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

Society for Immunotherapy of Cancer

Disclosures

- Research Funding:
  - Astrazeneca, Tesaro

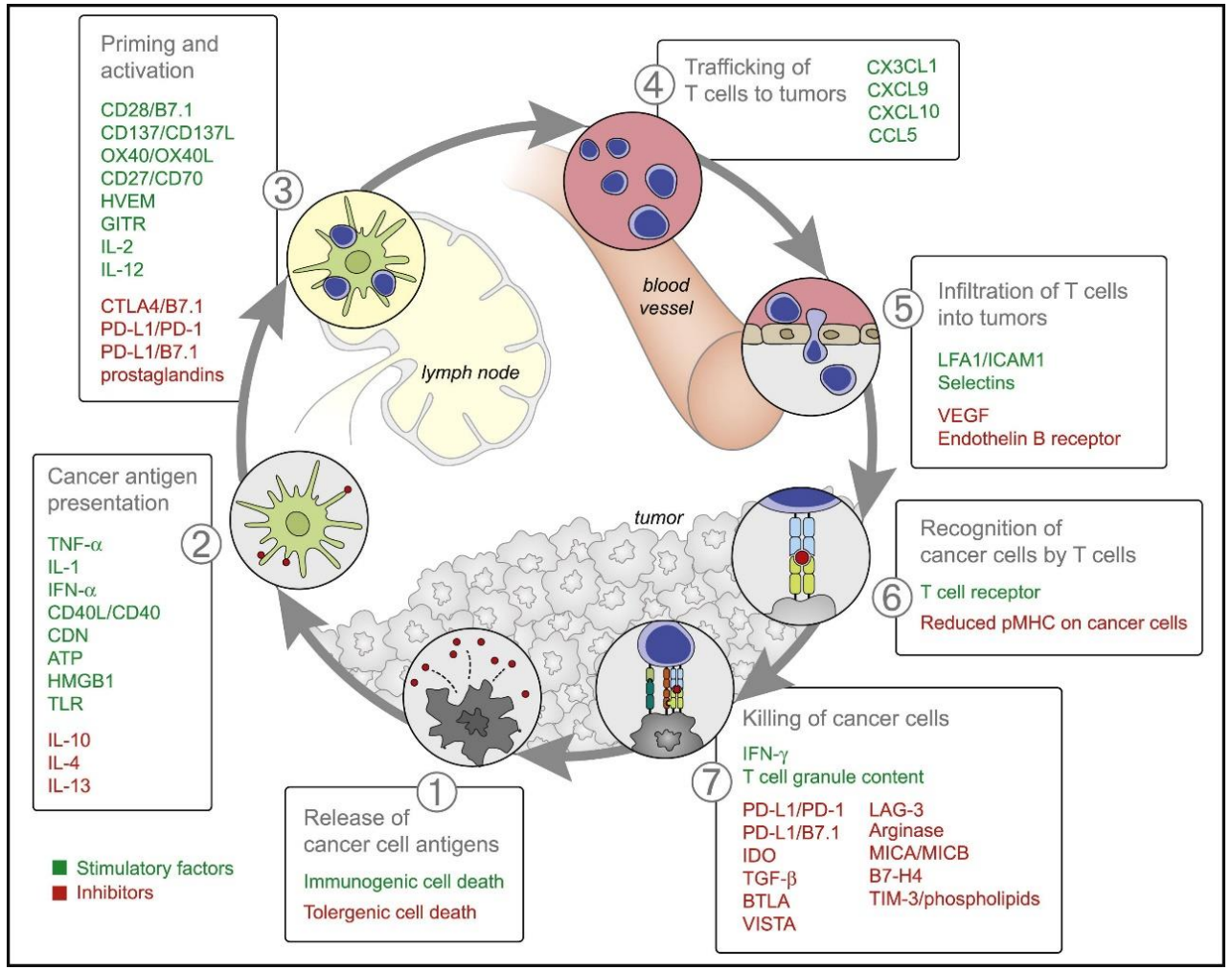
Reasons to explore beyond checkpoint inhibitors

- The fraction of patients responding to immune checkpoint blockers used as stand alone is generally around 20% (varies depending on indication).

- A variety of combinations are being investigated
  - To prevent escape resistance mechanisms, delay resistance
  - To further harness the power of the immune system, increase the number of patients benefitting
  - To elicit longer responses
  - To reduce toxicity

Gallucci et al Science Trans Medicine 2018

Stimulatory and inhibitory factors in the Cancer-Immunity Cycle

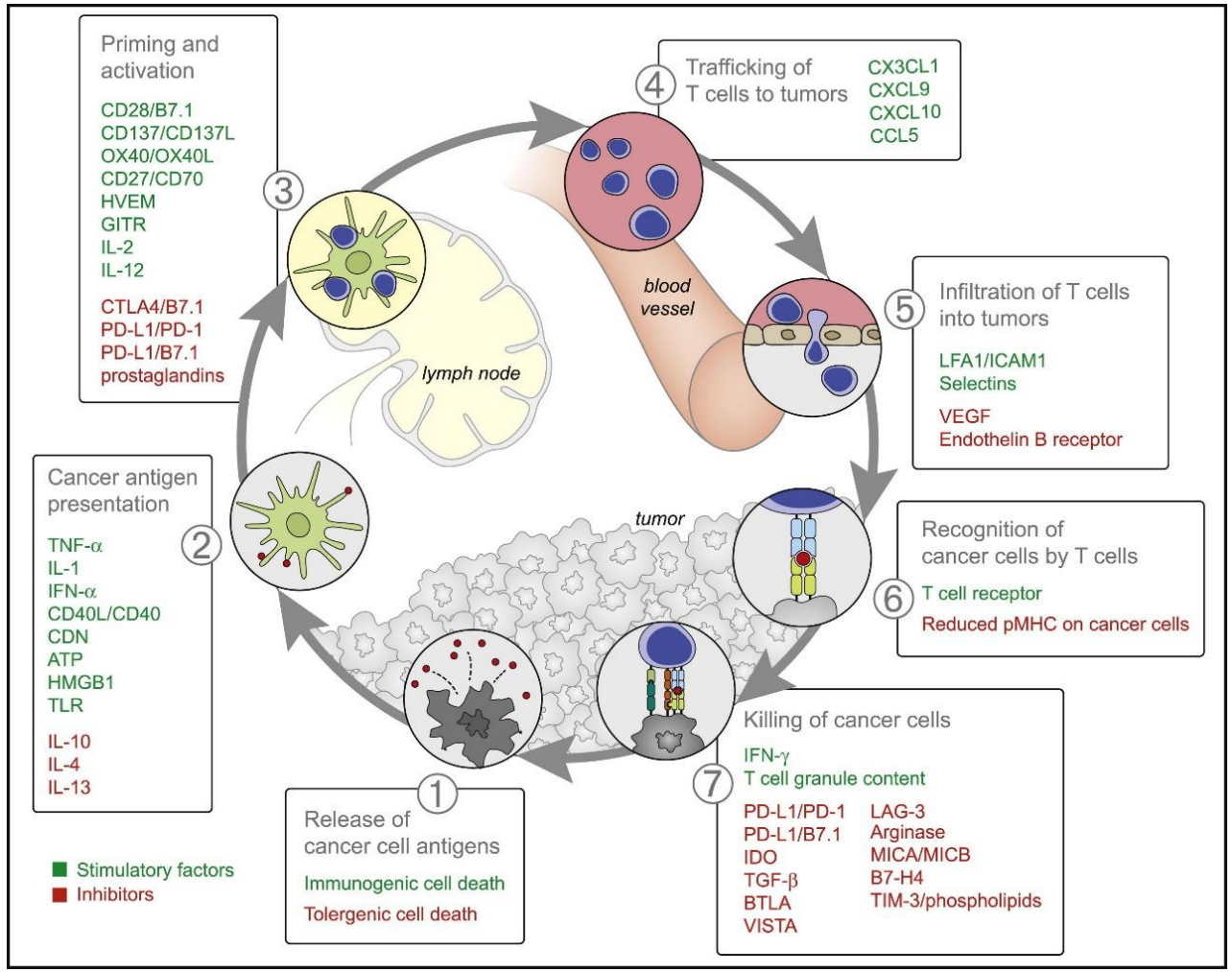


Chen & Mellman Nature 2013

Cancer Immunity Cycle- Clinical Trials available at IU

-**CTMX-M-072-001** (PDL1 probody)
-**EFT508-0010** (MNK inhibitor)
-**NKTR-214** (CD122 agonist)
-**HD IL-2 +Entinostat** (hypomethylation)
-**HD-IL2 + pembrolizumab**

