What's Next for Cancer Immunotherapy

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Financial Disclosures & COI

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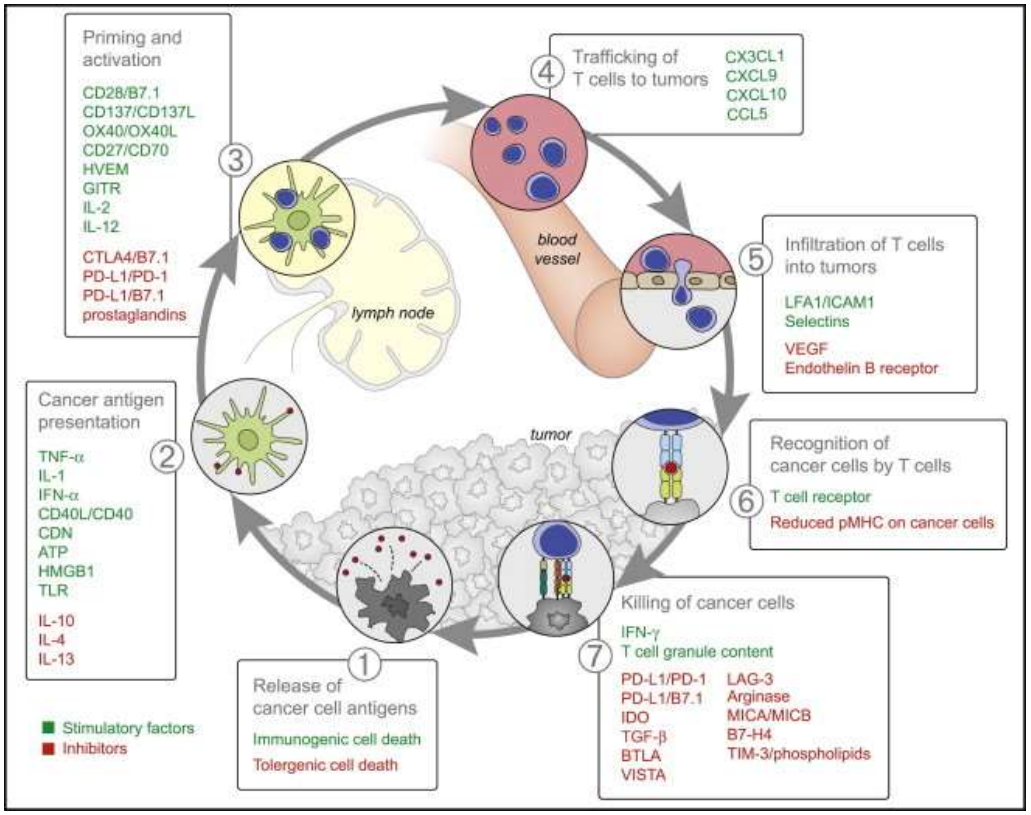
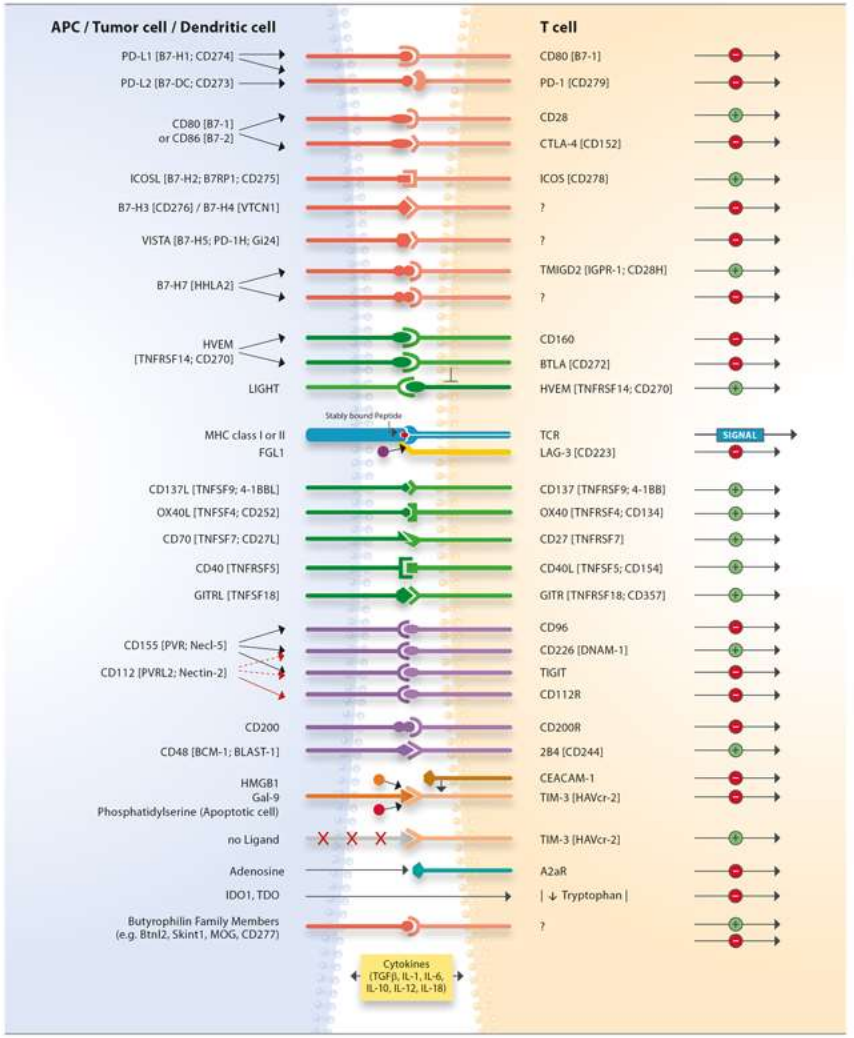
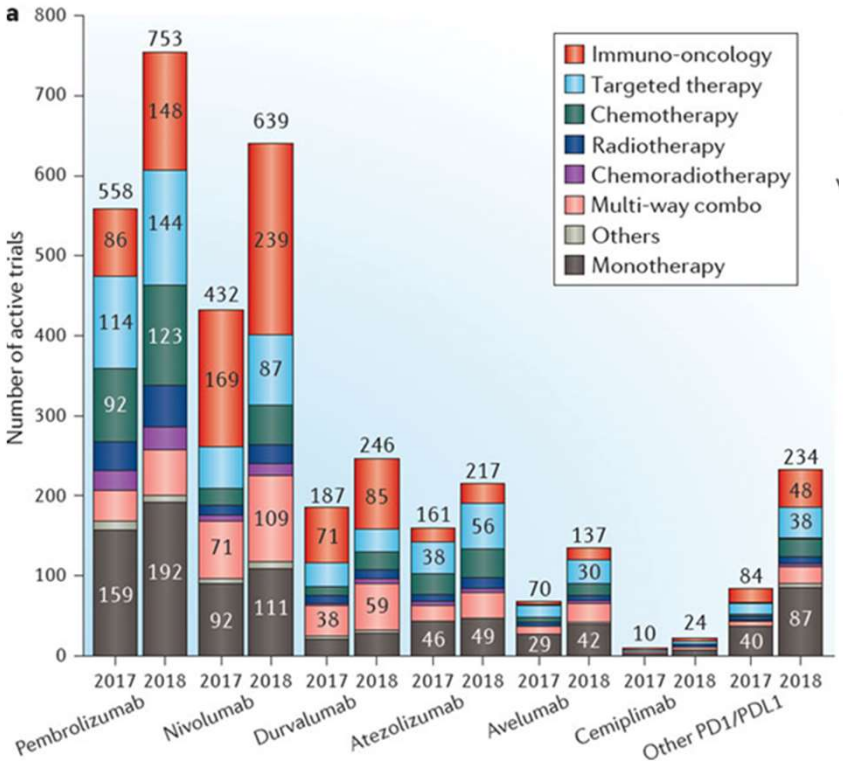
Stimulatory and Inhibitory Factors in the Cancer-Immunity Cycle

