2021 ESMO congress

Approaches and Early Results: Tackling Microenvironment Structures

Georgina V Long

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DECLARATION OF INTERESTS

Georgina V Long is consultant advisor for the following:

- Aduro Biotech, Inc.
- Amgen Inc.
- Array BioPharma Inc.
- Boehringer Ingelheim International GmbH
- Bristol Myers Squibb
- Evaxion Biotech A/S
- Hexal AG
- Highlight Therapeutics S.L
- Merck Sharp & Dohme
- Novartis Pharma AG
- OncoSec
- Pierre Fabre
- QBiotics Group
- Regeneron Pharmaceuticals, Inc.
- Specialised Therapeutics Australia Pty Ltd.

Overall Survival in Advanced Melanoma

CHECKMATE 067: Ipilimumab + nivolumab (n=314)[3]
CHECKMATE 067: Nivolumab (n=316)[3]
KEYNOTE-006: Pembrolizumab (n= 556)[2]
CA184-002: Ipilimumab (n=137)[1]

1. Hodi FS et al. NEJM 2010; 2. Robert et al Lancet Onc 2019; 3. Larkin NEJM 2019.

Presented by Georgina V Long @ProfGLongMIA

Outline

1. What is the ‘tumour microenvironment’?
2. PD1 biology → forcing a focus on the tumour microenvironment
3. Drug Targets
   - T cells
   - Antigen Presentation/Innate activation
   - Vasculature
   - Beyond PD1: Other Cells of the Microenvironment

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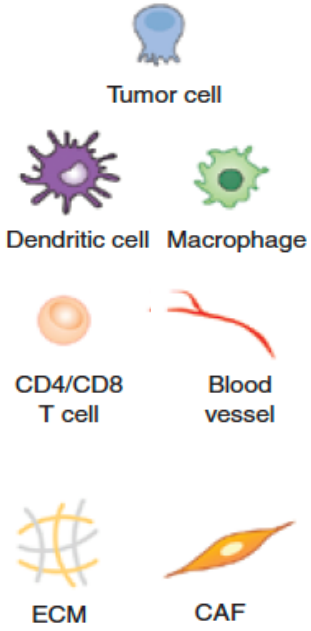
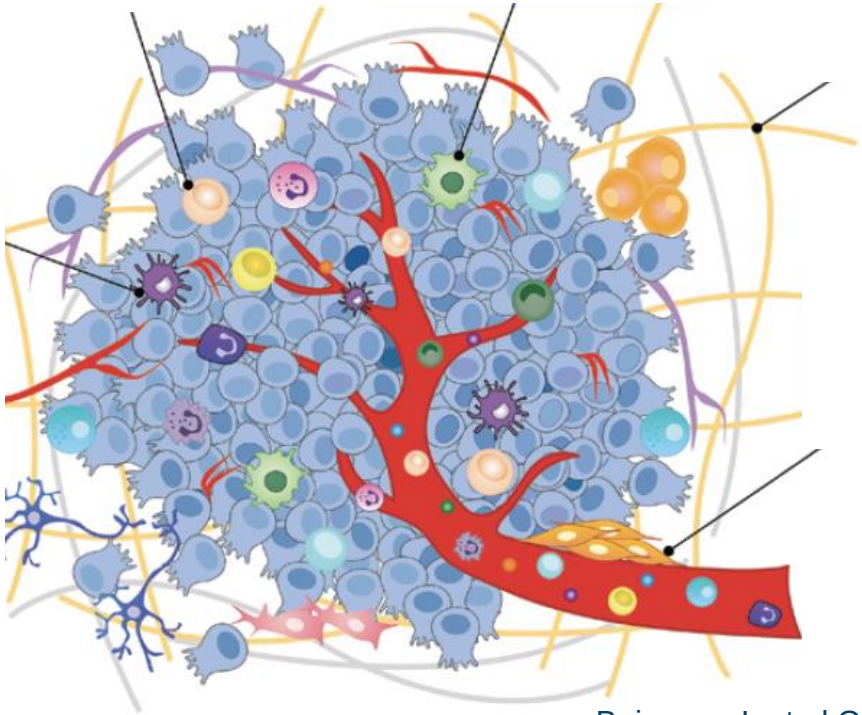
The Main Players in The Tumour Microenvironment





