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

Society for Immunotherapy of Cancer

Disclosures

- Honoraria: Pfizer/EmdSerono
- Consultant: Merck
- Advisory Board: Bristol Myers Squibb
- Research funding: Incyte, Merck, BMS, EMDSerono, AstraZeneca
- I will be discussing non-FDA approved indications during my presentation.

Audience Response Question

Which of the following are relevant considerations in early drug development?

A) Dose

B) Mechanism of Action

C) Characteristics of population enrolled to trials

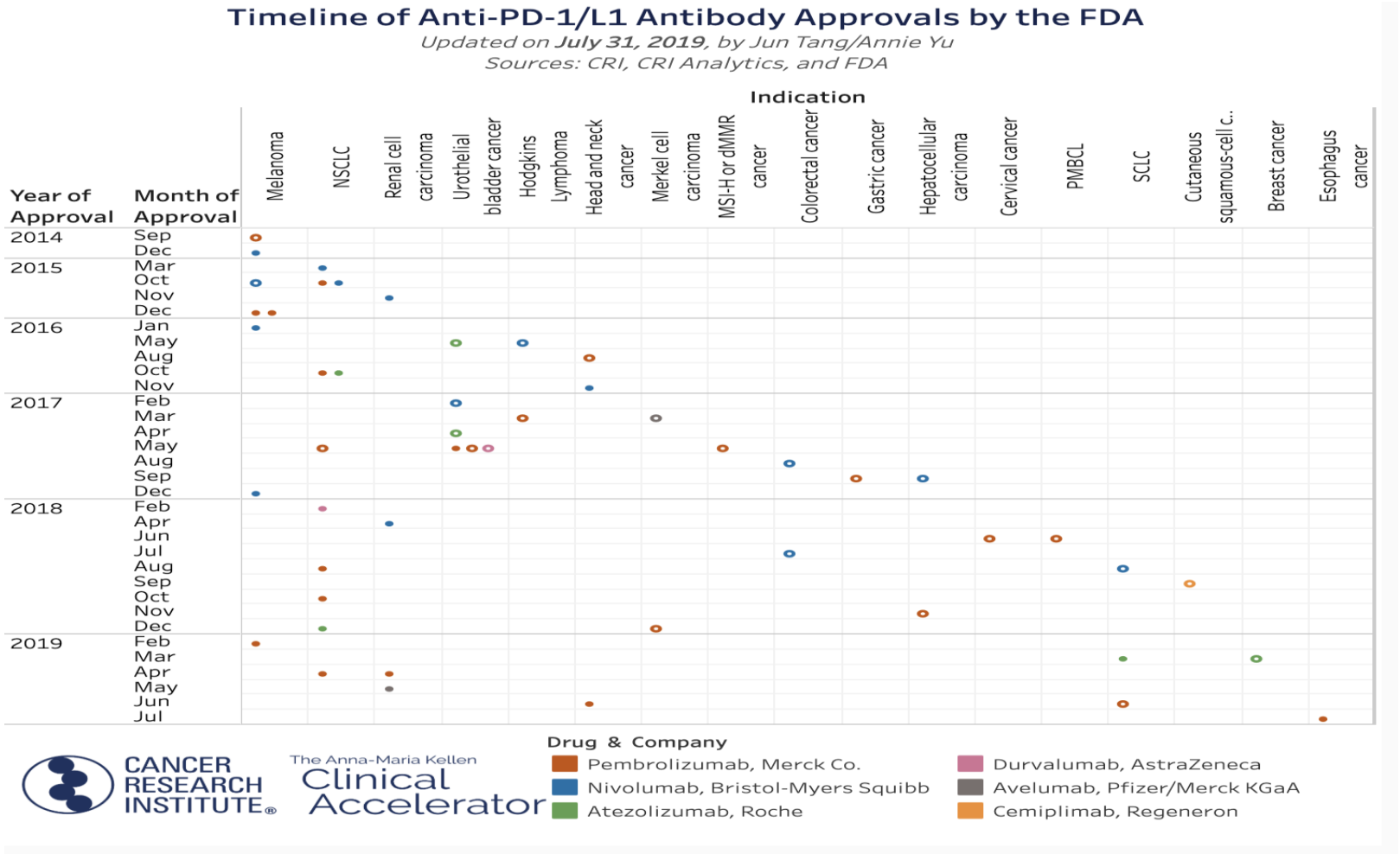
D) Preclinical data

Audience Response Question

Which of the following are active areas of therapeutic investigation?

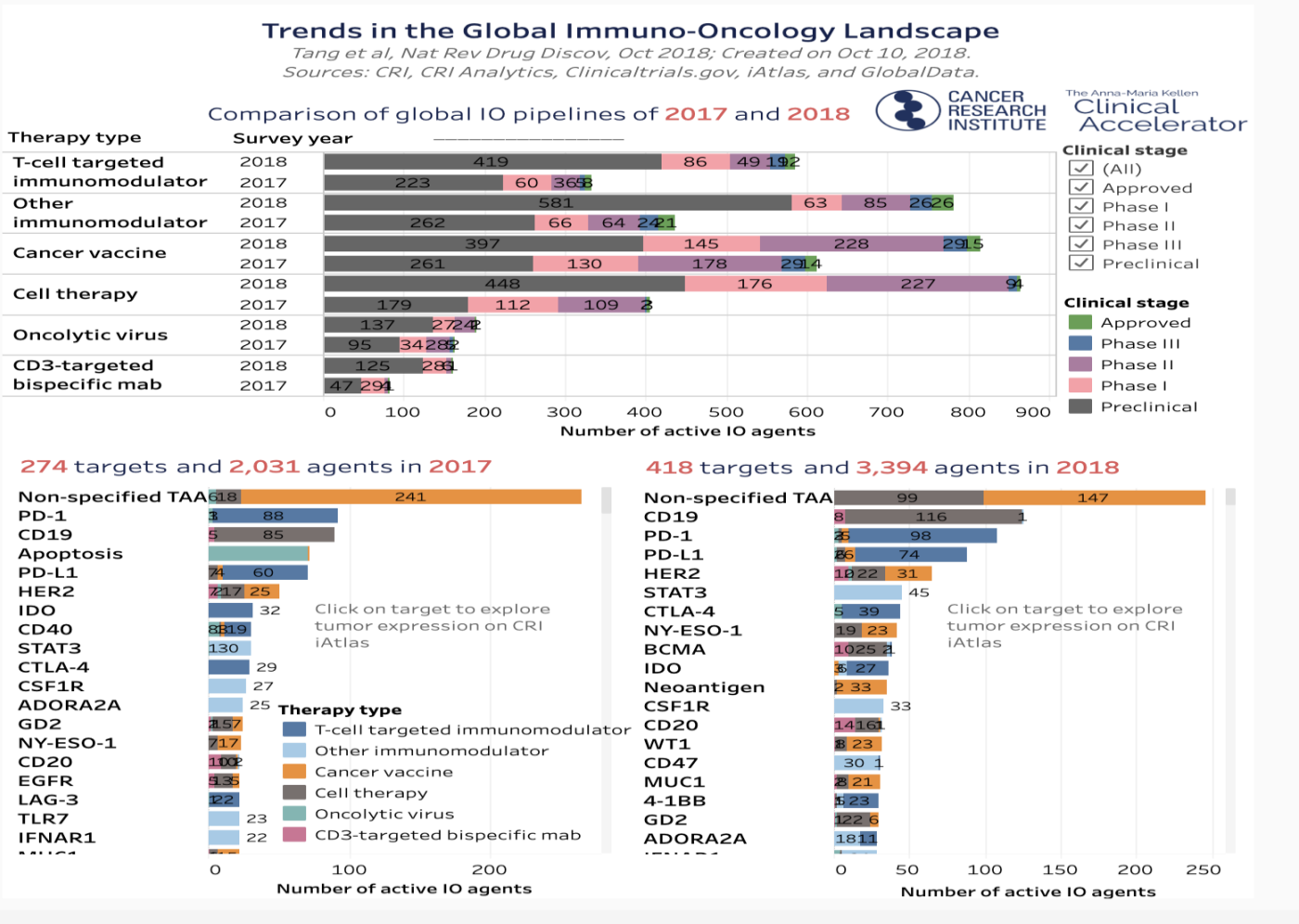
A) Oncolytic viruses
B) Epigenetic modulation
C) Adoptive cell therapy
D) Identification of novel checkpoints

The Excitement of Progress

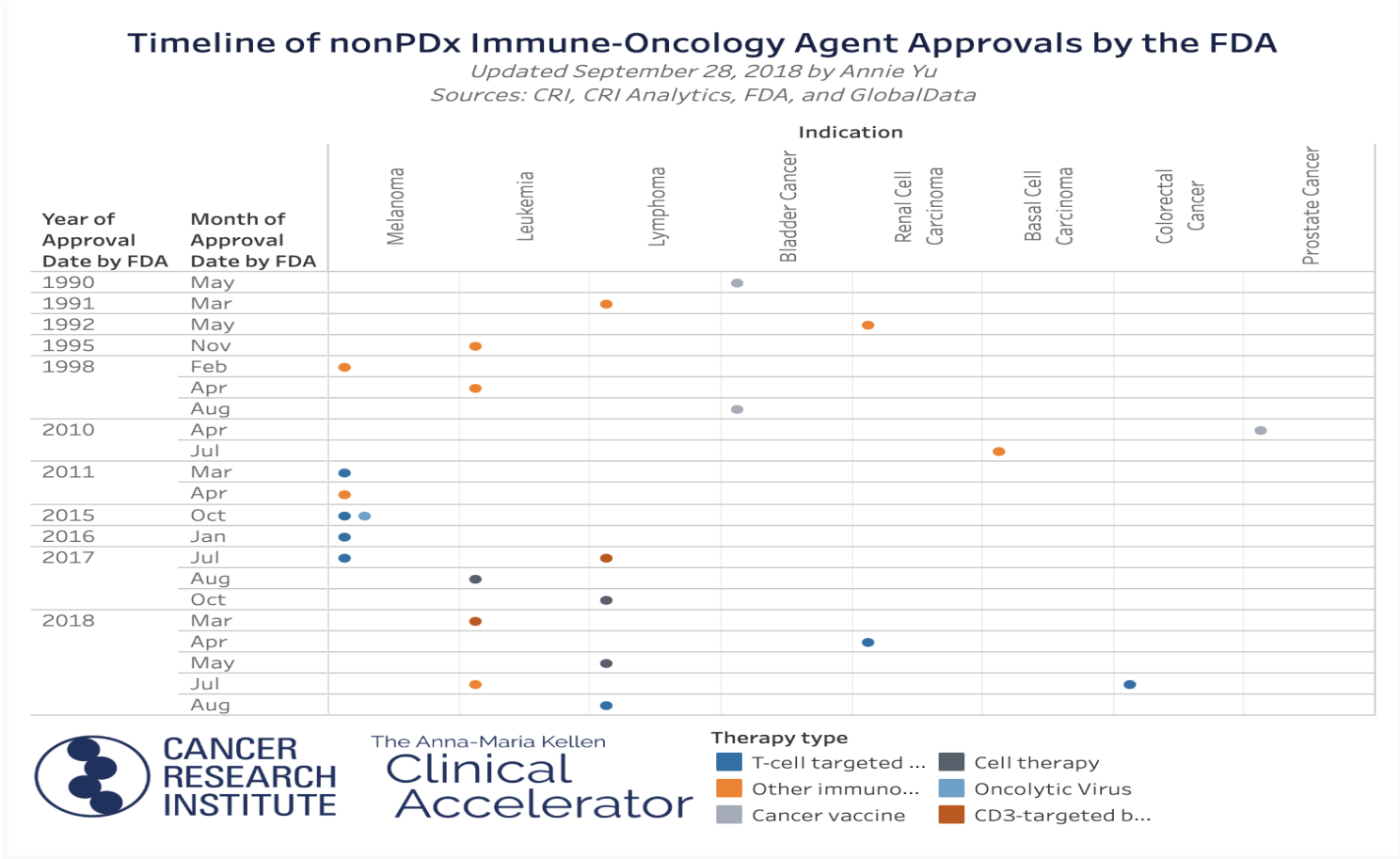


Klapper et al. Cancer 2008

What Comes Next



What Comes Next



Phase I Limitations and Challenges

- What's new and novel? (ICT + Drug X)
- Too many trials? (65,253 registered at clinicaltrials.gov quoted at ASCO)
- How does prior ICT toxicity affect both toxicity and response?
- How do you measure response….how to define ICT refractory?