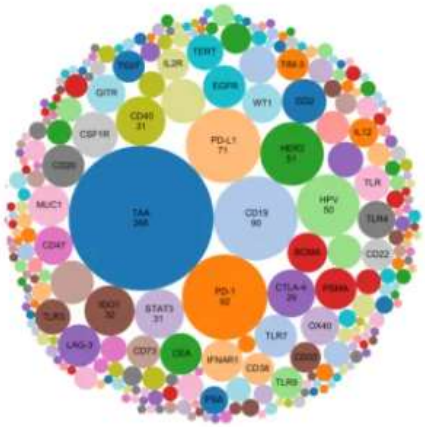


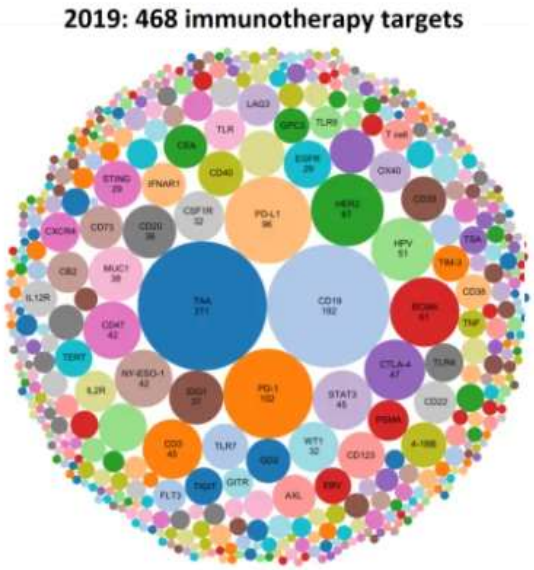


Chen DS, Mellman I; OncologyMeetsImmunology:TheCancer-ImmunityCycle; Immunity 39, July 25, 2013

Expanding Landscape in Immuno-Oncology



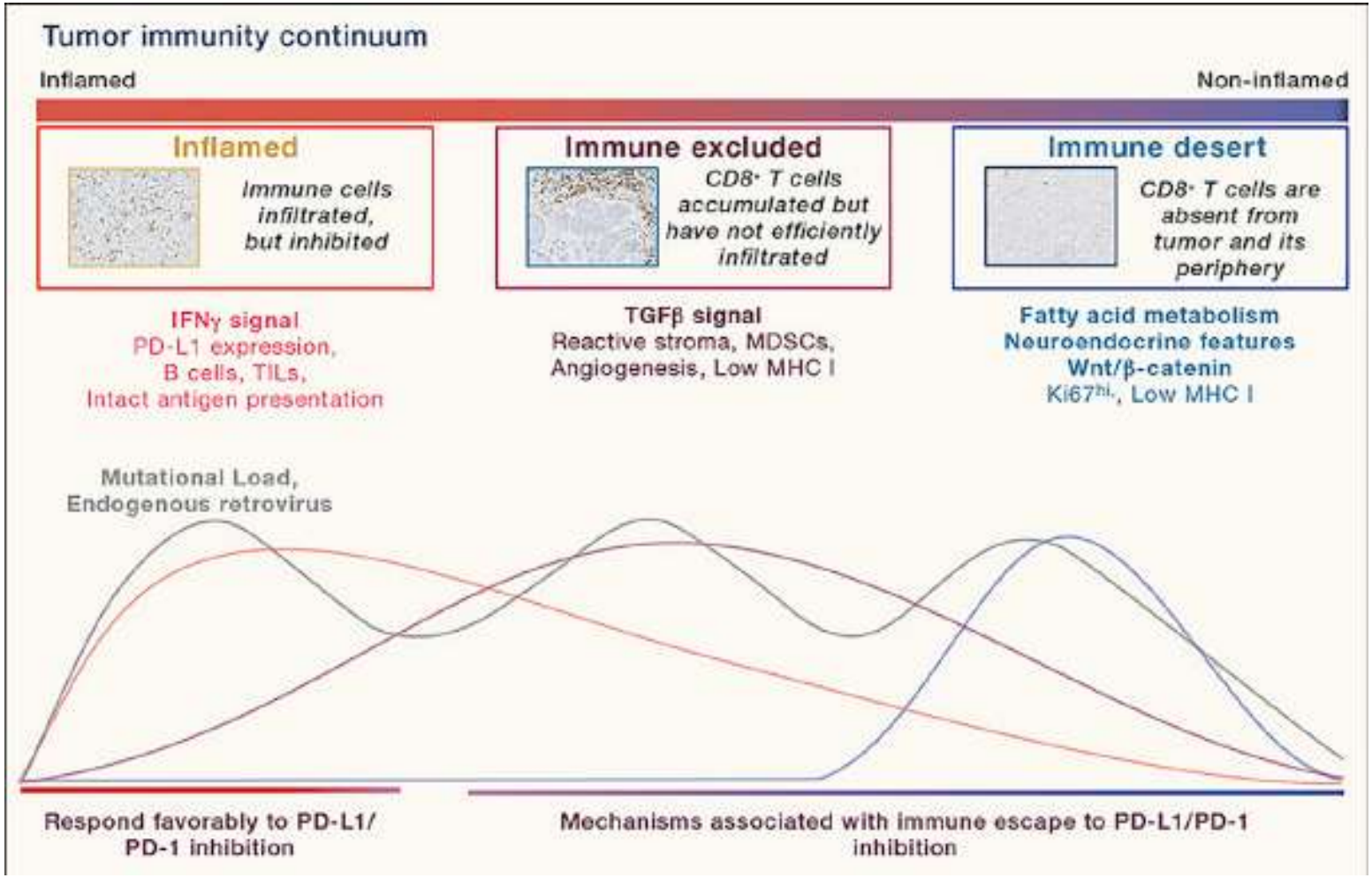




Tang, J., Yu, J., Hubbard-Lucey, V. et al. The clinical trial landscape for PD1/PDL1 immune checkpoint inhibitors. Nat Rev Drug Discov 17, 854–855 (2018).

Cancer Immunity and Resistance

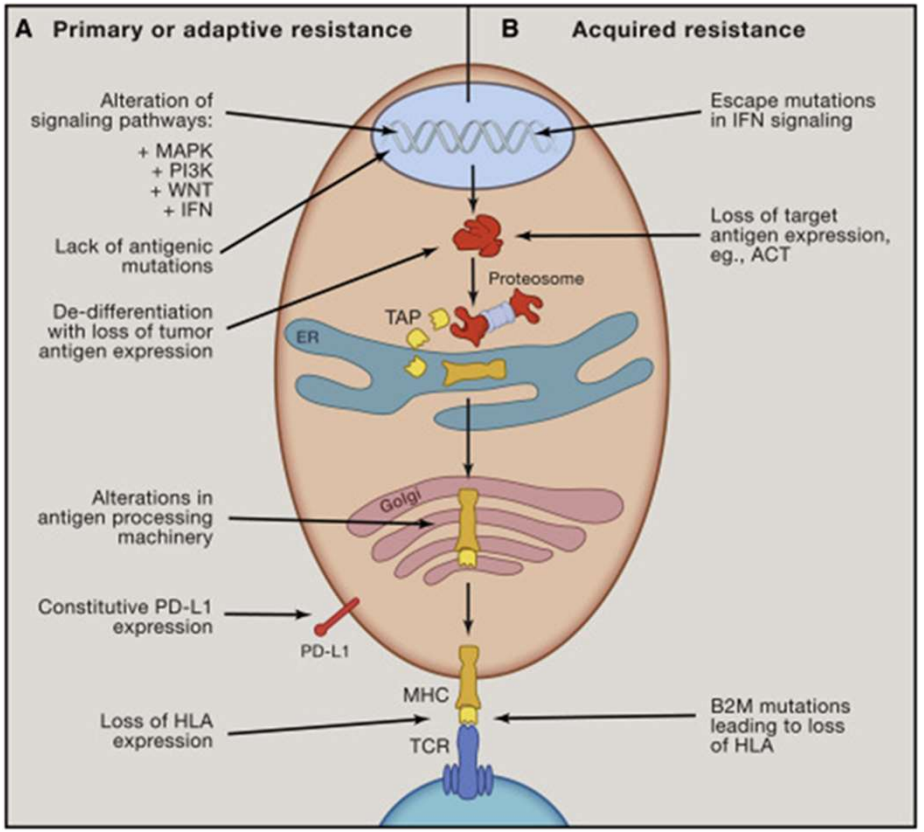
The Tumor Immunity Continuum



Hegde PS, Chen DS; Top 10 Challenges in Cancer Immunotherapy; Immunity 52, January 14, 2020