Bejarano L et al Cancer Discovery 2021

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Tissue Biomarkers - PD-L1 expression

Ph LETTER **Nature 2014**

doi:10.1038/nature13954

PD-1 blockade induces responses by inhibiting adaptive immune resistance

Paul C. Tumeh[1,2], Christina L. Harview[1], Jennifer H. Yearley[3], I. Peter Shintaku[1], Emma J. M. Taylor[1], Lidia Robert[1], Bartosz Chmielowski[1,2], Marko Spasic[1], Gina Henry[1], Voicu Ciobanu[1], Alisha N. West[1], Manuel Carmona[1], Christine Kivork[1], Elizabeth Seja[1], Grace Cherry[1], Antonio J. Gutierrez[1], Tristan R. Grogan[1], Christine Mateus[4], Gorana Tomasic[4], John A. Glaspy[1,2], Ryan O. Emerson[5], Harlan Robins[5,6], Robert H. Pierce[3], David A. Elashoff[1,2], Caroline Robert[4] & Antoni Ribas[1,2]

Personalized Medicine and Imaging

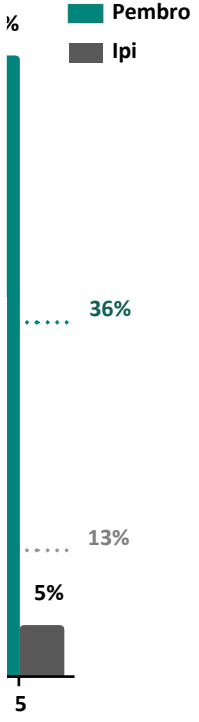
See related commentary by Ribas and Tumeh, p. 4982

Clinical Cancer Research

2014

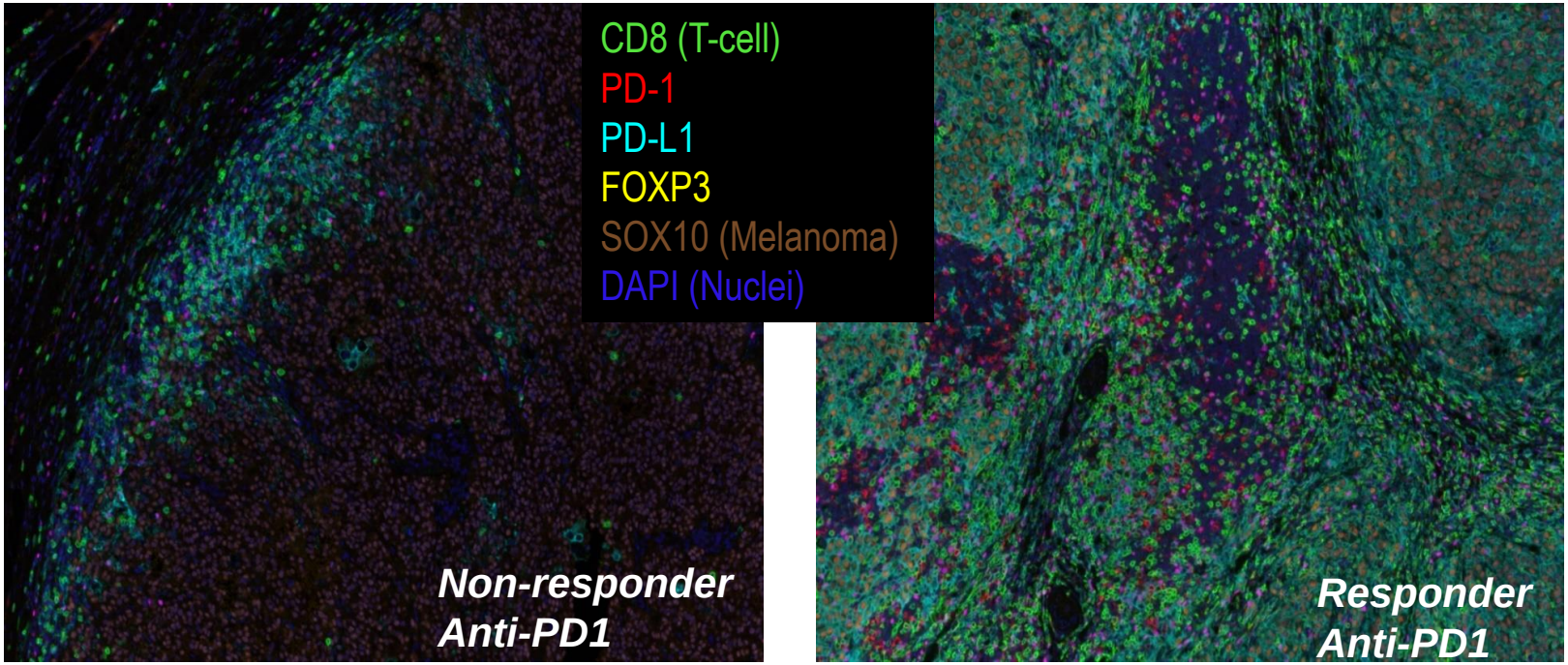
Association of PD-1, PD-1 Ligands, and Other Features of the Tumor Immune Microenvironment with Response to Anti–PD-1 Therapy