Phase I Key Considerations

- Preclinical Rationale
- Assessment of Dose
- Study Population Evaluated and Activity Seen
- Target Modulation/Understanding of Mechanism

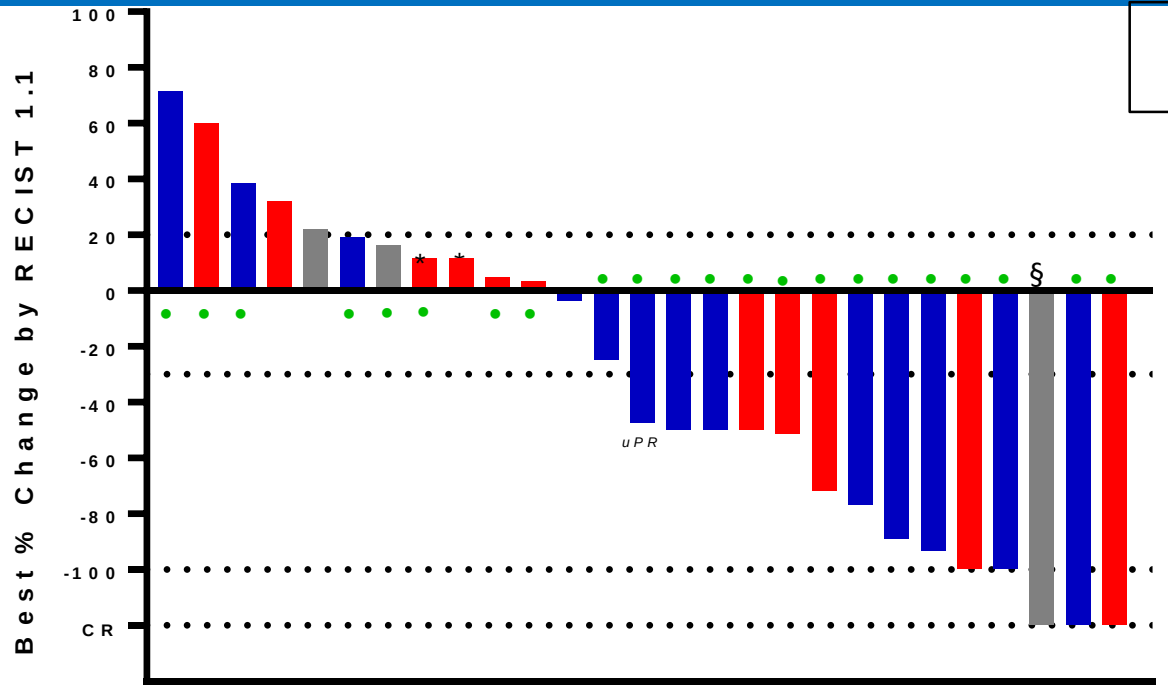
Improving Upon the Existing Standards

- Increase anti-tumor activity in naïve setting

- Develop effective approaches for primary and secondary resistance

Nivolumab + Pegylated IL-2 NKTR214: Stage IV IO-Naïve First Line Melanoma Cohort at RP2D Diab, A et al ASCO 2018

Stage 1: ORR 11/13 (85%)
Stage 2: Best Overall Response ORR=14/28 (50%); DCR=20/28 (71%)
Total ORR: 25/41=60%
ASCO 2019: ORR 53%; CR Rate 34%



Median Time on Study 4.6 Months (N=28)
As of May 29, 2018

PD-L1 Negative (<1%)
PD-L1 Positive (≥1%)
PD-L1 Unknown
Treatment Ongoing

ORR PD-L1 (-) 5/12 (42%)
ORR PD-L1 (+) 8/13 (62%)
ORR PD-L1 Unknown 1/3 (33%)

Data cut: May 29, 2018

Horizontal dotted lines indicate the thresholds for PD, PR and CR response according to RECIST (version 1.1) criteria. -100% is PR for complete clearance of target lesions. CR is a complete response. "u": Unconfirmed. *Best overall response is PD; SD for target lesions but PD due to a new lesion. §Off study treatment with confirmed CR due to patient decision.
One PD-L1(-) patient had PD due to non-target lesions and target lesions were not assessed, therefore 27/28 patients included in waterfall plot..

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Nivolumab + NKTR214 Treatment-Related Adverse Events (AEs) at RP2D Diab, A et al ASCO 2018

Preferred Term[1]	NKTR-214 0.006 q3w + Nivo 360 (N=283)
Treatment-Related Grade 3 or higher (≥1% listed below)	**40 (14.1%)**
Hypotension	5 (1.8%)
Syncope	5 (1.8%)
Increased Lipase	4 (1.4%)
Rash*	4 (1.4%)
Dehydration	3 (1.1%)
Treatment-Related Grade 1-2 in >15%	
Flu Like Symptoms**	166 (58.7%)
Rash*	126 (44.5%)
Fatigue	119 (42.0%)
Pruritus	89 (31.4%)
Nausea	62 (21.9%)
Decreased Appetite	54 (19.1%)
Diarrhea	43 (15.2%)
Patients who discontinued due to a TRAE	6 (2.1%)

Data cut: May 7, 2018 includes any AE deemed treatment-related by investigator and includes all available adjudicated safety data.
(1) Patients are only counted once under each preferred term using highest grade
*Rash includes the following MedDRA preferred terms: Rash, Rash Erythematous, Rash Maculo-papular, Rash Pruritic, Erythema, Rash Generalized, Rash Papular, Rash Pustular, Rash Macular
** Flu-like symptoms includes the following MedDRA preferred terms: Chills, Influenza, Influenza-like Illness, Pyrexia.

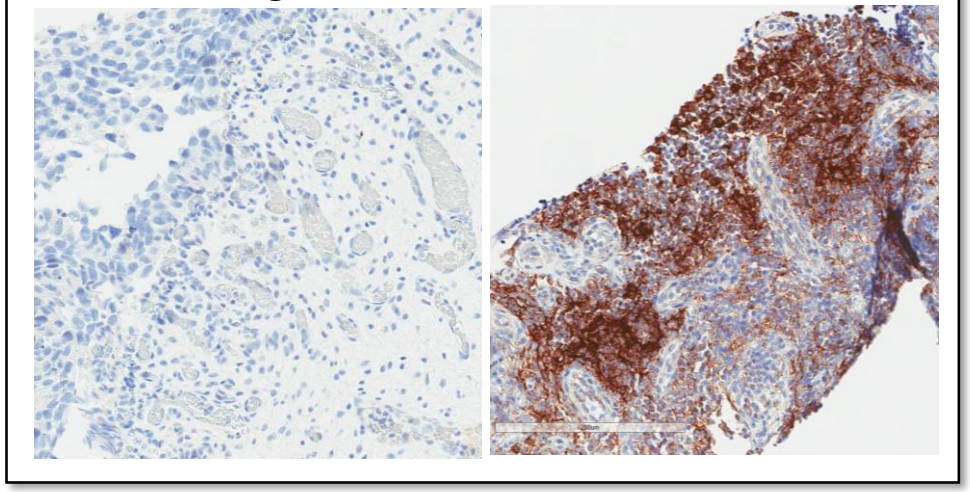
Adi Diab, M.D.

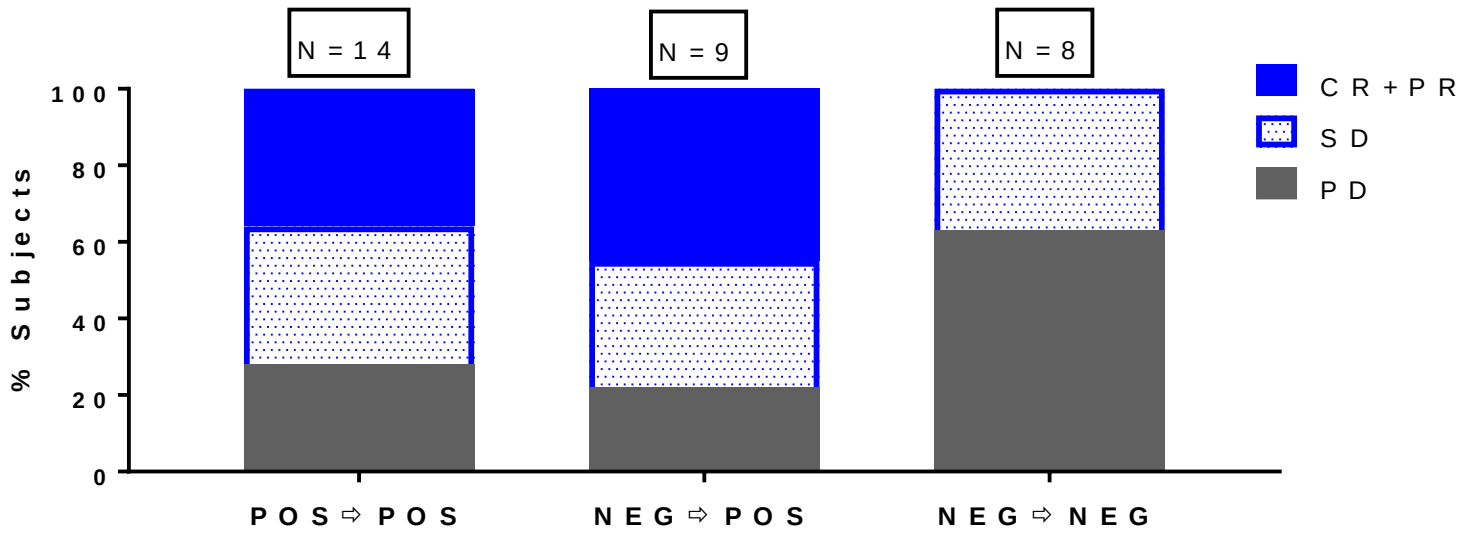
Conversion of PD-L1(-) to PD-L1(+) in Tumor Biopsies from Baseline to Week 3 is Associated with Clinical Benefit

Patient with Urothelial Carcinoma

Baseline:
PD-L1 Negative

Week 3:
PD-L1 Positive





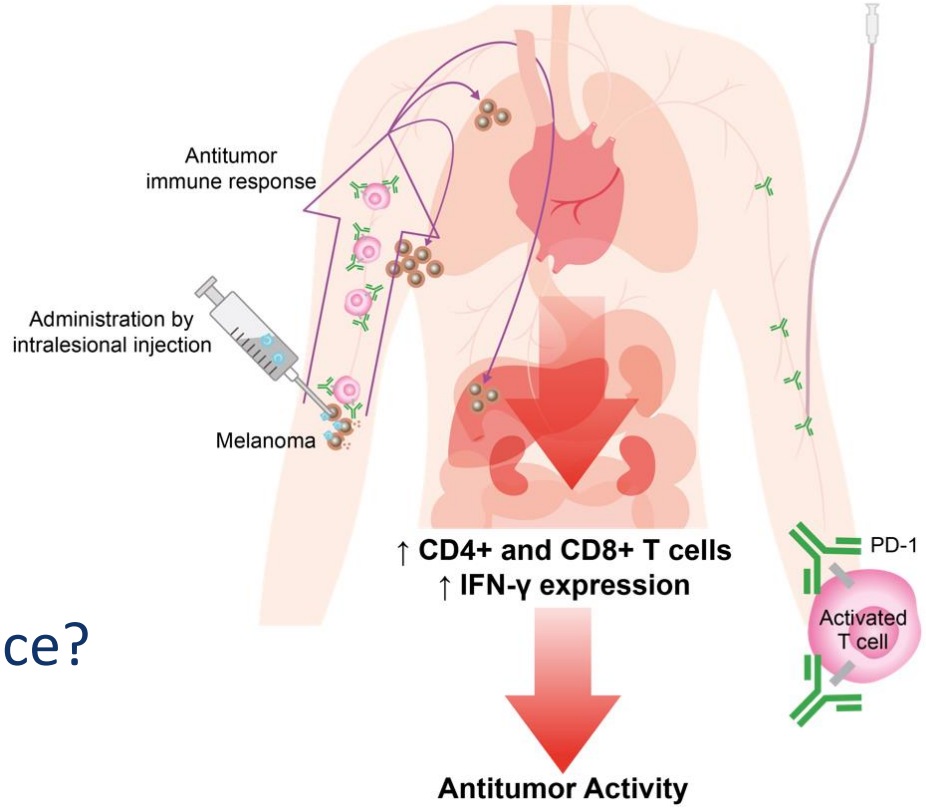
- NKTR-214 + nivolumab can convert PD-L1(-) tumors to PD-L1(+)
  - PD-L1 negative to positive conversion in 9/17 (53%) of patients
- Patients that were PD-L1(+) at baseline, or converted to PD-L1(+) after start of treatment showed greatest clinical benefit

31 patients were available with matched baseline and week 3 results for PD-L1 status. Of these, 17 were PD-L1 negative at baseline. PD-L1 was assessed on tumor cells using a validated 28-8 method. Example image shown for UC patient at baseline and week 3, 20x magnification. Diab, A et al ASCO 2018

Developing Intratumoral Injection Strategies

Pivotal Questions

- Intratumoral vaccination strategies show antitumor activity combined with ICT
- Will these combinations improve upon upfront checkpoint inhibitor activity?
- Can a cold tumor really become hot…especially once it has demonstrated ICT resistance?