Immune Resistance Mechanisms in Cancer Immunotherapy

- Primary resistance
  - cancer does not respond to an immunotherapy strategy
  - mechanism of lack of response to immunotherapy may include adaptive immune resistance
- Adaptive immune resistance
  - cancer is recognized by the immune system but it protects itself by adapting to the immune attack
  - could clinically manifest as primary resistance, mixed responses or acquired resistance
- Acquired resistance
  - cancer initially responds to immunotherapy but after a period of time it relapses and progresses



Sharma P; Primary, Adaptive, and Acquired Resistance to Cancer Immunotherapy; Cell 168, February 9, 2017

Mechanisms of Resistance to Immunotherapy

	Mechanism	Examples
Tumor cell intrinsic	absence of antigenic proteins	low mutational burden lack of viral antigens lack of cancer-testis antigens overlapping surface proteins
	absence of antigen presentation	deletion in TAP deletion in B2M silenced HLA
	genetic T cell exclusion	MAPK oncogenic signaling stabilized b-catenin mesenchymal transcriptome oncogenic PD-L1 expression
	insensibility to T cells	mutations in interferon gamma pathway signaling
Tumor cell extrinsic	absence of T cells	lack of T cells with tumor antigen-specific TCRs
	inhibitory immune checkpoints	VISTA, LAG-3, TIM-3
	immunosuppressive cells	TAMs, Tregs

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Combination Strategies

Combination Strategies to Overcome Resistance to Cancer Immunotherapy

Broad Approach	Specific Approach	Examples in Clinical Testing
CP blocking combinations: combination checkpoint blockade	anti-PD-1/L1 plus anti-CTLA4	Durvalumab + tremelimumab Nivolumab + ipilimumab Pembrolizumab + ipilimumab
	anti-PD-1 plus anti-PD-L1	MEDI0680 + durvalumab PDR001 + FAZ053
	anti-PD-1/L1 plus anti-TIM 3	Nivolumab + TSR022 PDR001 + MBG453
	anti-PD-1/L1 plus anti-LAG 3	Nivolumab + BMS 986016 PDR001 + LAG525 Pembrolizumab + IMP321 REGN2810 + REGN3767
	anti-PD-1/L1 plus anti-41BB/CD137	Avelumab + utomilumab Nivolumab + urelumab Pembrolizumab + utomilumab
checkpoint blockade plus immune-stimulatory agents	anti-CTLA4 plus anti-OX40 anti-PD-1/L1 plus anti-OX40 anti-CTLA4 plus Anti-PD-1/L1 plus anti-OX40 anti-41BB/CD137 plus anti-OX40	Atezolimumab + MOXR0916 ± bevacizumab Avelumab + PF-04518600 Durvalumab + MEDI0562 Pembrolizumab + GSK3174998 Tremelimumab + durvalumab + MEDI6469 Tremelimumab + MEDI0562 Utomilumab + PF-04518600
CP & agonist Ab	anti-CTLA4 plus anti-CD40 anti-PD-1/L1 plus anti-CD40	Atezolimumab + RO7009789 Tremelimumab + CP870893
	anti-PD-1/L1 plus anti-GITR	Nivolumab + BMS986156 PDR001 + GWN323
	anti-PD-1/L1 plus anti-ICOS	Nivolumab + JTX-2011
CP & metabolomics: checkpoint blockade plus metabolic modulators	anti-CTLA-4 plus IDO inhibitors anti-PD-1/L1 plus IDO inhibitors	Atezolizumab + GDC0919 Ipilimumab + epacadostat Ipilimumab + indoximid Nivolumab + BMS986205 Pembrolizumab+ epacadostat
	anti-PD-1/L1 plus A2AR inhibitors or anti-CD73	Atezolizumab + CPI-444 Durvalumab + MEDI9447 PDR001+ PBF509
	anti-PD-1/L1 plus TGFβ inhibitors	Nivolumab + LY2157299 PDR001 + NIS793
CP & immune modulators: checkpoint blockade plus other immune modulators	anti-PD-1/L1 plus CXCR4 inhibitors	Nivolumab + ulocuplumab Durvalumab + LY2510924
	anti-PD-1/L1 plus CCR4 inhibitors	Nivolumab + mogamulizumab
	anti-PD-1/L1 plus anti-CD27	Nivolumab + varlilumab Atezolizumab + varlilumab
	anti-PD-1/L1 plus CD122-biased cytokine	Nivolumab + NKTR-214
	anti-PD-1/L1 plus yeast-derived soluble β-glucan	Pembrolizumab + Imprime PGG
	anti-PD-1/L1 plus anti- TRAIL-DR5	Nivolumab + DS-8273a
	anti-PD-1/L1 plus glutaminase inhibitor	Nivolumab + CB839
	anti-PD-1/L1 plus IAP inhibitor	PDR001 + LCL161
CP & TAMs/MDSCs: checkpoint blockade plus macrophage inhibitors	anti-CTLA4 plus CSF1R inhibitors anti-PD-1/L1 plus CSF1R inhibitors	Durvalumab + Pexidartinib (PLX3397) Durvalumab + LY3022855 Nivolumab + FPA008 Pembrolizumab + Pexidartinib PDR001 + BLZ945 Tremelimumab + LY3022855

