LAG-3-MHC II Interaction: A New Validated Target In Immuno-Oncology

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Targets & Cell Types In Immuno-Oncology Europe 2023

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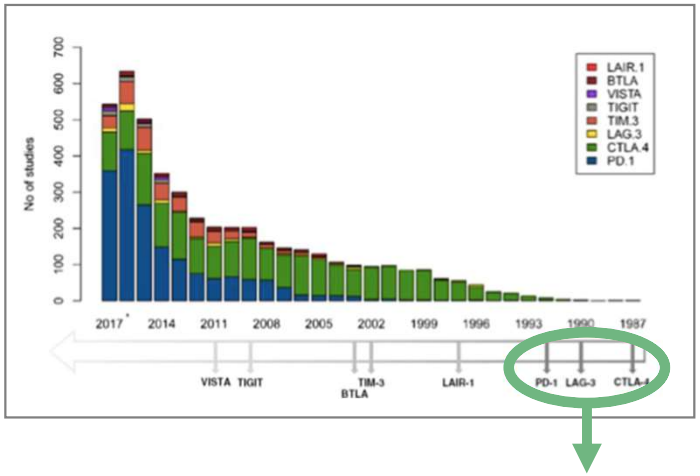
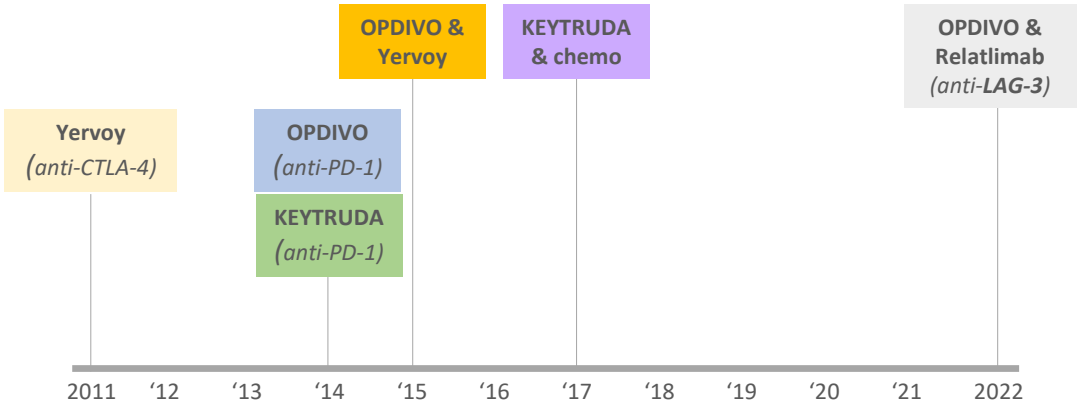
Immuno-Oncology (IO) Landscape

LAG-3 is one of three Immune Checkpoints with Regulatory Approvals

Timeline of Immune Checkpoint Discovery*



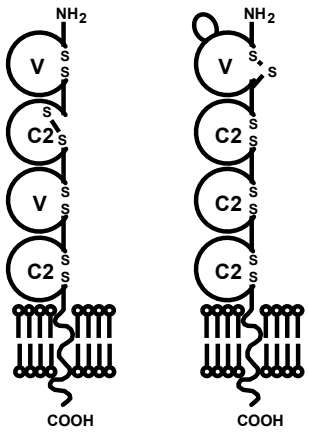
Evolution of Immuno-Oncology Therapies**

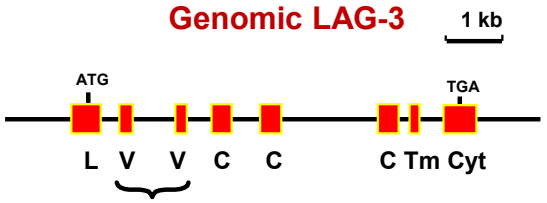


The immune system's role in fighting cancer has led to regulatory approval of immuno-oncology therapies targeting the immune checkpoints **CTLA-4**, **PD-1**, and **LAG-3**

*Checkpoint Inhibitors: Applications for Autoimmunity, Springer, September 2017Current Allergy and Asthma Reports 17(10) DOI:10.1007/s11882-017-0740-z. ** Yervoy (ipilimumab), OPDIVO (nivolumab), KEYTRUDA (pembrolizumab), Opdualag (nivolumab + relatlimab)

Lymphocyte Activation Gene-3
(LAG-3 or CD223)

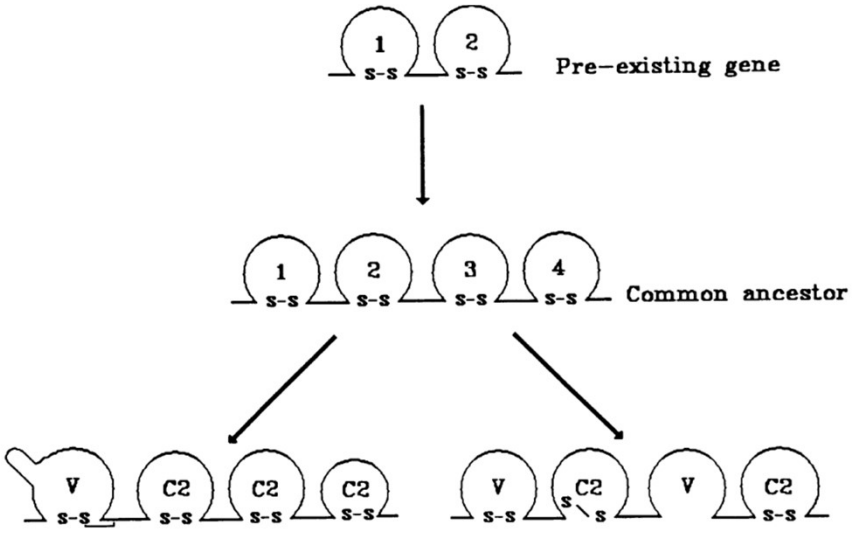




- 4-IgSF domain transmembrane proteins.
- Same genomic organization
  (intron in D1, duplication event D1D2 vs D3D4).
- Close proximity on 12p13.
- Share the same ligands (MHC class II)