-**BBI-DSP0509-101** (TLR-7 agonist)

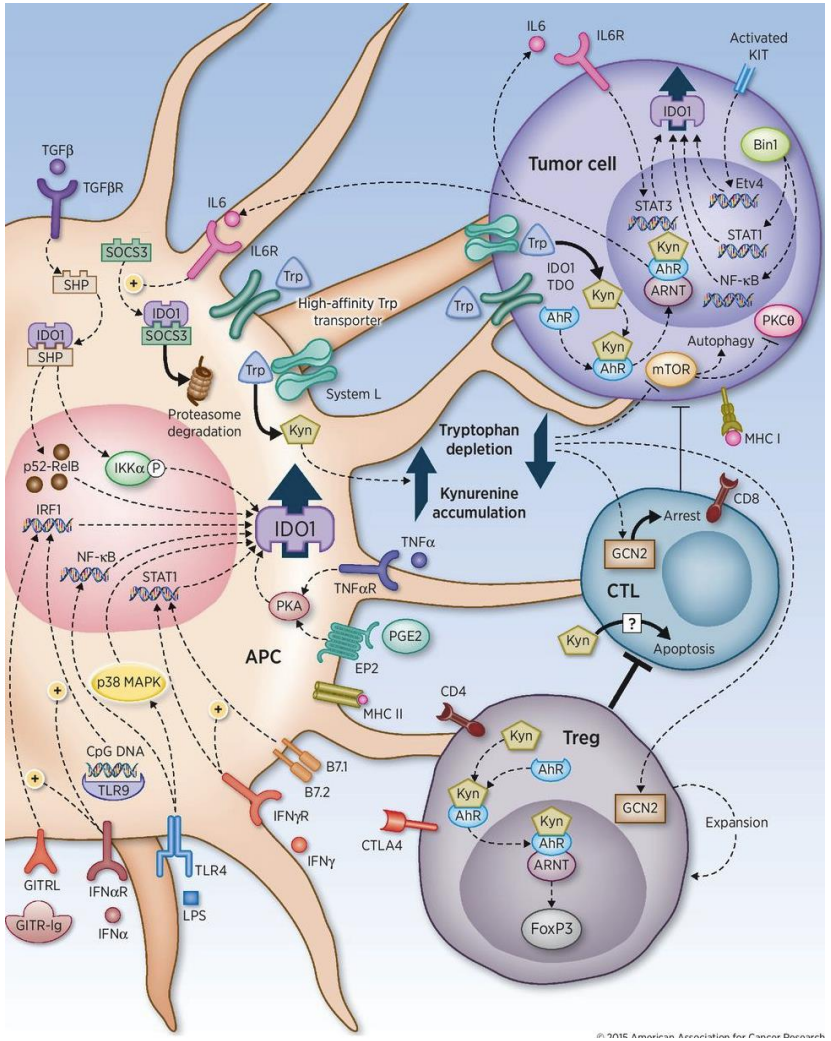


-**MAGE-A10^{c796}** (TCR)
-C144-01 (TILs)

-**I9L-MC-JZCA** (IDO1)
-**CPDR001XUS01** (LAG3 +PD1 inhibitor)

Beyond Receptors to Metabolites

- IDO1 is an enzyme that is expressed on tumor infiltrating lymphocytes and various tissues. Non-small cell lung cancer is one of the solid organ tumors with a high expression of IDO.
- IDO1 (Indoleamine 2,3-dioxygenase) regulates the immune response by degrading tryptophan to kynurenine. IDO pathway activity results in a shift of the ratio of tryptophan to kynurenine, which means suppressive immune phenotype.
- Tumors hijack the IDO pathway.



Johnson, Immunol Inves 2012;41

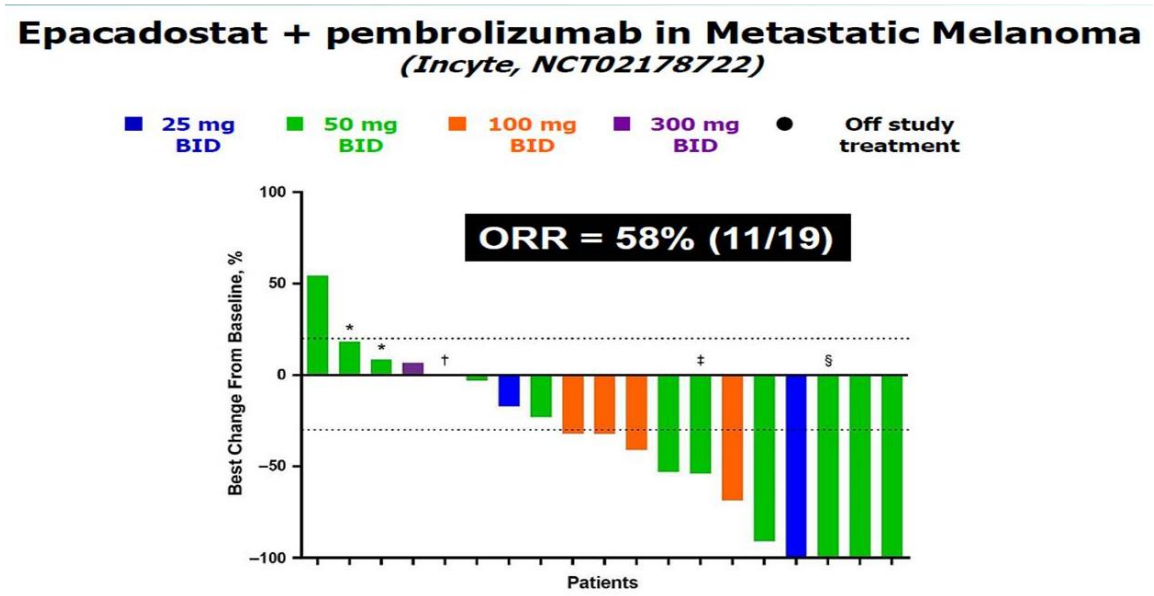
IDO1 inhibition strategies

Agent	Class
Indoximod	Selective IDO1 inhibitor
Epacadostat	Selective IDO1 inhibitor
GDC0919	Selective IDO1 inhibitor
IDO5 peptide	IDO peptide vaccine

