Society for Immunotherapy of Cancer

Advances in Cancer Immunotherapy™

Advances in Cancer Immunotherapy: Updates on IT Therapies in Melanoma and Other Cancers

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Disclosures

- **IP Rights:** US Patent Compositions and Methods for Treating Cancers, Compositions and Methods For Determining Responsiveness to Immune Checkpoint Inhibitors (ICI), Increasing Effectiveness of ICI and Treating Cancer

- **Consulting Fees:** Checkmate Pharmaceuticals, Finch, Shionogi, Vedanta Biosciences; Contracted Research: Arcus, BMS, Merck, Checkmate Pharmaceuticals, CellSight Technologies, Immunocore, Tesaro/GSK

- I will be discussing non-FDA approved indications during my presentation.

Scope

General

- Rationale for IT therapy
- MOA of IT therapies, differences among various classes

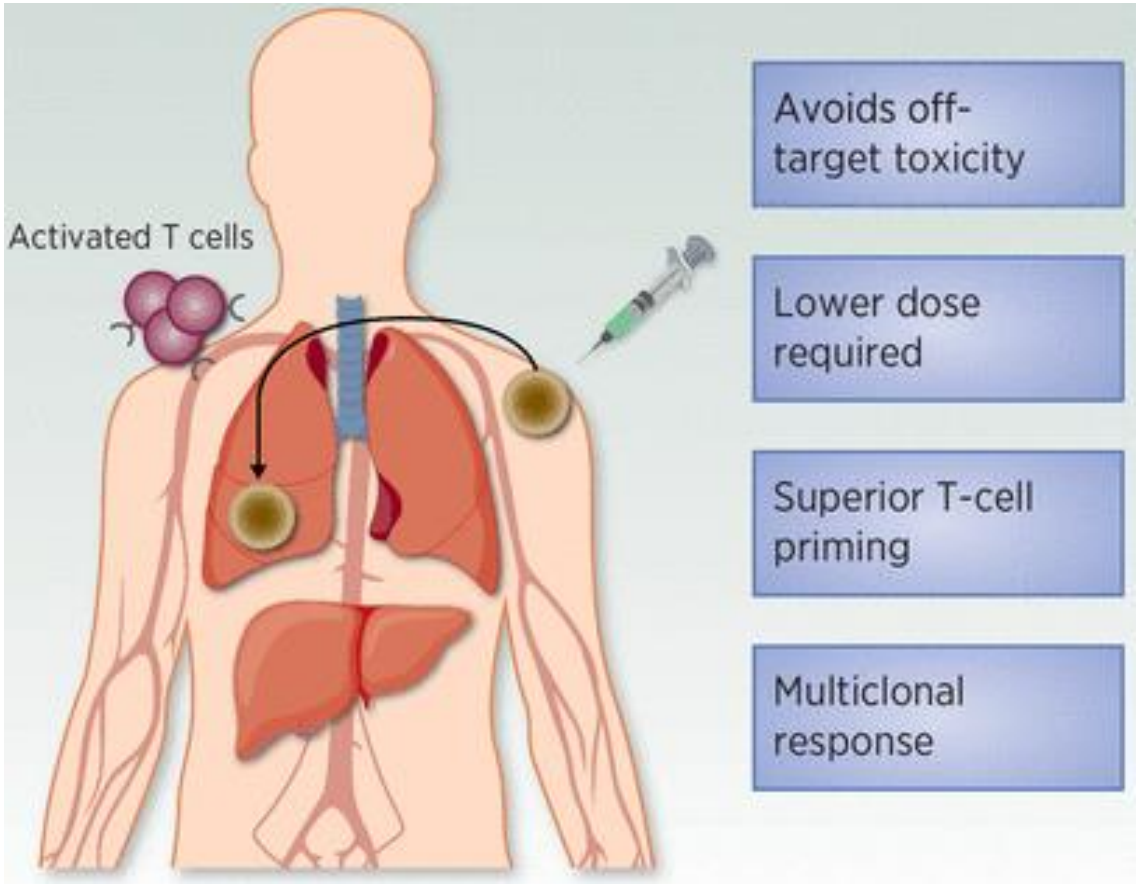
Challenges in Clinical Development

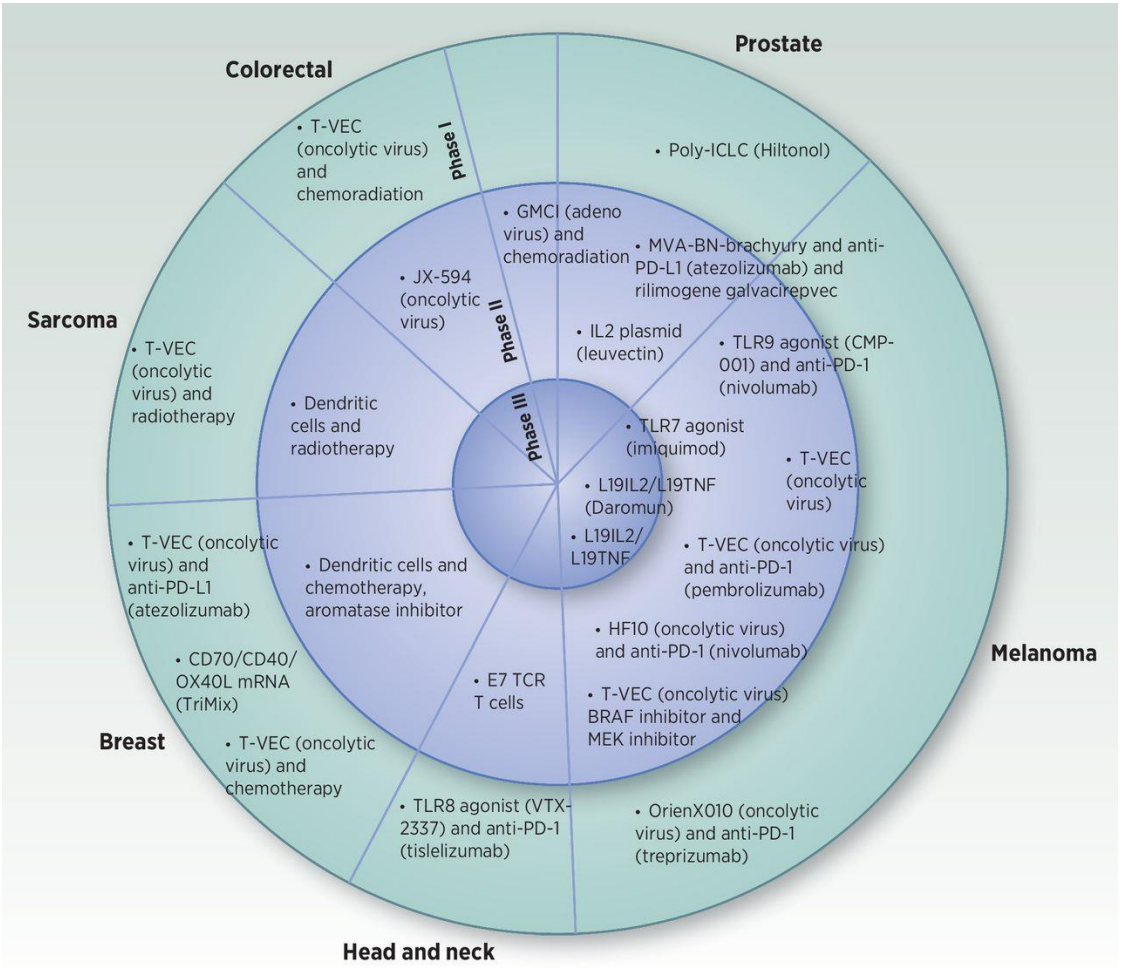
- Number and locations of lesions to inject
- Response assessment – itRECIST > RECIST/irRECIST
- Optimizing therapy in responding lesions
- Correlative analyses

