Redirecting T Cells for Prostate Cancer Immunotherapy

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Equity
Actym, Allector, Atreca, Bioalta, Bolt, Keyhole, Immunogenesis, Nutcracker, RAPT, Scribe, Senti, Soteria, TeneoBio

Immunotherapeutic approaches

Enhancing endogenous immunity

Blocking inhibitors

Stimulating effectors

- Vaccines
- Immune checkpoint modulators

Redirecting immune effectors

Engineering cellular specificities

Colocalizing effectors to tumors

- T cell engagers
- CART

PSMA
PSCA
STEAP
B7-H3

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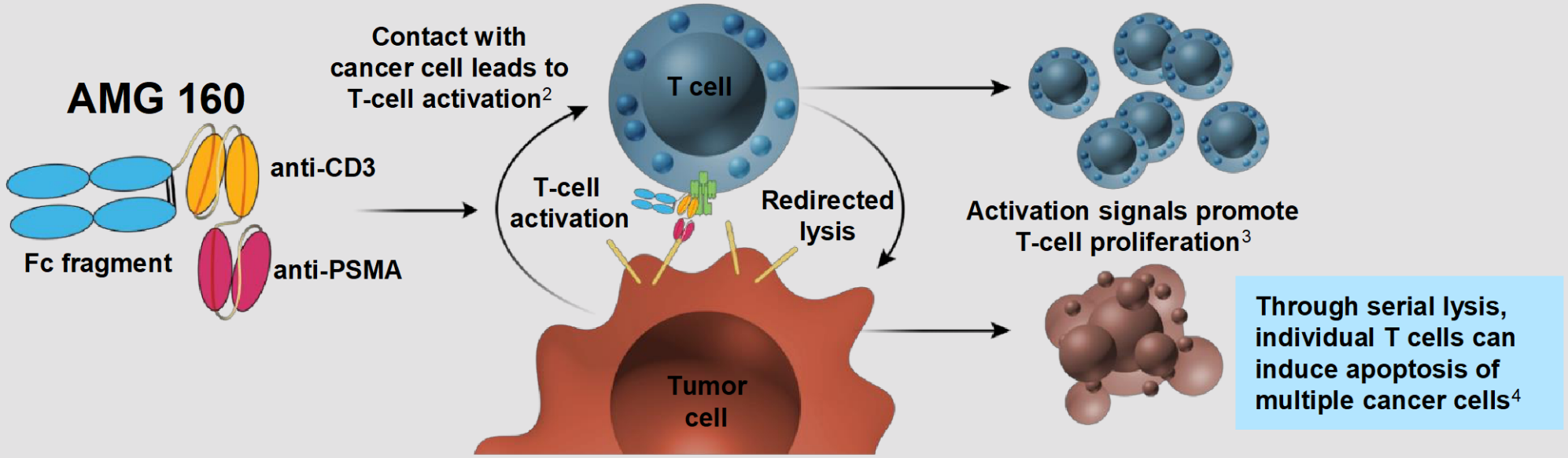
PSMA trispecific: AMG 160



- BiTE® molecules engage a patient's own T cells to attack and eradicate cancer cells[1]
  - T-cell activation induces transient cytokine release and tumor killing[1]
- Blinatumomab (BLINCYTO®, Amgen Inc.) is the first and only bispecific immunotherapy approved in oncology worldwide[1]
- AMG 160 is a half-life extended PSMA x CD3 BiTE® immunotherapy for mCRPC

Tran et al. ESMO 2020

AMG160: Adverse events

- 43 patients received ≥ 1 dose of AMG 160 monotherapy
  - 41 (95.3%) patients experienced TEAEs
  - 19 (44.2%) patients remained on AMG 160 at the time of data analysis
    - 6 (14.0%) received treatment ≥ 6 months

TRAEs

- 41 (95.3%) patients experienced TRAEs
  - No grade 5 events, and none resulted in treatment discontinuation
- 3 reversible dose-limiting toxicities occurred
  - Grade 3 rash (n = 2)
  - Grade 3 GI hemorrhage (n = 1)

ADAs

- 6 of 30 (20.0%) patients assessed developed ADAs affecting drug exposure between cycles 1 and 10
  - No AEs associated with ADAs were observed

TRAEs in ≥ 20% of patients (N = 43)*

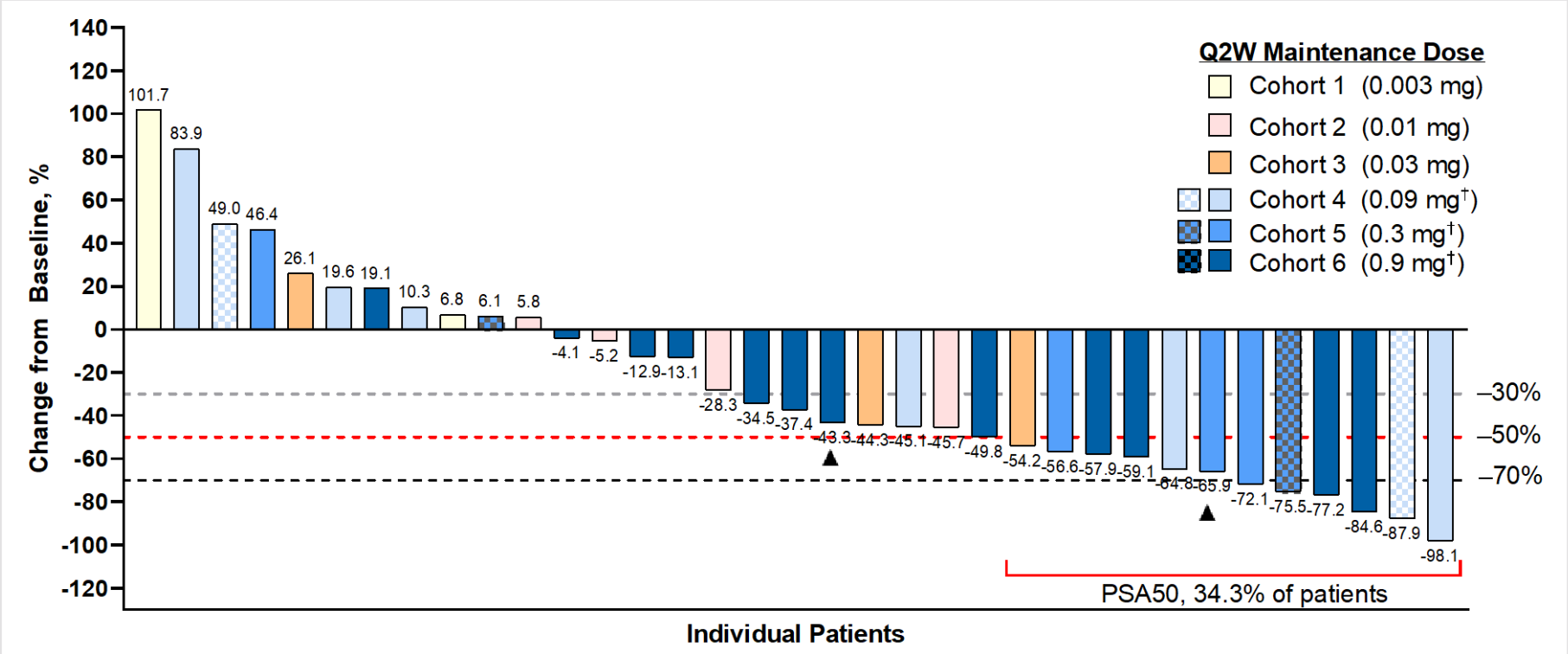
TRAE, n (%)	All Grade, n (%)	Grade 3, n (%)
CRS (Lee criteria)†	39 (90.7)	11 (25.6)
Fatigue	19 (44.2)	1 (2.3)
Vomiting†	19 (44.2)	0 (0)
Nausea†	17 (39.5)	0 (0)
Pyrexia†	16 (37.2)	0 (0)
Headache†	15 (34.9)	0 (0)
Diarrhoea†	14 (32.6)	2 (4.7)
Dry mouth	13 (30.2)	0 (0)
Rash†	12 (27.9)	4 (9.3)
Hypophosphataemia	11 (25.6)	4 (9.3)
Hypotension†	10 (23.3)	5 (11.6)
Chills†	10 (23.3)	0 (0)
Dysgeusia	10 (23.3)	0 (0)
Decreased appetite	9 (20.9)	0 (0)