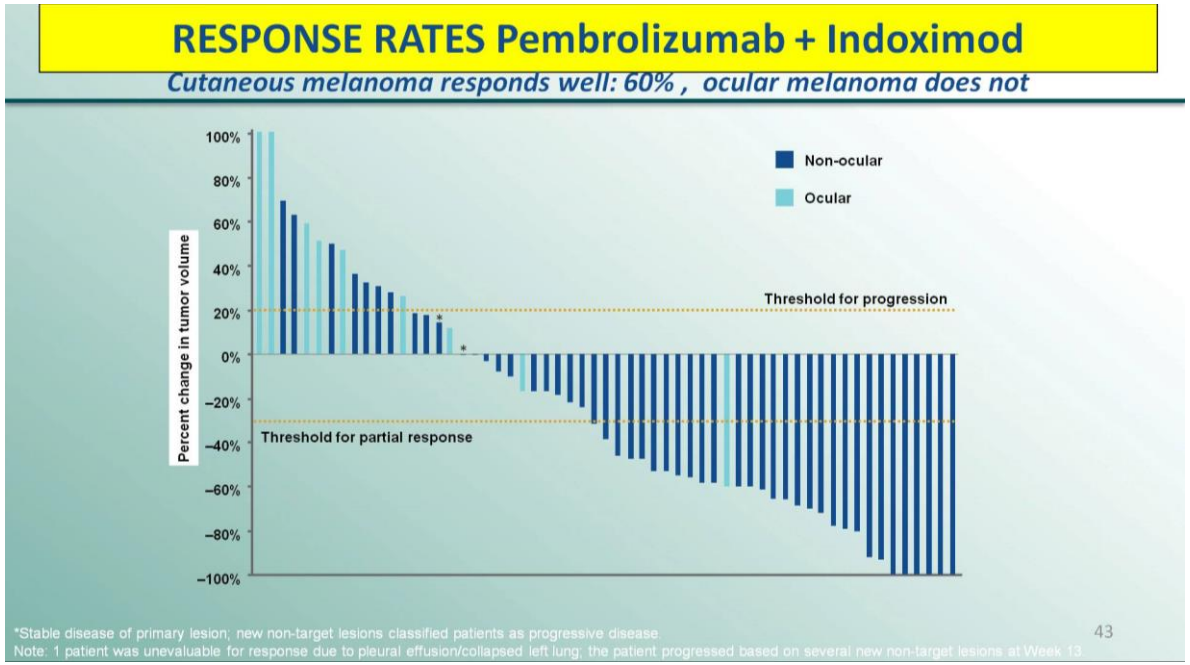
- IDO inhibitor monotherapy seems to have modest activity. It is still unclear if IDO1 inhibitors will be successful.
  - Multiple studies ongoing. This include a phase 1 trial we are participating in (LY3381916 alone or in combination with LY33000054) we are participating in.
  - Two distinct strategies: Direct IDO inhibition (Epacadostat) or reversal of IDO mediated suppression in the tumor (Indoximod)
  - ID05 peptide has shown some early promising activity in NSCLC

Zhai, CCR 2015, Soliman et al oncotarget 2016, Nayak et al, J Immunother Cancer 2014, Kjeldsen et al., Front Immunol 2018

IDO1(-) in combination with PD(-)



Phase 3 study negative

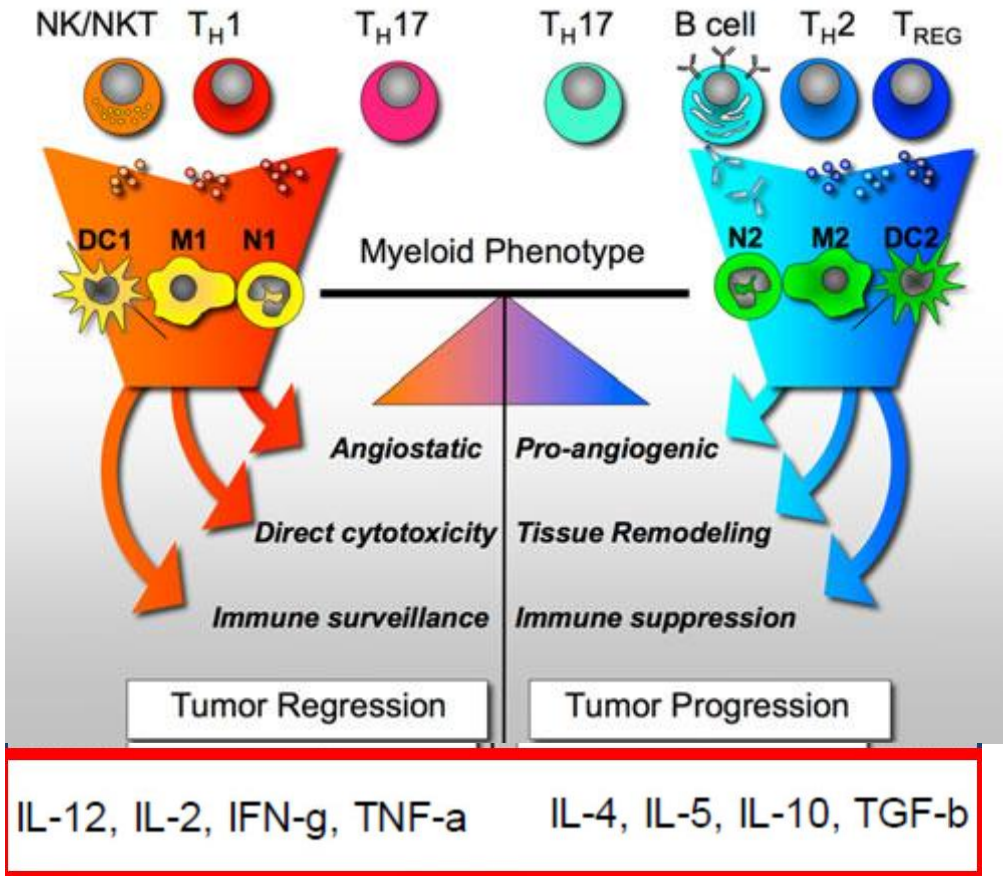


Phase 2 trial

Unclear if IDO1- will play out clinically!

Zakharia et al. AACR 2017, abs CT117
Alexander Eggermont at 2018 ASCO Annual Meeting

Do Not Forget Cytokines



Denardo et al, Cancer metastasis Rev 2010

Cytokines can directly stimulate T cells or NK cells

The History of IL-2

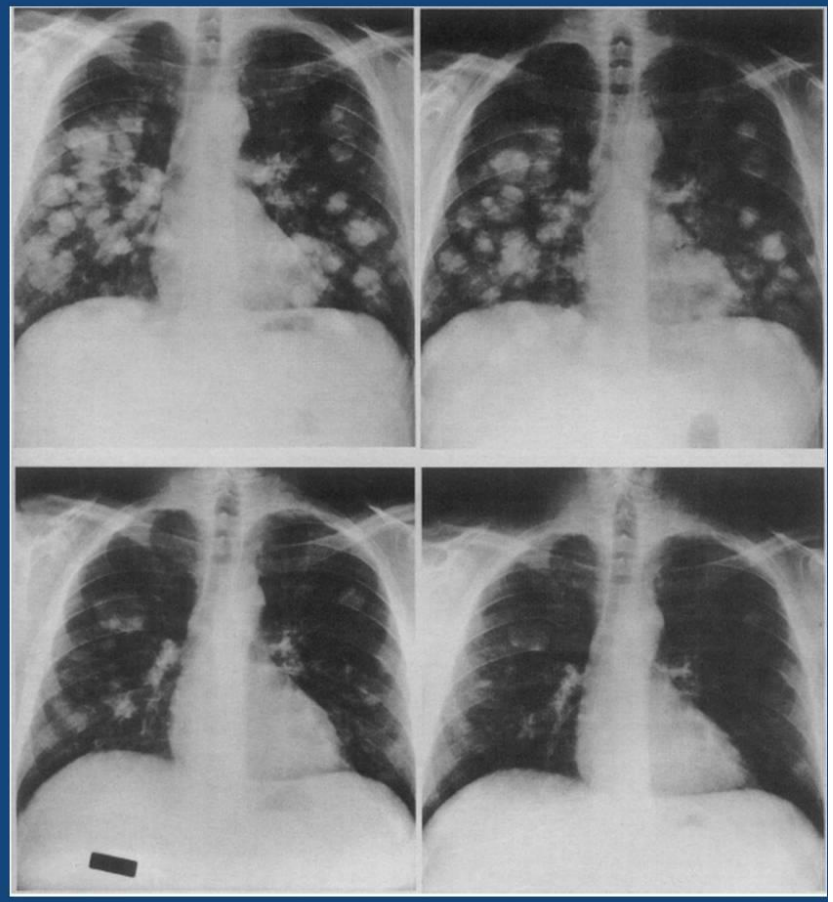
IL-2: the first effective human cancer immunotherapy