Janis M. Taube[1,2,3], Alison Klein[2,3,5], Julie R. Brahmer[3], Haiying Xu[1], Xiaoyu Pan[3], Jung H. Kim[1], Lieping Chen[6], Drew M. Pardoll[3], Suzanne L. Topalian[4], and Robert A. Anders[2]



Carlino M et al AACR 2016; EJC 2018

Multiplex IHC & Quantitative Pathology To Examine The Tumour Microenvironment



ONCOIMMUNOLOGY
https://doi.org/10.1080/2162402X.2019.1659093

2019

Taylor & Francis
Taylor & Francis Group

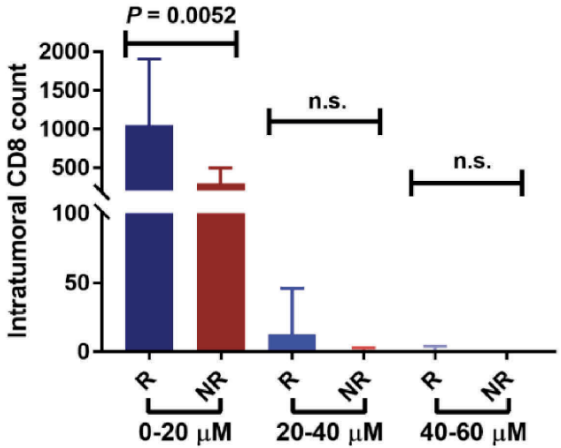
ORIGINAL RESEARCH

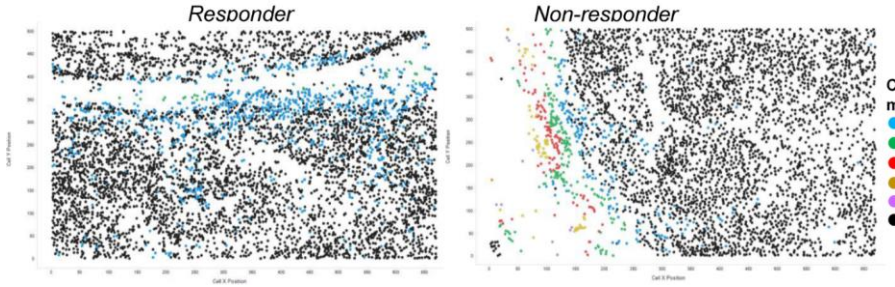
Check for updates

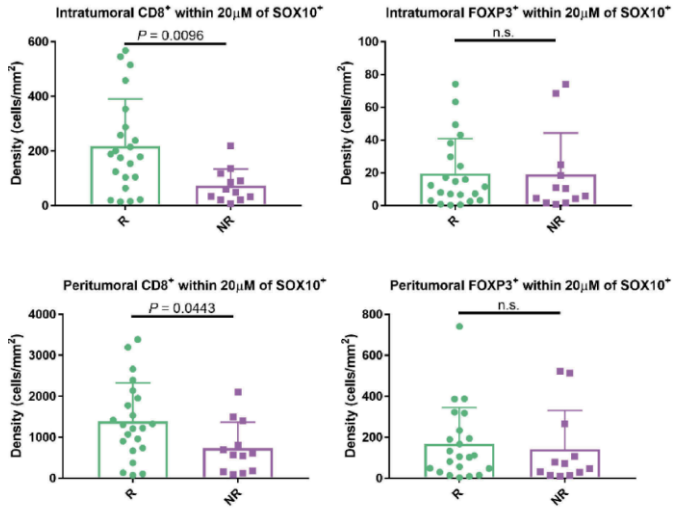
Close proximity of immune and tumor cells underlies response to anti-PD-1 based therapies in metastatic melanoma patients