Ribas A, Cell 2017

Previous Data

- Ipilimumab +/- talimogene laherparepvec:
  Randomized phase II trial: 39% ORR vs 18% ORR

- Pembrolizumab +/- talimogene laherparepvec:
  21 patient, phase 1b trial 63% ORR, 33% irCR

-NAIVE PATIENTS
-PHASE III DATA FORTHCOMING (MASTERKEY 265)

CVA21 (SITC 2017)

Oncolytic CVA21 increased PD-L1 expression and CD8+ T cell recruitment to the TME

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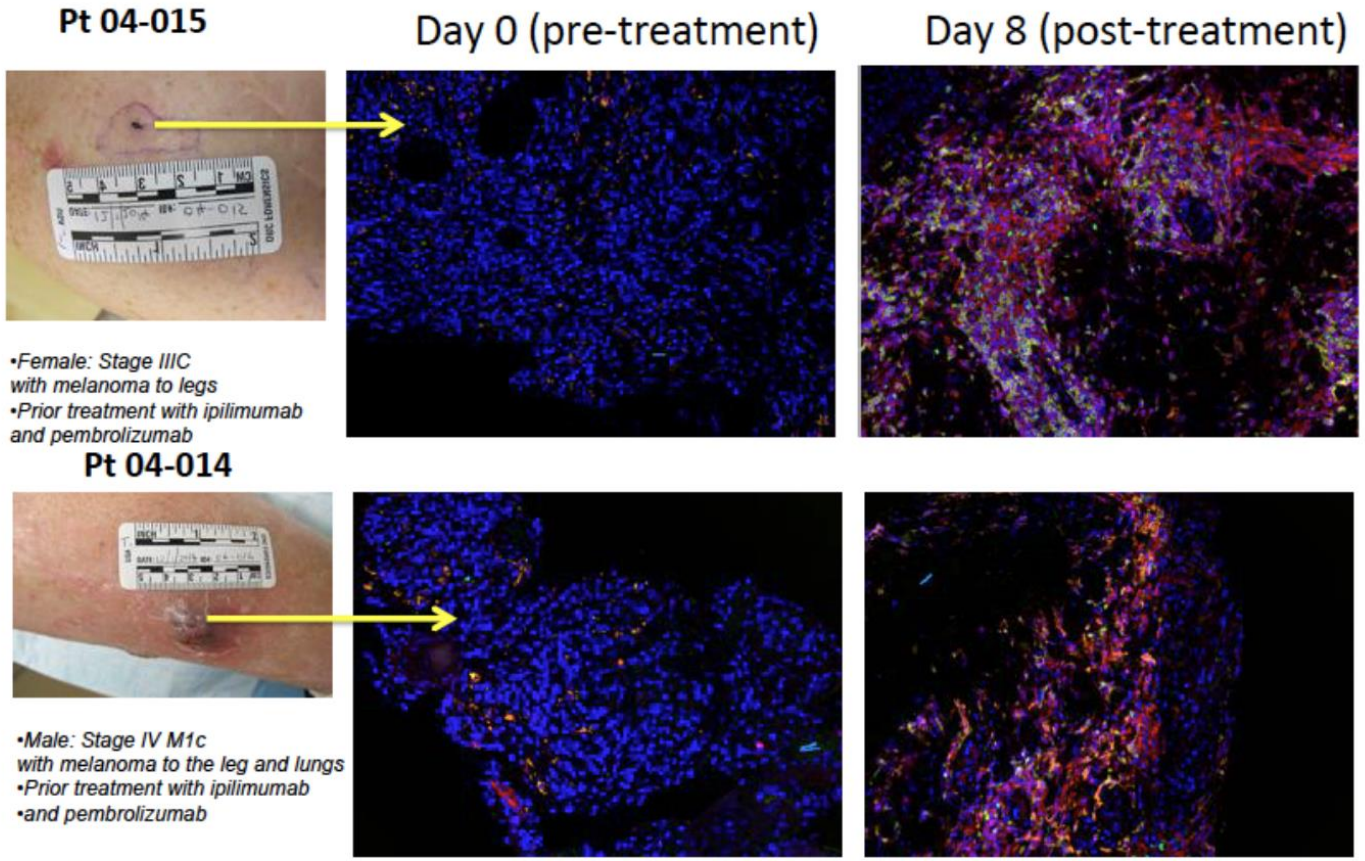


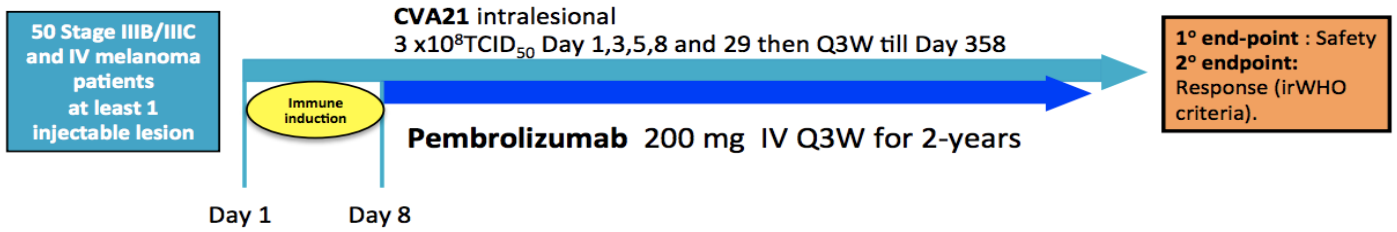
23 patients
61% ORR
78% DCR

D. Shafren, Viralytics

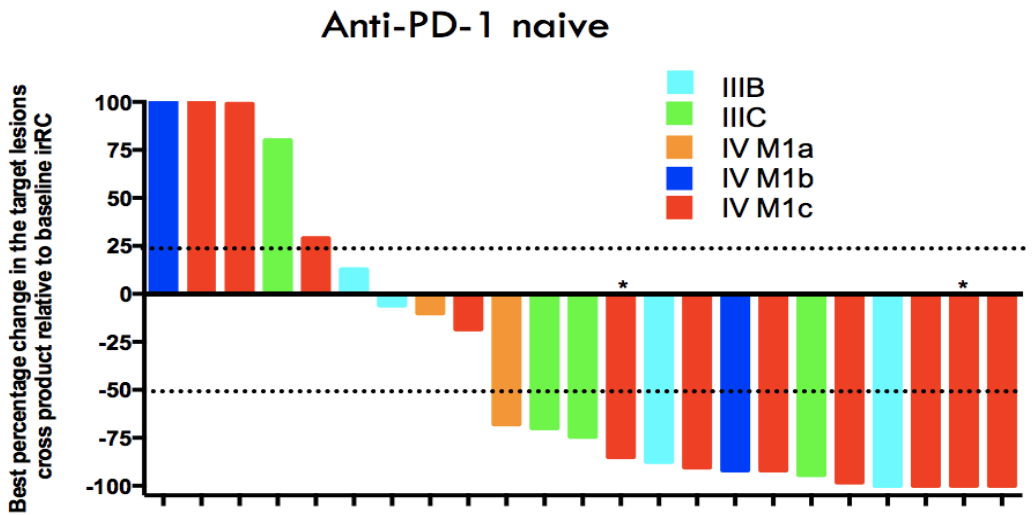
CAPRA PHASE 1 RESULTS (SITC 2017)

Intratumoral CVA21+ pembrolizumab

(CAPRA study : NCT02565992)



Preliminary Best percentage change in the sum of target lesions+



* **Prior ipilimumab treatment** +, Preliminary data , investigator assessed

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WHAT ABOUT ICT RESISTANT PATIENTS?

Phase 1b Study of Intratumoral CMP-001 + Pembrolizumab in PD-1 Resistant Melanoma

- 3+3 Dose Escalation / Expansion
- CMP-001 injected intratumorally / pembrolizumab administered IV
- Two CMP-001 schedules evaluated in escalation:

- Q12 week scans. RECIST v1.1 assessment per investigator
- Milhem, M et al AACR 2018

CMP-001 Dose Escalation Schema	
CMP-001 Dose (*concentration*)	Pembrolizumab Dose
1 mg *(1 mg/mL)*	Per label
3 mg *(1 mg/mL)*	Per label
5 mg *(1 mg/mL or 6 mg/mL)*	Per label
7.5 mg *(6 mg/mL)*	Per label
10 mg *(6 mg/mL)*^	Per label

*Dose can be increased to 10 mg (1mg/ml) based on investigator discretion

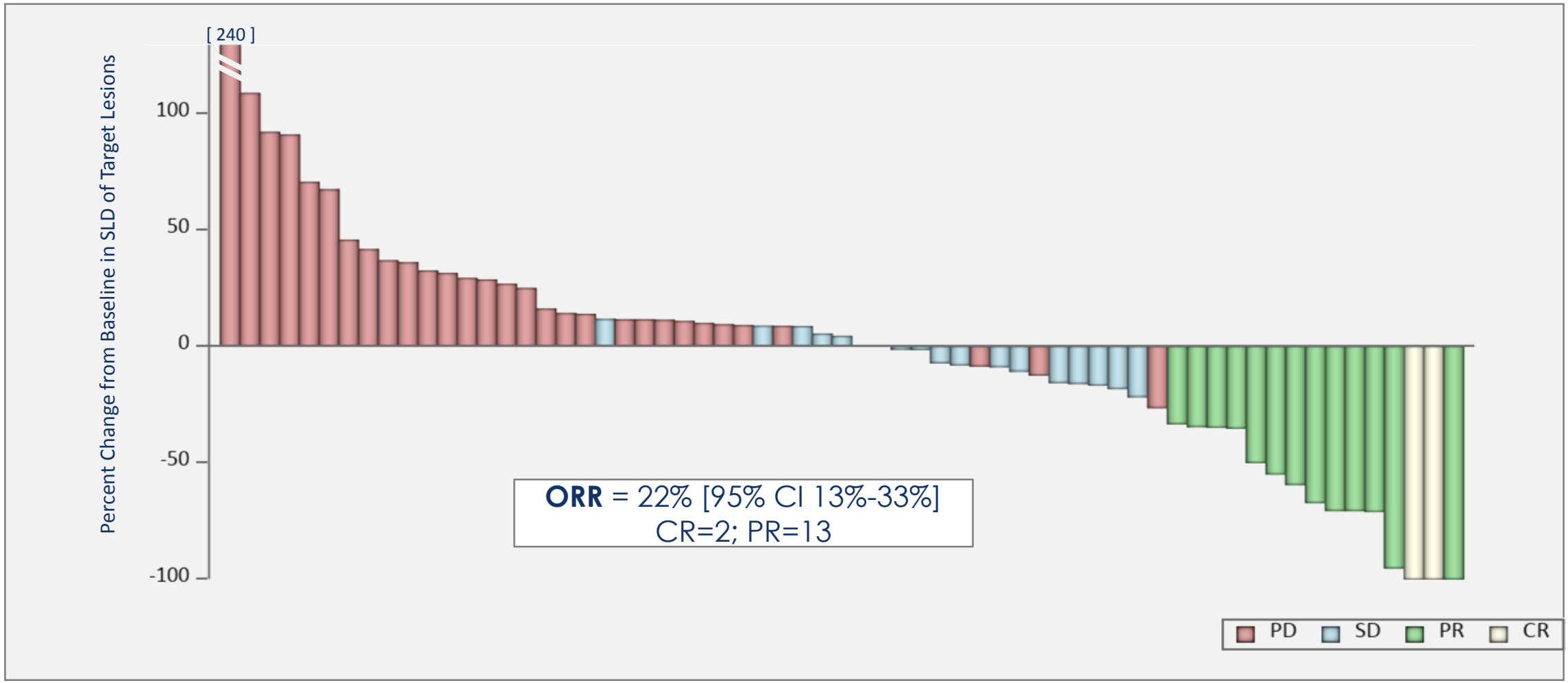
CMP-001+ Pembrolizumab Adverse Events

Adverse Event		N=69	
		Any Grade	≥ Grade 3
Flu-like Symptoms	Chills	53 (77%)	2 (3%)
	Pyrexia	42 (61%)	2 (3%)
	Nausea	38 (55%)	0
	Fatigue	34 (49%)	1 (1%)
	Headache	26 (38%)	0
	Vomiting	25 (36%)	0
Hypotension		20 (29%)	9 (13%)
Injection Site Pain		18 (26%)	0
Diarrhea		15 (22%)	0
Decreased Appetite		14 (20%)	0
Arthralgia		12 (17%)	1 (1%)
Dyspnea		7 (10%)	1 (1%)
Anemia		5 (7%)	2 (3%)
Hypertension		4 (6%)	2 (3%)
Hypophosphatemia		3 (4%)	2 (3%)