* 8 patients experienced grade 4 laboratory abnormalities that were clinically non-significant;
† CRS-related

Tran et al. ESMO 2020

AMG160: PSA modulation

- **PSA reductions (best response) were dose dependent and occurred in 24/35 (68.6%) evaluable patients (20 July 2020)**
- **PSA reductions > 50% occurred in 12/35 (34.3%) evaluable patients**



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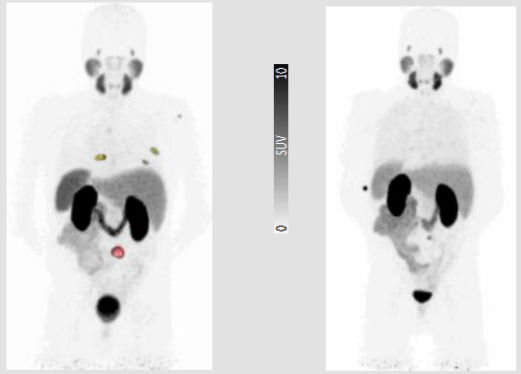
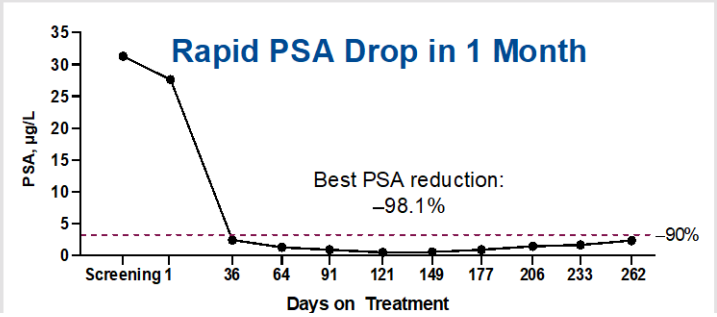
AMG 160: Clinical responses

Patient	10112001002
Prior Rx	Surgery, radiotherapy, docetaxel, enzalutamide, bicalutamide, and talazoparib
Cohort	4 (0.09 mg with cycle 1 priming)

PR by 3 Months
PSMA PET/CT

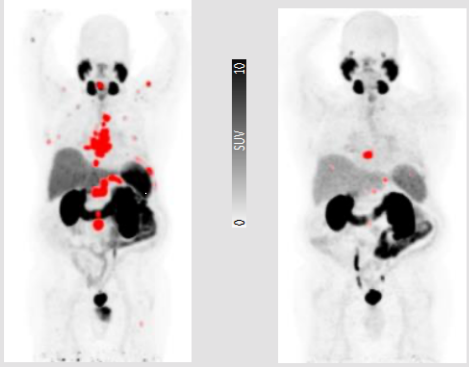


Baseline **Week 12**

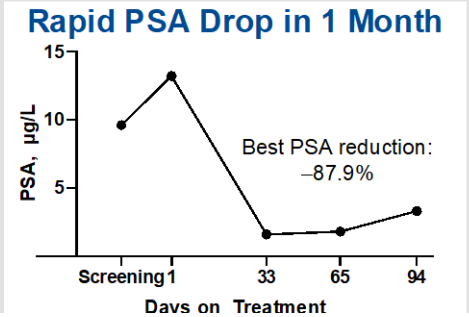


Patient	10166004005
Prior Rx	Surgery, docetaxel, enzalutamide, sipuleucel
Cohort	4 (0.09 mg with optimised cycle 1 priming)

Not RECIST evaluable
PSMA PET/CT

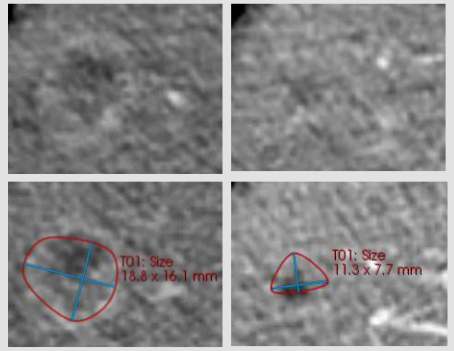


Baseline **Week 12**



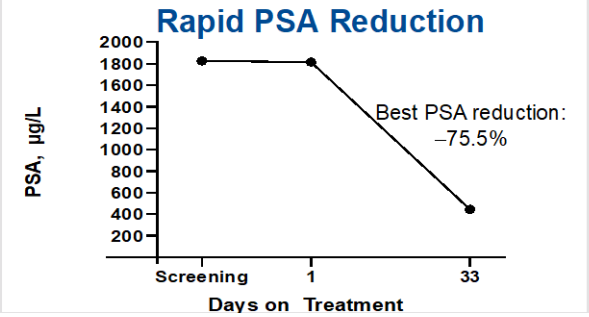
Patient	10166004006
Prior Rx	Radiotherapy, apalutamide, docetaxel, sipuleucel-T, radium-223
Cohort	5 (0.3 mg with optimised cycle 1 priming)

