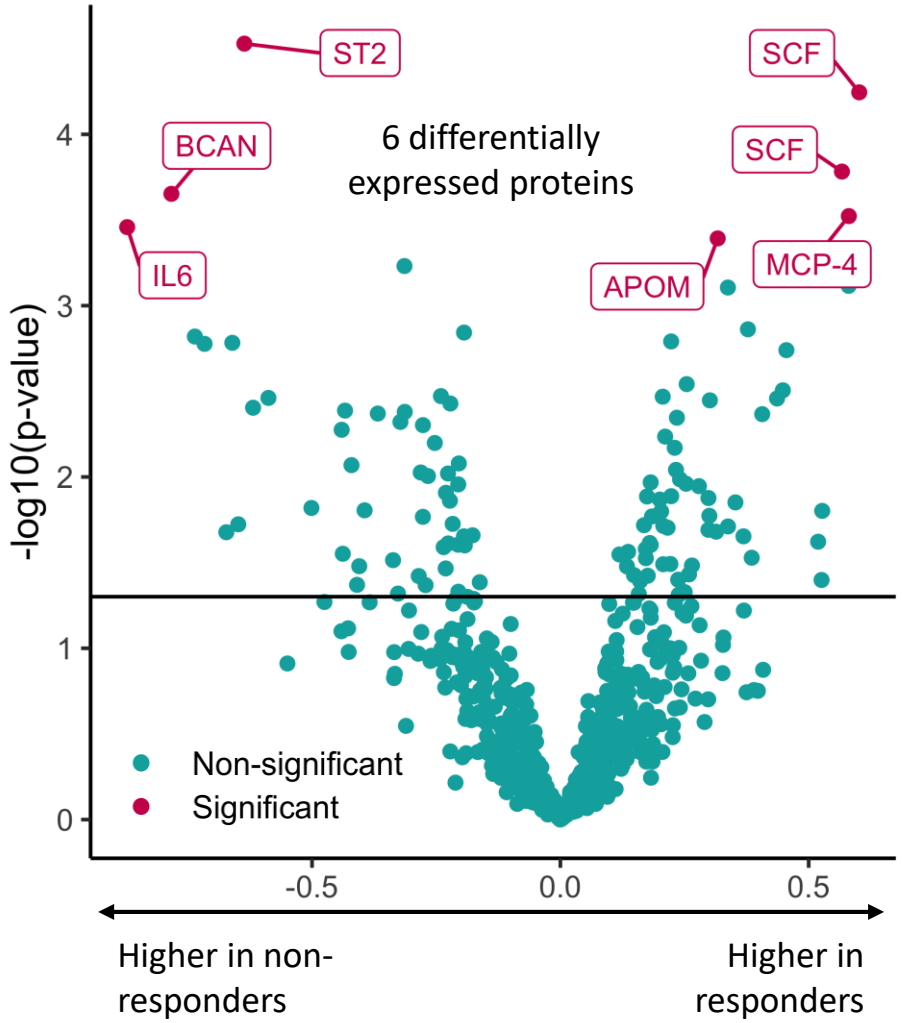


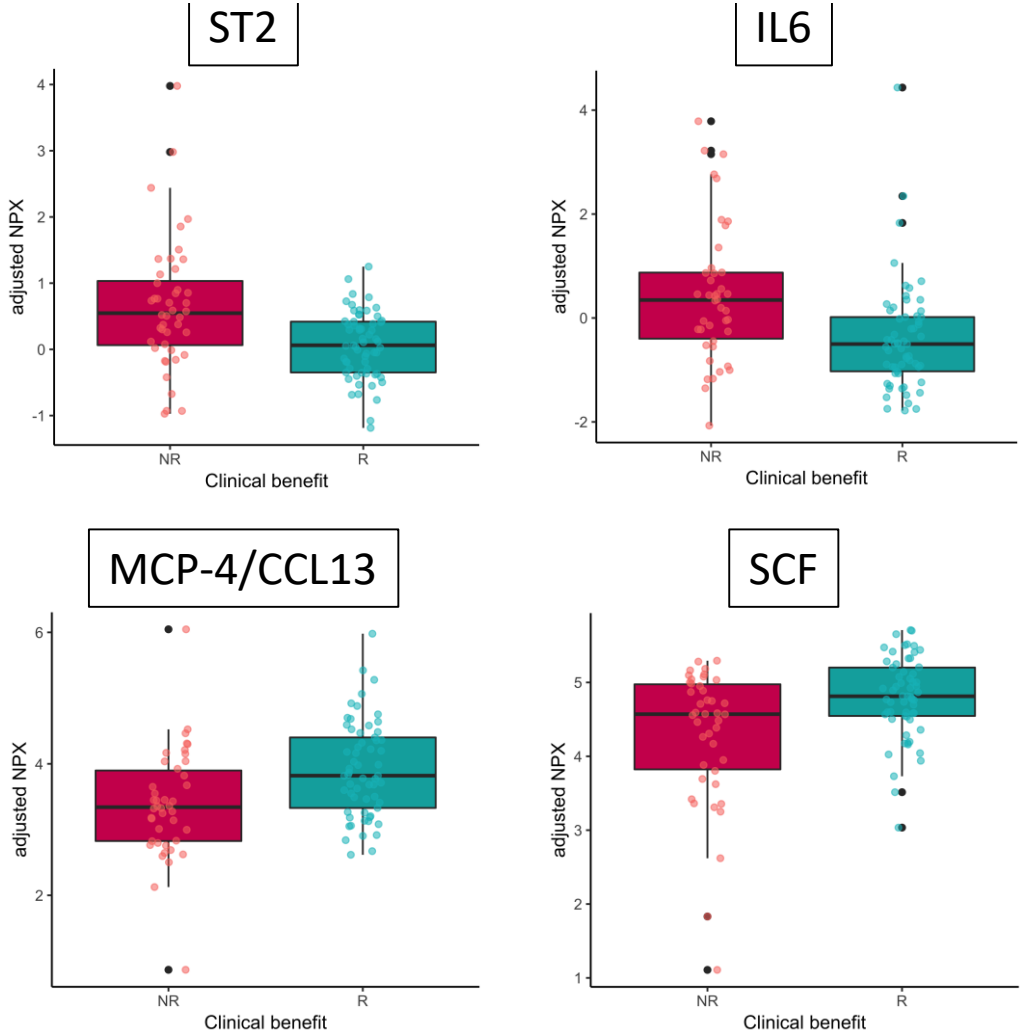
Arnav Mehta MD, PhD

In collaboration with Genevieve Boland, Nir Hacohen, Keith Flaherty, and Olink (Marijana Rucevic)

Mehta et al. ASCO 2020

Differentially expressed proteins between responders and non-responders at baseline