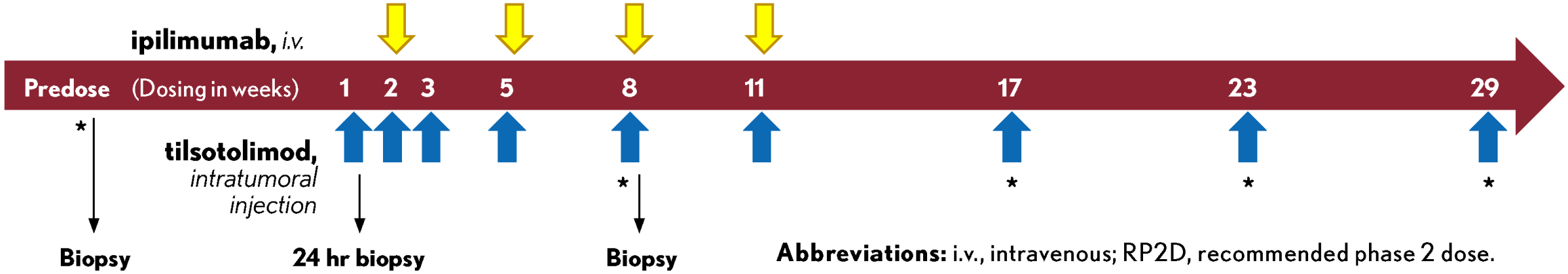
Includes TEAEs reported to be related to treatment in >20% of all subjects or Grade 3 or higher TEAES related to treatment in at least one subject.
2 Subjects discontinued due to AEs

CMP-001 + Pembrolizumab in PD-1 Resistant Melanoma

Best Tumor Response, All Subjects (ITT, RECIST v1.1)



TLR9 Agonist + Ipilimumab: second line ILLUMINATE-204 Study Design



Diab, A et al ASCO 2018

Best Overall Response in Patients Progressing on Anti-PD-1 Therapy

Best overall tumor response	Response rate (RECIST v1.1), N=26
Complete response (CR)	2 of 21 (9.5%)*
Partial response (PR)	6 of 21 (28.6%)
Stable disease (SD)	7 of 21 (33.3%)
Progressive disease (PD)	6 of 21 (28.6%)
Not yet assessed	5
Overall response rate (CR, uCR, or PR)	8 of 21 (38.1%)
Disease control rate (CR, PR, or SD)	15 of 21 (71.4%)

As of 9 May 2018.

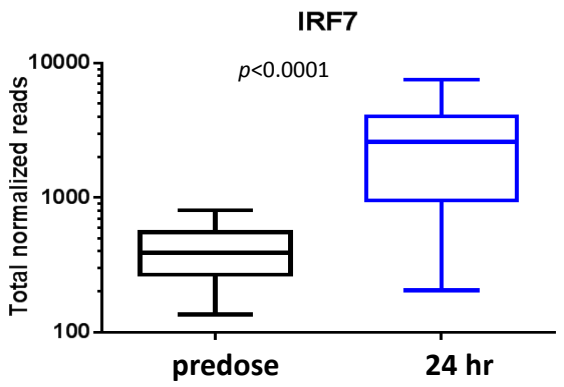
*One CR unconfirmed.

2019 Update:
34 patients
32.4% RR

Diab, A et al ASCO 2018

Tilsotolimod Activates Local IFNα-Response Gene Signature and in Combination With Ipilimumab Therapy Induces Proliferation of T Cells in Distant Lesion

tilsotolimod only (prior to ipilimumab)

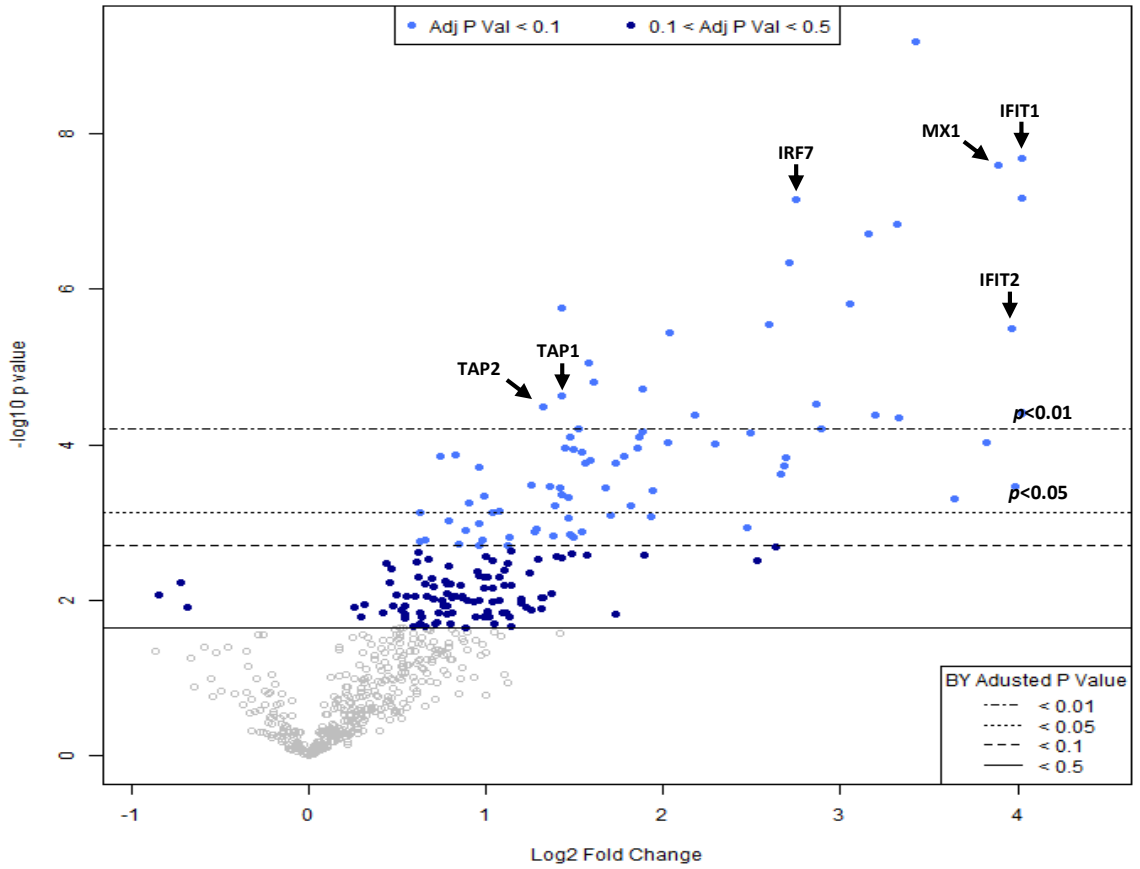


n=15

Injected lesion

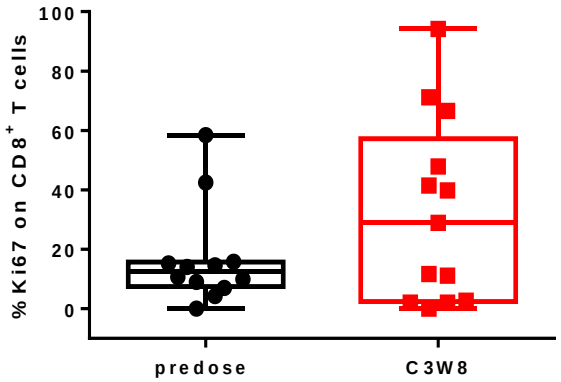
Figure shows translational analysis of biopsies obtained from patients at 24 hours predose (tilsotolimod only) and at week 8 (tilsotoliod plus ipilimumab). Figure 7a, Nanostring analysis shows significant increase in IRF7 (interferon regulatory factor 7) at 24 hours after tilsotolimod injection. Figure 7b, Nanostring analysis shows statistically significant increase in type 1 interferon pathway genes (eg, IFIT1 and IFIT2). Figure 7c, Fresh flow cytometry analysis demonstrates a significant increase in Ki67 positive CD8+ T cells in local and distant lesions.

tilsotolimod only (prior to ipilimumab)