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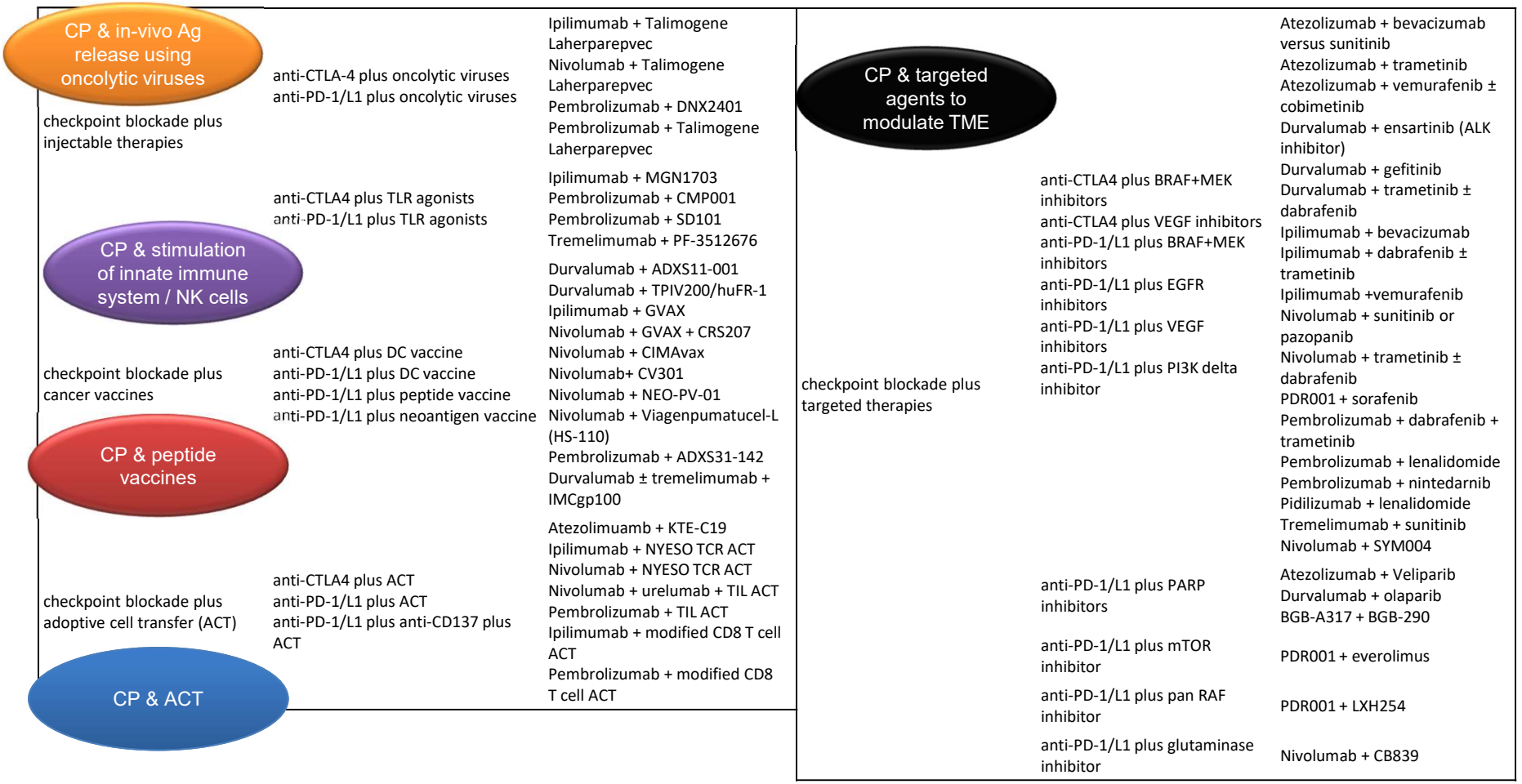
Combination Strategies to Overcome Resistance to Cancer Immunotherapy



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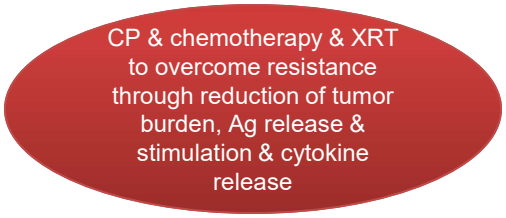
Combination Strategies to Overcome Resistance to Cancer Immunotherapy

checkpoint blockade plus radiation therapy (RT)	anti-CTLA4 plus RT anti-PD-1/L1 plus RT anti-CTLA4 plus Anti-PD-1/L1 plus RT	Atezolizumab + stereotactic radiation therapy Pembrolizumab + cisplatin/radiotherapy Pembrolizumab + sterotactic body radiotherapy Pembrolizumab + hypofractionated radiotherapy
checkpoint blockade plus chemotherapy	anti-CTLA4 plus chemotherapy anti-PD-1/L1 plus chemotherapy anti-CTLA4 plus Anti-PD-1/L1 plus chemotherapy	Atezolizumab + carboplatin/paclitaxel Atezolizumab + carboplatin/gemcitabine Durvalumab + paclitaxel Ipilimumab +carboplatin/paclitaxel Ipilimumab +dacarbazine Nivolumab + platinum doublets Pembrolizumab + carbo/paclitaxel or carbo/pemetrexed
checkpoint blockade plus epigenetic modifications	anti-PD-1/L1 plus histone deacetylase inhibitors anti-PD-1/L1 plus hypomethylating agents	Azacitidine + entinostat followed by nivolumab Atezolizumab + azacitidine Nivolumab + RRX001 Pembrolizumab + CC486 Pembrolizumab + CC486 + romidepsin Pembrolizumab + romidepsin Pembrolizumab + vorinostat + tamoxifen PDR001 + panobinostat
checkpoint blockade plus NK activation	anti-CTLA4 plus anti-KIR anti-PD-1/L1 plus anti-KIR	Ipilimumab + lirilumab Nivolumab + lirilumab



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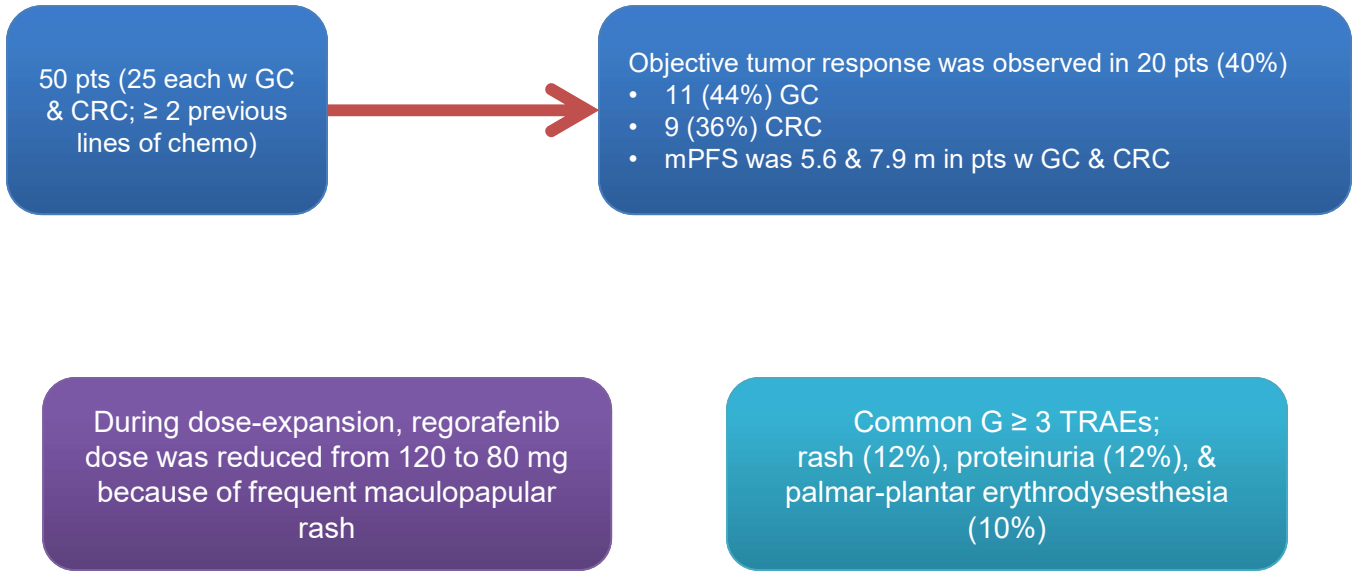
Clinical Data on Combination Strategies

Regorafenib Plus Nivolumab in Patients With Advanced Gastric or Colorectal Cancer: An Open-Label, Dose-Escalation, and Dose-Expansion Phase Ib Trial