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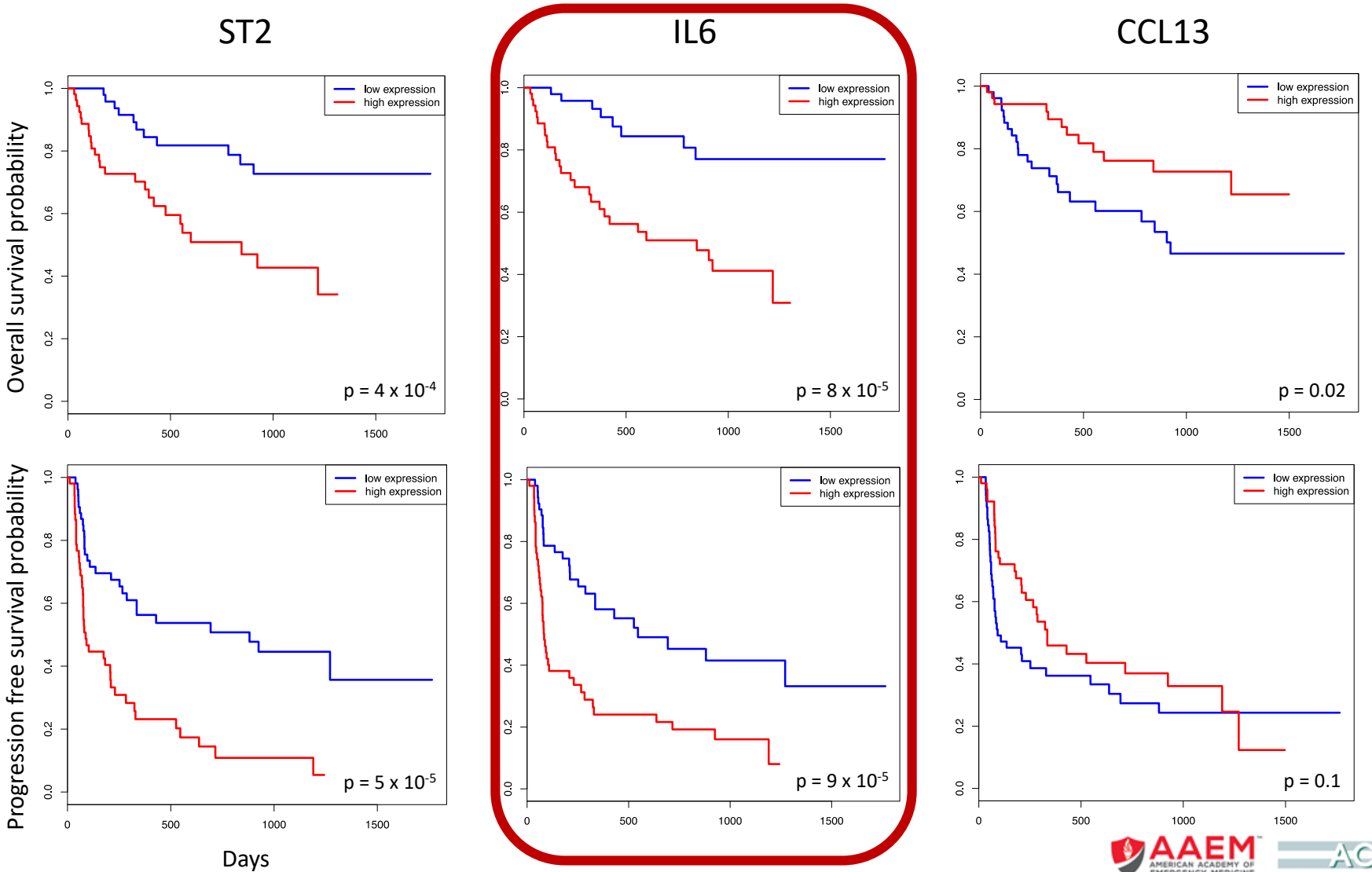
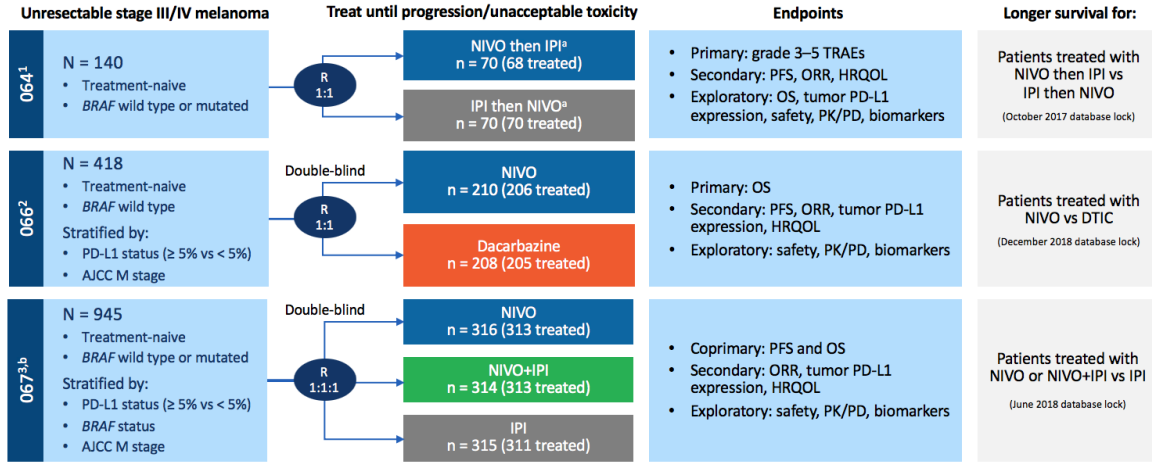
Baseline differentially expressed proteins are predictive of OS and PFS