n=15 Injected lesion

tilsotolimod + ipilimumab

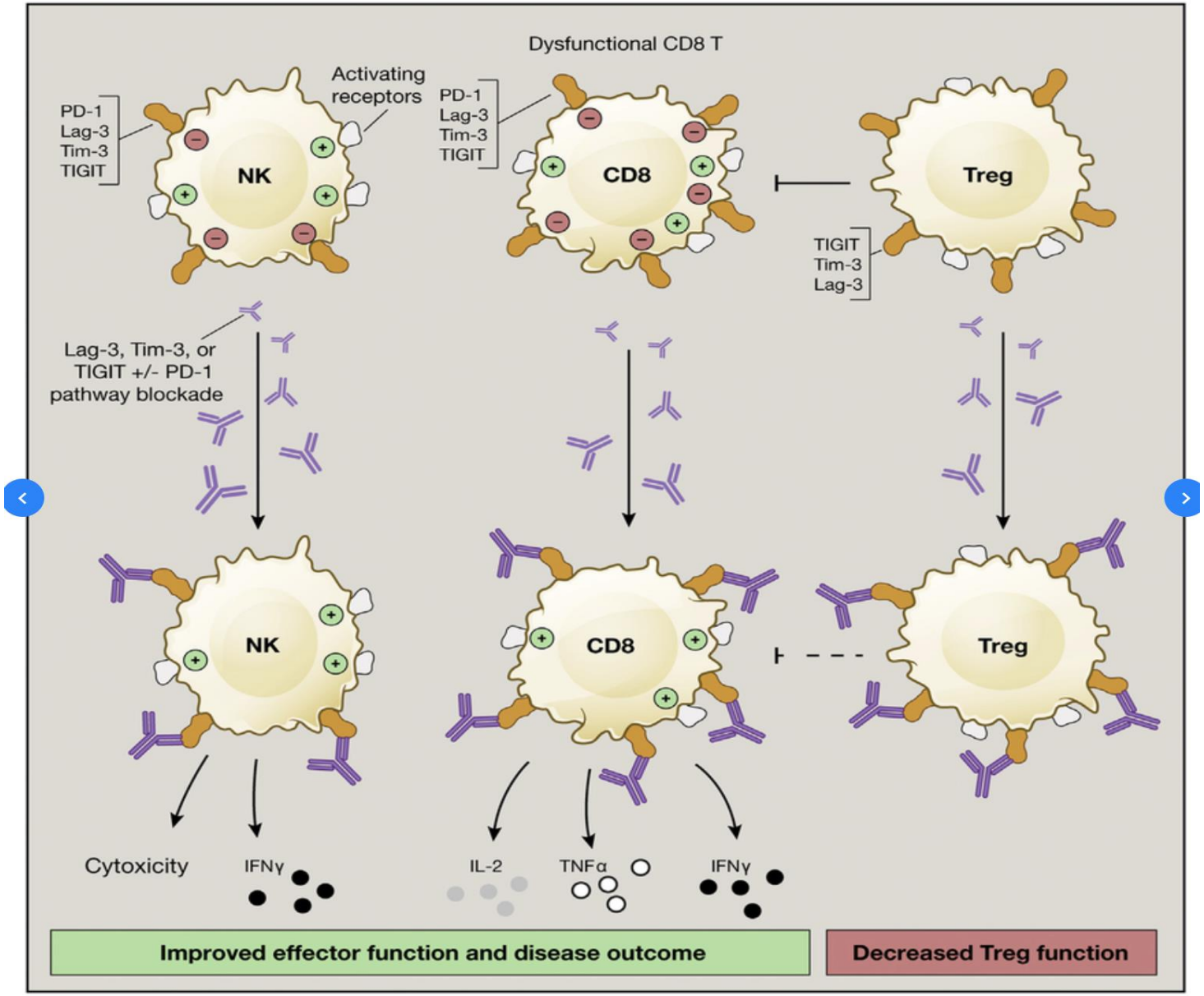


predose **week 8**

n=12

Distant lesion

Diab, A et al ASCO 2018



The Lag-3, Tim-3, and TIGIT Pathways in Chronic Diseases

Anderson 2016, Immunity

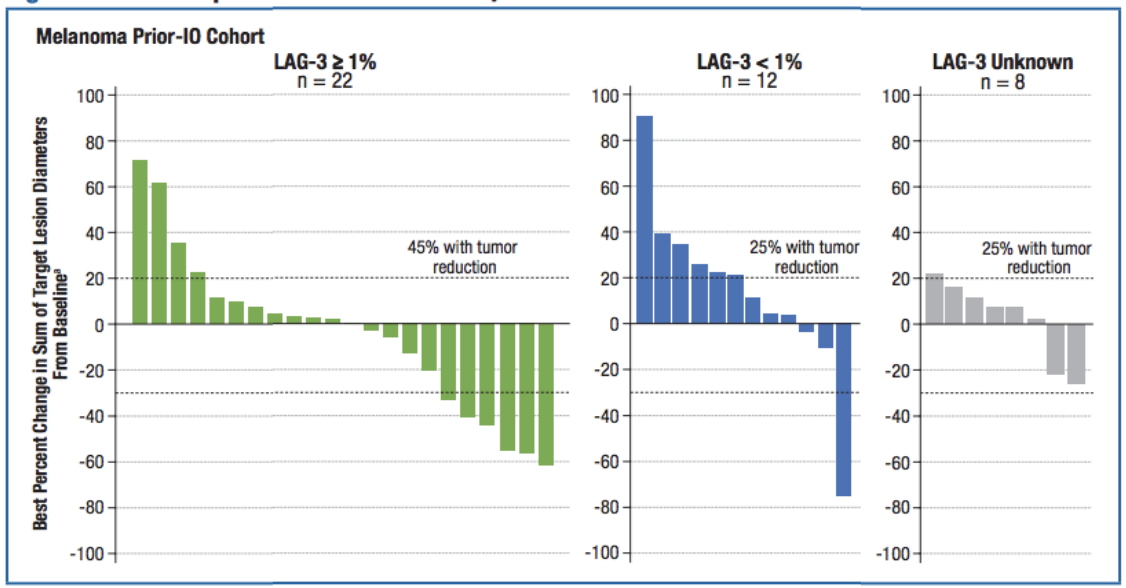
Initial Efficacy of Anti-Lymphocyte Activation Gene-3 (anti–LAG-3; BMS 986016) in Combination With Nivolumab in Patients With Melanoma Previously Treated

Table 4. Preliminary Evidence of Antitumor Activity

Patients, n (%)	Mel Prior IO (n = 48[a])
BOR	
CR	0
PR[b]	6 (13)
SD	20 (42)
PD	16 (33)
Clinical progressions[c]	6 (13)
ORR, 95% CI[b]	6 (13), 4.7, 25
LAG-3 ≥ 1% (n = 25)	5 (20), 6.8, 41
LAG-3 < 1% (n = 14)	1 (7.1), 0.2, 34
DCR (CR + PR + SD)[b]	26 (54)
LAG-3 ≥ 1% (n = 25)	16 (64)
LAG-3 < 1% (n = 14)	5 (36)

BOR, best overall response; DCR, disease control rate. [a]All response-evaluable patients; all progressed on prior anti–PD-1/PD-L1 therapy. [b]Two responses were unconfirmed. [c]Occurred prior to first radiographic scan.

Figure 3. LAG-3 Expression Enriches for Response

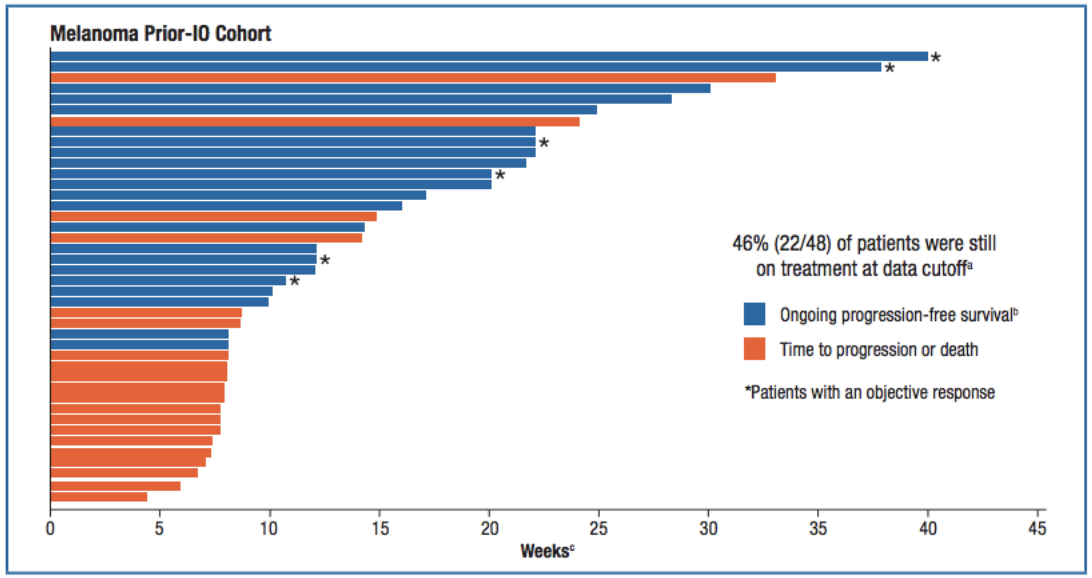


[a]Six patients had clinical progression prior to their first scan and are not included in the plot. One patient with best change from baseline > 30% had an unconfirmed best response of SD.

Efficacy in the Melanoma Prior-IO Cohort (cont)

- Of 48 evaluable patients, 46% remain on treatment without progression at data cutoff (**Figure 5**)
- There was nearly a 3-fold increase in ORR for patients with LAG-3 expression ≥ 1% (20%) vs LAG-3 expression < 1% (7.1%; **Table 5**)
- PD-L1 expression did not appear to enrich for response (**Table 5**)

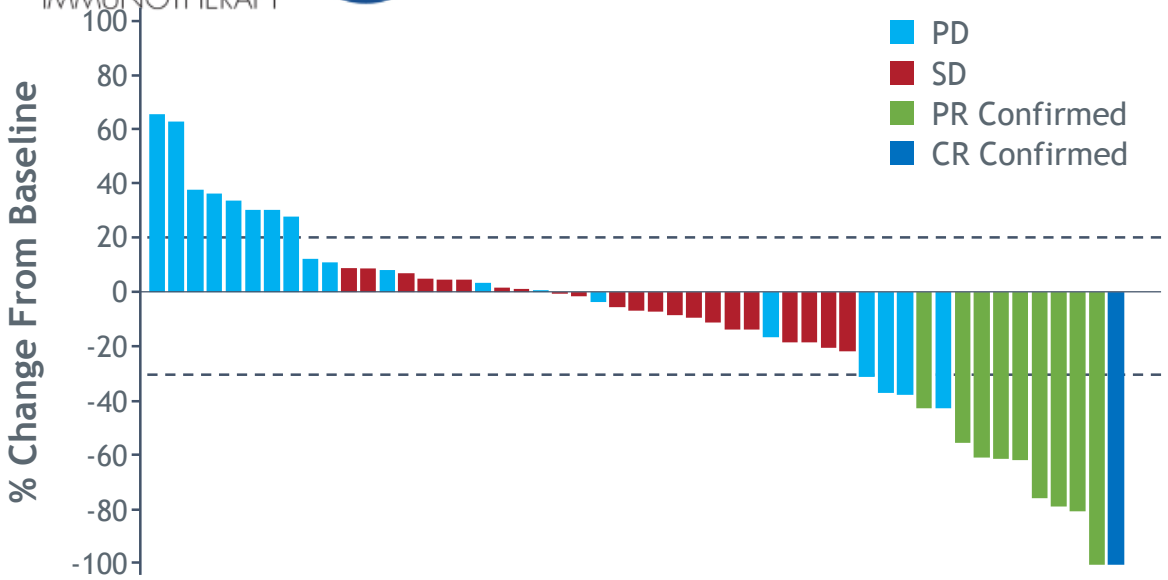
Figure 5. Ongoing Clinical Follow-Up

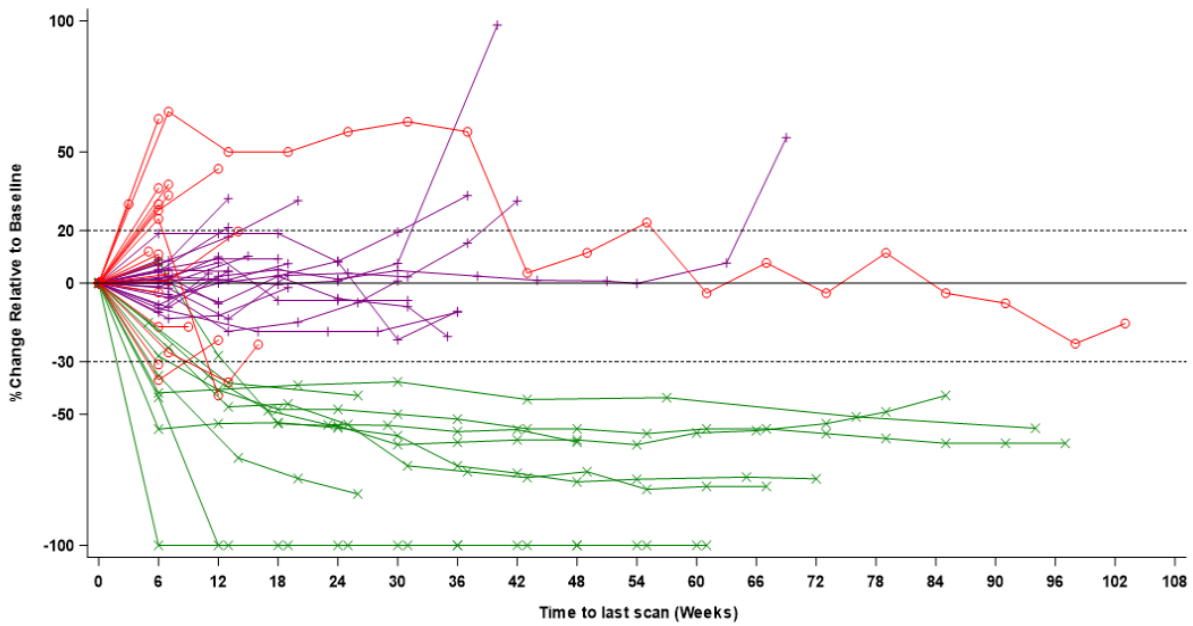


[a]Six patients had clinical progression prior to their first scan and are not included in the plot. [b]Censored on last visit. [c]Evaluations are planned for every 8 weeks.