Recent advances with IT therapies

- CMP-001 as a case study in melanoma

Rationale for IT therapy





Hong WX, CCR 2020

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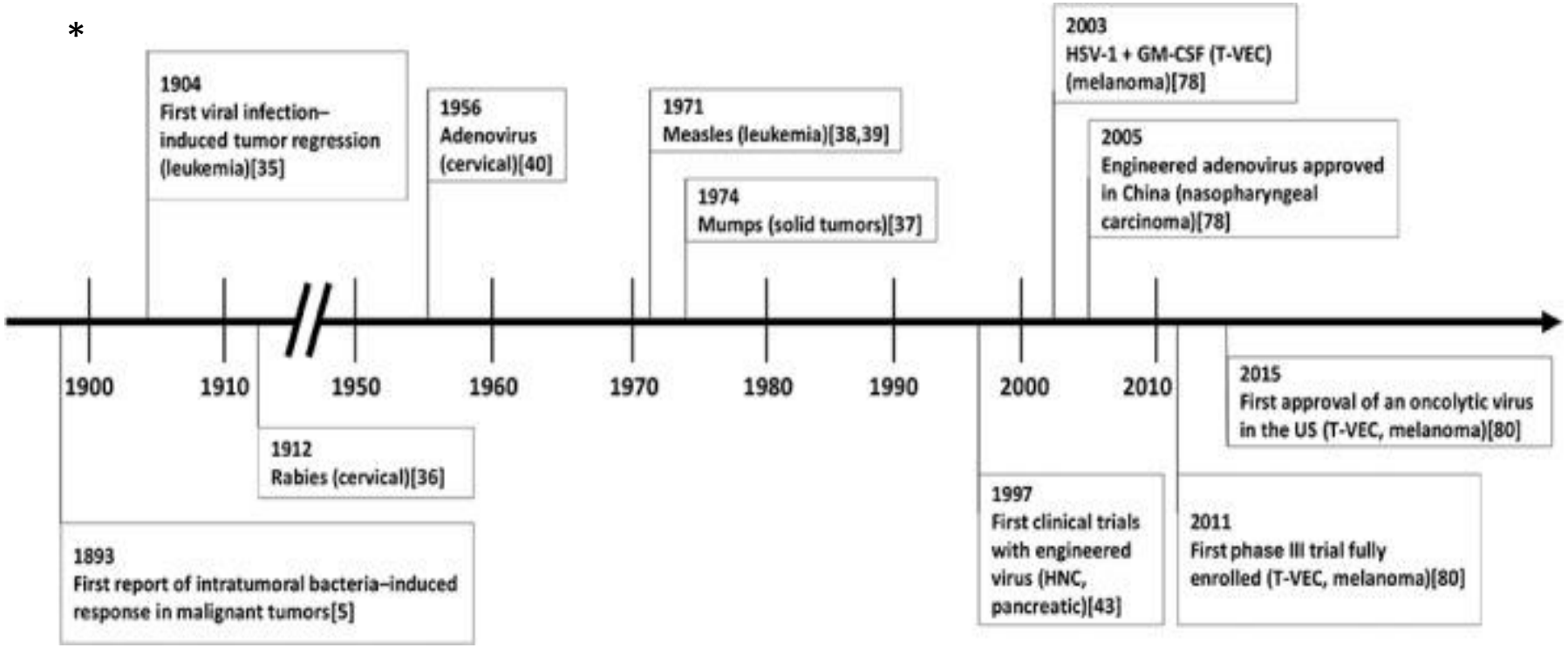
Landmarks in IT therapy



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*Hamid O, Oncologist 2020

MOA of IT therapies

PAMPs and analogs

Vidutolimod (CMP-001), Transcon TCTLR7/8, poly ICLC (hiltonol), BDB001, PV-10, NKTR-262, BO-112

STING

E7766, BMS-986301, MK-2118

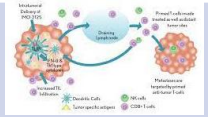
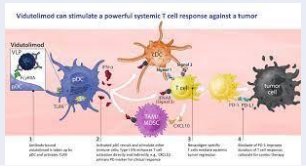
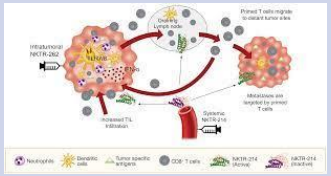
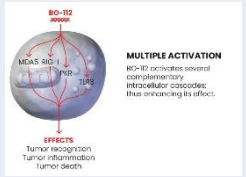
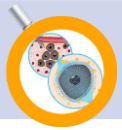
OVs

TVEC, PVS-RIPO, C-REV/HF-10, DNX-2401/Tasadenoturev, VCN-01, Reolysin , JX-594, GMCI, OrienX010

Gene therapy

Daromun (L19IL2/L19TNF), Leuvectin (IL2 plasmid), TriMix (CD70/CD40/OX40L mRNA)

Differences among IT Agents (PAMPs and analogs)

IT Agent (Sponsor)	Class	Completed studies (patient population) (activity)	Recent/ongoing studies (patient population) (activity)
Tilsotolimod/IMO-2125 (Idera) 	TLR9 agonist	R/R mel (+ipi): ORR 22.4%[1]	R/R mel (+ipi): 8.8% (+ipi) vs. 8.6% (ipi)[2]
Vidutolimod/CMP-001 (Checkmate) 	TLR9 agonist	R/R mel (+pembro): ORR 25%[3] Naïve mel (neoadj) (+nivo): pCR 47%, MPR 57%[4]	R/R mel (+nivo, 10 study): ongoing Naïve mel (+nivo, 11 study): ongoing
NKTR-262 (Nektar Therapeutics) 	TLR 7/8 agonist	R/R tumors (+NKTR-214): ORR 18.2%[5]	REVEAL-01 active, not recruiting
BO-112 (Highlight Therapeutics) 	dsRNA	R/R mel (+pembro): ORR 27%[6]	SPOTLIGHT203 active, recruiting
Tavo-EP (Oncosec) 	IT IL-12	Naïve mel (+pembro): ORR 41%[7]	R/R mel (+pembro): ongoing Neoadjuvant mel (+pembro): ongoing