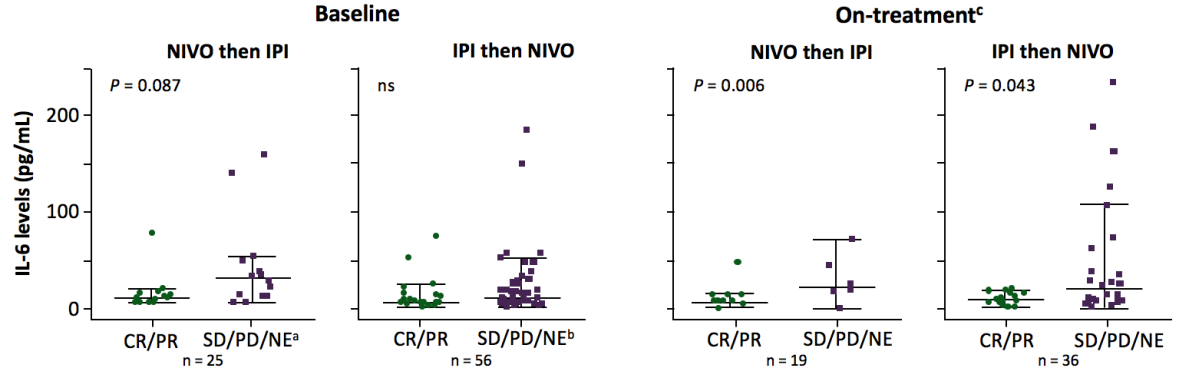
Mehta et al. ASCO 2020

Study Design and Survival Outcomes: CheckMate 064, 066, and 067



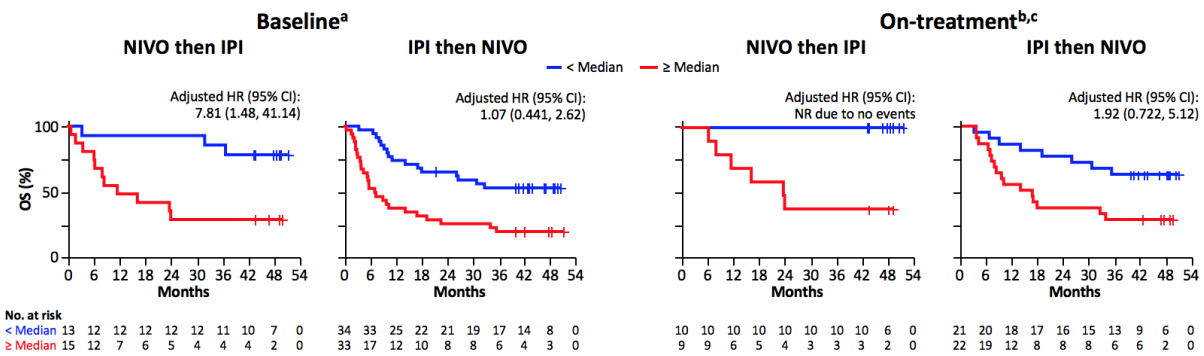
[a]Switch in treatment at week 13; [b]CheckMate 067 was not designed for a formal statistical comparison between NIVO+IPI and NIVO monotherapy. AJCC, American Joint Committee on Cancer; HRQOL, health-related quality of life; ORR, objective response rate; OS, overall survival; PD, pharmacodynamics; PFS, progression-free survival; PK, pharmacokinetics; R, randomized; TRAE, treatment-related adverse event. 1. Weber JS, et al. *Lancet Oncol* 2016;17:943–955; 2. Robert C, et al. *N Engl J Med* 2015;372:320–330; 3. Larkin J, et al. *N Engl J Med* 2015;373:23–34.