PR (u)* by 2.5 Months



Baseline
T01 Liver Segment VIII

Week 10
40% reduction vs baseline



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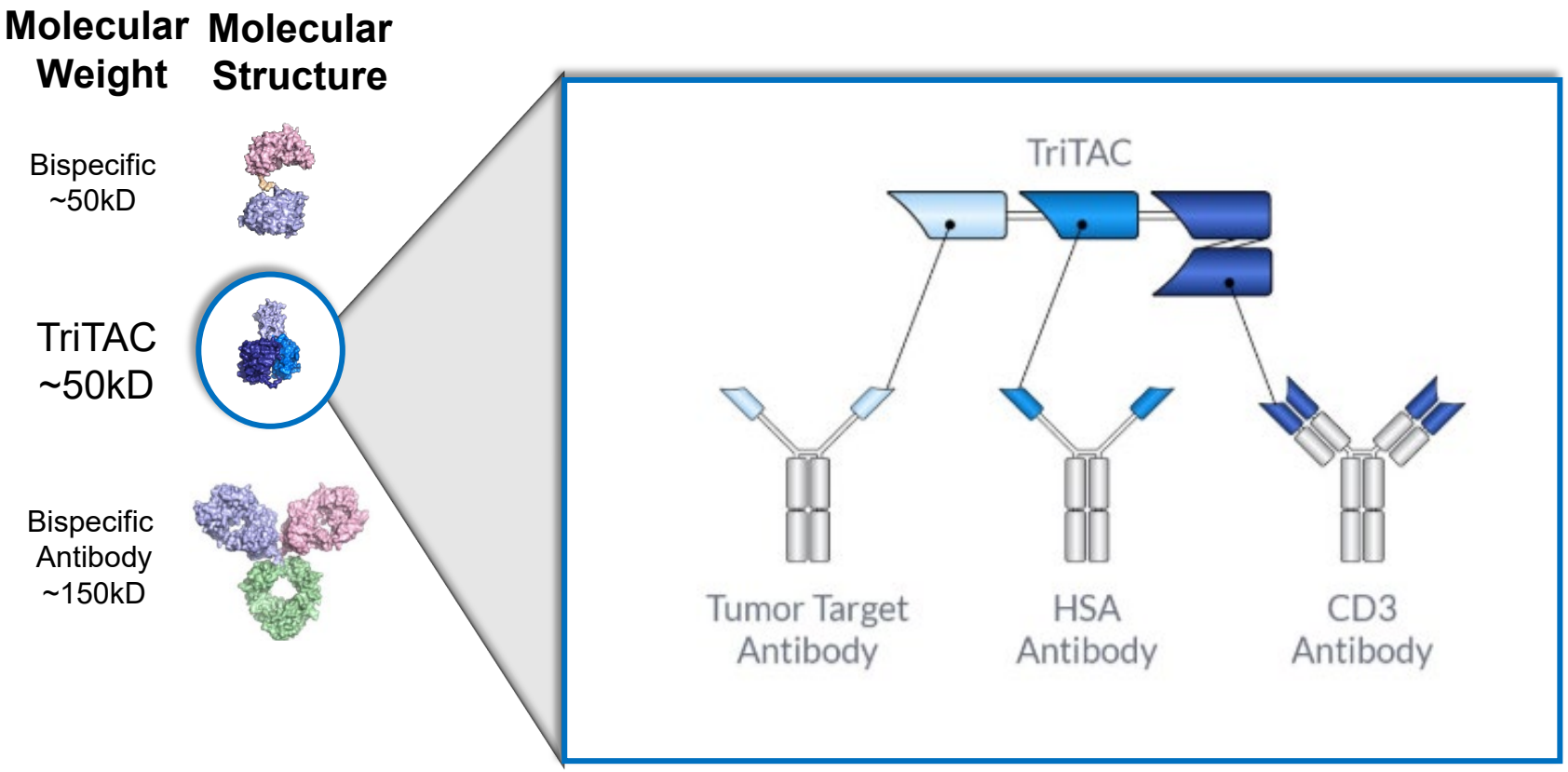
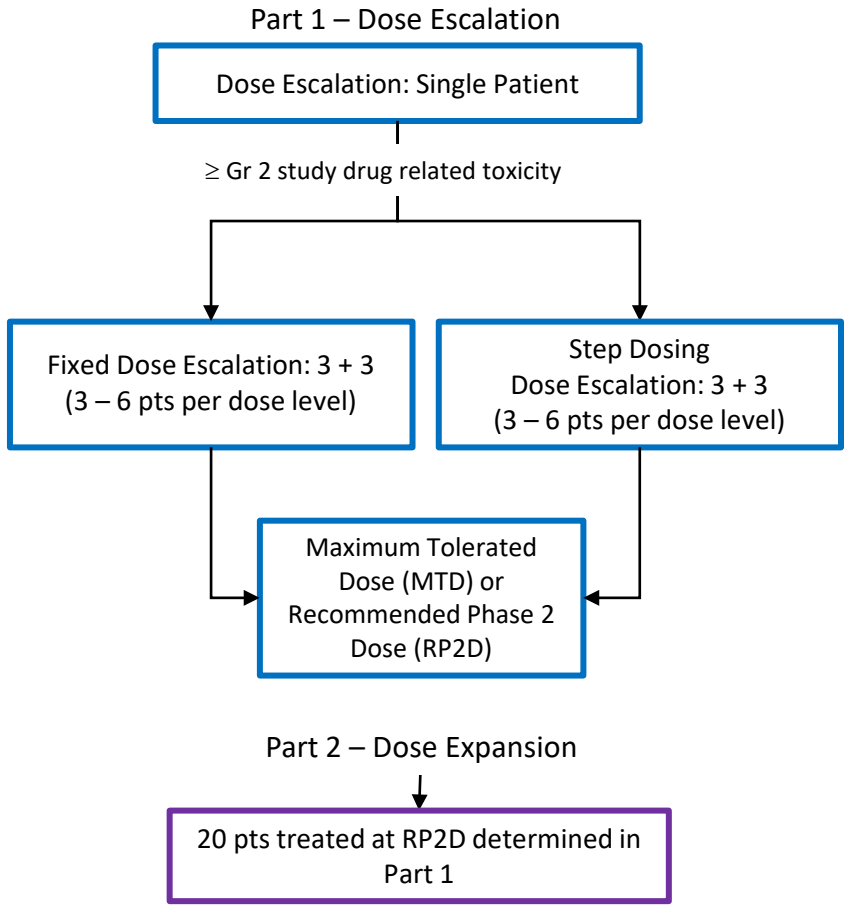
PSMA “Trispecific”: HPN424