J. Exp. Med. 171:1393-1405, 1990

Proposed evolutionary pattern for LAG-3/CD4



LAG-3

Co-inhibitory

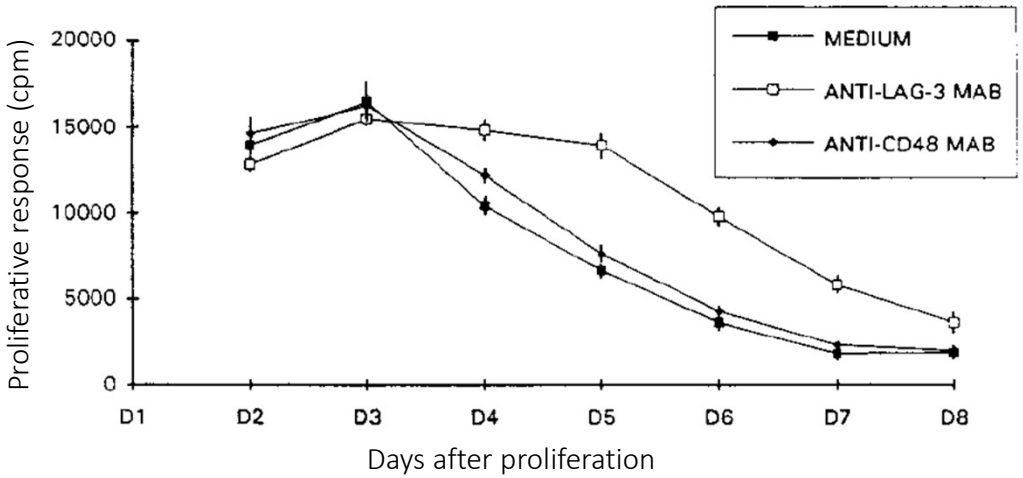
CD4

Co-stimulatory

- Duplication of a 2-IgSF domain ancestor
- The LAG-3/CD4 subfamily has evolved like the CTLA-4/CD28 subfamily: one inhibitory and one stimulatory receptor modulating TCR signaling
- A yin/yang modulatory machinery on T cells

Immunogenetics 39:213-217, 1994

First evidence for LAG-3 being a coinhibitory receptor on T cells



The antigen-specific proliferative response of an influenza-specific CD4 T cell clone is increased by the addition of a blocking anti-LAG-3 mAb

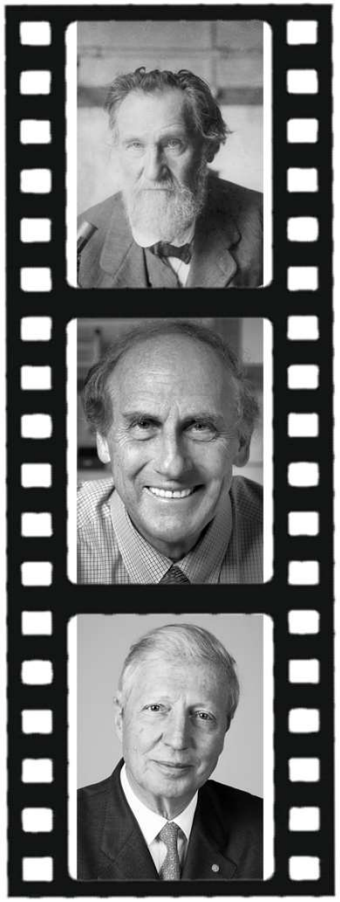
Eur. J. Immunol. 24:3216-3221, 1994

From phagocytes to danger signals delivered to dendritic cells: a historical perspective

- **Elie Metchnikoff:** Nobel prize in 1908 for the discovery of cellular immunity (innate immunity mediated by phagocytes/**macrophages**)

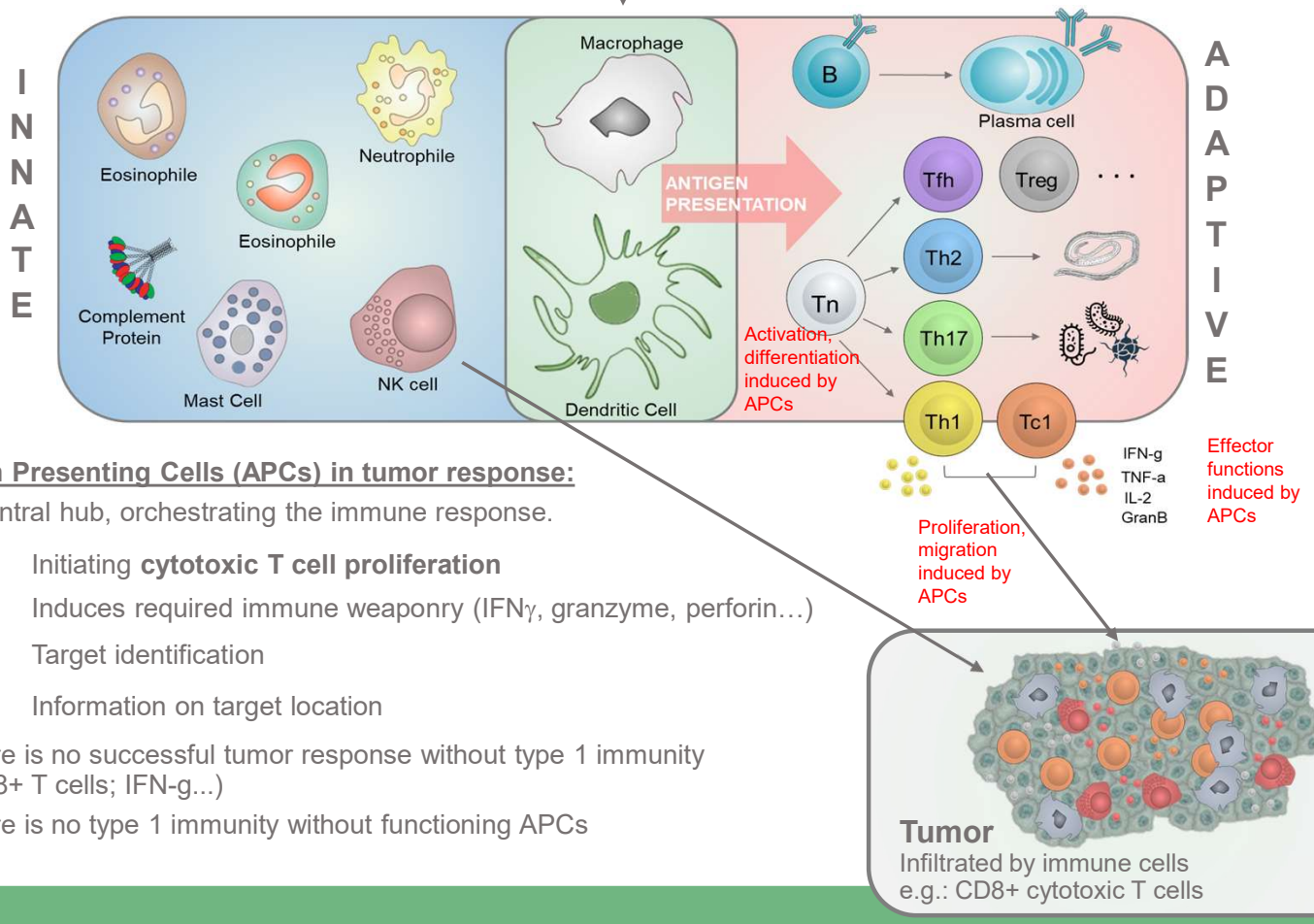
- **Ralph Steinman:** Nobel prize in 2011 for the discovery of the dendritic cell as a professional **Antigen Presenting Cell (APC)** and its role in directing adaptive immunity