CheckMate 064: Association of Baseline and On-Treatment IL-6 Levels With BOR



Lower baseline and on-treatment IL-6 levels were observed in patients with CR/PR vs SD/PD/NE

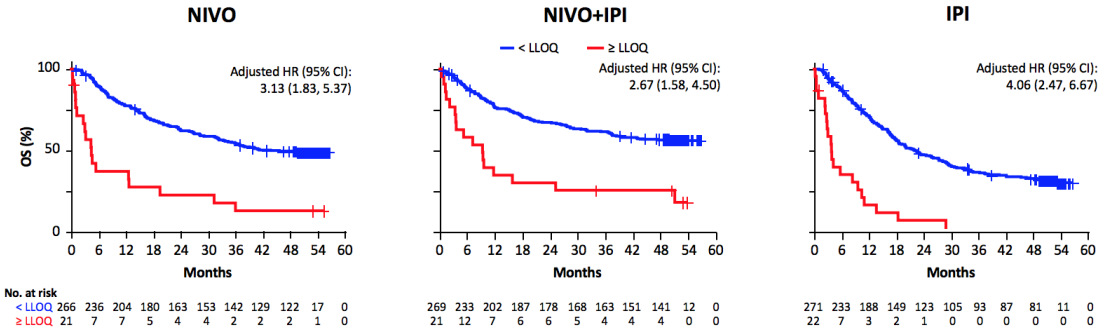
CheckMate 064: Association of Baseline and On-Treatment IL-6 Levels With OS Across Treatment Arms



High baseline and on-treatment IL-6 levels were associated with shorter OS

[a]Median IL-6 at week 0: 13.3 pg/mL; [b]Median IL-6 at week 13: 13.6 pg/mL; [c]On-treatment at week 13; switch in treatment occurred at week 13.
HR adjusted for The Eastern Cooperative Oncology Group performance status (ECOG), *BRAF* status, M stage, and baseline lactate dehydrogenase (LDH). NR, not relevant.