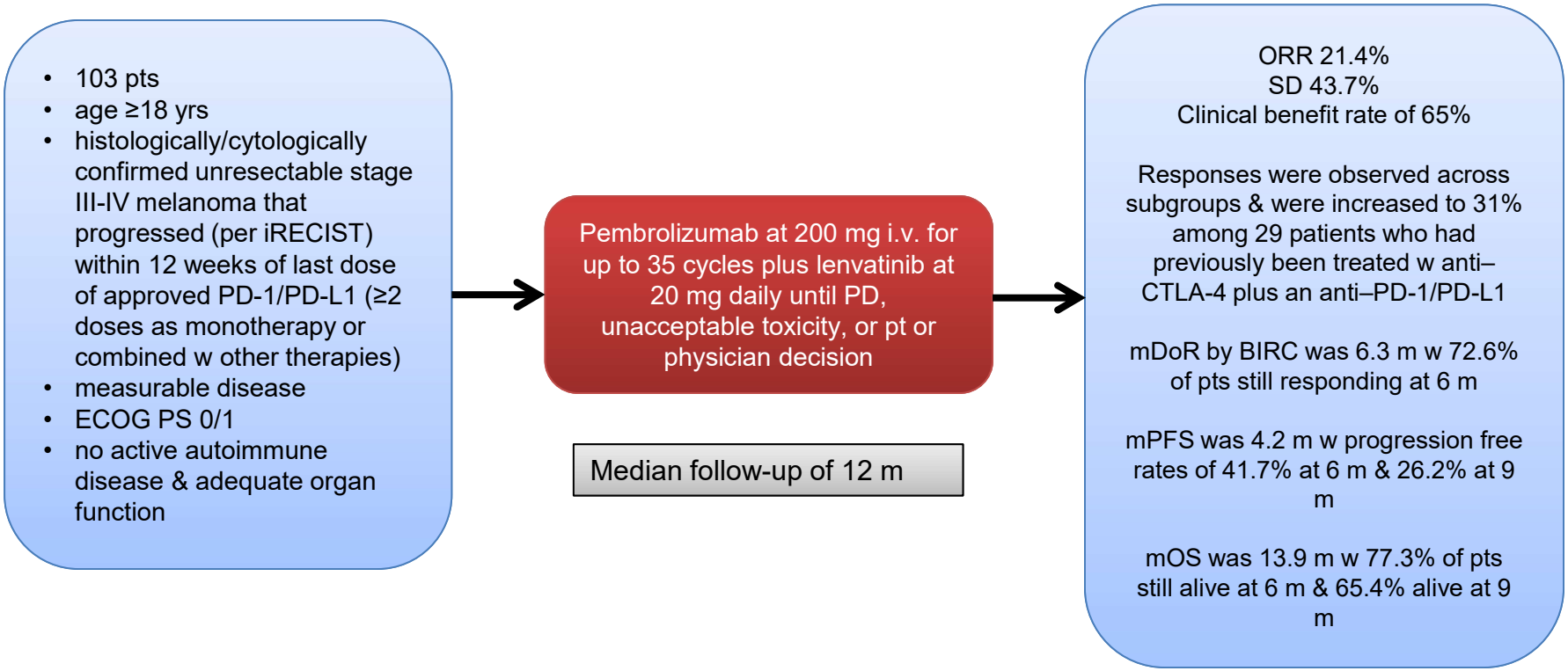
Regorafenib of 80-160 mg was administered once daily for 21 days on/7 days off with nivolumab 3 mg/kg every 2 weeks.



Fukuoka S, et alRegorafenib Plus Nivolumab in Patients With Advanced Gastric or Colorectal Cancer: An Open-Label, Dose-Escalation, and Dose-Expansion Phase Ib Trial (REGONIVO, EPOC1603).
J Clin Oncol. 2020 Jun 20;38(18):2053-2061. doi: 10.1200/JCO.19.03296. Epub 2020 Apr 28. PMID: 32343640.

Lenvatinib (len) plus pembrolizumab (pembro) in patients (pts) with advanced melanoma previously exposed to anti–PD-1/PD-L1 agents: Phase 2 LEAP-004 study

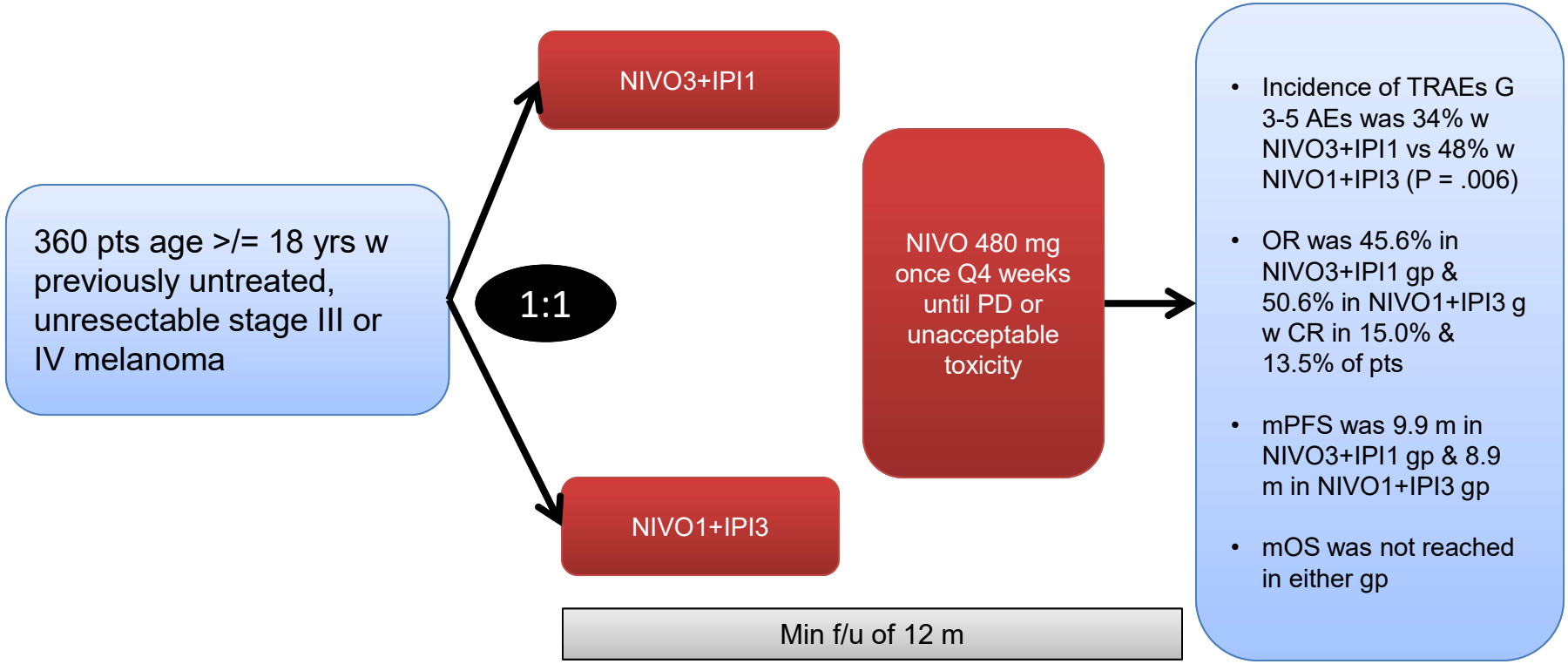
- Len - potent inhibitor of VEGF receptors 1-3, FGF receptors 1-4, PDGF receptor α, RET, & KIT
- Phase 1b/2 KEYNOTE-146 trial: Len plus pembro showed anti-tumor activity & was well-tolerated (24-wk ORR, 47.6%; TRAE: gr 3/4, 67%; gr 5, 0%) in pts w advanced melanoma previously treated w 0-2 therapies



Arance Fernandez AM, O'Day SJ, de la Cruz Merino L, et al: Lenvatinib plus pembrolizumab for advanced melanoma that progressed on a PD-1 or PD-L1 inhibitor: Initial results of LEAP-004. ESMO Virtual Congress 2020: Abstract LBA44

Evaluation of Two Dosing Regimens for Nivolumab in Combination With Ipilimumab in Patients With Advanced Melanoma: Results From the Phase IIIb/IV CheckMate 511 Trial

Ph IIIb/IV study to determine if nivolumab 3 mg/kg plus ipilimumab 1 mg/kg (NIVO3+IPI1) improves the safety profile of the combination



DOI: 10.1200/JCO.18.01998 Journal of Clinical Oncology 37, no. 11 (April 10, 2019) 867-875.