- **Jules Hoffmann:** Nobel prize in 2011 for the discovery of the function of the fruit fly Toll gene in insect innate immunity, leading to the cloning of many Toll Like Receptors (TLR) in mammals



Antigen Presenting Cells

Dendritic Cells, Macrophages



Antigen Presenting Cells (APCs) in tumor response:

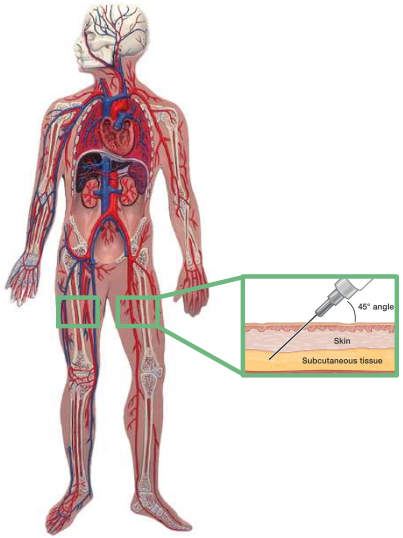
- A central hub, orchestrating the immune response.
  - Initiating **cytotoxic T cell proliferation**
  - Induces required immune weaponry (IFNγ, granzyme, perforin…)
  - Target identification
  - Information on target location
- There is no successful tumor response without type 1 immunity (CD8+ T cells; IFN-g...)
- There is no type 1 immunity without functioning APCs

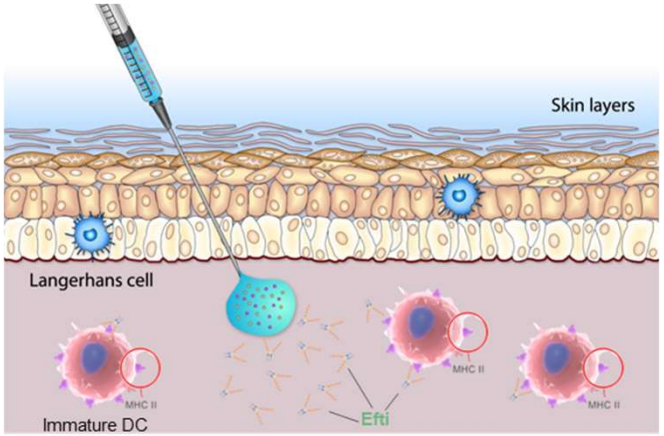
Step #1:

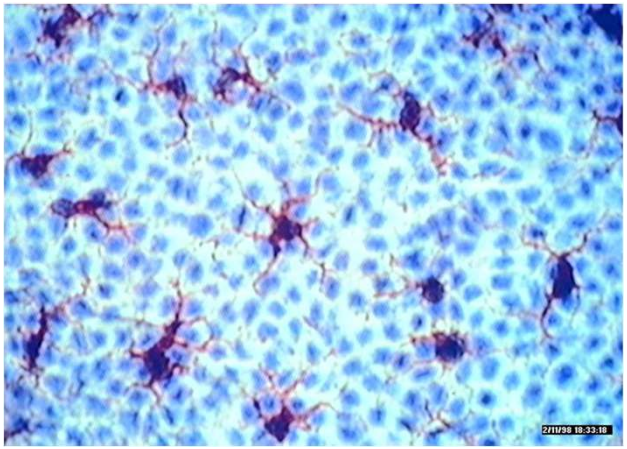
Efti binds MHC-II molecules expressed on APCs

Dosing:

- Efti is given **s.c. every 2 weeks at 30 mg** (1.2 ml) in the anterior face of the thigh
- **Low effective dose**: Efti is an agonist; high receptor (MHC II) occupancy is not needed







MHC II staining (skin section)

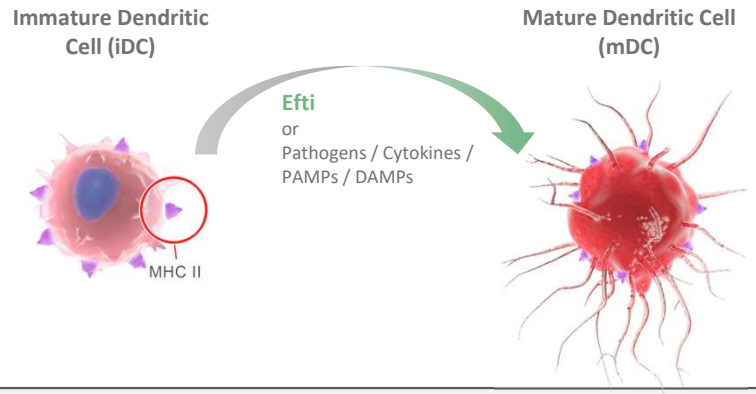
APCs in the skin:

- The skin is the primary defense system against foreign pathogens and therefore hosts a variety of antigen presenting cells (DCs, macrophages)
- The skin is well connected to lymphatic system and blood circulation.
- More about APCs: Malissen B et al. The origins and functions of dendritic cells and macrophages in the skin. *Nat Rev Immunol* **14**, 417–428

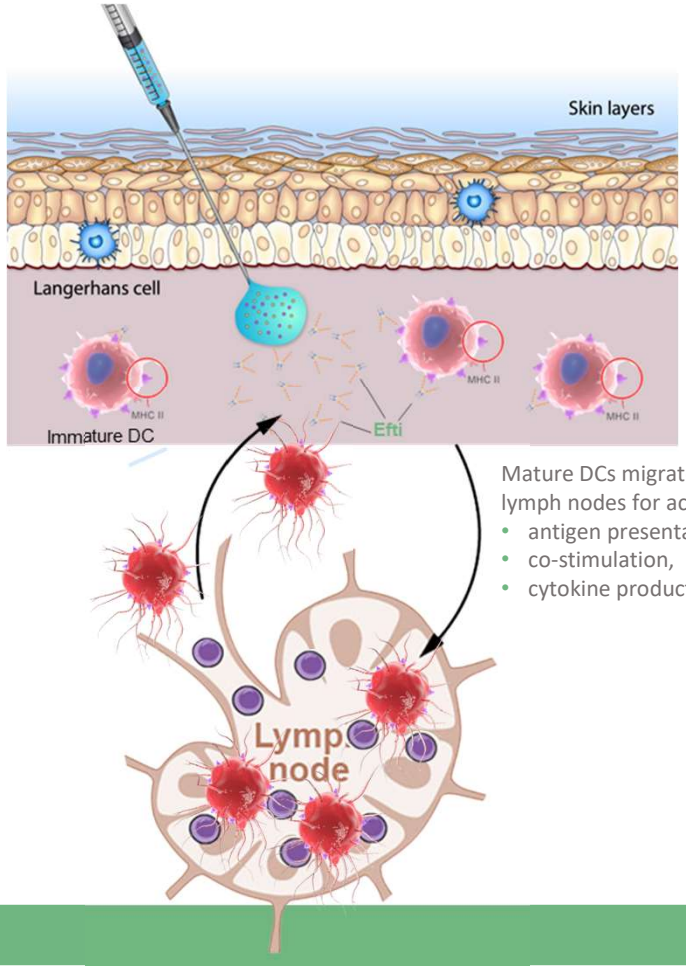
Step #2

Efti binding induces APC maturation

DC maturation after Efti binding:



Round shape without dendrites	Large dendrites
↓ Co-stimulatory molecule expression for T cell activation (CD80, CD83, CD86, CD40)	↑ Co-stimulatory molecule expression for T cell activation (CD80, CD83, CD86, CD40)
↓ MHC I and II expression for antigen presentation.	↑ MHC I and II expression for antigen presentation.
↓ Secretion of pro-inflammatory cytokines (e.g.: IL-12), chemokines	↑ Secretion of pro-inflammatory cytokines (e.g.: IL-12, TNF-a), chemokines
↓ $CCR7^{-}$ $CCR4^{-}$ $CCR5^{+}$ expression	↑ $CCR7^{+}$ $CCR5^{-}$ expression
↑ Phagocytic capacity to pick up antigens	↓ Phagocytic capacity to pick up antigens



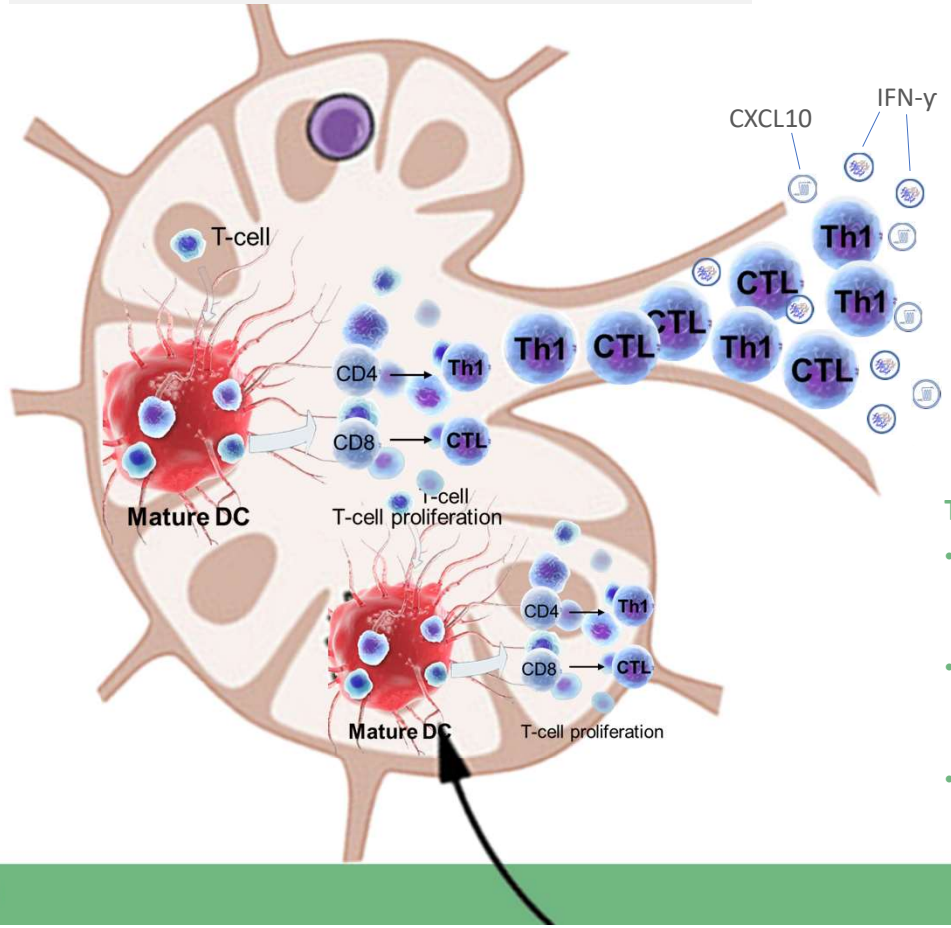
Mature DCs migrate to the draining lymph nodes for activation of T cells via
- antigen presentation,
- co-stimulation,
- cytokine production.

More about Dendritic Cell maturation: Front. Immunol., 21 January 2019, Volume 9 - 2018 | https://doi.org/10.3389/fimmu.2018.03176

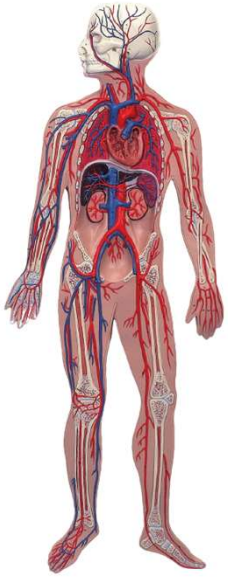
Step #3

Mature APCs induce T-cell response

Lymphoid organs



Activated CD4⁺ Th1 and CD8⁺ cytotoxic T cells (CTLs) entering the circulation and can be recruited to tumor sites



T-cell activation by mature APCs:

- Mature APCs equipped with co-stimulatory molecules, inflammatory cytokine production etc… activate effector, effector-memory and memory T-cells in lymphoid organs.
- In Efti pre-clinical and clinical studies: significantly increased number of activated T-cells and their cytokines (e.g. IFN-g) can be measured in the blood. The increase is sustained over months → **elevated TH1 immune status**.
- Additionally, NK cell and monocyte numbers also increased.