Ascierto et al, ASCO 2017

Change in Tumor Volume and Change in Tumor Volume Over Time per irRECIST in ENCORE-601: Pembrolizumab + Entinostat

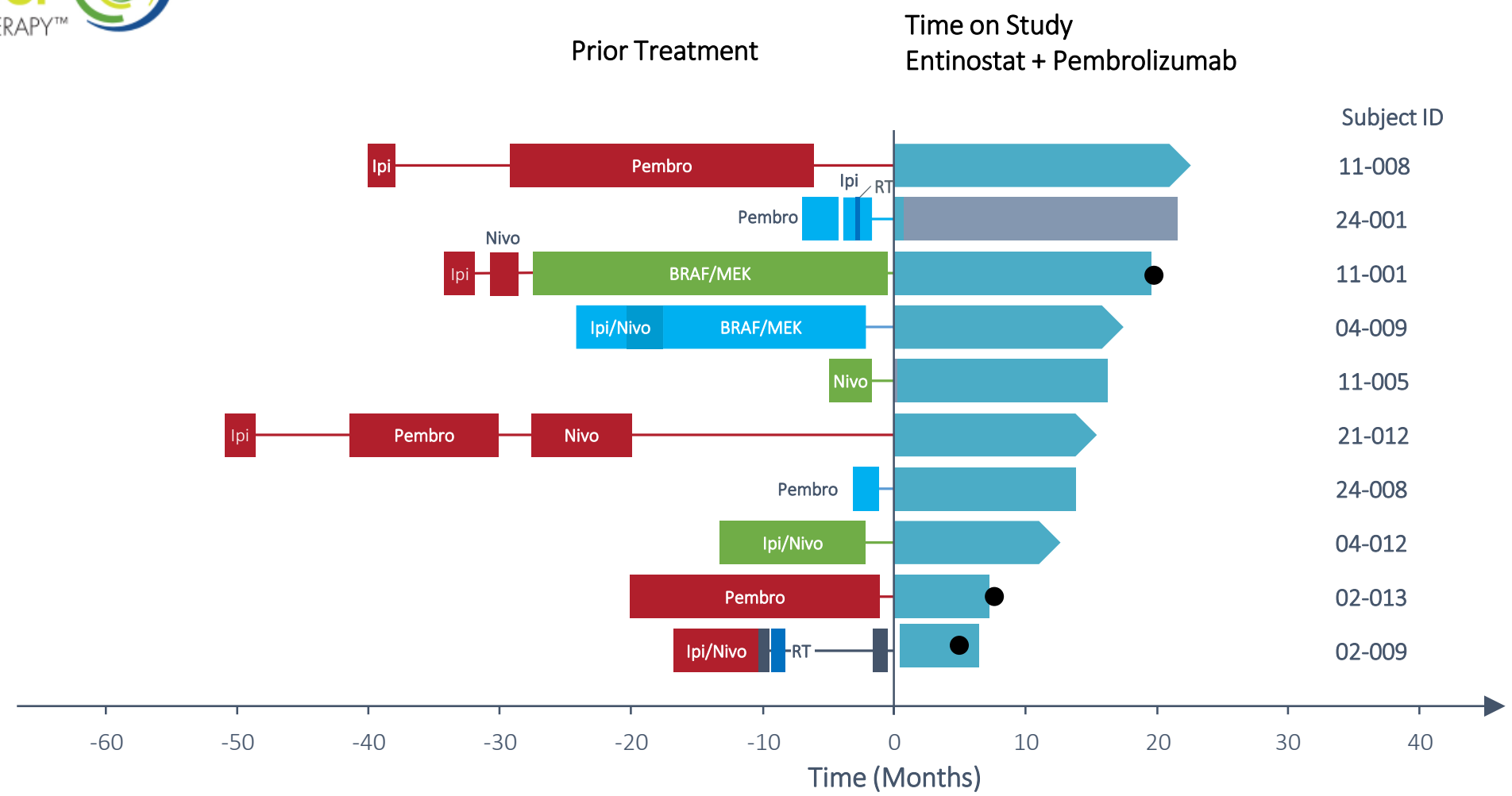




- 10 confirmed responses of 53 treated [19% ORR (95% CI: 9%-32%)]
  - 1 CR, 9 PRs
- Median duration of response: 13 months (range 3-20)
  - 4 responders ongoing
- An additional 9 patients have had SD for >6 months
  - 36% CBR (95% CI: 23%-50%)

CBR, clinical benefit rate; CI, confidence interval; CR, complete response; irRECIST, immune-related Response Evaluation Criteria in Solid Tumors; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

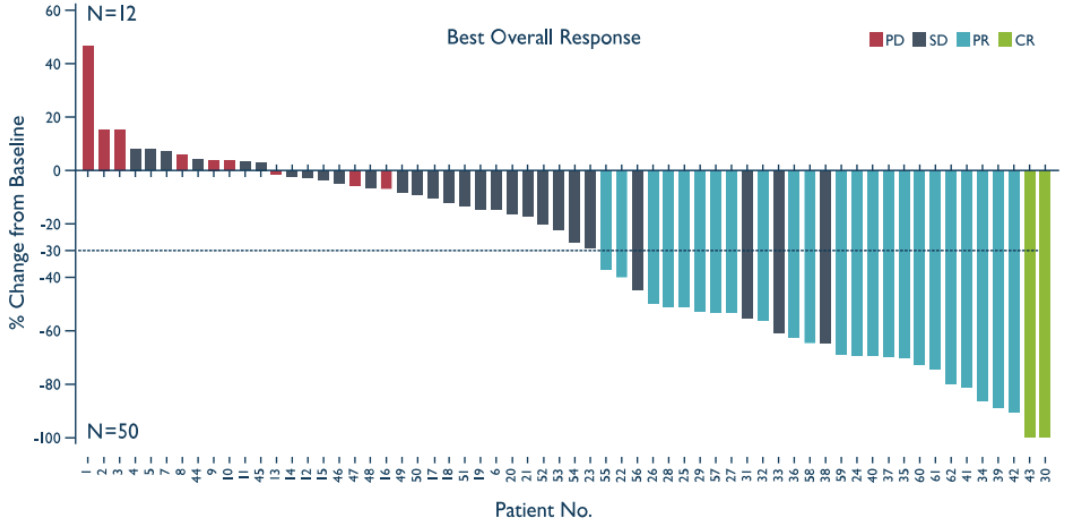
Responses Observed Regardless of Prior Treatment History



Ipi, ipilimumab; Nivo, nivolumab; RT, radiotherapy.

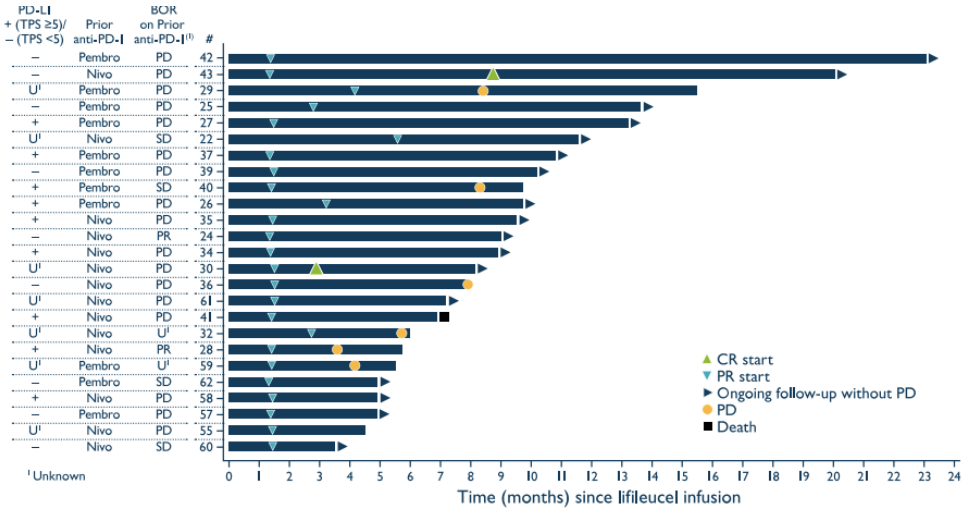
LN-144, Lifileucel

- Complex administration
- Select candidates



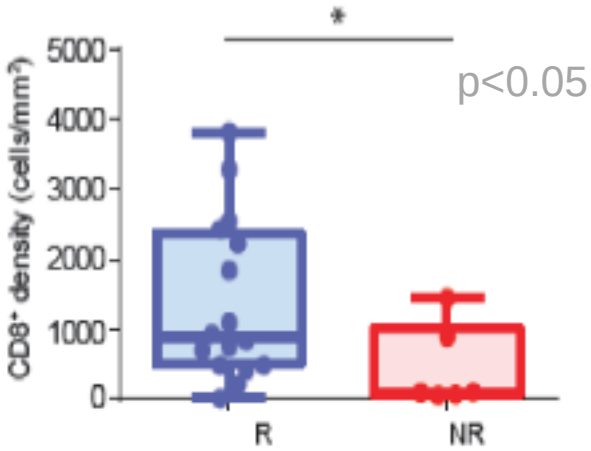
Three subjects had no post TIL disease assessment due to early death; one subject had no post-TIL disease assessment due to new cancer therapy. For subject #30,100% change from baseline is displayed for the CR visit involved lymph nodes.

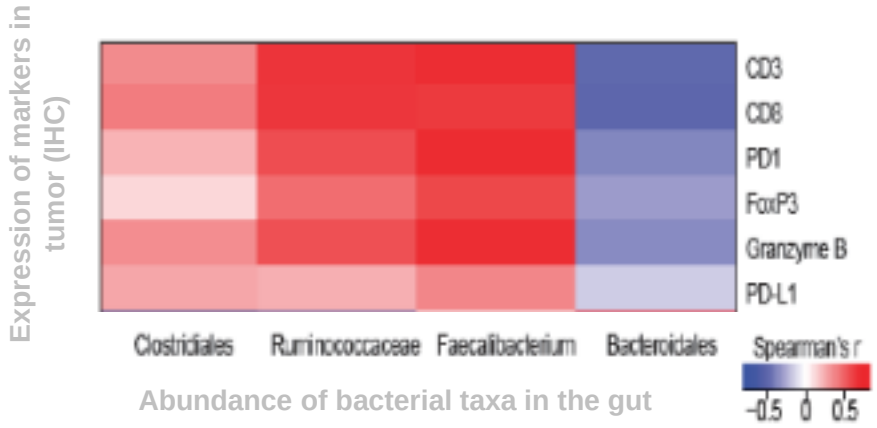
- 81% of patients had a reduction in tumor burden
- Mean Time to response 1.9 months (range 1.3-5.6)

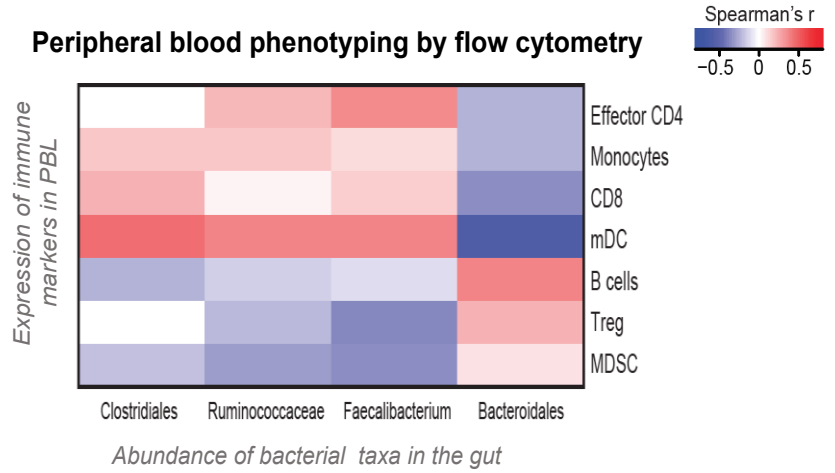


- 68% of responders have ongoing response

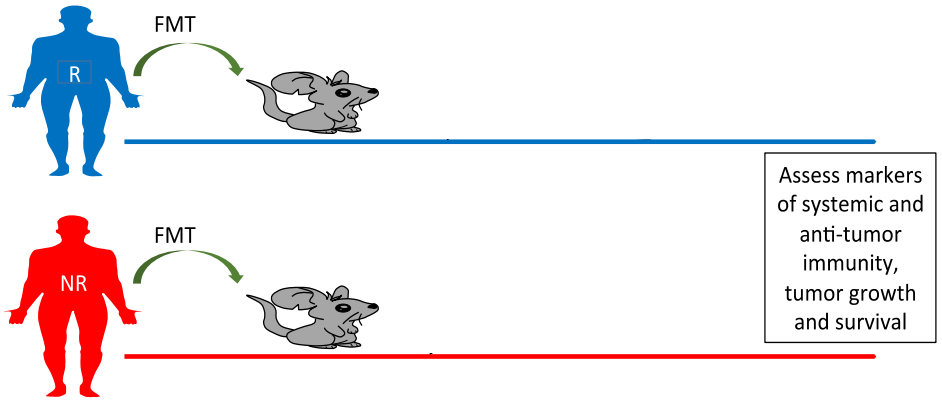
"Favorable" signatures in the gut microbiome associated with enhanced immune responses in the tumor microenvironment