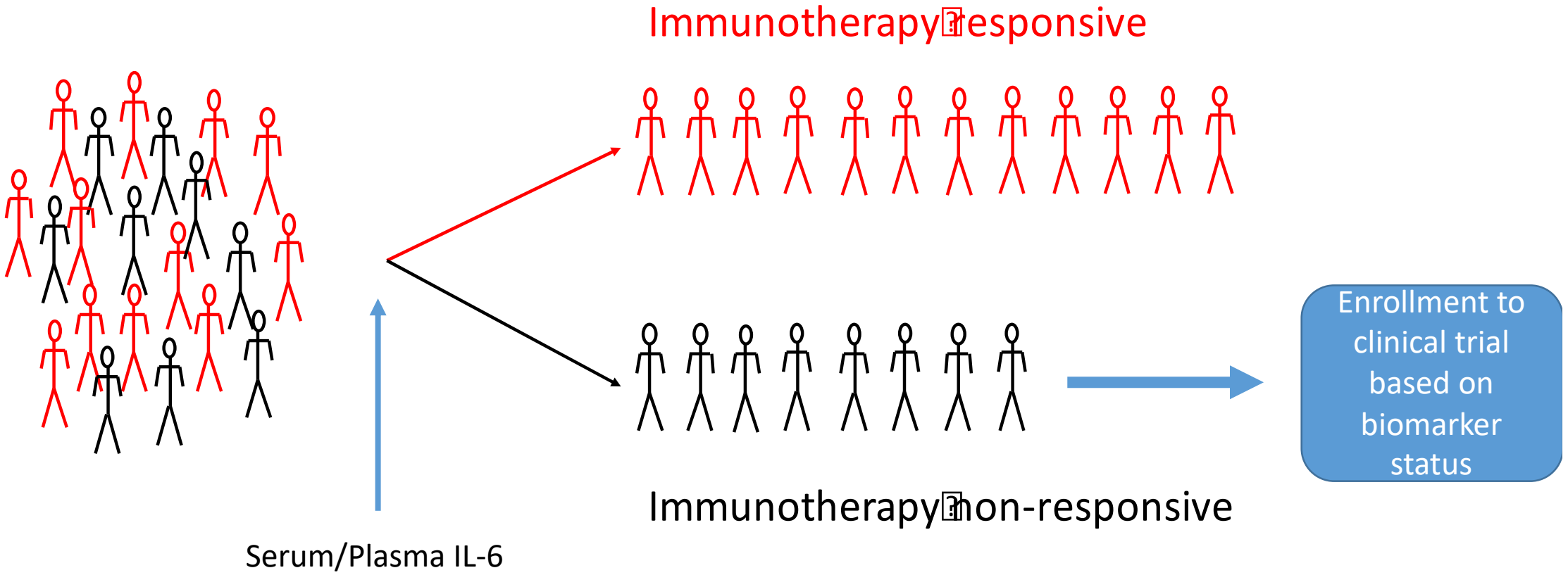
CheckMate 067: Association of Baseline IL-6 Levels With OS Across Treatment Arms



High IL-6 levels were associated with shorter OS

IL-6 LLOQ: 11 pg/mL.
HR adjusted for ECOG, *BRAF*, M stage, and baseline LDH.

Biomarker Enrichment?



Tocilizumab (anti-IL6) + Nivo + Ipi (TOY1?)
PI Weber; NCT03999749

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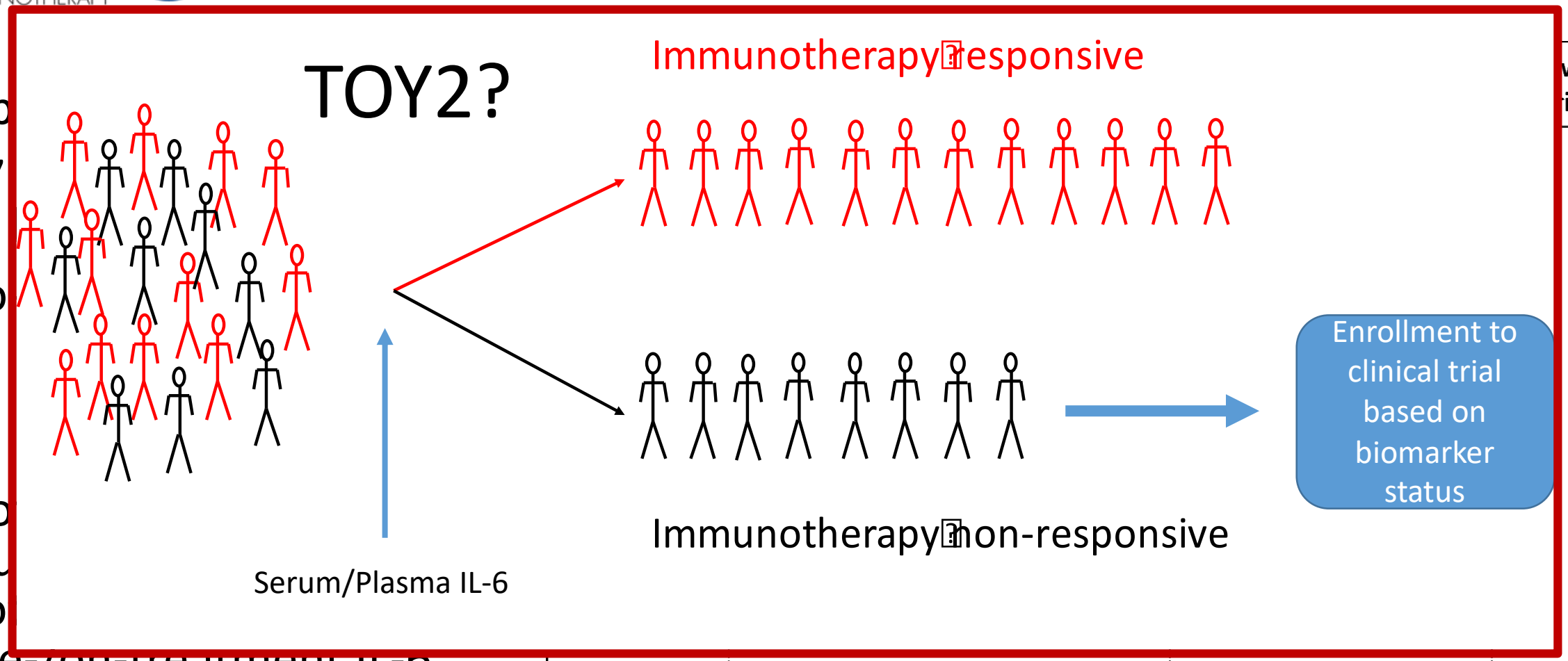