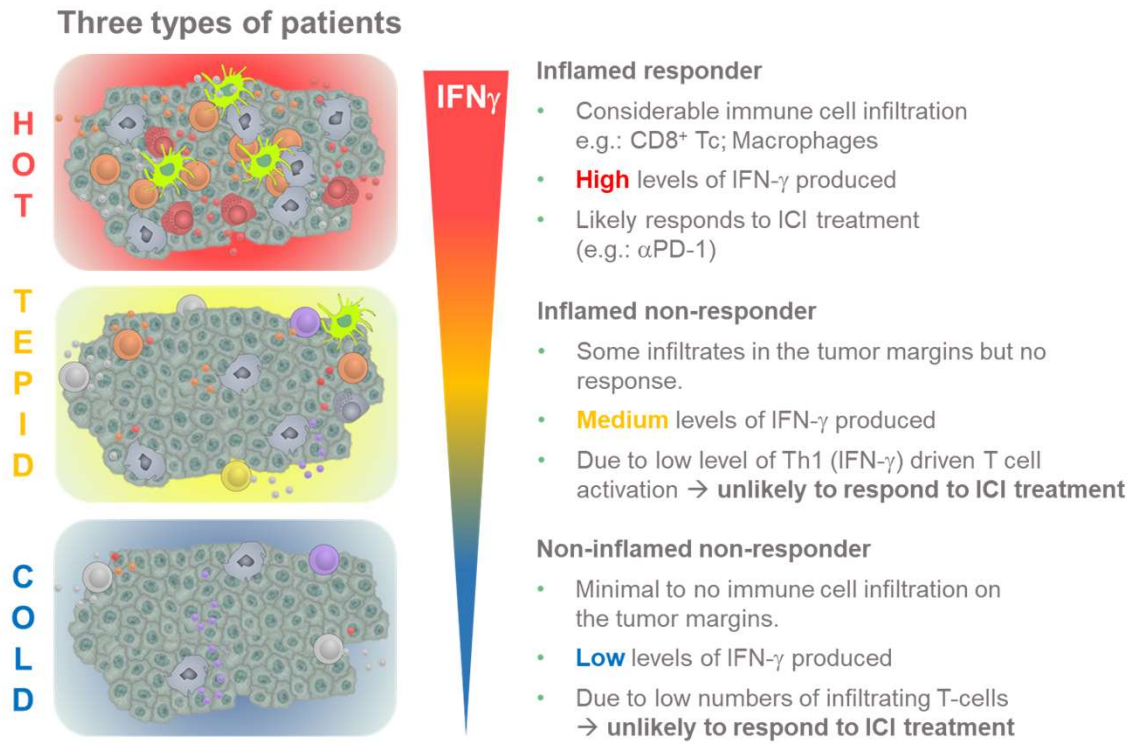
Step #4

Cytotoxic T and NK Cells Killing Tumor Cells

Turning a COLD tumor into HOT tumor:

- Activation of effector (T_{eff}), effector-memory (T_{EM}) and memory T cells (T_{CM}) is non-specific and efti induces differentiation/proliferation of these T cells in the absence of any antigen in vitro.
- But the patient is loaded with tumor antigens and potentially there are several tumor-specific memory T cells that can differentiate into proliferating effector T cells, thanks to the activated, more mature APCs. Efti works as a wake-up call in a sense.
- Elevated NK cell activity is also expected at tumor site due to increased inflammatory immune status.

Due to the synergistic MoA of Efti, patients with tepid / cold tumors could also respond to ICI treatment



immutep
LAG-3 IMMUNOTHERAPY

TACTI-002 Phase II Trial – Part A

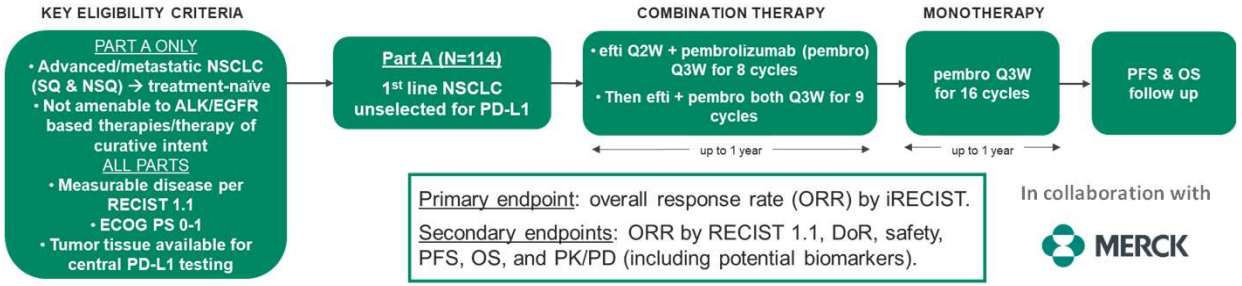
Efti + Pembrolizumab Combination in First Line Treatment of Metastatic Non-Small Cell Lung Cancer

TACTI-002 / KN-798 Trial Overview and Baseline Characteristics

Part A: Large Phase II trial (N=114) in metastatic 1st Line non-small cell lung cancer (1L NSCLC)

Trial Design (Part A)

- Phase II, open label, Simon's two stage
- Six countries (US, UK, ES, PL, UA, AU)
- 18 sites
- 114 patients enrolled



Baseline characteristics

- Trial enrolled 1L NSCLC patients regardless of PD-L1 Tumor Proportion Score (TPS) expression
- ~75% of patients have PD-L1 TPS of <50%
- Lower proportion of patients with PD-L1 TPS ≥50% than would be expected

Safety

- No new safety signals compared to pembrolizumab monotherapy

Baseline characteristics for TACTI-002 Part A		N=114	
Age, median (range), years		67 (44-85)	
Sex, n (%)	Female / Male	30 (26.3) / 84 (73.7)	
ECOG PS score, n (%)	0 / 1	43 (37.7) / 71 (62.3)	
Smoking status, n (%)	Current or Ex-smoker / Non-smoker	108 (94.7) / 6 (5.3)	
Histology, n (%)	Squamous / Non-squamous / Unknown	40 (35.1) / 72 (63.2) / 2 (1.8)	
Metastatic disease, n (%)	Yes / No	113 (99.1) / 1 (0.9)	
		Central only	*Central + local*
PD-L1 expression TPS, n[1] (%)	< 1%	32 (35.6)	37 (34.3)
	1-49%	38 (42.2)	42 (38.9)
	≥ 50%	20 (22.2)	29 (26.9)
Previous therapy, n (%)	Radiotherapy	38 (33.3)	
	Surgery	23 (20.2)	
	Systemic therapy for non-metastatic disease	26 (22.8)	

Note: Patients were recruited according to Simon's optimal two-stage design: during the first stage, 17 pts were recruited; second stage recruitment (n=19) was opened only after the number of responses was above 4. An extension stage (n=78) could be added if there were above 12 responses. In total, 114 pts were enrolled.

Data cut-off August 15, 2023

[1] N=90; Central assessment of PD-L1 TPS using Dako IHC 22C3 pharmDx. [2] N=108; Central assessment as per footnote 1 for 90 pts. For 18 patients, local assessment used predominantly Dako IHC 22C3 pharmDx due to non-evaluable central assessment results.