First IL-2 responder treated in 1984 and had a durable, decades-long response

US FDA approval:

Advanced dz	Approved	ORR
Renal Cell	1992	16%
Melanoma	1998	15%

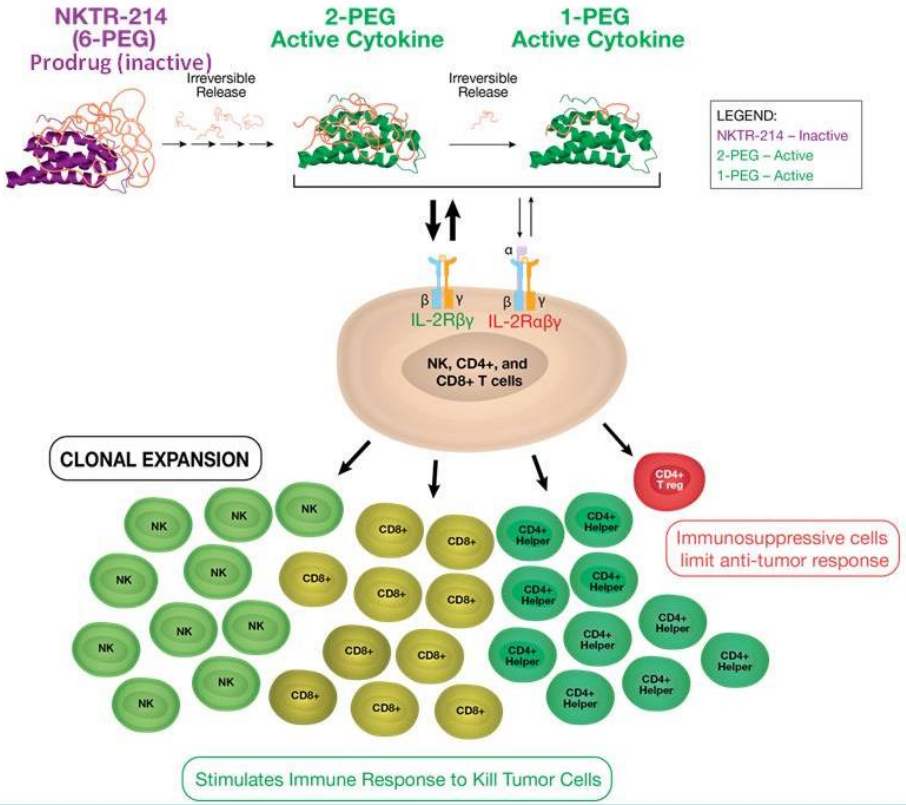
mRCC estimated 10y OS of ~10%[1,2]



PROCLAIM registry confirmed durability of HD IL-2

Alva t al. 2016, Donskov et al ASCO 2010, Fisher et al Cancer J Science 2000, Lotze et al. JAMA 1986

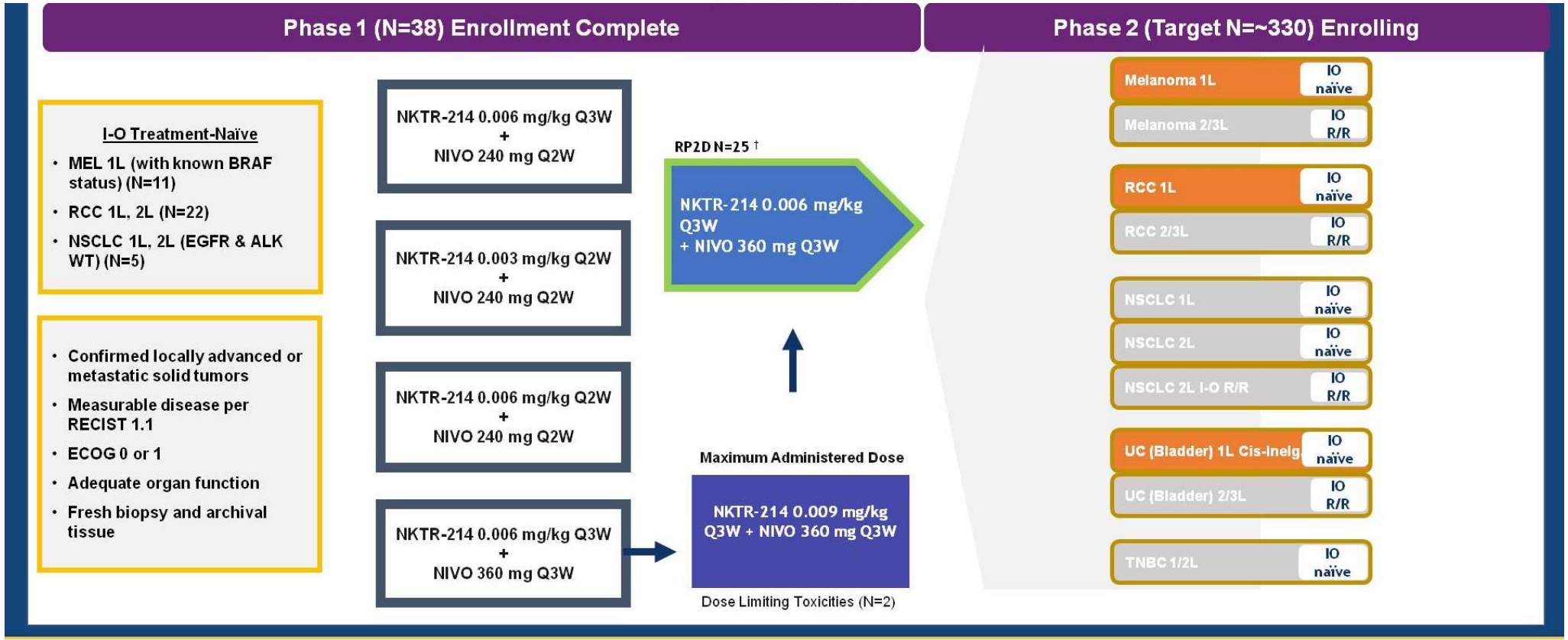
NKTR-214 Background: Harnessing IL-2 to increase TILs



- NKTR-214 prodrug design with sustained signaling
- Mitigation of rapid immune stimulation to achieve safe, outpatient regimen administered every 3 week IV dosing
- Biased signaling preferentially activates and expands effector T cells and NK cells over Tregs in the tumor microenvironment
- NKTR-214 increases proliferation of TILs and PD-1 expression on the surface of CD8+ T cells providing a mechanistic rationale for combining with nivolumab

Presented By Adi Diab at 2018 ASCO Annual Meeting

PIVOT-02 Dose Expansion Cohorts in 5 Tumor Types



PRESENTED AT: 2018 ASCO ANNUAL MEETING #ASCO18

PRESENTED BY:

Diab ASCO 2018

Preliminary Results

- NKTR-214 showed encouraging antitumor activity
  - RR melanoma 42%
  - RCC 53%
  - Urothelial 60%

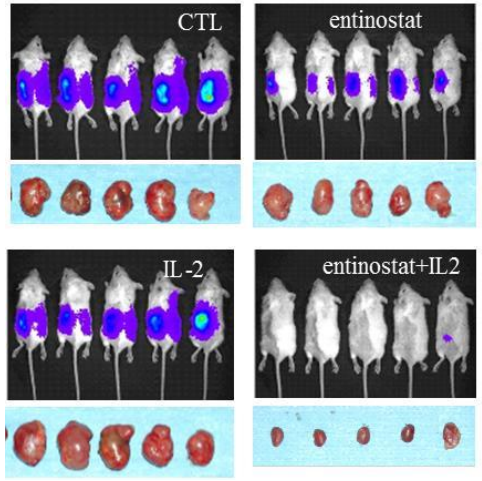
- Incidence of grade ≥3 immune mediated events was low (3.5%)

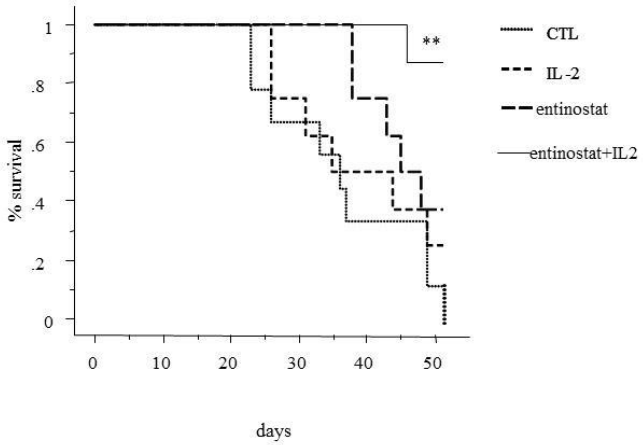
- There was a significant rate of conversion of PDL1(-) to PDL1 (+)tumors.