- Constructed as a small, globular protein (~50kDa)
- Binds monovalently to CD3 and PSMA

Bendell, Fong et al. ASCO 2020

Trial Schema



- **Target Population**
  - Disease progression on the prior systemic regimen
  - At least two prior systemic therapies approved for mCRPC
  - Prior chemotherapy allowed, but not required
- **Trial Design**
  - Objectives include characterization of safety, PK, pharmacodynamics and identification of expansion dose
  - Tumor assessments performed q9w and include conventional CT and bone scans and PSA
- **Dosing, Administration & Exposure**
  - HPN424 administered qw, 1 hour IV infusion (one cycle = 3 weeks)
  - Starting dose of 1.3ng/kg established by minimally anticipated biological effect level

DeBono, Fong et al. ASCO 2021

Baseline Demographics

Age (Years)	
Median	70
Range	43 - 91
Race	
White	69 (78%)
Black	8 (9%)
Asian	2 (2%)
Other / Not reported	10 (11%)
ECOG Performance Status	
0	39 (44%)
1	50 (56%)
PSA (ng/mL)	
Mean	464
Median	129
Range	0.1 – 5000

Time Since Diagnosis (Years)	
Mean	8.5
Median	6.9
Range	0.9 – 27.1
Stage at Diagnosis (n=75)[a]	
M0	37 (49%)
M1	38 (51%)
Location of Metastases	
Bone	78 (88%)
Lymph Node	43 (48%)
Lung	12 (14%)
Liver	10 (11%)
Other Visceral	10 (11%)
Other Non-visceral	4 (5%)

Prior Therapies	n (%)	Median (Range)
All Prior Therapy	89 (100%)	5 (1 – 12)
Novel Hormonal Therapy	87 (98%)	2 (0 – 4)
Chemotherapy (mCRPC)	65 (73%)	1 (0 - 3)
Immunotherapy	30 (33%)	0 (0 – 3)

Reason for Entering Study (n=64)[a]	
PSA Progression	27 (42%)
PSA & Clinical Progression	3 (5%)
PSA & Radiographic Progression	10 (16%)
Radiographic Progression	24 (38%)

[a] Actual n is indicated where full dataset not available

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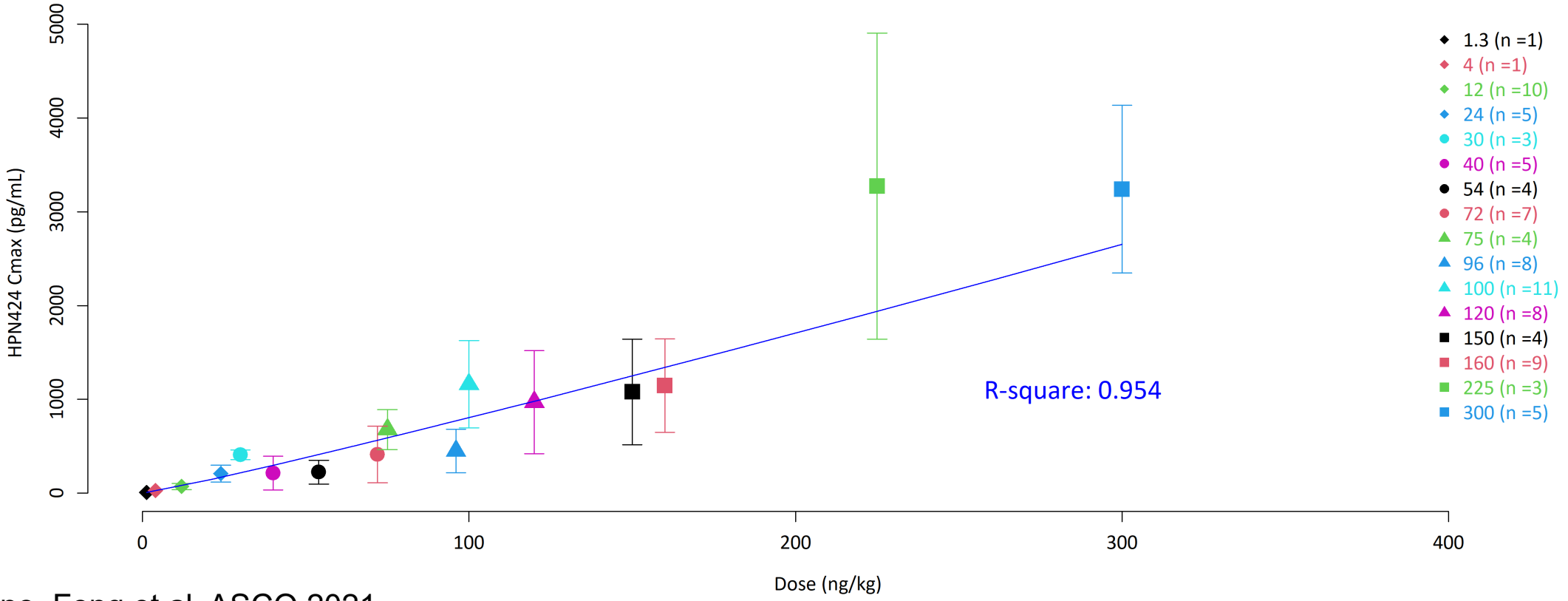
Pharmacokinetics

- Dose proportional increase in Cmax
- Mean T1/2 with dose group of N>2 is 24 hrs (range of 9 – 70 hrs)
- PK parameters: T1/2, CL, and volume of distribution are dose independent suggesting linear PK kinetics



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Adverse Events

Event, n (%)	All Grades	Grade 3+
Cytokine-Related AEs[a]		
Cytokine Release Syndrome (CRS)[b]	61 (69%)	4 (4%)
Chills	60 (67%)	0 (0%)
Pyrexia	58 (65%)	2 (2%)
Hypotension	35 (39%)	6 (7%)
Infusion Related Reaction (IRR)	20 (22%)	0 (0%)
Flushing	13 (15%)	0 (0%)
Hypoxia	11 (12%)	4 (4%)
Liver Function Tests		
AST Increase	28 (31%)	19 (21%)
ALT Increase	26 (29%)	14 (16%)
Other Adverse Events		
Fatigue	45 (51%)	3 (3%)
Nausea	40 (45%)	1 (1%)
Vomiting	34 (38%)	1 (1%)
Anemia	28 (31%)	10 (11%)
Headache	24 (27%)	0 (0%)
Back Pain	21 (24%)	4 (4%)
Tachycardia	20 (22%)	1 (1%)
Constipation	20 (22%)	0 (0%)
Decreased Appetite	20 (22%)	0 (0%)