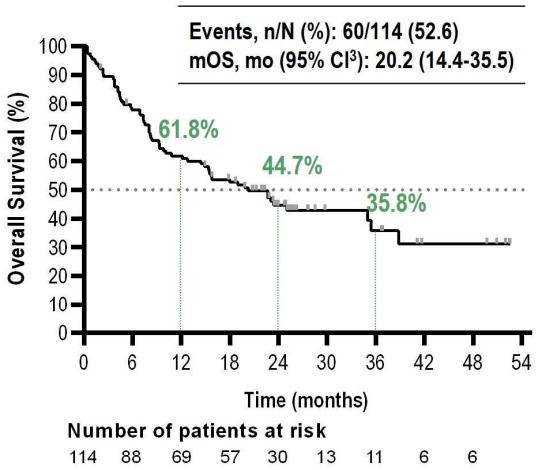
True response rates sources/assumptions: KN-001 &-042 (KN-001: Lancet Respir Med, 2019; 7(4): 347-357; KN-042: Lancet 2019;393(10183:1819-1830), expecting that ~70% of patients had PD-L1 TPS <50%.

Key Efficacy Data in ITT Population

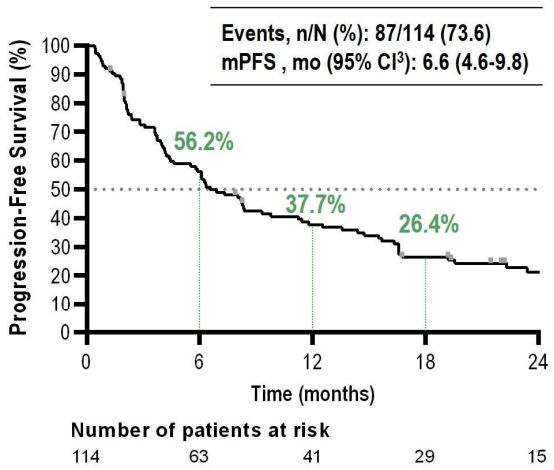
Intent-to-treat (ITT) population (N=114) includes ~75% patients with TPS <50% and ~35% with TPS <1%

- Strong response rate of 40.4%[1] [95% CI[3]: 31.3-50.0] in conjunction with high median DoR of 21.6 months[2]
- Median OS of 20.2 months (with median follow up of 25.1 months!)
- Excellent 12-month PFS (37.7%) and 36-month OS (35.8%) rates

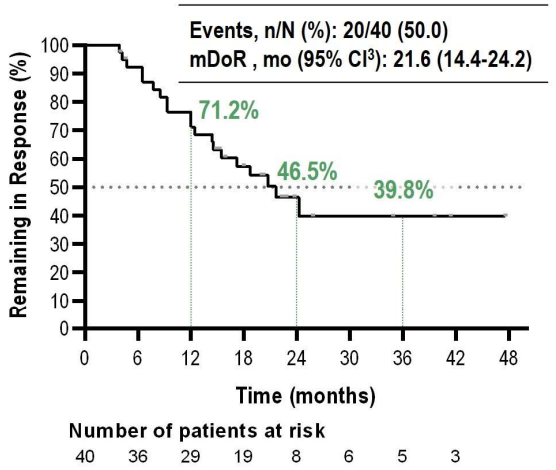
Overall Survival, ITT (N=114)



Progression Free Survival[1], ITT (N=114)



Duration of Response[3], (N=40)



Data cut-off August 15, 2023 with median follow-up of 25.1 mo.; ITT: Intention-to-treat (N=114). 45/114 (39.5%) received 2nd line therapy, mostly chemotherapy-based (42/45; 93.3%). Note: mOS for squamous and non-squamous histology was 20.2 and 19.8 mo. |
[1] according to iRECIST. [2] by iRECIST including only patients with confirmed response. [3] 95% confidence intervals calculated using Clopper-Pearson method or using Kaplan-Meier survival analysis method.

Excellent Survival Benefit across all PD-L1 Expression Levels

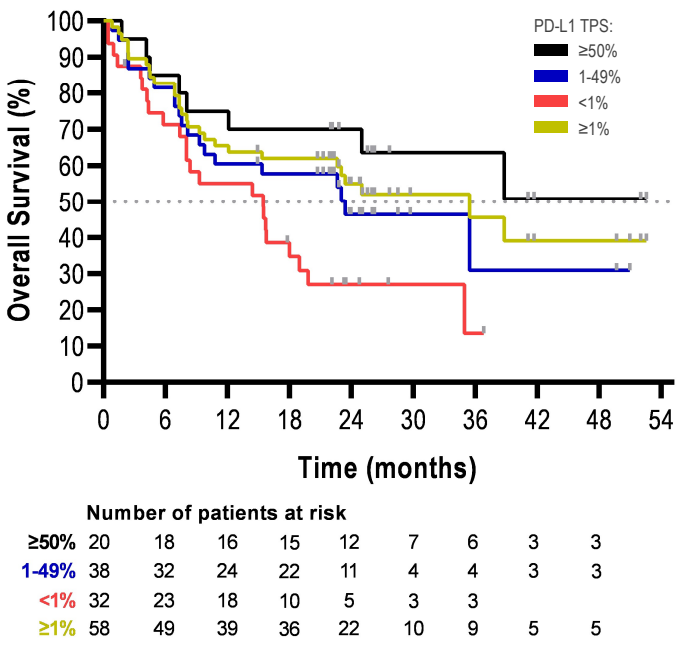
Strong efficacy with any PD-L1 (TPS≥1%) and PD-L1 negative (TPS <1%), low (TPS 1-49%), high (TPS ≥50%)

Promising efficacy with strong Overall Response Rate (ORR), Progression Free Survival (PFS), Duration of Response (DOR), and Overall Survival (OS) visible across all PD-L1 TPS subgroups including negative and low expressing patients[1,2]

Tumor Response by Central PD-L1[1], N=90

Efficacy parameter	TPS <1% n (%), N=32	TPS 1-49% n (%), N=38	TPS ≥50% n (%), N=20	TPS ≥1% n (%), N=58
ORR[2,3], % (95% CI)[4]	31.3 (16.1-50.0)	44.7 (28.6-61.7)	55.0 (31.5-76.9)	48.3 (35.0-61.8)
mPFS[2], months (% events)	4.2 (90.6)	9.3 (71.1)	16.5 (70.0)	11.2 (70.7)
mDoR[2], months (% events)	20.7 (57.1)	NR (35.7)	18.7 (63.6)	24.2 (48.0)
mOS, months (% events)	**15.5** (71.9)	**23.4** (52.6)	**NR** (40.0)	**35.5** (48.3)

Overall Survival by central PD-L1[1]