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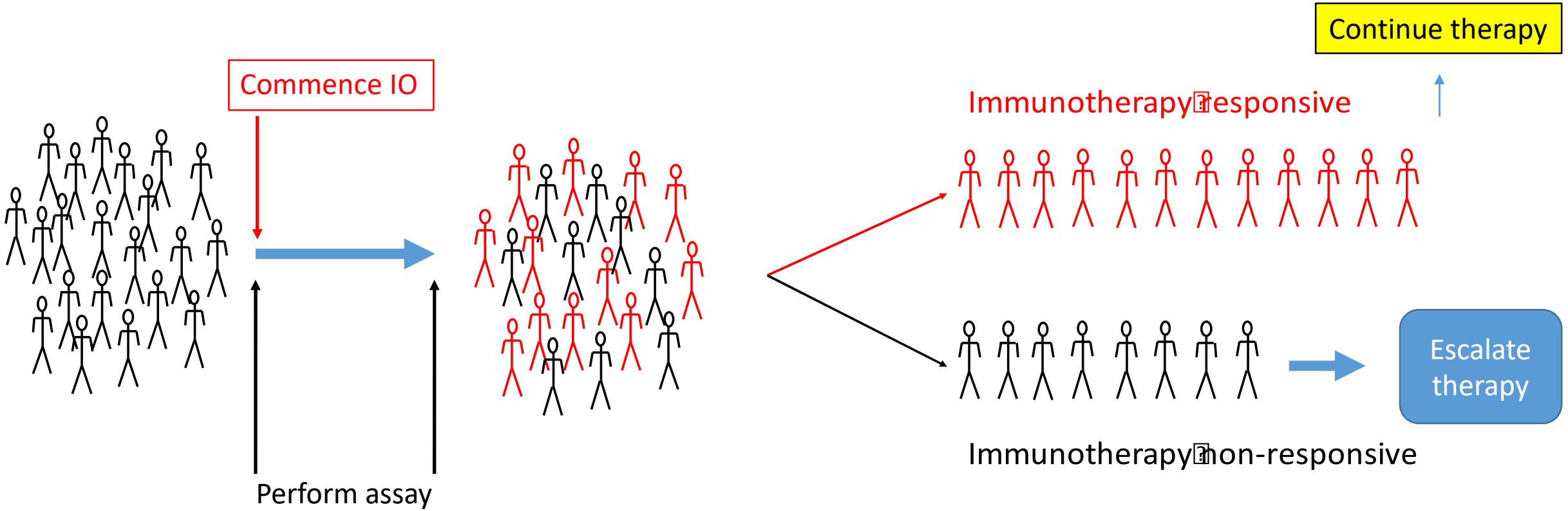
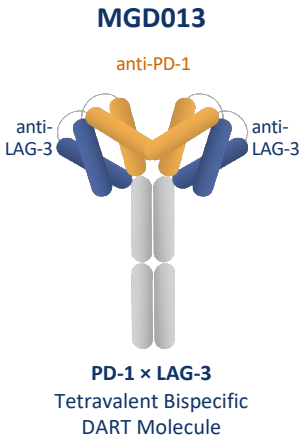
Biomarker-Directed Escalation?