Tuba N. Gide[a,b,c], Ines P. Silva[a,b,c], Camelia Quek[a,b,c], Tasnia Ahmed[a], Alexander M. Menzies[a,b,c,e,f], Matteo S. Carlino[a,c,g], Robyn P.M. Saw[a,c,d,f], John F. Thompson[a,c,d,f], Marcel Batten[a,b,c], Georgina V. Long[a,b,c,e,f*], Richard A. Scolyer[a,b,c,d*], and James S. Wilmott[a,b,c*]

[a]Melanoma Institute Australia, The University of Sydney, Sydney, Australia; [b]Charles Perkins Centre, The University of Sydney, Sydney, Australia; [c]Sydney Medical School, The University of Sydney, Sydney, Australia; [d]Royal Prince Alfred Hospital, Sydney, Australia; [e]Royal North Shore Hospital, Sydney, Australia; [f]Mater Hospital, North Sydney, Australia; [g]Crown Princess Mary Cancer Centre, Westmead and Blacktown Hospitals, Sydney, Australia





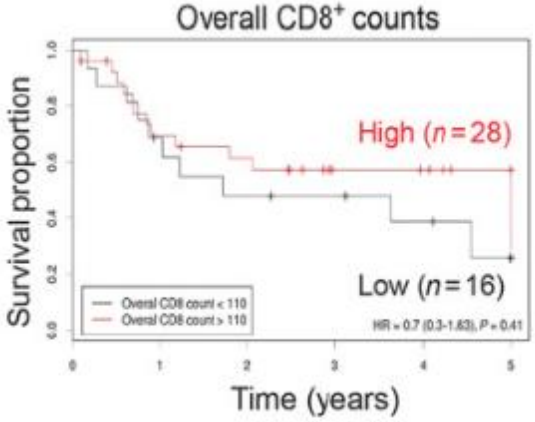


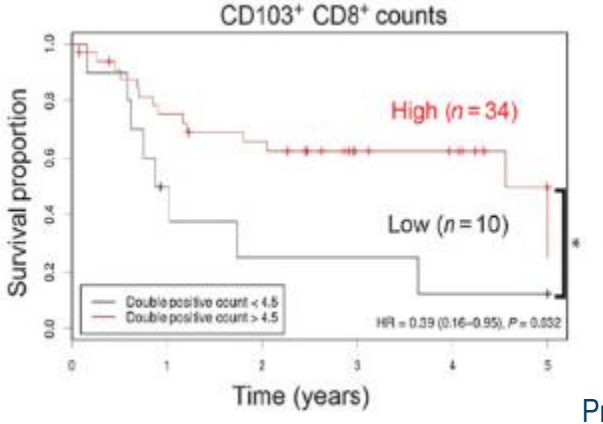
Cancer Therapy: Clinical

Clinical Cancer Research

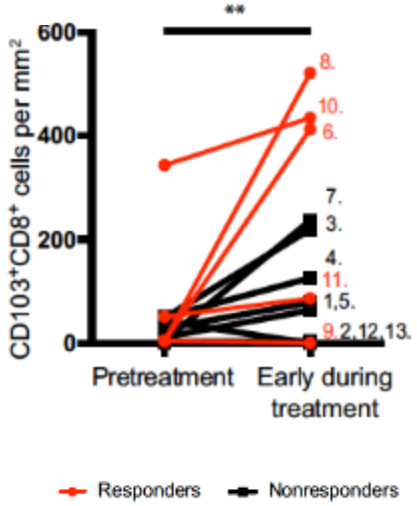
CD103$^+$ Tumor-Resident CD8$^+$ T Cells Are Associated with Improved Survival in Immunotherapy-Naïve Melanoma Patients and Expand Significantly During Anti–PD-1 Treatment