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[1]Haymaker C, Cancer Discov 2021; [2]Idera Press Release; [3]Ribas A, Cancer Discov 2021; [4]Davar D, SITC 2020 and 2021; [5]Diab A, ASCO 2021; [6]Rodas IM, SITC 2021; [7]Algazi AP, CCR 2020

Differences among IT Agents (STING)

IT Agent (Sponsor)	Mode of Delivery	Completed studies (patient population) (activity)	Recent/ongoing studies (patient population) (activity)
ADU-S100 (Aduro)	IT	Phase I R/R solid tumors: 3/47 responses, no DLT[1]	None planned
BMS-986301 (BMS)	IV	Not reported	Active, recruiting
E7766 (Eisai)	IT	Not reported[2]	Active, recruiting
MK-1454 (Merck)	IT	Phase I R/R solid tumors and lymphomas: 0/26 (Arm 1), 6/34 (Arm 2)[3]	1L HNSCC (MK-1454-002): active, not recruiting
MK-2118 (Merck)	IT	Not reported	Active, recruiting
SB 11285 (F Star)	IV	Not reported[4]	Active, recruiting

[1]Meric-Bernstam F, CCR 2021; [2]Gualberto A, AACR-NCI-EORTC 2021
[3]Harrington KJ, ESMO 2018; [4]Janku F, ASCO 2020;

Differences among IT Agents (OVs)

IT Agent (Sponsor)	Class	Completed studies (patient population) (activity)	Recent/ongoing studies (patient population) (activity)
T-VEC (Amgen)	HSV-1 with GM-CSF transgene	Phase III OPTIM (mel, vs. GM-CSF): ORR 26% vs. 6%[1] Phase II mel (+ipi): ORR 62%[2]	Phase II neoadj (mel, vs. surg): 17%, pCR; 2-year RFS 30% vs. 17%[3] Phase III MASTERKEY-265 (mel, +pembro): 49% vs. 41%[4]
PVS-RIPO (Istari)	OGM poliovirus with tropism for cells expressing Necl-5 (GBM etc.)	Phase I (GBM): OS 21%[5]	Phase II PD-1 R/R mel: LUMINOS-102
Canerpaturev/HF-10 (Takara)	Spontaneously mutated HSV-1	Phase II PD-1 R/R mel (+ipi): ORR 41% vs. 6%[6]	SPOTLIGHT203 active, recruiting
DNX-2401/Tasadenoturev	OGM adenovirus	Phase II rGBM (+pembro): 12% responses, mOS 12.5 months[7] Phase I DIPG: 75% responses by RAPNO[8]	Phase III rGBM planned

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[1]Andtbacka RHI, J Clin Oncol 2015; [2]Chesney J, J Clin Oncol 2018; [3]Dummer R, Nat Med 2021; [4]Gogas H, ESMO 2021; [5]Desjardins A, NEJM 2018; [6]Andtbacka RHI, ASCO 2017; [7]Zadeh G, SNO 2020; [8]Perez-Larraya JG, SNO 2021

Challenges: Number and locations of lesions to inject

No. of injected lesions

- 1 vs. 1-2 vs. 1-4 vs. up to 8
- Dead volume

Location of injected lesions

- Subcutaneous, LN
- ?deeper LN
- ?visceral

Different doses within same trial

- Factors: drug concentration; no. of injected lesions
- Confounds assessment of total dose administered

IMO-2125 + ipilimumab safety population (N=18)

IMO-2125 dose	4 mg (N=3)	8 mg (N=9)	16 mg (N=3)	32 mg (N=3)	Total (N=18)
≥ 1 TEAE	3 (100)	9 (100)	3 (100)	3 (100)	18 (100)
Related TEAE	2 (67)	9 (100)	3 (100)	3 (100)	17 (94)
≥ 1 SAE	2 (67)	4 (44)	2 (67)	1 (33)	9 (50)
Discontinued for AE	0	0	0	0	0
Death from AE	0	0	0	0	0
DLT	0	0	0	0	0
irAE[1]	1 (33)	3 (33)	2 (67)	0	6 (33)

RP2D

MTD (no DLT)

Discrepancies in drug delivery and dose exposure

Ideally:

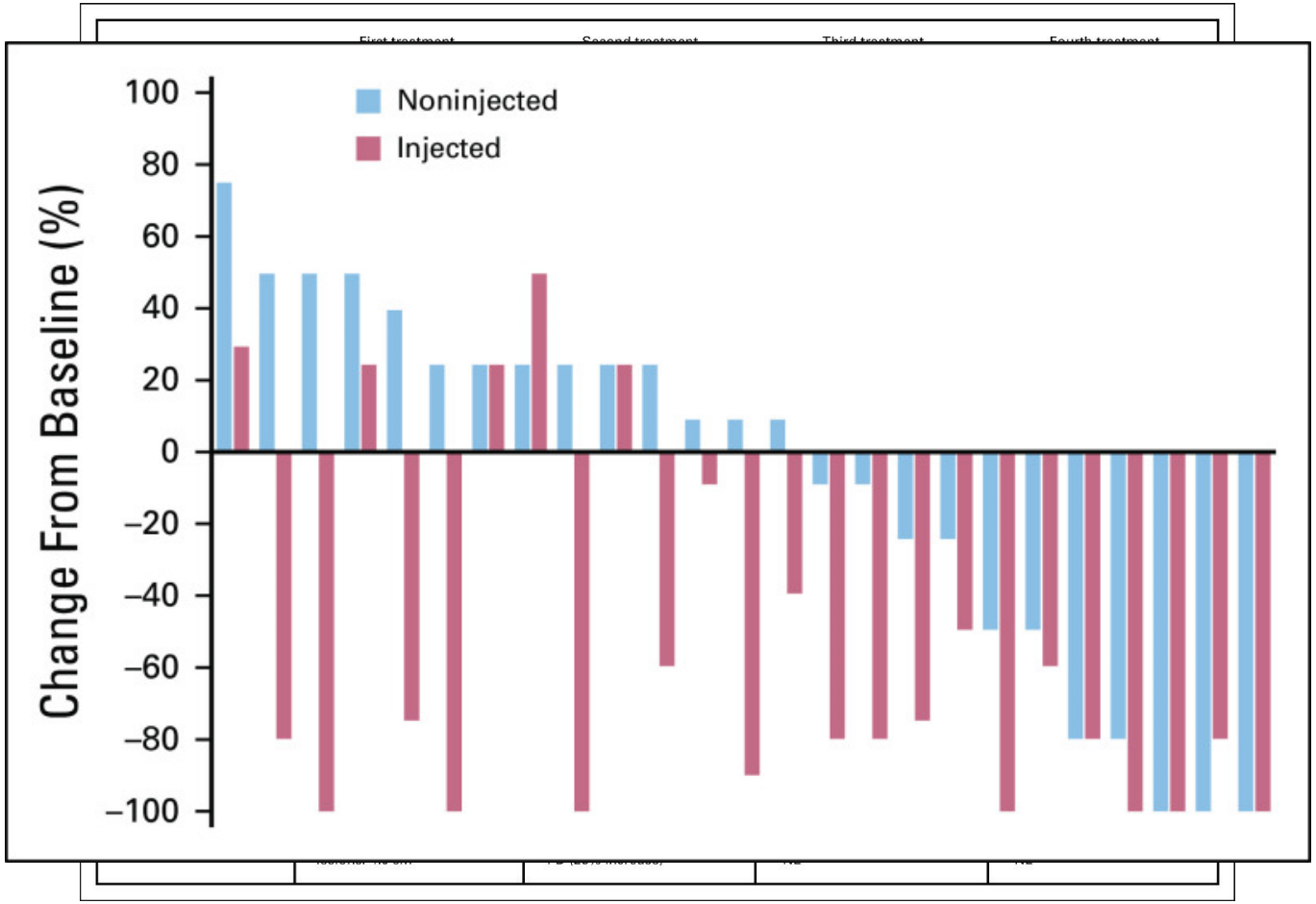
- Highest dose permissible should be administered
- Dose calculation based on the size of the largest lesion (and if feasible lesions should be reimaged prior to each dose)
- Lesion selection is important

Uemura MI, ASCO 2017; Diab A, ASCO 2018

Challenges in Clinical Development: Assessing Response with IT Therapies

Challenges with response assessment

- What is the maximal effect of IT therapy (+/- systemic therapy) on non-injected lesions?
- What is the maximal effect of IT therapy (+/- systemic therapy) on injected lesions?
- What is the overall response?



Goldmacher GV, J Clin Oncol 2020

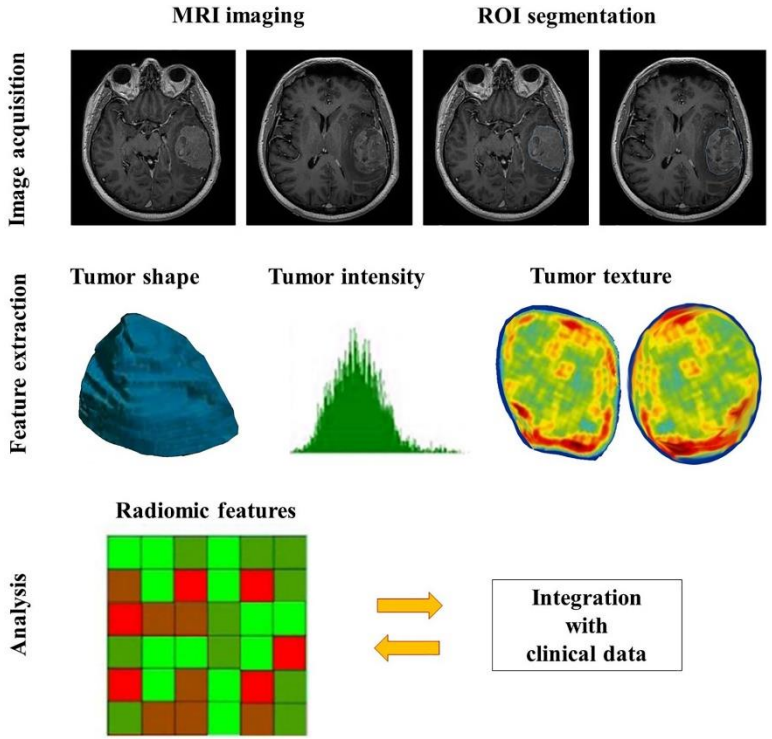
Challenges in Clinical Development: Optimizing Therapy In Responding Lesions