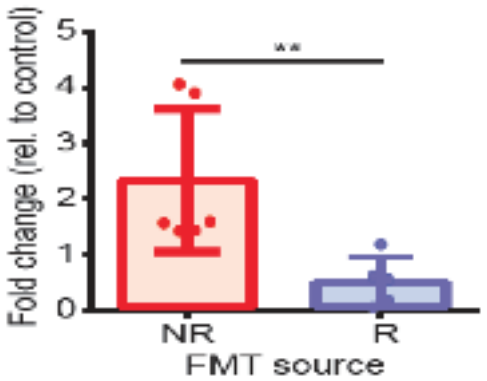


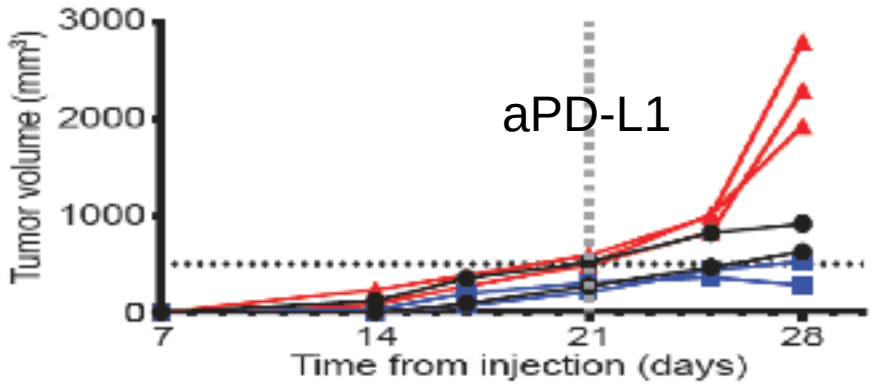




And mechanistic studies in germ free mice showed that fecal transplant could recapitulate the phenotype



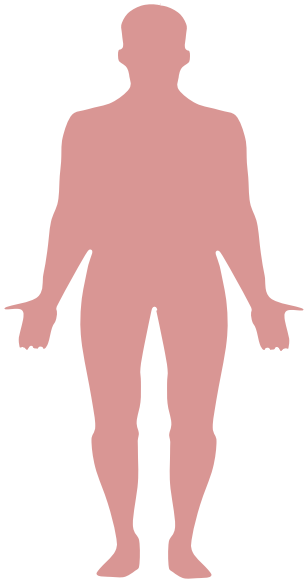




Mechanistic insights suggest that this is mediated both at the level of the gut and mesenteric lymph node, and also via metabolites produced by gut microbes potentially mediating distant effects (needs validation)

Gopalakrishnan et al, Science 2018

Numerous studies are now underway incorporating modulation of the gut microbiome in combination with response to immune checkpoint blockade



Clinical studies are testing whether cancer immunotherapy drugs work better when patients receive a fecal transplant. JEFF MCINTOSH/THE CANADIAN PRESS/AP PHOTO

Fecal transplants could help patients on cancer immunotherapy drugs

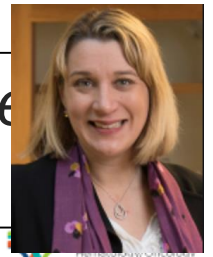
By **Jocelyn Kaiser** | Apr. 5, 2019 , 1:45 PM

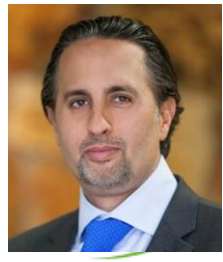
erapy
cebo)

Ongoing

In preparation

Promising data from 2 ongoing clinical trials was presente
at AACR Annual Meeting (March 2019)





MDACC PIs: Tawbi & Glitza

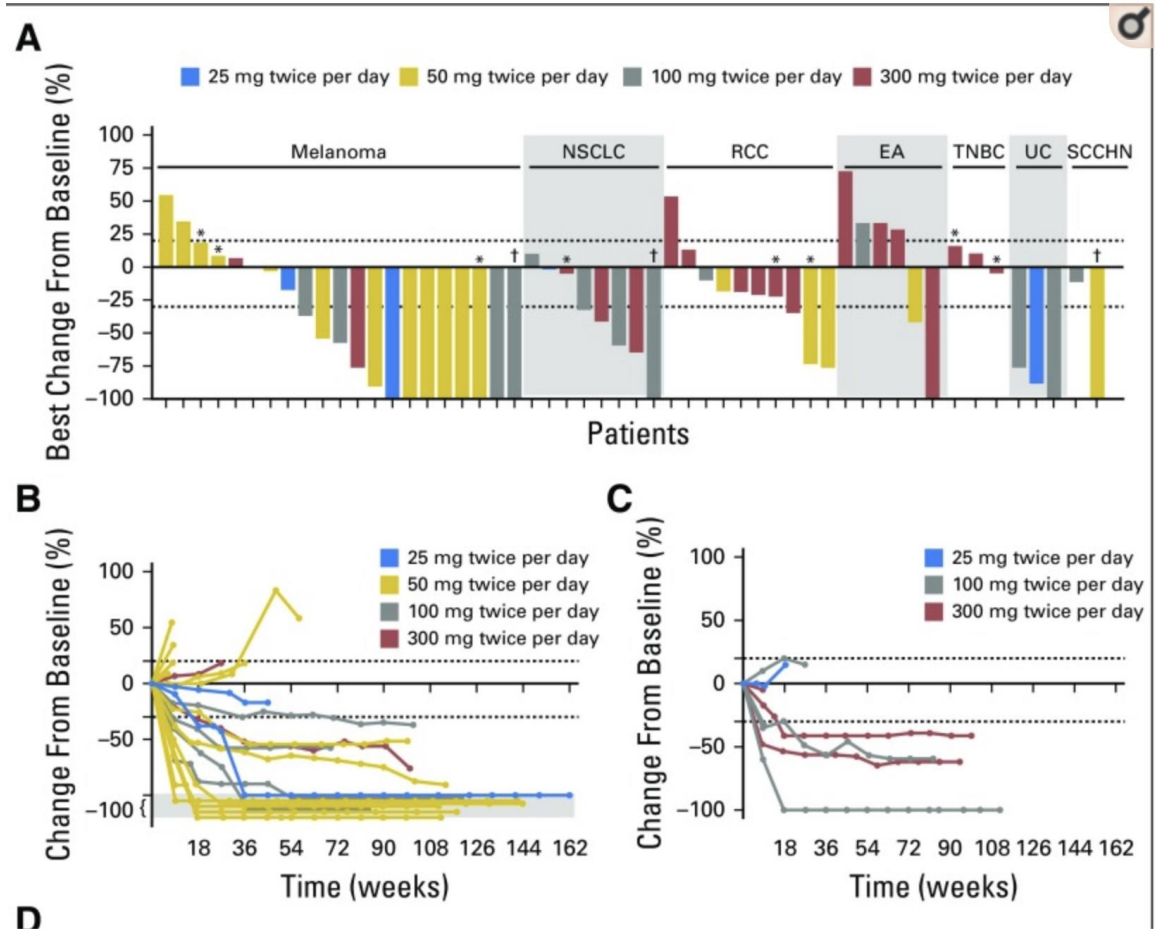
Rutgers and Angeles Clinic PIs: Mehnert & Hamid

LESSONS LEARNED IN PHASE 1

Phase I Key Considerations

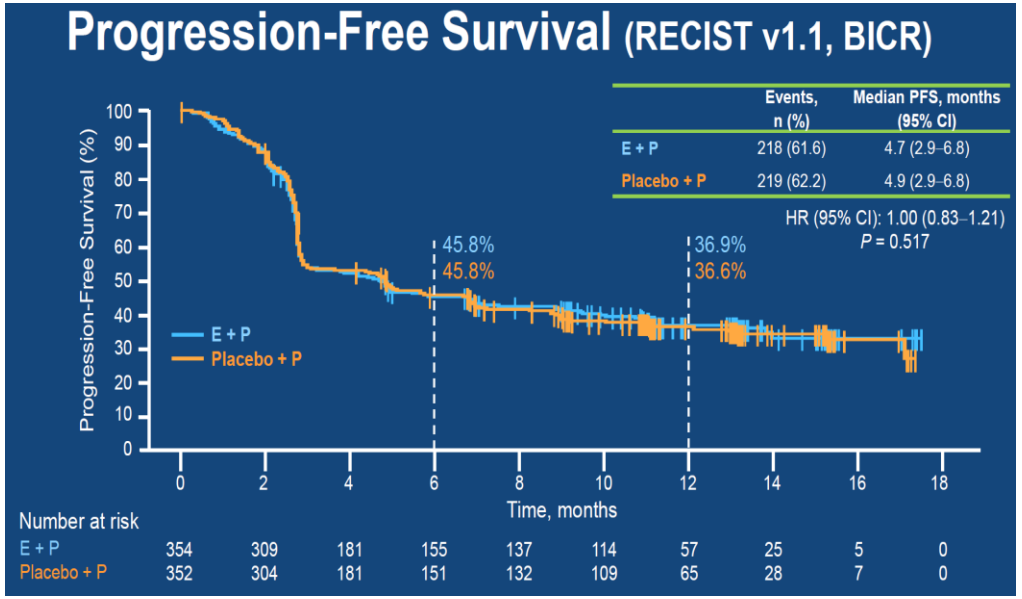
- Preclinical Rationale
- Assessment of Dose
- Study Population Evaluated and Activity Seen
- Target Modulation/Understanding of Mechanism