[a] Includes AEs that were reported as concurrent symptoms of the CRS events
[b] CRS Grading according to ASTCT 2019 criteria

- Maximum-tolerated dose (MTD) not yet reached
- Dose Limiting Toxicities (DLTs):
  - Observed at doses ranging from 96 to 300ng/kg
  - Did not limit escalation
  - Most Common: Transaminitis G4 (n=6); Cytokine Release Syndrome G3 (n=4)
    - Majority of events occur with first dose
- No Grade 4 or 5 CRS, no Grade 5 treatment-related AEs
- Two of 89 (2%) pts discontinued treatment due to treatment-related AEs

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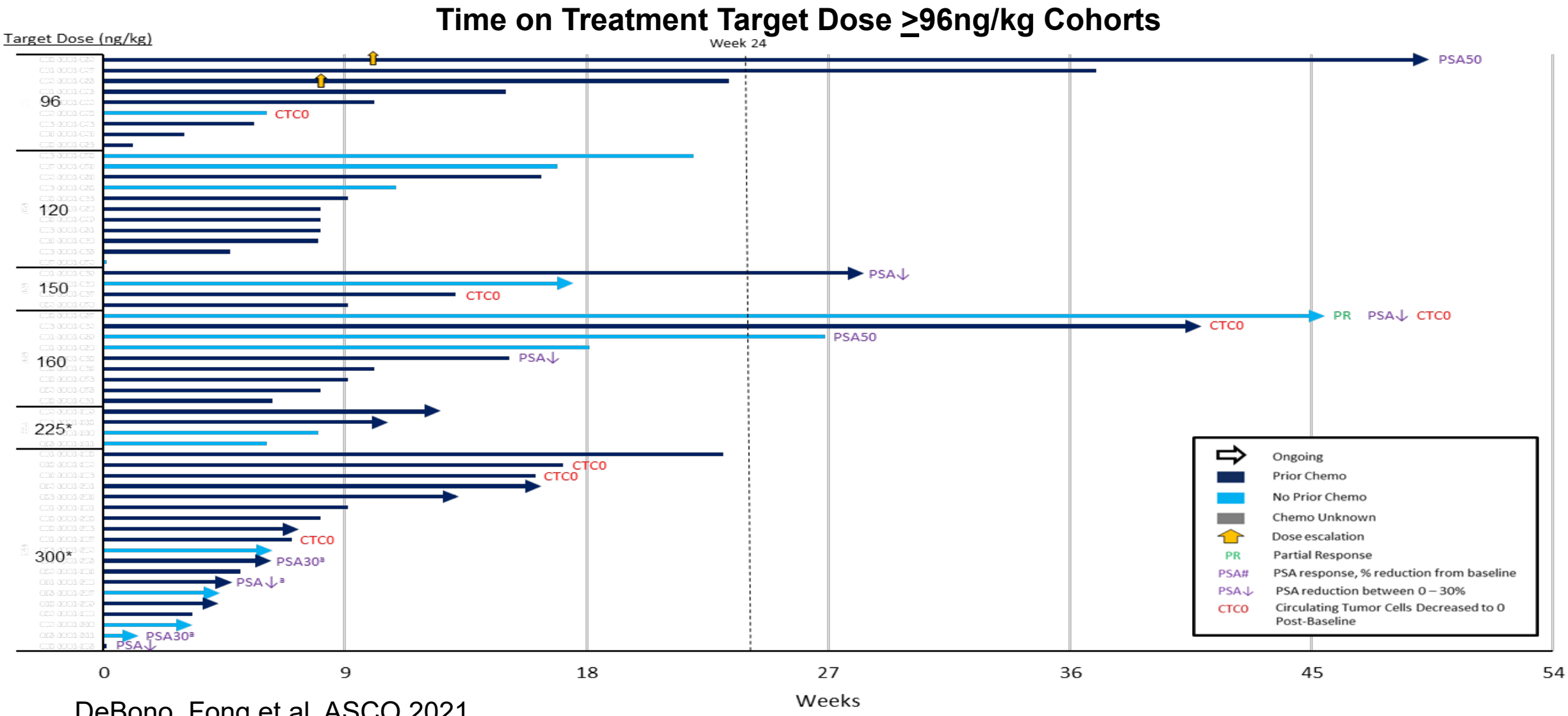
HPN424 Clinical Activity



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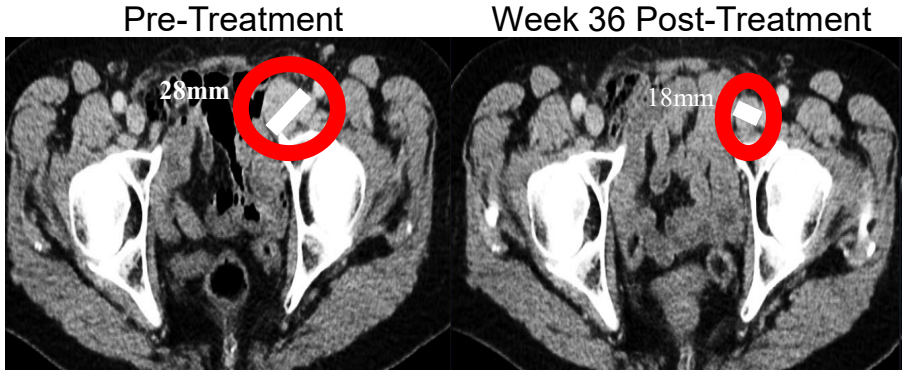
HPN424-1001 RECIST Response

Baseline Characteristics			
ECOG	1	Reason for Study Entry	Radiographic Progression
PSA (ng/mL)	39	Location of Metastases	Lymph Node
Stage at Diagnosis	M0	Prior Therapies	ADT, Bicalutamide, Apalutamide



- Initiated HPN424 at 160ng/kg
- Demonstrated RECIST partial response (-32%) at 1st post-baseline scan (Week 9), confirmed PR (-43%) at Week 18, response maintained at Week 36
- Remains on study after 41 weeks of treatment

HPN424-1001 Summary

- HPN424, a novel half-life extended PSMA-targeting T cell engager, is active and generally well tolerated.
- CRS has been transient and manageable with 4% of patients experiencing Grade 3 CRS, no Grade 4 or 5.
- CRS and transaminitis events observed most often in Cycle 1, with diminished frequency and severity in subsequent cycles.
- HPN424 has antitumor activity including a confirmed PR per RECIST, PSA declines and CTC reductions.
- Treatment duration $\geq$ 24 weeks observed in 15 of 74 (20%) pts, including 8 of 17 (47%) chemo-naïve patients.
- Assessment of optimal target dose and patient population for expansion ongoing.