What to do if lesions shrink or resolve?

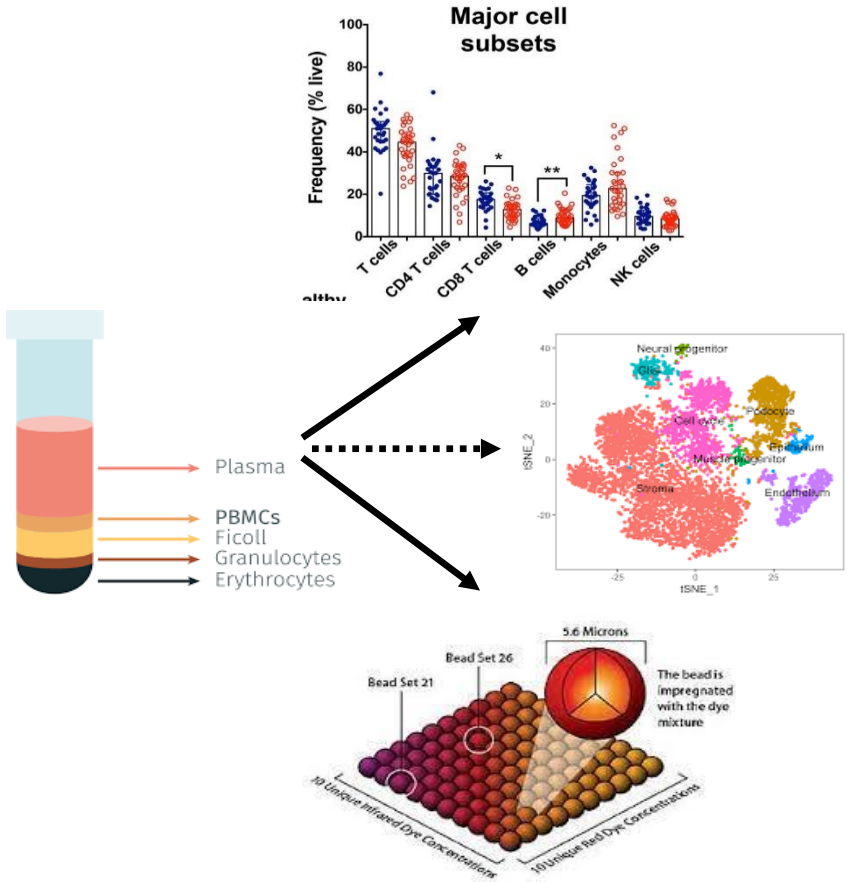
- Lesions smaller
  - Reduce dose
  - Add a new lesion(s)
- Lesions resolve
  - Add a new lesion(s)
- Duration of therapy
  - ?2 years

Challenges in Clinical Development: Correlative analyses

Radiomics



Circulating biomarkers



Tumor and TME

Injected Non-injected

Immune cell populations: flow cytometry, scRNAseq

Spatial orientation: IHC, IF,

Transcriptional state: RNAseq

Emerging technologies: Spatial transcriptomics, computational integration of multi ‘omic data

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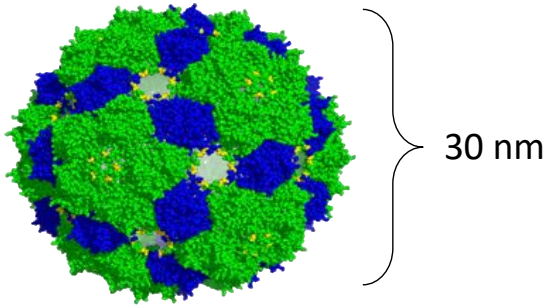
Recent Advances: CMP-001 Case Study (1)