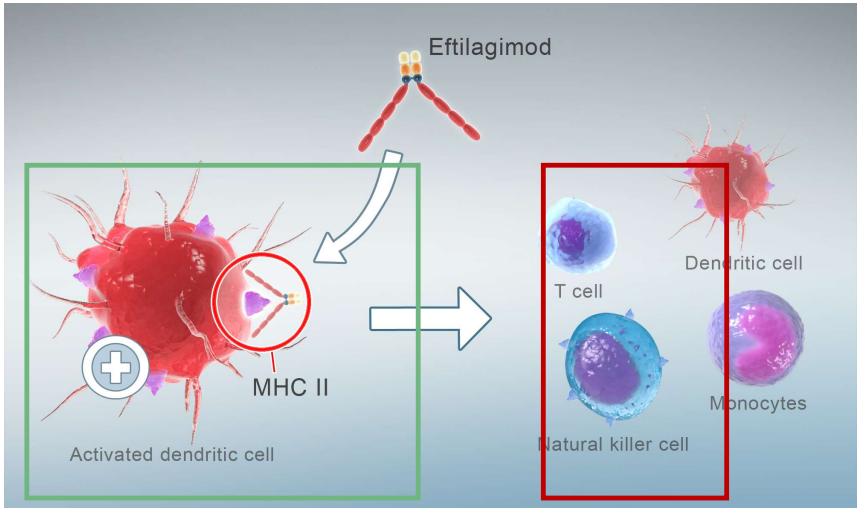
Data cut-off date: August 15, 2023. [1] N=90; Central assessment of PD-L1 TPS using Dako IHC 22C3 pharmDx; [2] iRECIST; [3] unconfirmed; [4] calculated using Clopper Pearson method; NR: not reached.
Note: results for PD-L1 central + local (N=108) were as follows (<1% / 1-49% / ≥50% / ≥1%): mOS, mo: 14.4 / 23.4 / 38.8 / 35.5; mPFS[2]: 4.2 / 8.3 / 16.3 / 9.8; mDoR[2]: 20.7 / 21.6 / 18.7 / 21.6.

Efti Pharmacodynamic Activity

Pharmacodynamic effects observed in NSCLC (TACTI-002 trial)

PD Activity in Clinical Trials

Primary and Secondary Target Cells of **efti**



Primary Target Cells of efti

- Cells expressing MHC-II
- Dendritic Cells
- Macrophages / Monocytes

Measurement

- Increase in target cell count
- Expression of activation markers on the surface of APCs

Secondary Target Cells of efti

- Cells activated by APCs
- T Cells ($CD4^+$, $CD8^+$)
- Natural Killer Cells (NK)

Measurement

- Increase in target cell count
- Increased activation status
- Shift to effector-memory phenotype

Additional Biomarkers

- Increase of soluble factors of type-1 immune response

→ **IFN-γ**

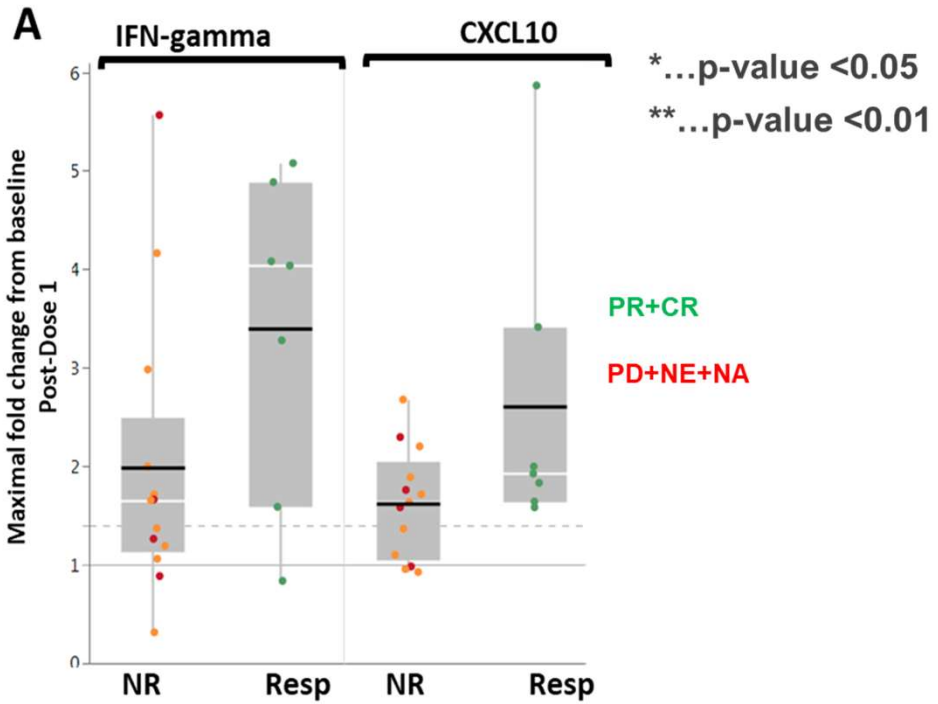
- Increase of IFN-induced chemokines

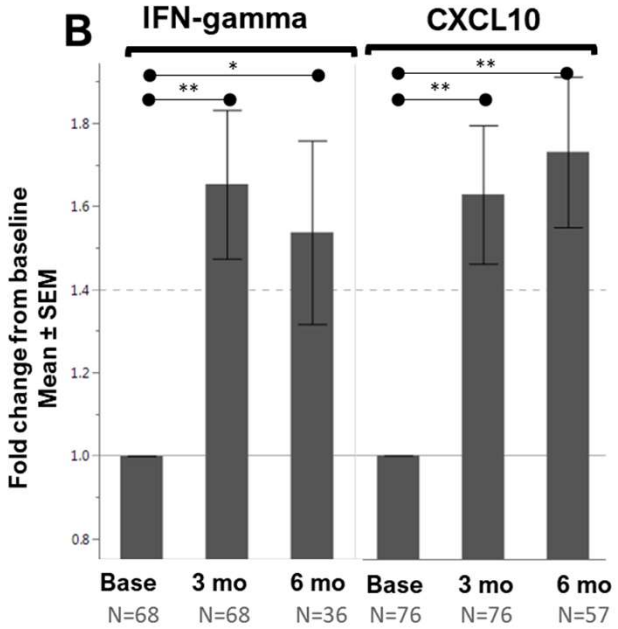
→ **CXCL10**

Key factors for T cell infiltration and generation of „hot“ tumor microenvironment

Reschke & Gajewski, *Sci. Immunol.* 2022

TACTI-002: an increase in Th1 cytokines that is correlated with clinical responses

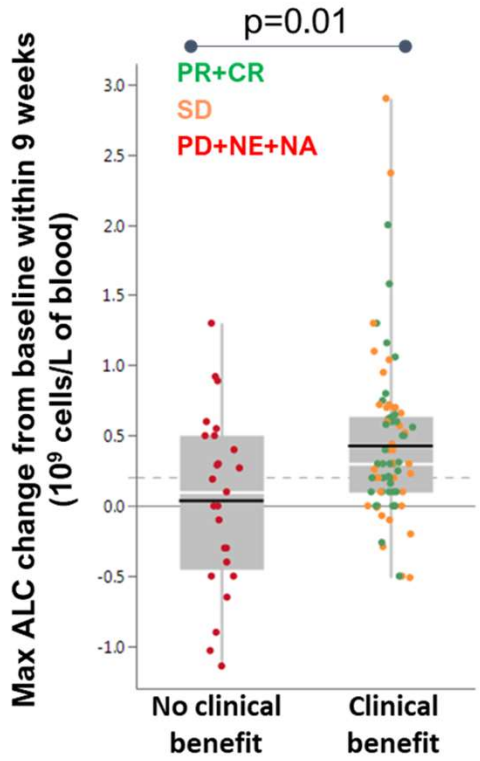




A) Early (within 96 hours of 1st efti dose) Th1 biomarker change from baseline by BOR (iRECIST) for patients with PK sampling;
B) Th1 biomarker change from baseline in all patients with samples.