ALKS 4230 monotherapy and in combination with pembrolizumab (pembro) in patients (pts) with refractory solid tumours (ARTISTRY-1)

- ALKS 4230 is a fusion protein of circularly permuted IL-2 & IL-2Rα designed to selectively bind to the intermediate-affinity IL-2 receptor
- Being investigated as monotherapy & in combination with pembro in pts with solid tumors
- Ongoing 3-part phase I/II study. In Parts A (dose escalation) and B (expansion)
- ALKS 4230 is administered as IV monotherapy on days 1-5 of 14- or 21-day cycles
- In Part C (combination therapy), ALKS 4230 is administered via the same 5-day regimen q21d with pembro on day 1

Part B
9 pts (5 melanoma, 4 RCC) received 6 µg/kg (RP2D)

→

1 pt w metastatic urethral melanoma (recurred following adj nivo) achieved PR w normalization of serum LDH

Part C
46 pts (13 tumor types) received ALKS 4230 (3 µg/kg) & pembro
Most common tumors (≥5 each) were CRC, OC & sarcoma

→

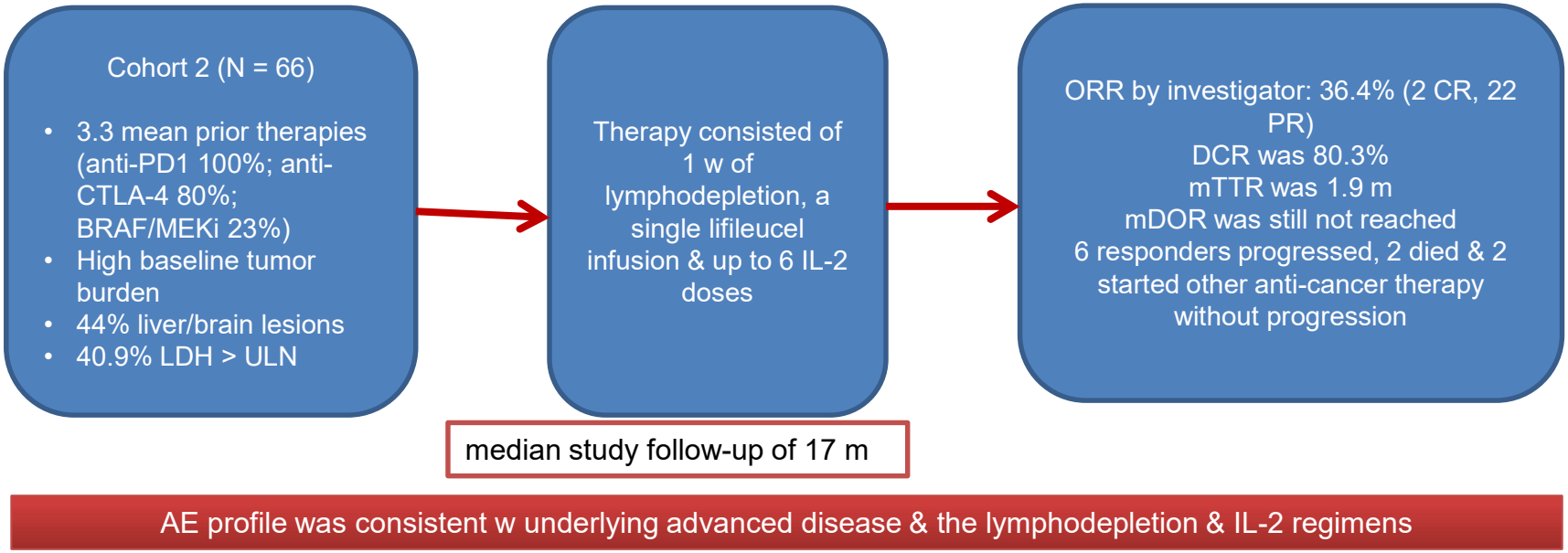
1 heavily pretreated pt w OC : CR (per RECIST)
PR : 2 other OC pts
iPR : 1 pt w TNBC
All 4 responders were CPI naive

Annals of Oncology (2020) 31 (suppl_4): S645-S671. 10.1016/annonc/annonc279

ATC with tumor-infiltrating lymphocytes

Global Phase 2 open-label, multicenter study of efficacy & safety of lifileucel (cryopreserved autologous TIL therapy) in pts w unresectable metastatic melanoma who have progressed on CPIs & BRAF/MEKi, if BRAFv600 m

Tumors were resected at local institutions, processed in central GMP facilities for TIL production, manufactured, cryopreserved & shipped back to sites in a 22-day process

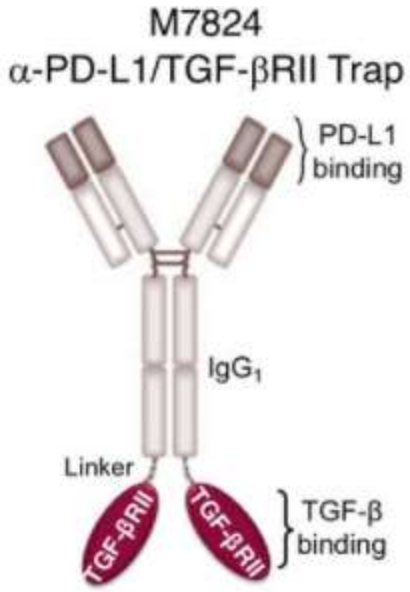


J Clin Oncol 38: 2020 (suppl; abstr 10006)

Dual targeting of TGF-β and PD-L1 via a bifunctional anti-PD-L1/TGF-βRII agent

- Bintrafusp alfa consists of an IgG1 targeting PD-L1 moiety fused via peptide linkers to ECD of 2 TGF-β receptor II molecules designed to 'trap' TGF-β in the TME
- Able to bring the TGF-β trap to the TME via its anti-PD-L1 component, thus simultaneously attacking both immunosuppressive PD-L1 & TGF-β entities

- Preclinical studies have shown bintrafusp alfa capable of ;
    1. preventing or reverting TGF-β-induced EMT in human carcinoma cells – thus rendering human tumor cells more susceptible to immune-mediated attack as well as to several chemotherapeutic agents
    2. altering the phenotype of NK & T cells, thus enhancing their cytolytic ability against tumor cells
    3. mediating enhanced lysis of human tumor cells via ADCC
    4. reducing the suppressive activity of Treg cells
    5. mediating antitumor activity in numerous preclinical models
    6. enhancing antitumor activity in combination with XRT, chemotherapy and several other immunotherapeutic agents