Jarem Edwards[1], James S. Wilmott[2,3], Jason Madore[2], Tuba Nur Gide[2], Camelia Quek[2], Annie Tasker[1], Angela Ferguson[1,3], Jinbiao Chen[1], Rehana Hewavisenti[1], Peter Hersey[1], Thomas Gebhardt[4], Wolfgang Weninger[1], Warwick J. Britton[1,3], Robyn P.M. Saw[2,3,5], John F. Thompson[2,3,5], Alexander M. Menzies[2,3,6], Georgina V. Long[2,3,6], Richard A. Scolyer[2,3,5], and Umaimainthan Palendira[1,3]

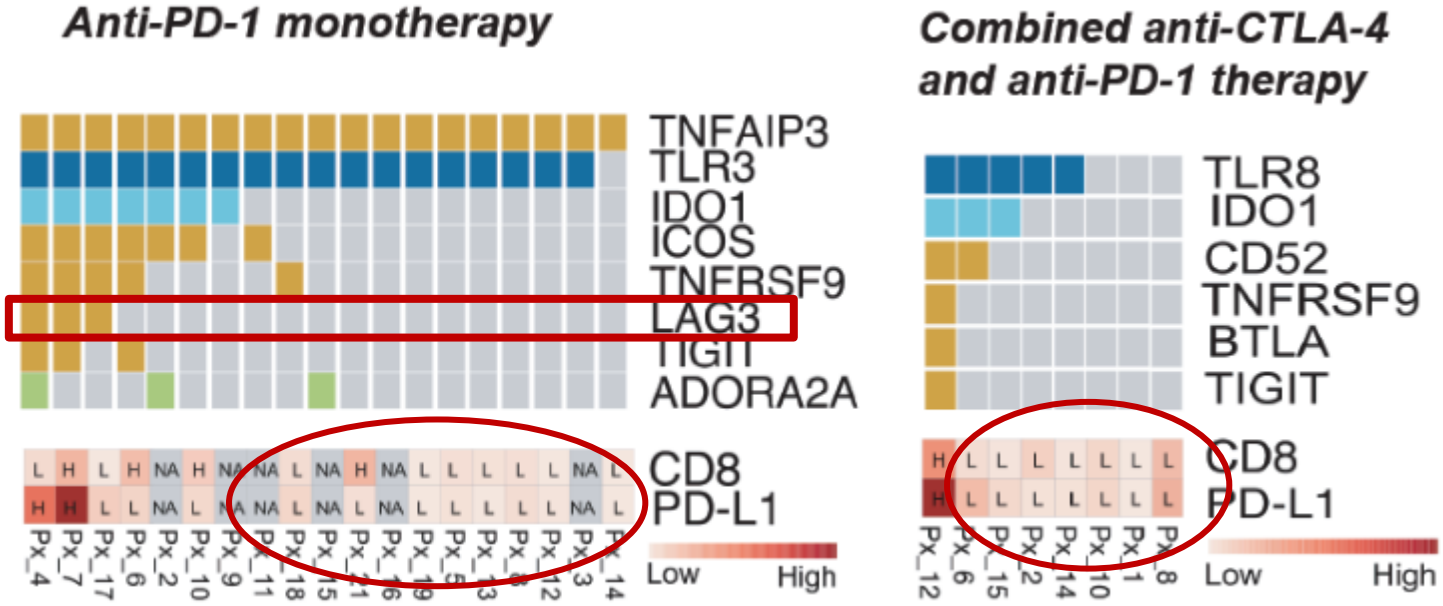




Anti-PD-1



RNA Expression and IHC of Baseline Melanoma Tissue Non-Responders n=34



↓ TILS
↓ PDL1