CMP-001



Qb coat protein

- Capsid protein from Qb bacteriophage; 180 subunits form an icosahedral virus-like particle (VLP)
- Protects the G10 inside the VLP from degradation *in vivo*
- Immunogenic protein induces Ab response after first injection in humans and mice
- Anti-Qb Ab opsonize the VLP, facilitate its uptake into pDC via FcR with enhanced induction of systemic CD8 T cell response[8]

G10: A CpG-A TLR9 agonist

Poly G and CpG motifs mimic retroviral, viral DNA, induce systemic T cell responses

CpG-A is strongest known activator of tumor-associated pDC for IFN, CTL induction[1-4]

Synthetic native DNA (phosphodiester) drives strongest pDC response[5]

CpG-A induces pDC differentiation into distinct subset vs. other TLR9 agonists[6]

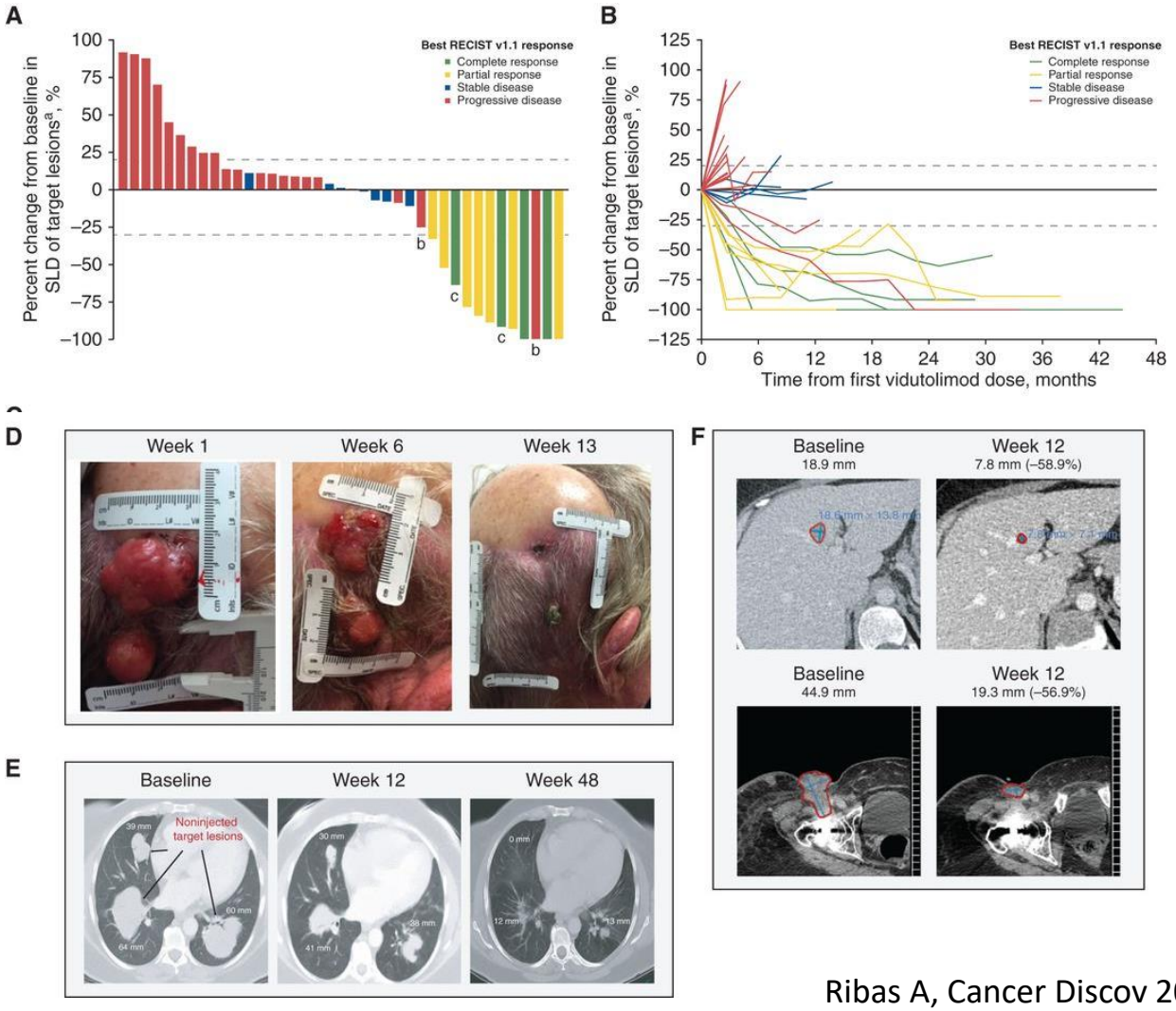
Lower induction of inflammatory cytokines vs. other innate immune activators[7]