Diab et al ASCO 2018

HD IL-2 in combination with Entinostat

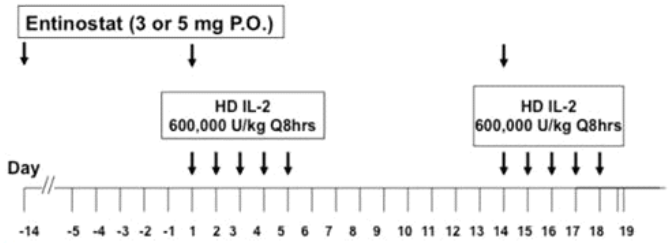
- Epigenetic modulation of gene expression as been shown to influence signaling and expression of proteins involved in innate and acquired immunity.
- Histone deacetylase inhibitors in combination with IL-2 were shown to have activity in a renal cell animal model.
- Entinostat is a selective oral HDAC inhibitor that has shown promising activity in combination with high dose IL-2 in renal cell carcinoma patients
- Randomized study of high dose IL-2 alone or in combination with Entinostat is treatment naïve clear cell RCC is ongoing at IU.

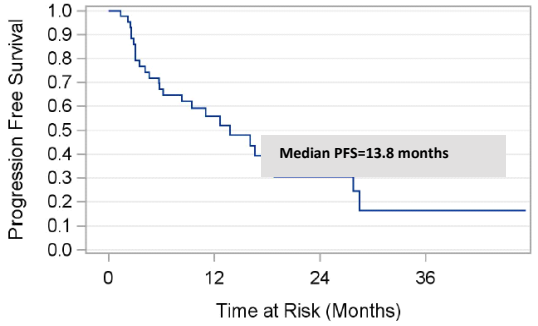


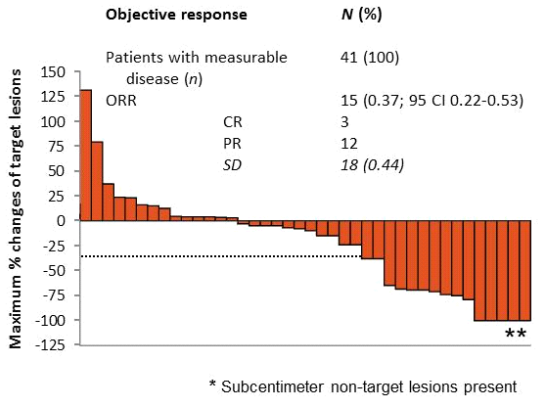


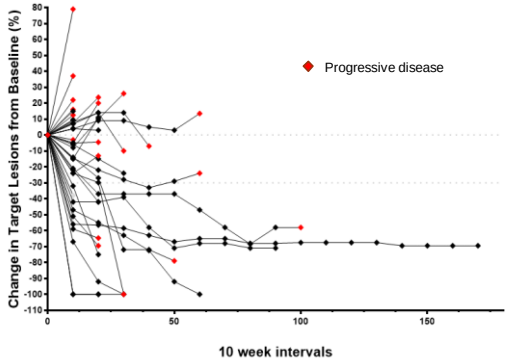
Kato et al. CCR 2007
Pili et al CCR 2017

High dose IL-2 in combination with Entinostat









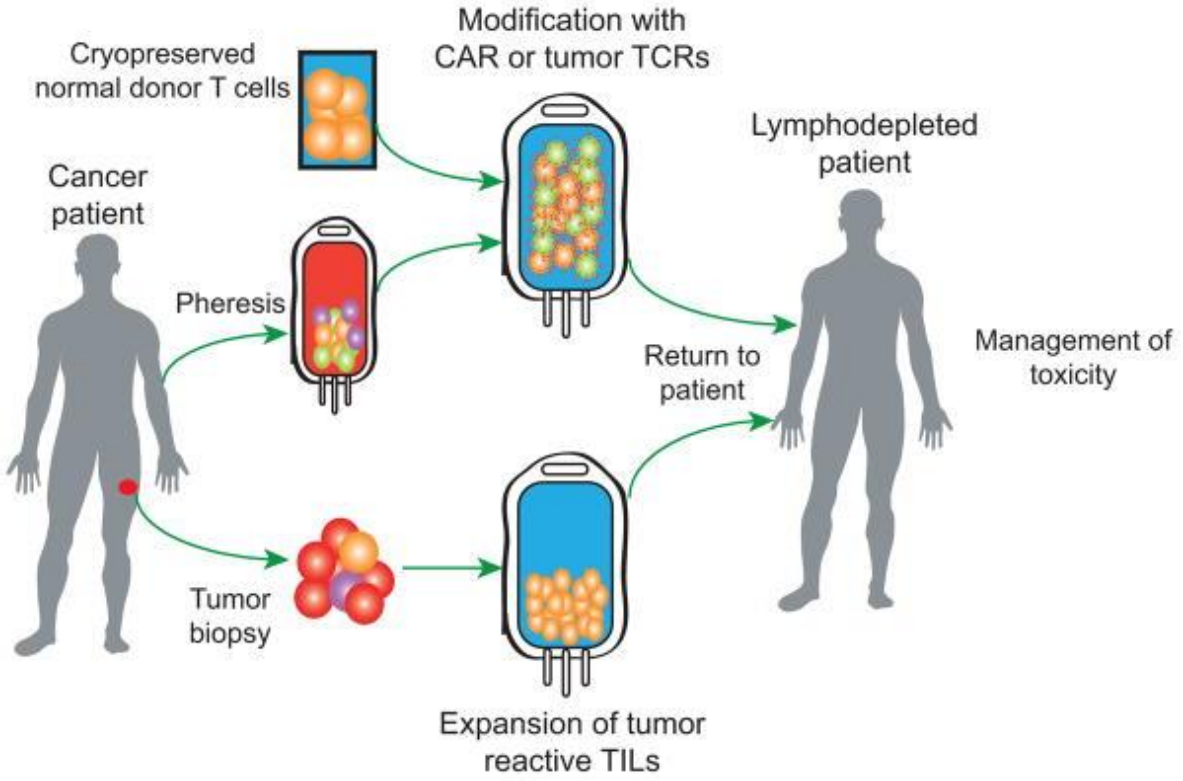
Patients with metastatic kidney cancer

Clinical Trial Enrollment

Randomized Phase II study of HD-IL2 +/- entinostat (HCRN)