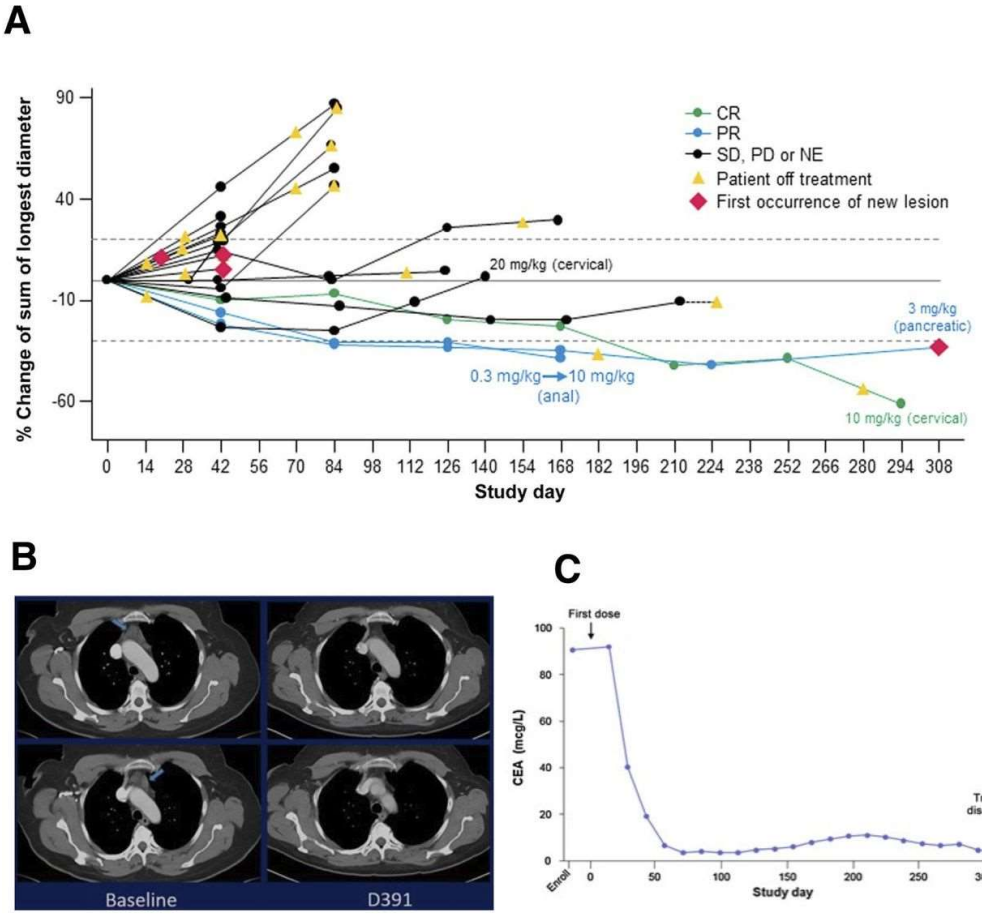


Lind H, Gameiro SR, Jochems C, et alDual targeting of TGF-β and PD-L1 via a bifunctional anti-PD-L1/TGF-βRII agent: status of preclinical and clinical advancesJournal for ImmunoTherapy of Cancer 2020;8:e000433. doi: 10.1136/jitc-2019-000433

Dual targeting of TGF-β and PD-L1 via a bifunctional anti-PD-L1/TGF-βRII agent

Dose-escalation portion of a ph I, open-label clinical trial of bintrafusp alfa (MSB0011359C) has been completed

- 19 heavily pretreated pts w metastatic or locally advanced solid tumors w/o prior CPI - pancreatic, cervix uteri, colorectal, anal & adenoid cystic carcinoma, among others
- Bintrafusp alfa showed a safety profile similar to other anti-PD-1/PD-L1 monotherapies w/ the addition of skin-related AEs characteristic of TGF-β blockade
- Evidence of clinical activity was seen;
  - 1 case (cervical cancer) demonstrated a dCR
  - 2 pts (pancreatic cancer, anal cancer) had dPR
  - 2 cases (pancreatic cancer, carcinoid) experienced prolonged SD



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Anti-TIGIT (T-cell immunoreceptor with immunoglobulin and ITIM domains)

- TIGIT is expressed on multiple immune cell types;
    - Expression of TIGIT on Tregs, particularly tumor-infiltrating Tregs, enhances their immunosuppressive function, with indirect effects that include inhibition of proinflammatory cytokine production
    - Also directly suppresses the antitumor effector function of CD8 T cells
    - Immune activation of TIGIT-expressing CTLs & NK cells is suppressed when TIGIT interacts w 1 of its ligands, CD155 (PVR) or CD112 (PVRL2; Nectin 2) expressed on tumor cells

Phase 1a/1b GO30103 trial (NCT02794571) demonstrated efficacy of atezolizumab plus the anti-TIGIT antibody tiragolumab in patients with PD-L1–pos NSCLC

The study enrolled 73 pts;

- Phase 1a included 24 pts, of whom 67% experienced TRAEs
- Phase 1b included 49 pts, w/ 59% experiencing TRAEs; anemia (31%)
- 3 tumor responses were observed in pts treated in phase 1b
- All had PD-L1–pos tumors, included 2 pts w NSCLC, including 1 CR & 1 pt w/ H&N SCC w/ PR

Expansion cohorts of immunotherapy-naïve pts w/ PD-L1–pos

- 14-pt mNSCLC expansion cohort had ORR of 46%, including 2 CRs & 4 PRs
- DCR was 85%, and the safety profile was similar to that seen in the dose-escalation cohort

OX 40 Agonist Monoclonal Antibody

Safety and Clinical Activity of MEDI0562, a Humanized OX40 Agonist Monoclonal Antibody, in Adult Patients with Advanced Solid Tumors

- Ph I, multicenter, open-label, single-arm, dose-escalation (3+3 design) study, patients received 0.03, 0.1, 0.3, 1.0, 3.0, or 10 mg/kg MEDI0562 through intravenous infusion every 2 weeks, until confirmed PD or unacceptable toxicity
    - 55 patients received ≥1 dose of MEDI0562
    - Most common tumor type was SCC H&N (47%).
    - Median duration of treatment was 10 weeks (range, 2–48 weeks).
    - TRAEs occurred in 67% of patients, most commonly fatigue (31%) & IRRS (14%)
    - G 3 TRAEs occurred in 14% of pts with no apparent dose relationship; no TRAEs resulted in death
    - 2 pts had IR PR per protocol & 44% had SD
    - Increased Ki67+ CD4+ & CD8+ memory T-cell proliferation in the periphery & decreased intratumoral OX40+ FOXP3+ cells

Clin Cancer Res October 15 2020 (26) (20) 5358-5367; DOI: 10.1158/1078-0432.CCR-19-3070

Cancer Vaccines - PVSRIPO

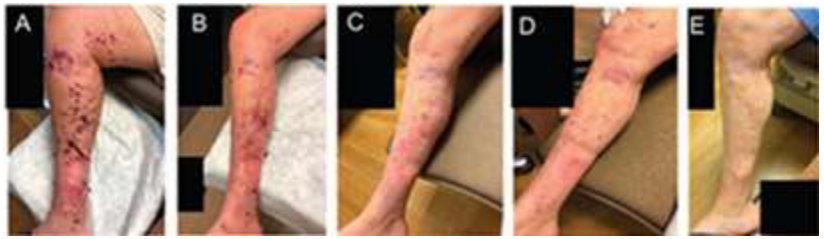
- Ph 1 open-label trial (clinicaltrials.gov NCT03712358) enrolled 12 pts w unresectable &/ metastatic melanoma, who failed ≥1 anti-PD-1-based regimen; pts w $BRAF^{V600}$ failed ≥1 BRAF-targeted therapy

- PVSRIPO: novel immunotherapy consisting of non-neurovirulent rhinovirus: poliovirus chimera that activates innate & adaptive immunity to facilitate targeted anti-tumor immune response

    - 4 (33%) met criteria for ORR per iRRC, including 4/6 (67%) who received 3 injs
    - Path CR : 2 of 4 (50%) pts w in-transit disease - evidence of abscopal response
    - Following the study's completion, majority of pts received additional ICI-based therapy & 6 / 12 pts (50%) remained progression free at data cutoff

- IT PVSRIPO was well tolerated (all adverse events grade 1 or 2)
- No SAEs or DLTs
- No evidence of viral spread from IT inoculation site; pre-existing anti-poliovirus immunity & CD155 targeting are the likely mechanisms responsible for restricting viral spread & systemic IR AEs

- LUMINOS-102 Ph 2 study evaluating the safety & efficacy of PVSRIPO w & w/o anti-PD-1 therapy in advanced anti-PD-1 refractory melanoma population



Georgia M. Beasle et al; A Phase I Trial of Intratumoral PVSRIPO in Patients with Unresectable Treatment Refractory Melanoma; SITC 2020

Cancer Vaccines - UV1

A phase I/IIa clinical trial investigating the therapeutic cancer vaccine UV1 in combination with ipilimumab in patients with malignant melanoma: Four-year survival update

- UV1 targets the enzyme telomerase (hTERT) which is expressed in almost all cancer types and is essential for the immortality of cancer cells and a hallmark of cancer
- UV1 consists of three synthetic long peptides and vaccination induces Th1 responses in most patients irrespective of HLA type
- Pts w/ metastatic melanoma received treatment with UV1 (300 µg) + GM-CSF (75 µg) as an adjuvant, combined with ipilimumab (3 mg/kg)
- 12 patients were treated from Feb to Nov 2015
- Adverse events mainly included injection site reactions & diarrhea
- Immune responses occurred very early & 10/11 evaluable patients showed an immune response
    - 3 pts obtained PR & 1 had CR
    - 3-y OS)was 67%

DOI: 10.1200/JCO.2020.38.5_suppl.62 Journal of Clinical Oncology 38, no. 5_suppl (February 10, 2020) 62-62.