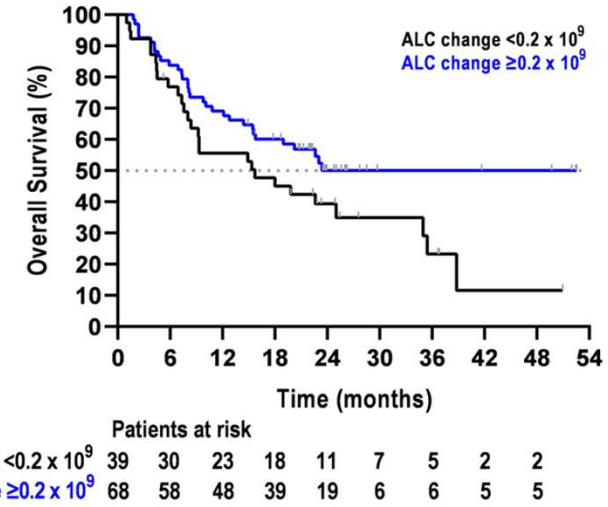
TACTI-002: an increase in ALC that is correlated with tumor responses and overall survival

A



B

OS by iRECIST (N=114)	ALC Change <0.2	ALC Change ≥0.2
	Early ALC increase (within 9 weeks)	
Events, n/N' (%)	27/39 (69.2%)	32/68 (47.1%)
Median, months (95% CI[1])	15.7 (8.02-34.96)	NR (15.51-)
HR	0.60 (0.36-1.02), p=0.029	



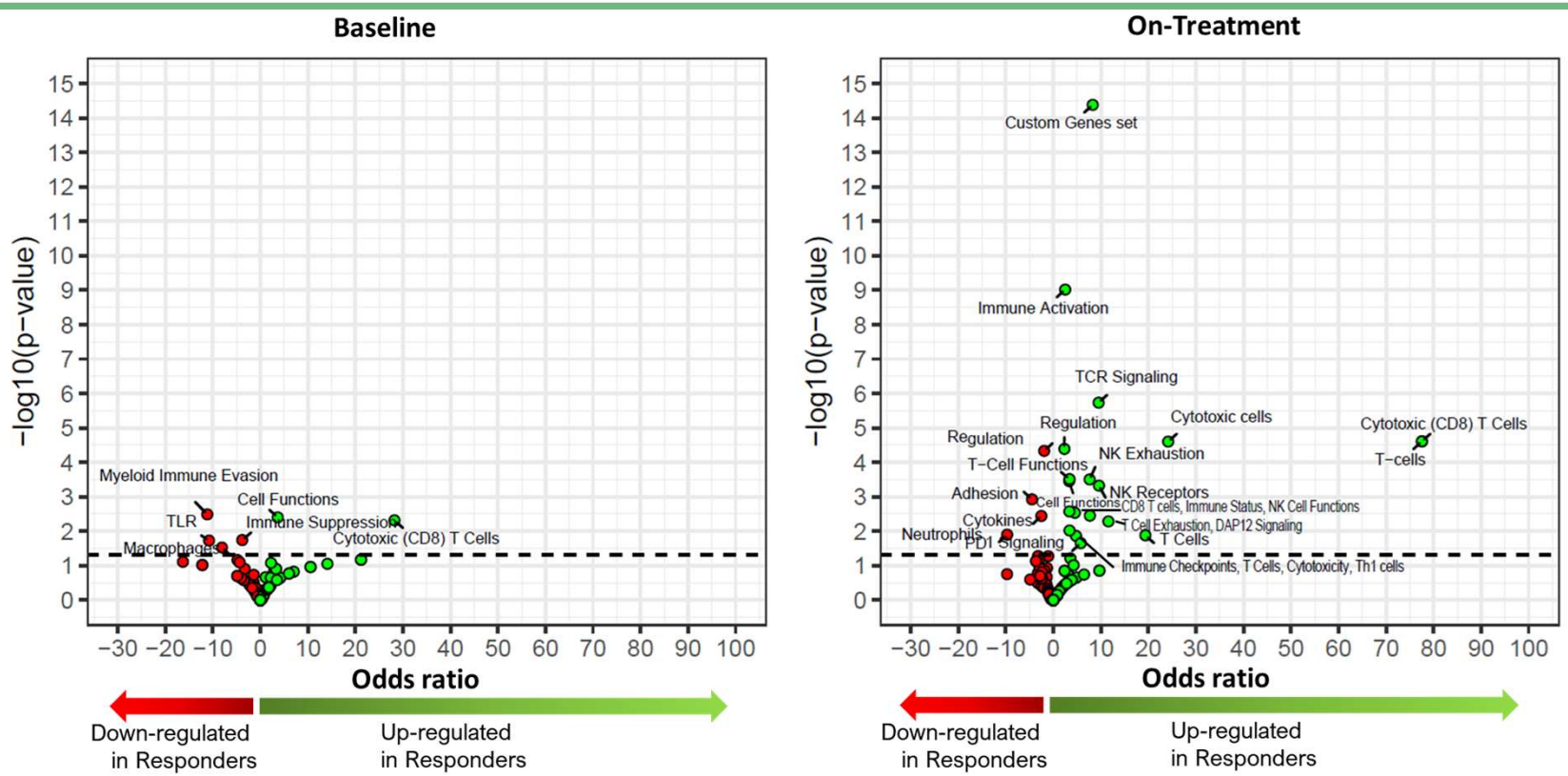
Patients at risk

ALC change <0.2 x 10^9	39	30	23	18	11	7	5	2	2
ALC change ≥0.2 x 10^9	68	58	48	39	19	6	6	5	5

A) Maximal Absolute Lymphocyte Counts change from baseline within the first 9 weeks (before the 4th cycle) is shown in patients with no clinical benefit (UPD+NE+NA, n=25) and clinical benefit (CR+PR+SD, n=82); per iRECIST

B) Kaplan Meyer survival curves for OS per subgroups of patients with ALC change within the first 9 week < or ≥ 0.2. 10^9/L

Diving deeper: gene expression analysis in liquid biopsies comparing Responders vs Non-Responders



Volcano plot of pathways and cell types at Baseline and On-treatment (at 3 months) comparing Responders vs Non-Responders

Thank you!