[1]Hartmann E, Cancer Res 2003; [2]Labidi-Galy SI, Cancer Res 2011; [3]Sisirak V, Cancer Res 2012; [4]Rothenfusser S, Blood 2004; [5]Chan et al., Nature Comm. 2015; [6]Alculumbre SG, Nat Immunol 2018; [7]Checkmate, in preparation; [8]Lemke et al., in revision

Recent Advances: CMP-001 Case Study (2)

Phase IB study of **CMP-001/pembrolizumab** in **PD-1 R/R melanoma**

- N = 44, no of responders = 11/44 for **ORR 25%** using RECIST
- With iRECIST, -2 additional responders, no of responders = 13/44 for **ORR 29.5%**
- **Safety profile manageable**
- **Clinical activity promising**

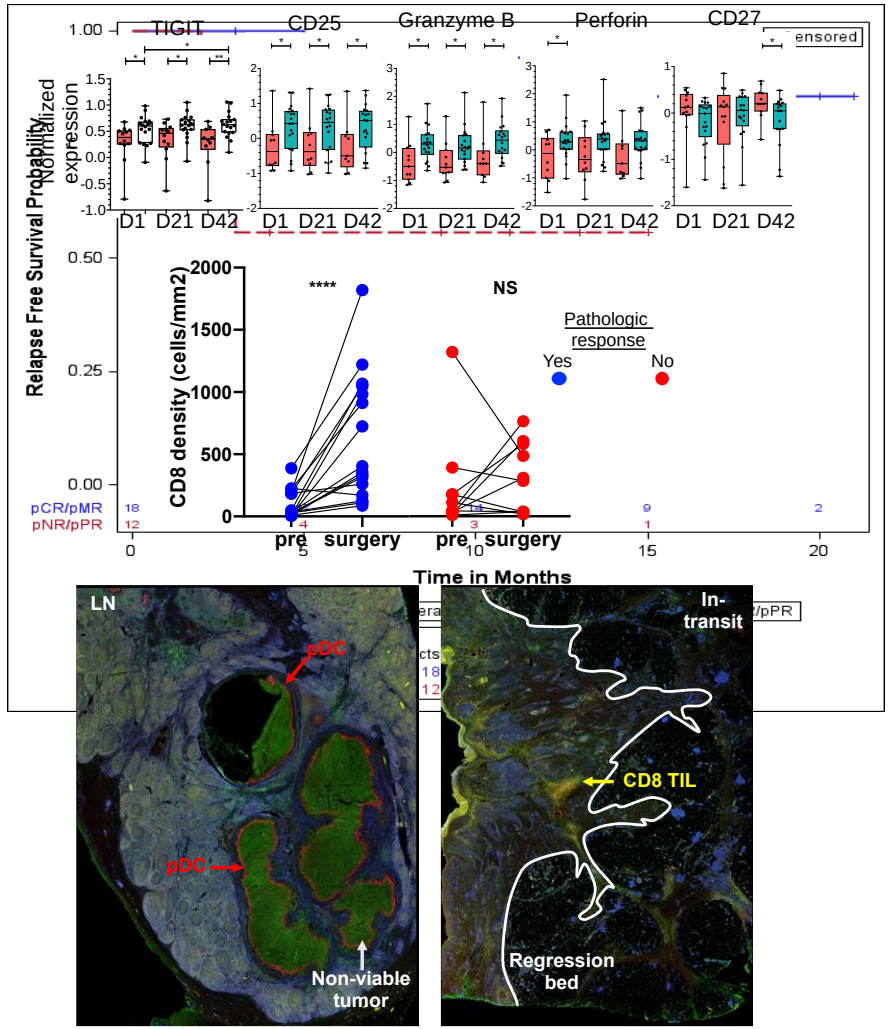


Ribas A, Cancer Discov 2021

Recent Advances: CMP-001 Case Study (3)

Phase II study of neoadjuvant **CMP-001/nivolumab** in **high-risk resectable** melanoma

- N = 31, 30 evaluable for path response
- Response: **pCR** (0% residual tumor) **47%**, **pMR** (<10% residual tumor) **10%** → **57% MPR**
- **Safety profile manageable**
- **MPR** → **durable RFS (1-year RFS 93%)**
- **Clear evidence of immune activation within tumor and peripherally including pDC activation**



Davar D, SITC 2020 and SITC 2021

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Conclusions

- IT therapies including PRR agonists, OVs and gene therapy span a range of MOAs → central role is to augment innate and adaptive immunity.
- Practical considerations, including number/location of lesions, response assessment and methods to optimize local delivery play an important role in safety and efficacy of this approach.
- Recent setbacks include tilsotolimod/IMO-2125 in PD-1 R/R melanoma and T-VEC in PD-1 naïve 1L melanoma; although several agents have demonstrated promising phase II data and are in pivotal trials (CMP-001) or have novel MOAs (PVS-RIPO, Tavo-EP).