Cancer Vaccines - ilixadencel

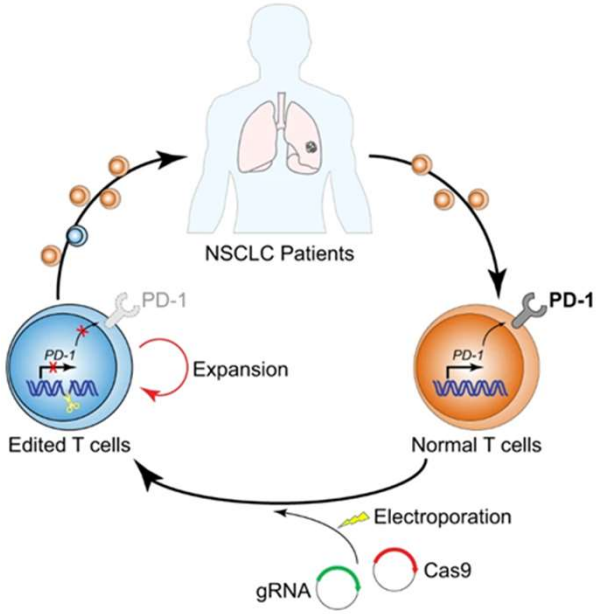
A randomized phase II study with ilixadencel, a cell-based immune primer, plus sunitinib versus sunitinib alone in synchronous metastatic RCC

- Ilixadencel is a cell-based allogeneic off-the-shelf product aimed to prime anti-cancer immune response when injected intratumorally
- Pts were randomly assigned at 2:1 ratio to the combination (COMBO) or sunitinib (SUN) arm
- From April 2014 to January 2017, 88 patients (58 COMBO, 30 SUN) were randomized
    - 5 pts (11%) in the COMBO arm had a CR as best response versus 1 patient (4%) in the SUN arm
    - Confirmed ORR was 42.2 % (19/45) versus 24.0% (6/25)
    - Median DoR was 7.1 months versus 2.9 months
    - Median PFS was 11.8 months versus 11.0 months
    - Median OS has still not been reached in either group
    - As of July 2019, 57% and 43% were alive in the COMBO and SUN arms, respectively
    - Treatment with ilixadencel did not add any treatment-related Grade 3-4 Adverse Events.

DOI: 10.1200/JCO.2020.38.5_suppl.11 *Journal of Clinical Oncology* 38, no. 5_suppl (February 10, 2020) 11-11.

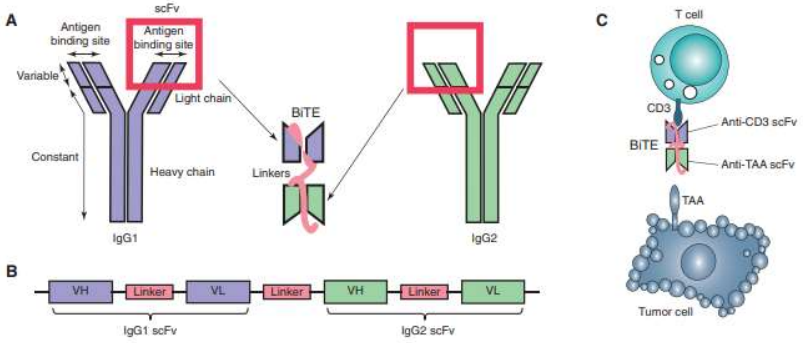
CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats)

- *Lu et al* conducted the first-in-human trial of CRISPR-edited, PD-1-ablated T cells in pts with advanced NSCLC
- 12 pts were transfused edited T cells & were monitored for up to 96 w for TRAEs
- Transfected cells were expanded ex vivo for 17–40 days
- Editing efficiency & in vivo persistence of edited T cells were monitored by NGS of mutations at the *PD-1* locus in infused cells for up to 1 year
- Relatively low levels of editing efficiency (median = 5.81%) in infused cells was observed & as a result, edited T cells did not persist long term in most patients
- Off-target editing by CRISPR was rare
- Infused pts were monitored for up to 2 years for TRAEs
- G 1/2 AEs occurred in 11 of the 12 patients and no grade 3+ AEs were reported
- No treatment-related dose-limiting toxicities were observed during the 2-yr follow-up
- No objective responses were in the treated patients, which may be due to a combination of low editing efficiency, poor T cell expansion, and/or lack of antigen specificity by the edited T cells
- 1 patient with the highest PD-1 editing efficiency showed long-term persistence of edited T cells in vivo & SD for 76 weeks, suggesting higher editing efficiency may be associated with improved clinical outcomes



He, S. The first human trial of CRISPR-based cell therapy clears safety concerns as new treatment for late-stage lung cancer. Sig Transduct Target Ther 5, 168 (2020).

CARs versus BiTEs



	CAR T cell	BiTE
Structure	A synthetic gene construct encoding an scFv against tumor antigen linked to activation and costimulatory motifs.	A recombinant protein composed of two linked scFvs; one binds to CD3 on T cells and the other to target a tumor antigen on tumor cells.
Effector cell types	Engineered $CD8^+$ and $CD4^+$ T cells (5). Less-differentiated subsets displaying better antitumor activity *in vivo* (T_{SCM} and T_{CM}; ref. 10).	Endogenous $CD8^+$ and $CD4^+$ T cells (13). Antigen-experienced T_{EM} but not T_N effective (14).
Immune synapse	Atypical (15).	Typical (17–19).
Serial killing	Yes (16).	Yes (22).
Killing mechanisms	Perforin and granzyme B (16), Fas/Fas-L, or TNF/TNF-R.	Perforin and granzyme B (17).
Trafficking	Active. Trafficking of CAR T cells involves comprehensive interactions between various molecules and cell–cell interactions (57).	Passive. Biodistribution depends on factors related to rates of diffusion through vascular endothelium, fluid flow rates, and interaction with target.
Toxicity	CRS, neurotoxicity, B-cell aplasia (31, 49).	CRS, neurotoxicity, B-cell aplasia (62, 64).
Clinical applications	Pretreatment lymphodepleting regime using cyclophosphamide and fludarabine. Premedicate with acetaminophen and an H1-antihistamine. One infusion.	No lymphodepletion regime required. Premedicate with dexamethasone. Repeat administration necessary, including continuous i.v. infusion regimens.
FDA approval	Yescarta was approved to treat adult patients with relapsed/refractory large B-cell lymphoma in 2017. Kymriah was approved to treat patients up to 25 years of age with refractory/relapsed B-ALL in 2017.	Blinatumomab was approved to treat relapsed/refractory B-ALL in 2014 and 2017.
Other characteristics	Individually produced for each patient.	"Off the shelf" reagents.

For treating solid tumors, CD3-coupled BiTEs specific for EPCAM (solitomab), CEA, and prostate-specific membrane antigen (PSMA)

New constructs, such as bifunctional checkpoint-inhibitory T cell engagers (CiTEs), simultaneous multiple interaction T cell engagers (SMITEs), trispecific killer engagers (TriKEs) and BiTE-expressing chimeric antigen receptor (CAR) T cells (CART.BiTE cells), have been developed to integrate various immune functions into one therapeutic approach or cellular vector, thereby enhancing anticancer activity without substantially increasing the risk of immune-related adverse effects

Slaney CY, et al; CARs versus BiTEs: A Comparison between T Cell–Redirection Strategies for Cancer Treatment; Cancer Discovery; Aug 2018
Goebeler, ME., Bargou, R.C. T cell-engaging therapies — BiTEs and beyond. Nat Rev Clin Oncol 17, 418–434 (2020)