Pili R *et al* Clin Cancer Res 2017

Adoptive Cell Transfer

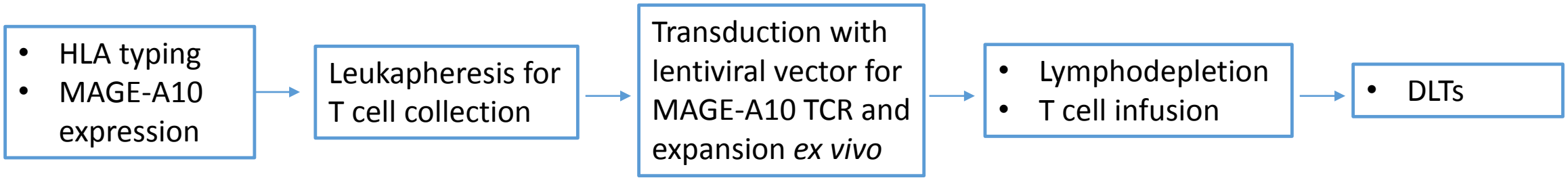


Chimeric antigen receptor (CAR) recognition is limited to membrane antigens which represent around 1% of the total proteins expressed, whereas T cell receptor modified T cells (TCRs) have the advantage of targeting any peptide resulting from cellular protein degradation. TILs are another strategy

Walseng et al. Scientific report, 2017
Barrett et al, J Immunol 2016

MAGE-A10^{c796} TCR

- MAGE-A10 is expressed in 10-50% of melanomas, H/N, NSCLC tumors
- Specific peptide-enhanced affinity receptor (SPEAR) autologous MAGE-A10 T cells directed toward MAGE-10 tumor antigen are being tested in clinical trials



Lam et al ASCO 2018

MAGE-A10^{c796} TCR Initial Safety Results

- MAGE-A10 protein expression was noted in 41% of squamous cell lung cancers, 39% large cell lung cancers and 47% bladder cancers
- Transduced T cells were detectable in peripheral blood of treated patients
- Serious adverse events included dyspnea, hematologic toxicities, cytokine release syndrome, sepsis

Lam et al ASCO 2018

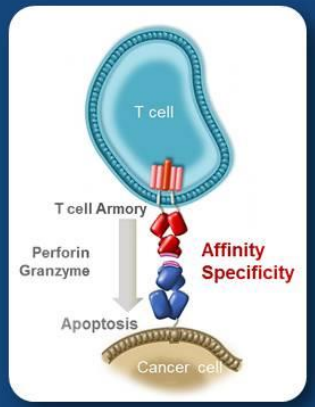
NY-ESO-1^{c259} TCR Initial Efficacy results in Myxoid/ Round cell Liposarcoma

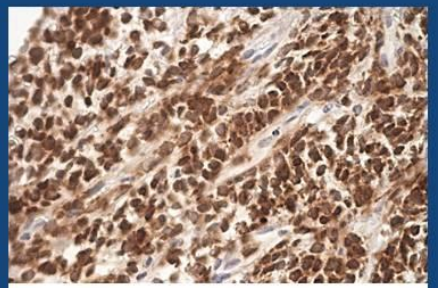
NY-ESO-1^{c259}TCR is an affinity-matured HLA-A*02-restricted TCR recognizing NY-ESO-1 peptide (*SLLMWITQC*)

NY-ESO-1^{c259}TCR led to responses in 50% of synovial sarcoma patients (D'Angelo *et al. Cancer Discovery*, in press)

NY-ESO-1 is expressed in 80-90% of MRCLS

This experience prompted interest in exploring a similar approach in MRCLS



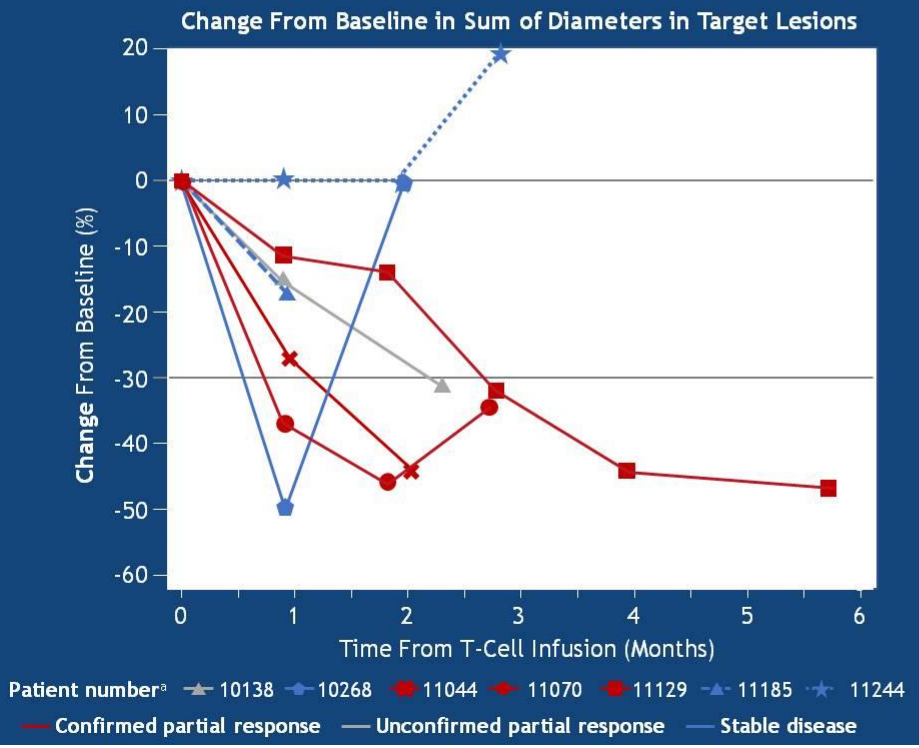


NY-ESO-1 IHC staining of MRCLS tissue

Presented By Sandra D''Angelo at 2018 ASCO Annual Meeting

NY-ESO-1^{c259} TCR Initial Efficacy results in Myxoid/ Round cell Liposarcoma

Response Summary



Best Overall Response (BOR)	N=8
Confirmed complete response	0
Confirmed partial response	3
Unconfirmed partial response	1
Stable disease	3
Progressive disease[b]	0
Not assessed[a]	1
Overall (Unconfirmed) Response	4

[a]Patient 11832 recently treated and post-infusion disease assessment is not yet available
[b]Three patients have progressed

Data cutoff May 30, 2018

Presented By Sandra D''Angelo at 2018 ASCO Annual Meeting

Anti-PD (L)1 Plus Targeted therapy might be rational combinations with timing being Key

- Targeted treatments can
  - Enhancing tumor antigen release and expression
  - Increased T-cell activity
  - Modulate tumor microenvironment

- BRAF inhibition leads to increased CD8+ T cell infiltration
- Pro-angiogenic factors can modulate immune response
  - Reducing T cell infiltration
  - Inhibition of Treg proliferation, dendritic cell maturation