How can we improve the therapeutic index of these T cell engagers?

- The majority of the T cell engagers in development use an anti-CD3 from: SP34, OKT3, UCHT1.

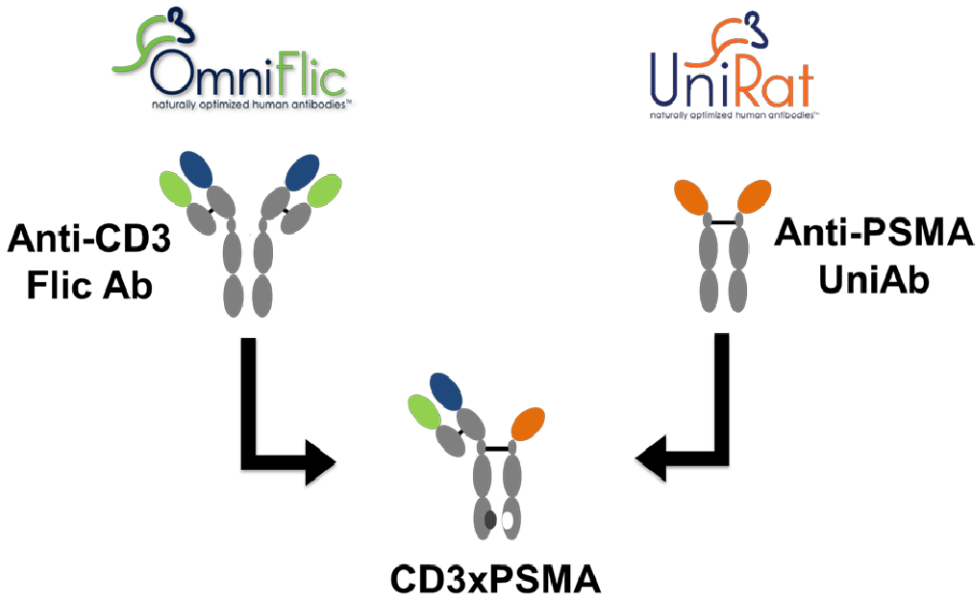
All high affinity…

- Could lower affinity anti-CD3 domains reduce toxicity without compromising efficacy?

Development of TNB-585

Activating αCD3 Ab

- Retained Efficacy, Reduced Cytokine Secretion
- Reduced Treg activation
- Unique CD3 δε epitope



αPSMA UniAb

- High affinity
- Heavy chain only

Fc Tail

- Silenced human IgG4 Fc
- Engineered to prevent arm exchange
- Knob/Hole design
- No off-target T-cell activation