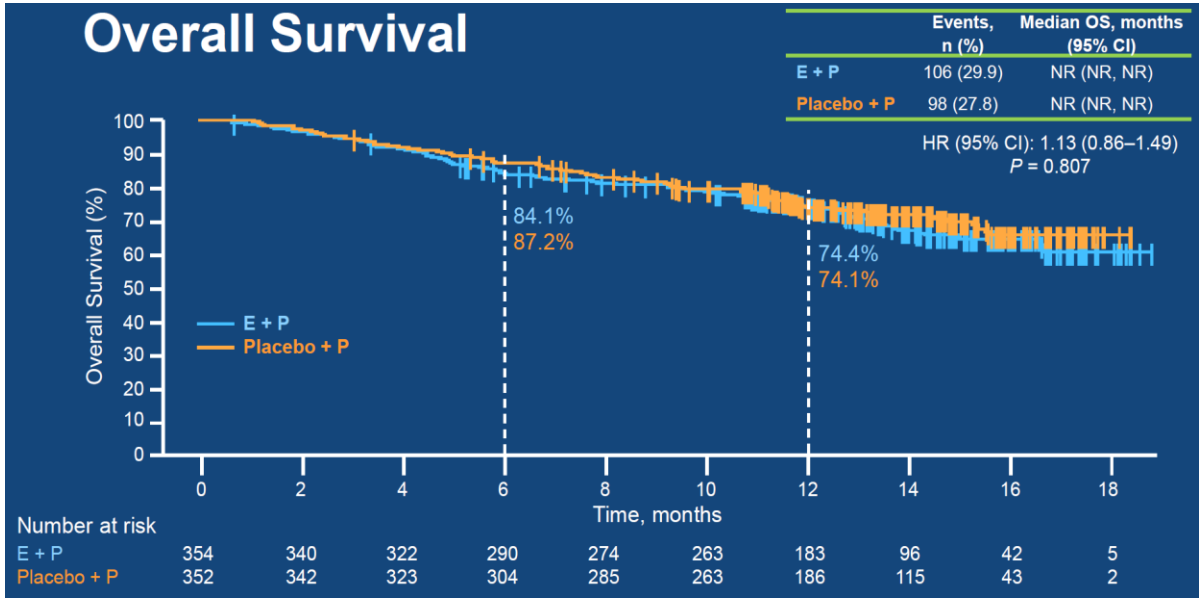
ECHO 202-KEYNOTE037



Mitchell T JCO 2018

ECHO 301

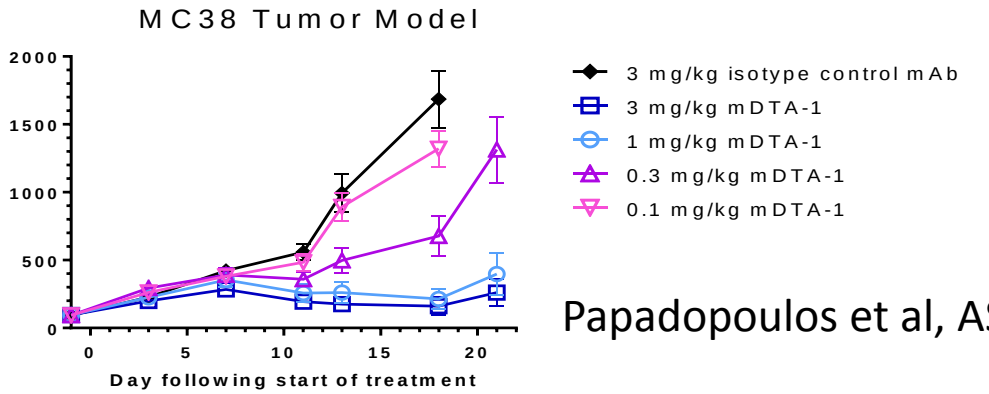




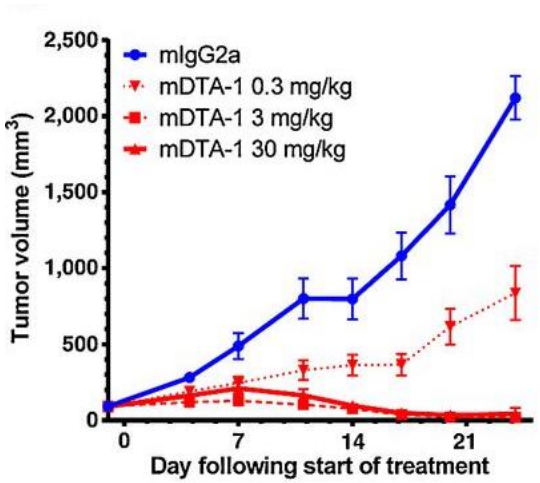
Long *et al*. ASCO 2018

GITR AGONIST MK-4166

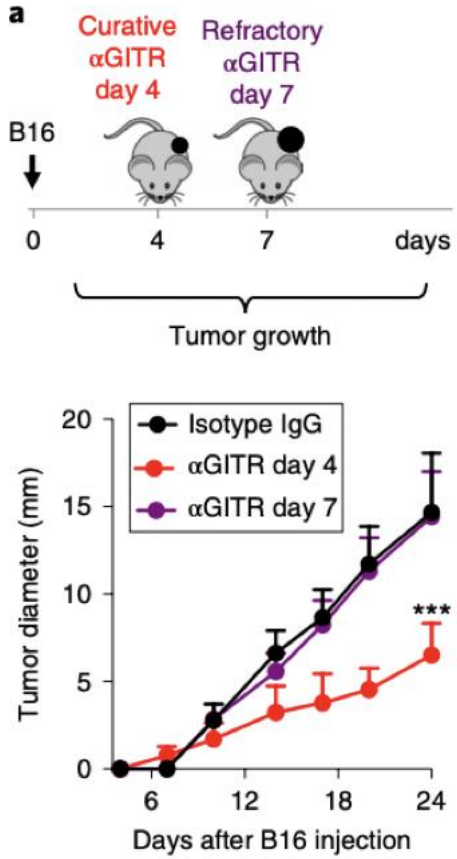
Efficacy of a Single Dose of mDTA-1 IgG2a in Syngeneic MC38 Mouse Tumors



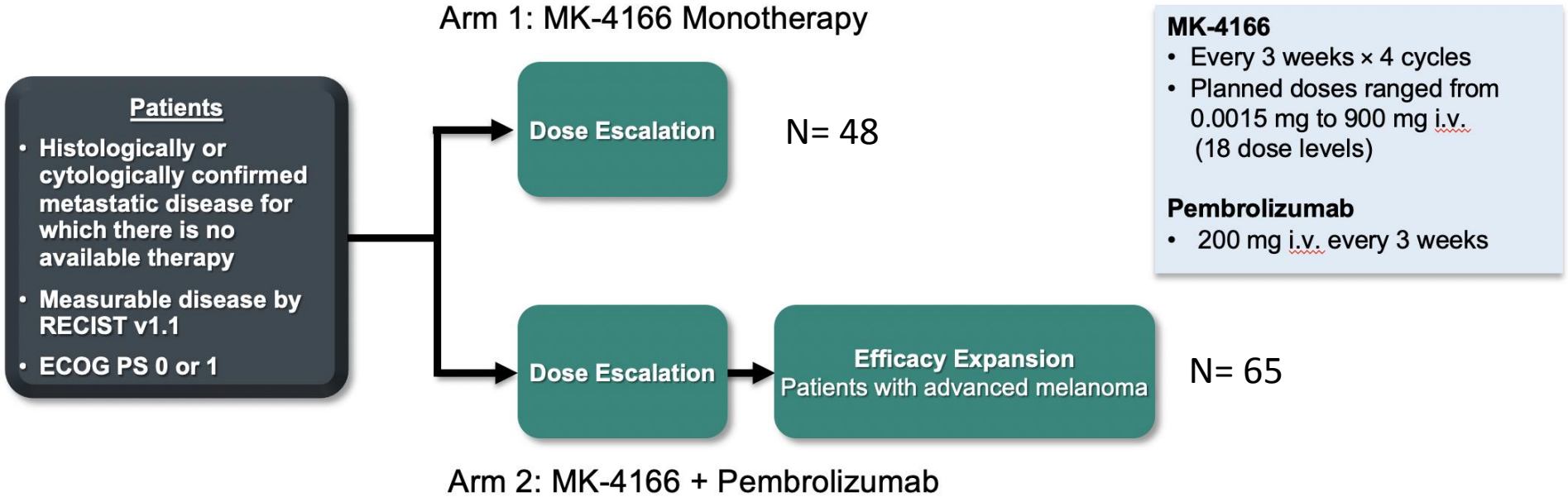
Papadopoulos et al, ASCO 2019



Mahne et al, Cancer Res 2017

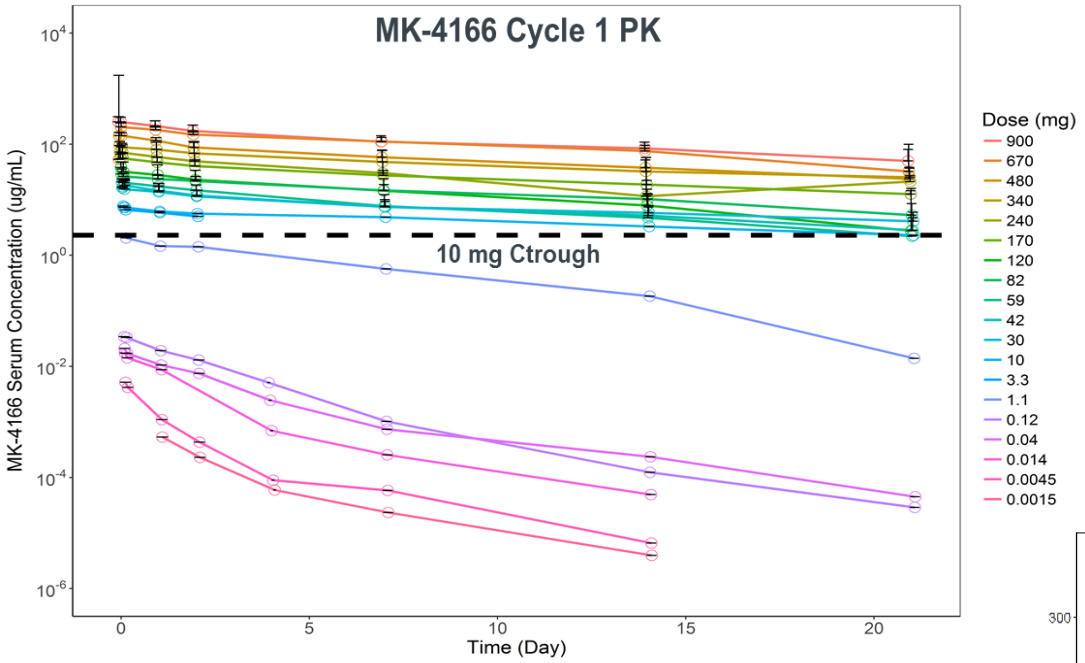


Zappasodi et al, Nat Med



- MK-4166 at a dose up to 900 mg as monotherapy and in combination with pembrolizumab 200 mg every 3 weeks was well tolerated
  - 7.7% of patients experienced TRAEs with the combination of MK-4166 plus pembrolizumab
- Responses were observed with MK-4166 in combination with pembrolizumab
  - High response rate (9/13 with 4 CRs and 5 PRs) was observed in patients with melanoma naive to ICIs

MONOTHERAPY NOT AN EFFECTIVE APPROACH!

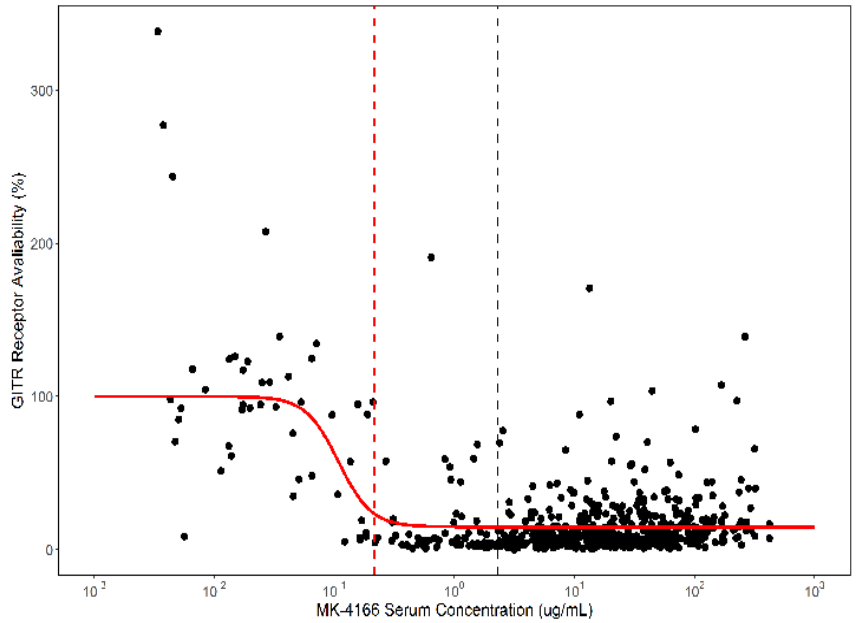


Horizontal dash line marks cycle 1 trough concentration at 10 mg dose

Target Mediated Drug Disposition Concomitant with Decreased GITR Availability on T Cells

90% GITR engagement achieved at MK-4166 0.217 µg/mL

MK-4166 10 mg achieves >90% GITR engagement at trough



Vertical red dashed line marks concentration needed for 90% target engagement

Vertical black dashed line marks cycle 1 trough concentration at 10 mg dose

- 0% Monotherapy Response Rate
  Noted Also with Other In-class Agents (AMG228, TRX518)
- Well Tolerated Agent…MTD not reached
- 69% intriguing ORR…AGAIN?
- Target Modulation Not Demonstrated
- How Do We Know How Much Dose Matters?

Conclusions

- Multiple exciting compounds and approaches
- Clinical trial design must be as inclusive as possible of population seen
- Attention to preclinical rationale, biomarker development, and mechanistic studies is critical