Frederick et al CCR 2013
Moya-Horno et al., Ther Adv Med Oncol 2018

Anti-PD (L)1 Plus Targeted in Melanoma

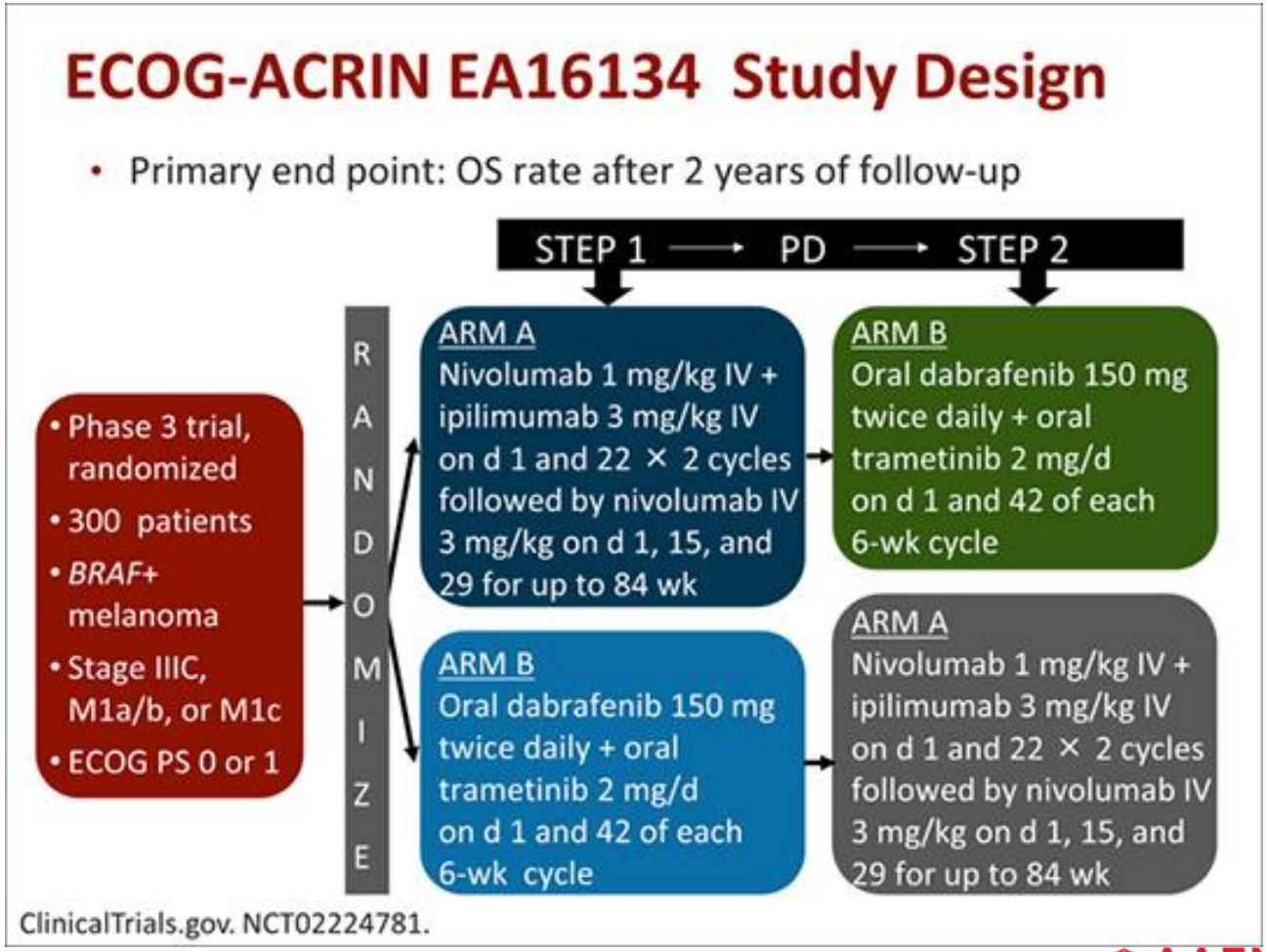
- Approximately 50% of melanomas as BRAF V600 mutant

- Traditional thinking suggests combination might overcome the rapid but short response with BRAF targeted therapy and the durable but less frequent response with immunotherapy

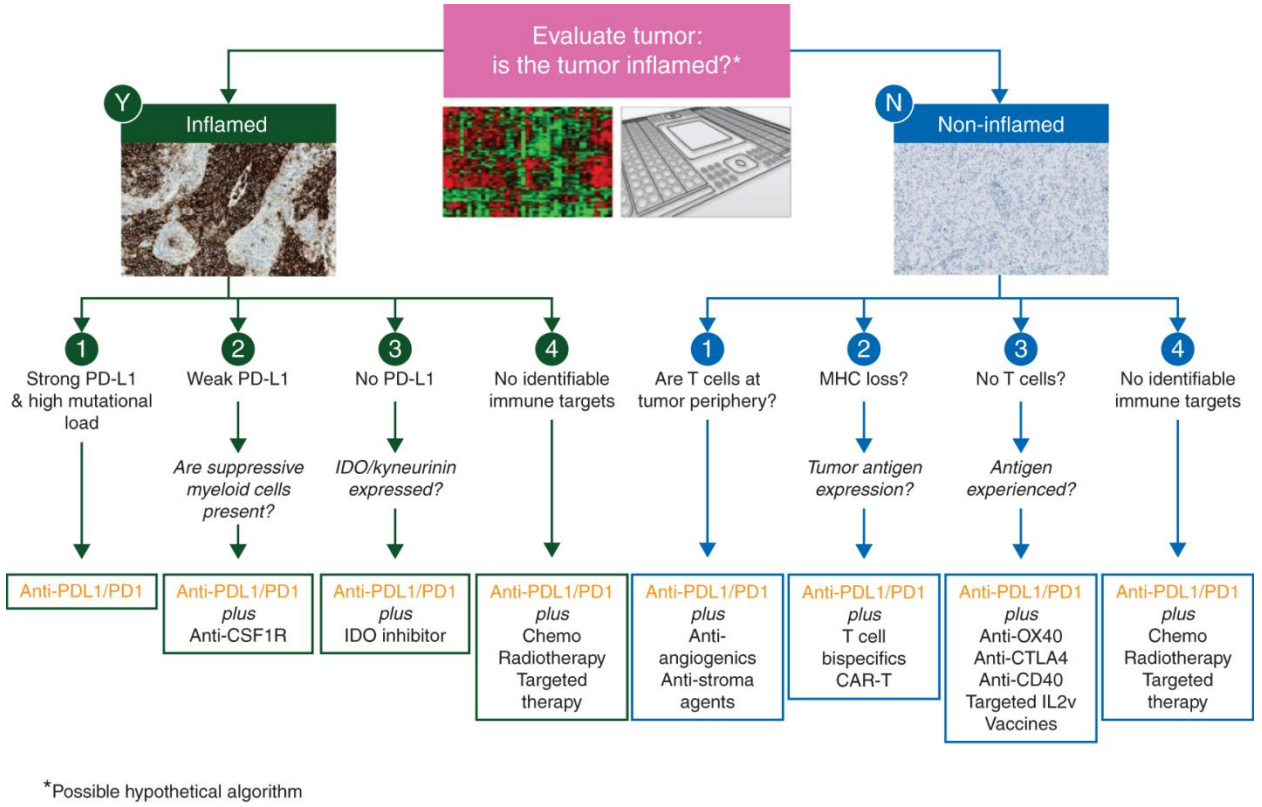
- Promising phase 1 data including
  - Atezolizumab+ cobimetinib+vemurafenib in BRAF mut melanoma led to RR 83%. Toxicity might be an issue
  - Axitinib in combination with pembrolizumab in advanced RCC with DCR 86%

Sullivan et al. ASCO 2017, abstract 3063
Atkins, lancet oncology 2018

Anti-PD (L)1 Plus Targeted in Melanoma



Defining the cancer-immune phenotype



From: Immune escape to PD-L1/PD-1 blockade: seven steps to success (or failure)

Ann Oncol. 2016;27(8):1492-1504. doi:10.1093/annonc/mdw217

Personalizing Immunotherapy (ADVISE Study)

Pt number	LAG-3	CSF-1R	GITR	IDO	NKp46	FOX-P3	Treatment
1	Low	Low	Low	Low	Low	Med	Nivo+Ipi
2	Low	Low	Low	Low	High	Low	Nivo+Lirilumab
3	Med	Med	Med	High	Low	Med	Nivo+anti-GITR
4	Med	Med	Med	Med	Med	Med	Randomize
5	low	low	low	low	low	Low	Nivo+SBRT

Luke et al, ASCO 2018, TPS3101

Many questions remain in the era of Immunotherapy

- What is the optimal Duration of treatment?
- Can we stop treatment in setting of CR?
- What do we do in setting of mixed response?
- Is toxicity a reason to stop treatment?
- Are steroids the best or only way to manage toxicities?
- What are causes of acquired resistance?
- What do we know about hyper-progression?
- Should we offer checkpoint inhibitors to PS 2 patients? Or patients with AI conditions?