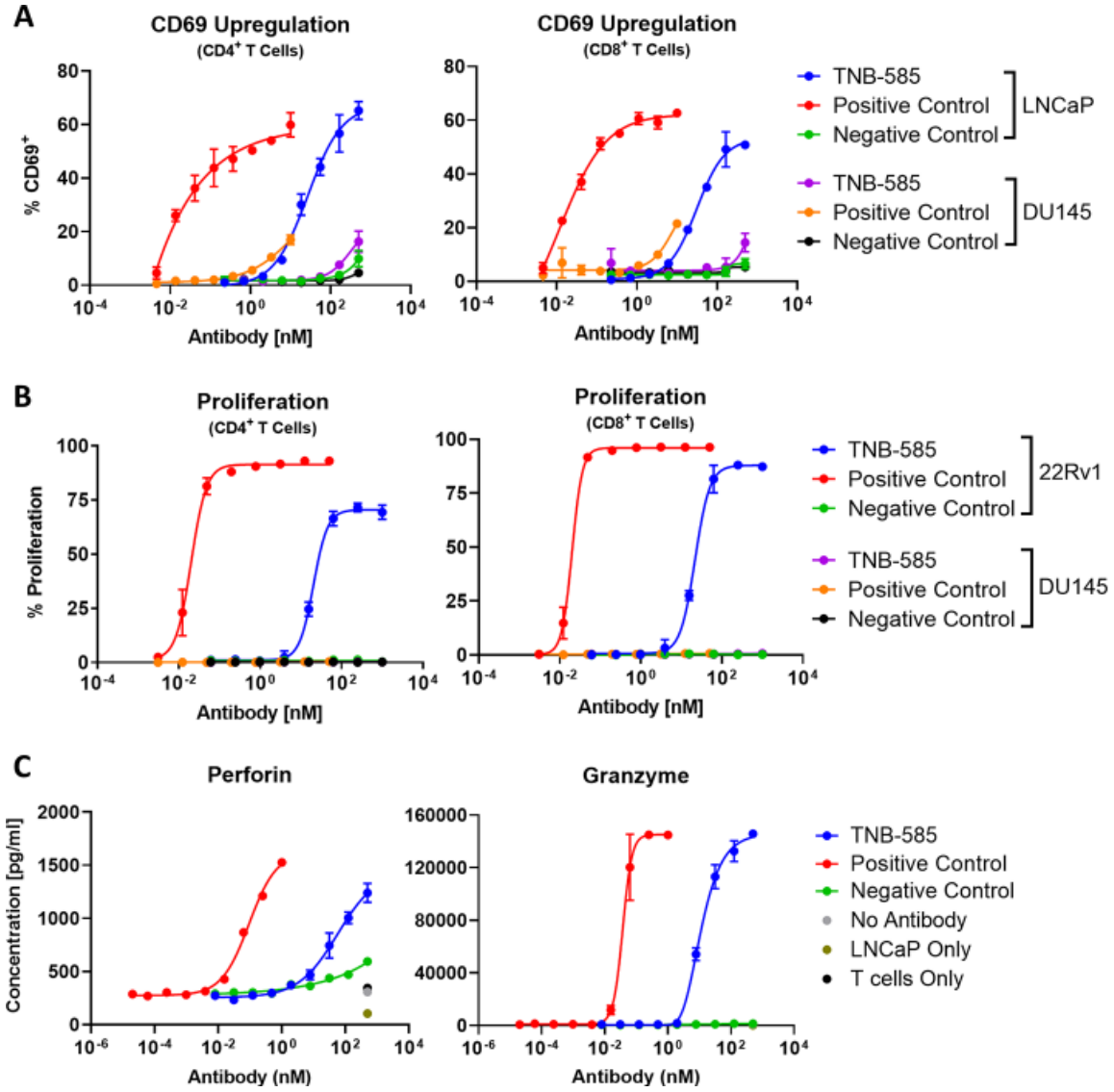
Dang et al. PCF 2019

TNB-585 activates T cells *in vitro*

PSMA+: LN-CAP, 22Rv1
PSMA-: DU145

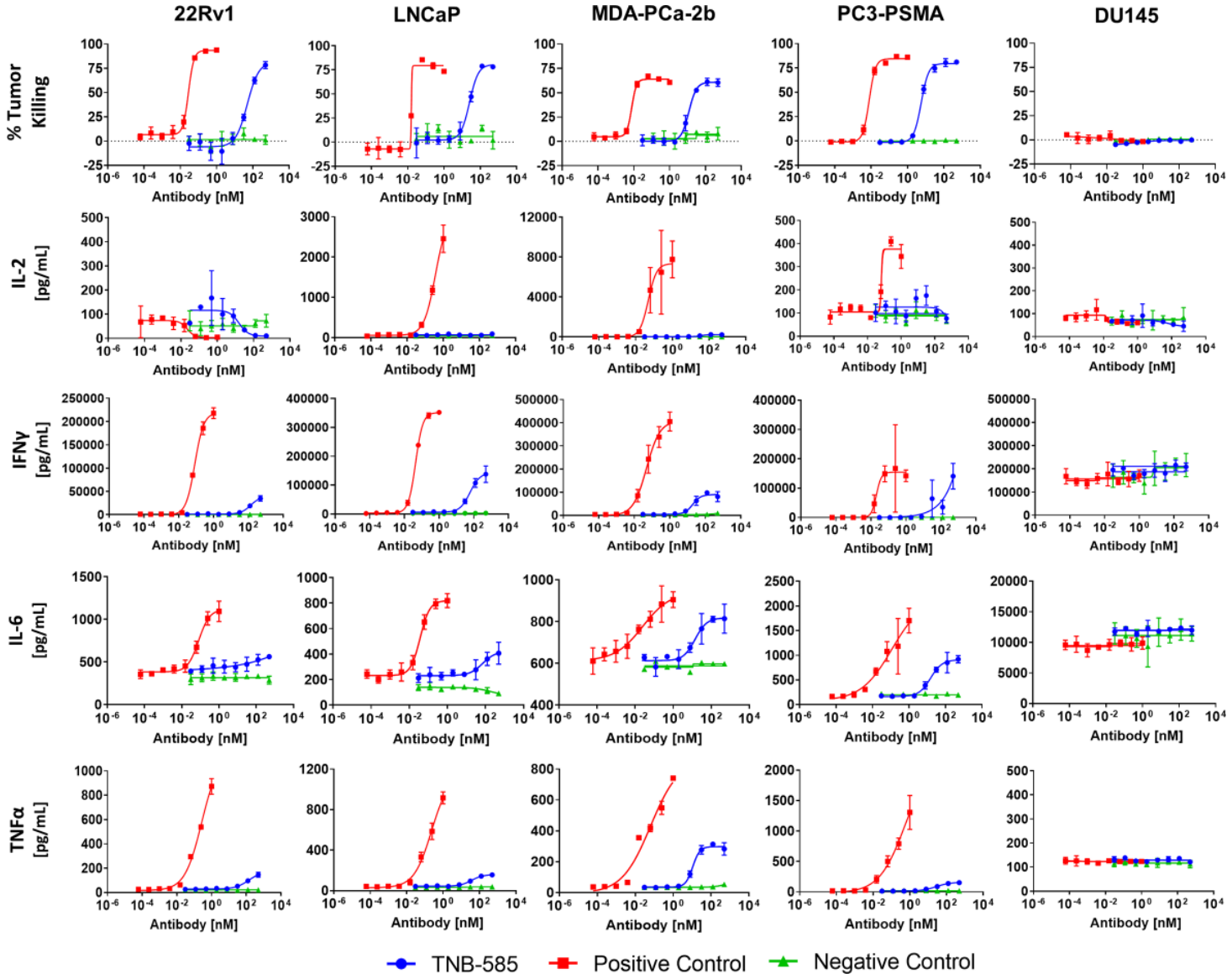
Positive Control: OKT3-like

T cell/tumor/drug cocultures



Dang … Fong, Dalvi. JITC 2021

TNB-585 attenuates cytokine production



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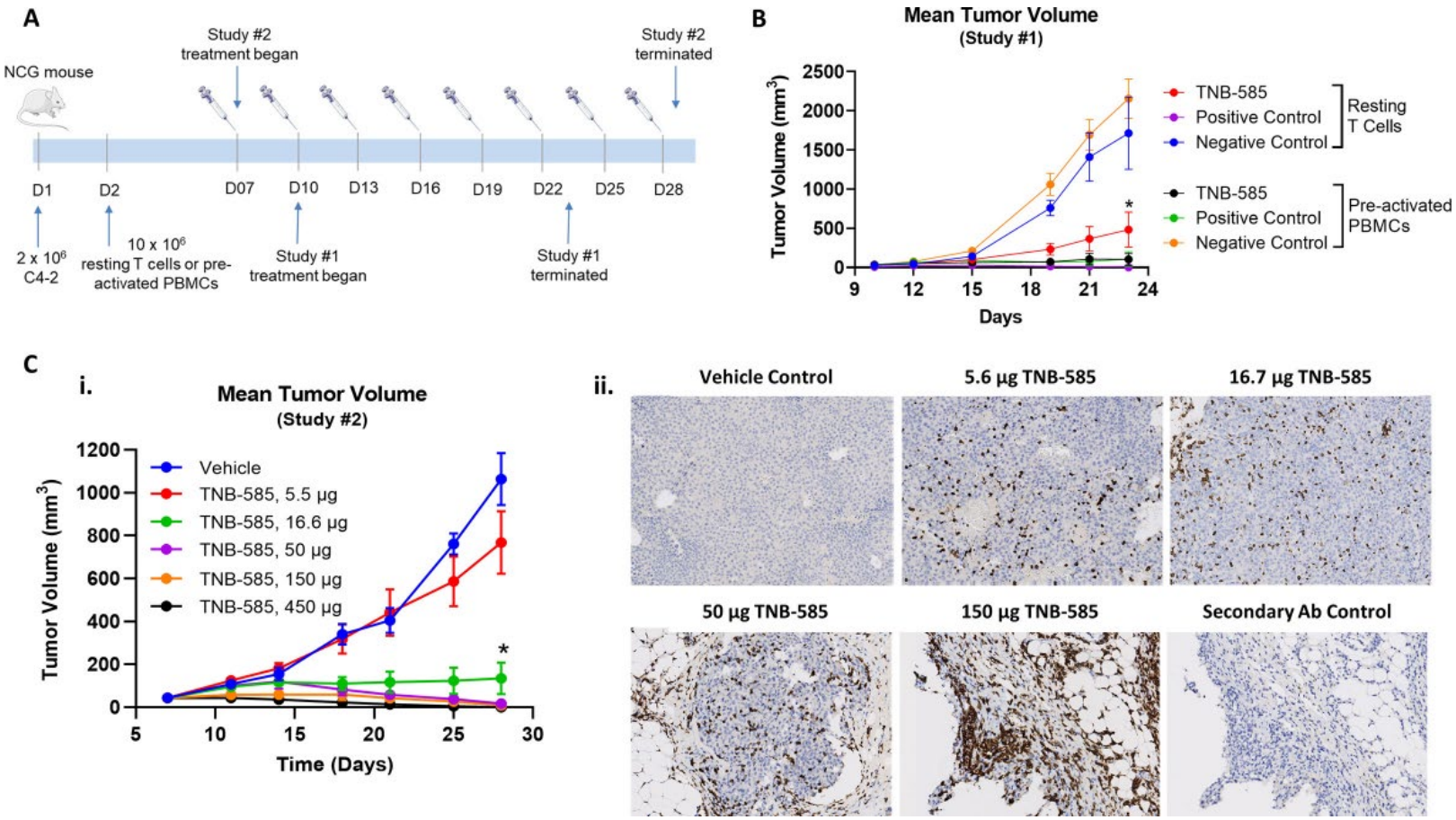
TNB-585 induces tumor regression *in vivo*



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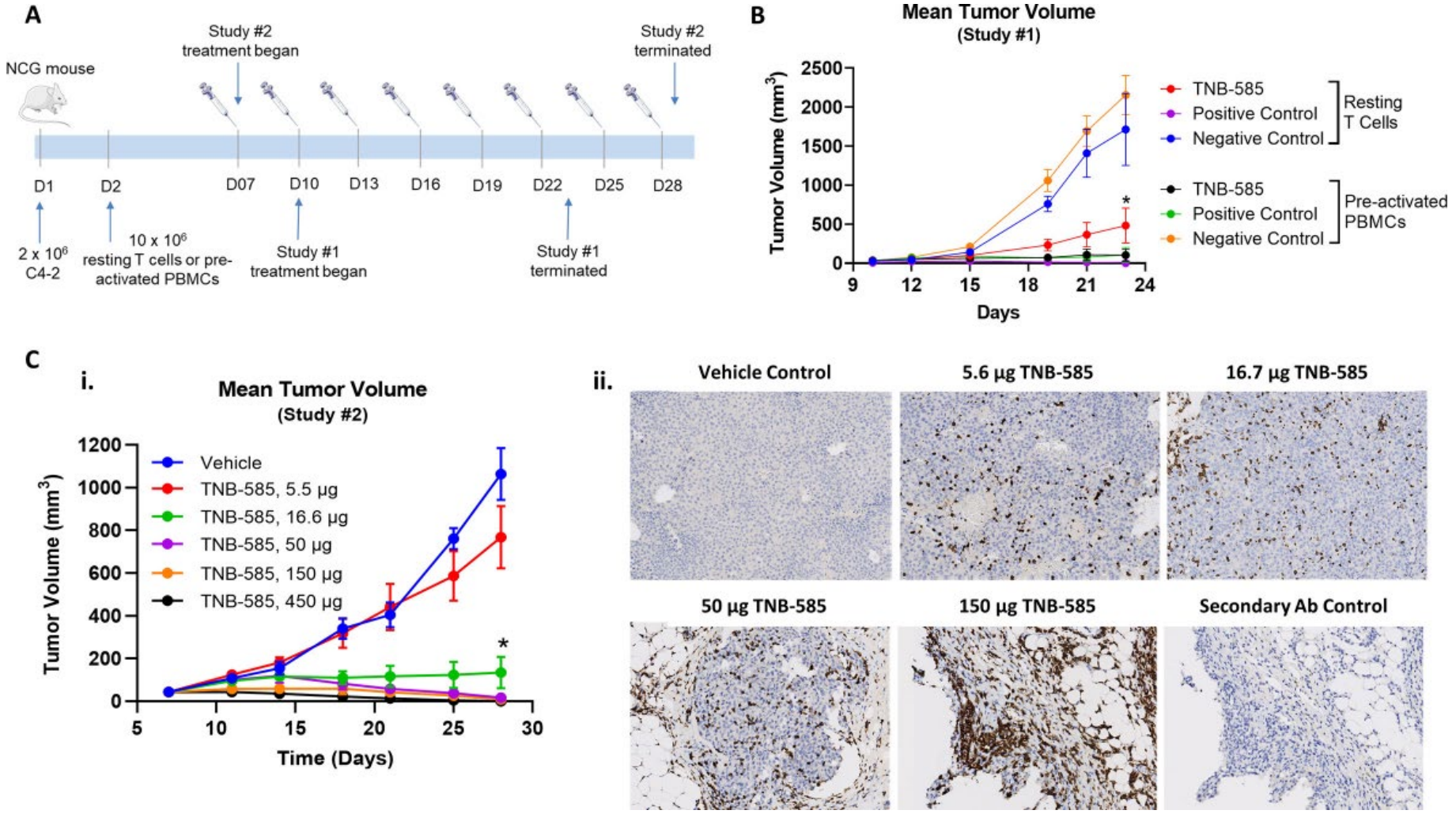
TNB-585 induces tumor regression *in vivo*



Dang … Fong, Dalvi. JITC 2021

Conclusions

- Attenuating the affinity of the anti-CD3 binding domain of T cell engagers may allow for:
  - Maintenance of anti-tumor efficacy
  - Reduction in cytokine release and potential for toxicities

- The clinical trial is now accruing…

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Take-home

- PSMA targeting T cell engagers are showing early signs of clinical activity, but with toxicities.
- Dosing and premedication with steroids are being used to ameliorate these toxicities.
- Stay tuned for clinical data from multiple novel T cell engagers targeting PSMA.

- This is just targeting PSMA…

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Patients and their families

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