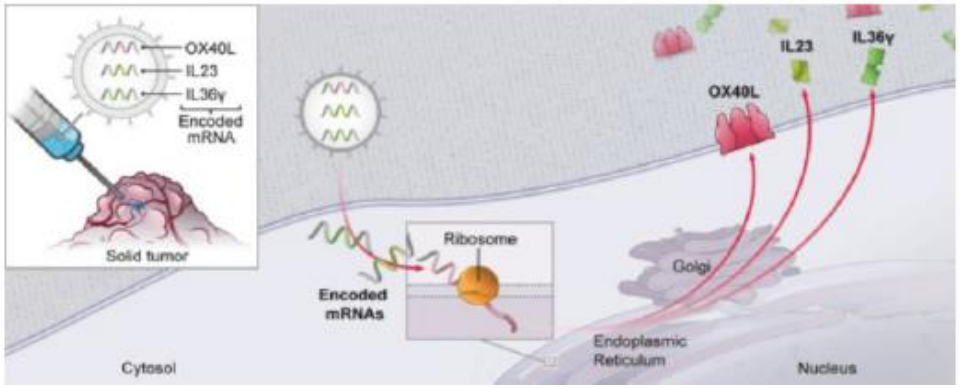
Concluding remarks

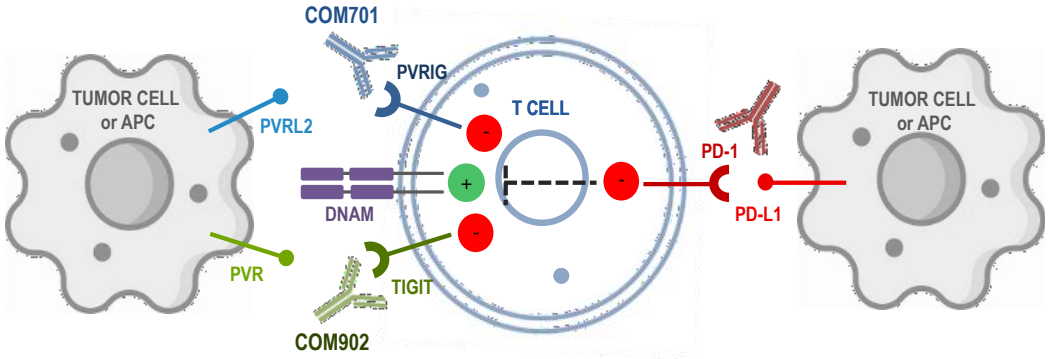
Year	Drugs	Approvals	Diseases	Combos
2011	1	1	1	
2014	2	2	1	
2015	3	4	3	1
2016	3	5	4	
2017	4	10	7	
2018	5	12	10	5
2019	4	7	5	6
2020	6	8	8	3

Checkpoint inhibitor combinations are the present and future



New constructs are capable of delivering combination therapy safely and preliminarily effectively





New targets are being discovered and clinical trials have been launched