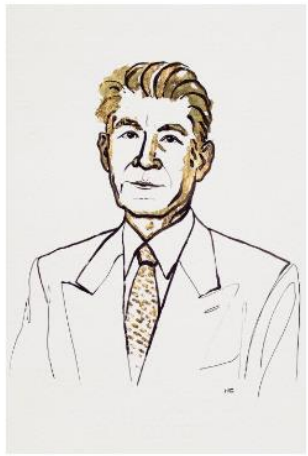
Many clinical questions…

- What is the optimal Duration of treatment?
  - Unknown
- Can we stop treatment in setting of CR?
  - *Some suggestion of feasibility in melanoma*
- What do we do in setting of mixed response?
  - Isolated areas of progression should be treated with local modalities
- Are steroids the best or only way to manage toxicities?
  - It is currently
- What are causes of acquired resistance?
  - They are diverse!
- What do we know about hyper-progression?
  - It is a real phenomena (Ferrara et al. JAMA oncology 2018)
- Should we offer checkpoint inhibitors to PS 2 patients? Or patients with AI conditions?
  - Risk-benefit ratio discussion

Ill. Niklas Elmehed. © Nobel Media

James P. Allison

Prize share: 1/2

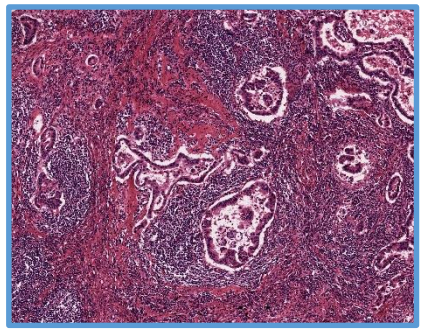


Ill. Niklas Elmehed. © Nobel Media

Tasuku Honjo

Prize share: 1/2

The Nobel Prize in Physiology or Medicine 2018 was awarded jointly to James P. Allison and Tasuku Honjo "for their discovery of cancer therapy by inhibition of negative immune regulation."



TUMOR + PATIENT +MICROENVIRONMENT

↓

Rx

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Thank you for your attention!

Society for Immunotherapy of Cancer

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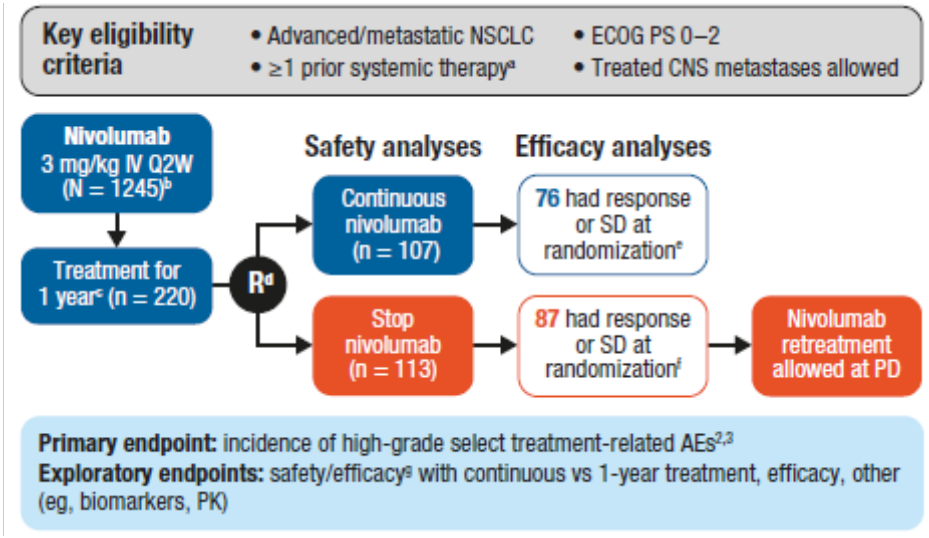
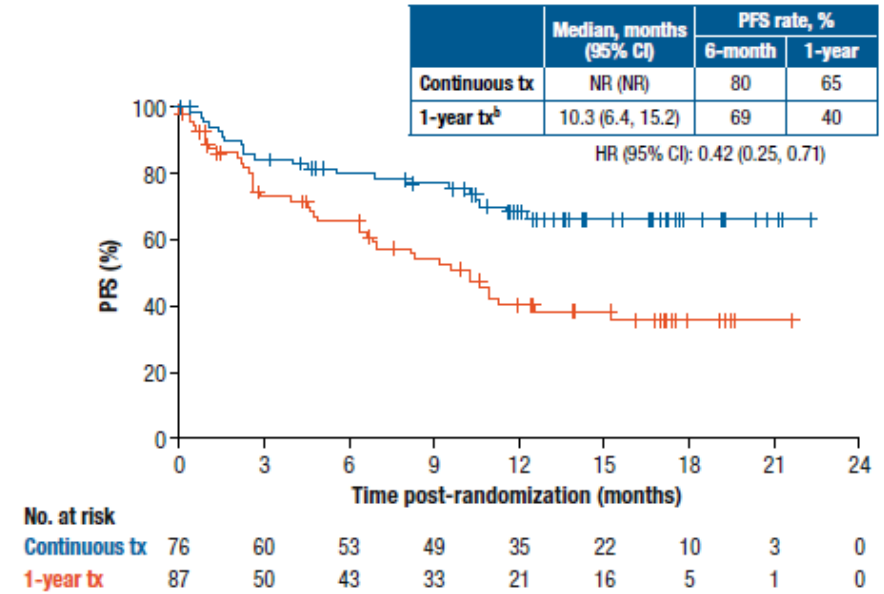
BACKUP

Nivolumab continuation beyond 1 year improves PFS





Responses on KEYNOTE-010 NSCLC arm showed durability after 2 years of pembrolizumab

Spigel et al, German Cancer Congress 2018
Herbst et al. KEYNOTE-010, 2016 World Conference on Lung Cnacer

LAG3 Inhibition as a potential therapy

- LAG3 or lymphocyte activation gene-3 is a receptor that is expressed on activated and regulatory T cells, NK cells and a subset of dendritic cells.
- LAG3 is frequently co-expressed with PD1 on dysfunctional or exhausted T cells.
- LAG3 inhibition shows synergy with PD1 inhibition in animal models.
- LAG3 is expressed on TILs of melanoma, gastric and NSCLC

Villanueva et al, Therapeutic advances in Resp Disease, 2018

LAG 3 Inhibitors in development

LAG 3	BMS-986016 (mAb)	Bristol Myers	Monotherapy and in combination with nivolumab
	LAG525 (mAb)	Novartis	Monotherapy, combination with anti-PD-1 mAb (PDR001)
	MGD013 (mAb)	Macro-genics	Monotherapy
	REGN3767 (mAb)	Regeneron Pharma	Monotherapy, combination with anti-PD-1 mAb (REGN2810)
	TSR-033 (mAb)	Tesaro	Monotherapy, combination with anti-PD-1 mAb
	INCAGN022385 (mAb)	Incyte Corp	Monotherapy

Phase 2 trial was open at IU, enrolled SCLC, Gastric, NET, B-cell lymphoma, STS, ovarian, prostate cancer

Villanueva et al, Therapeutic advances in Resp Disease, 2018

Initial Efficacy Results of anti-LAG 3 BMS-986016+Nivolumab in melanoma patients previously treated with anti PD(L)1

- 212 patients were treated
  - 55 patients had melanoma and were previously treated with anti PD(L)1
  - PD was best response to PD1 inhibition in 40%

- RR were promising
  - LAG-3≥1%, RR 20%
  - LAG-3<1% ,RR 7.1%

- Grade ¾ events were noted in 9% of patients

Ascierto et al. ASCO 2017, abstract 9520

Do ECOG PS2 patients have similar benefit?

- Atezolizumab was evaluated as first line treatment in cisplatin ineligible patients with metastatic urothelial cancers
  - 20% were ineligible due to PS 2
  - RR 25%

- Retrospective data from CheckMate 171 suggests tolerability of nivolumab in patients with ECOG PS 2 was comparable to overall population

Balar et al. Lancet 2017
Popat et al. ESMO 2017