Gide T et al Cancer Cell 2019: Melanoma Translational Lab

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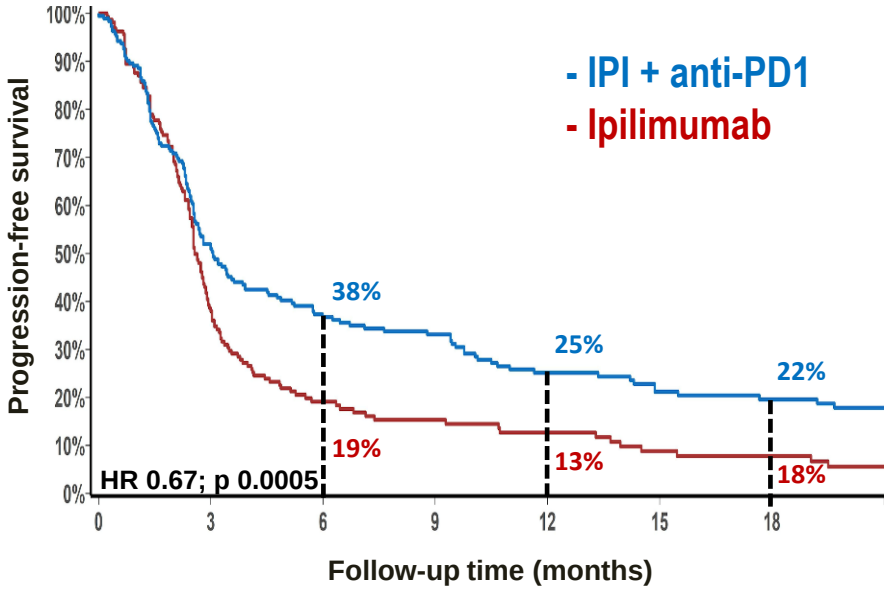
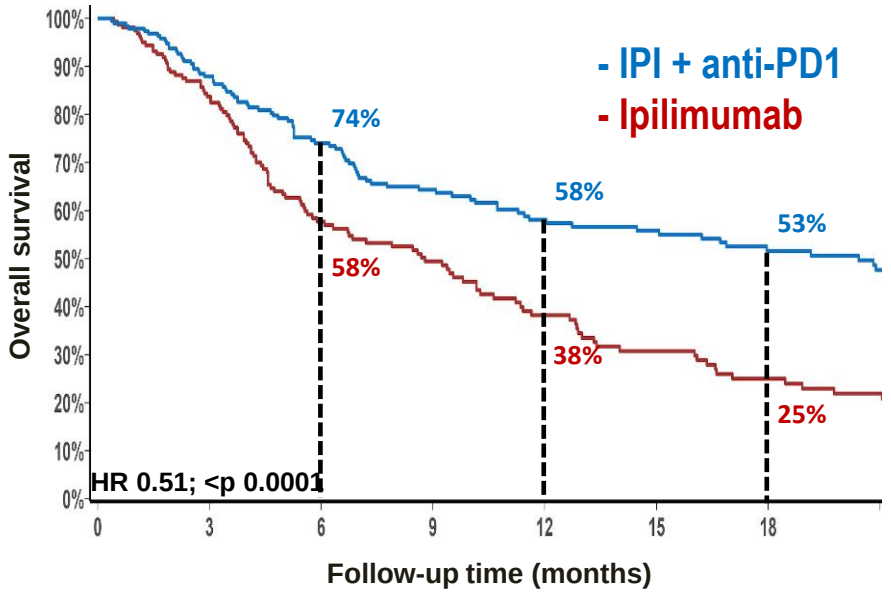
Progression on Anti-PD1 → Ipilimumab+/- Anti-PD1



No. at risk								
IPI	162	60	25	20	13	9	7
IPI+anti-PD1	193	97	63	52	35	27	24



IPI	162	131	79	63	43	33	26
IPI+anti-PD1	193	165	125	98	80	69	56

Silva, I et al Lancet Onc 2021

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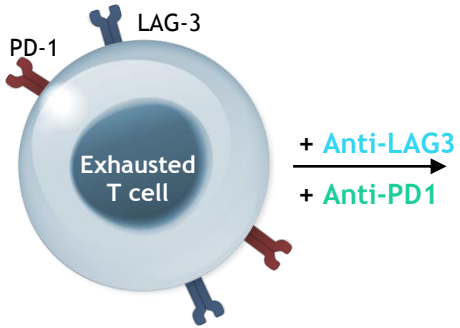
Anti-LAG-3 - Another Immune Checkpoint Inhibitor



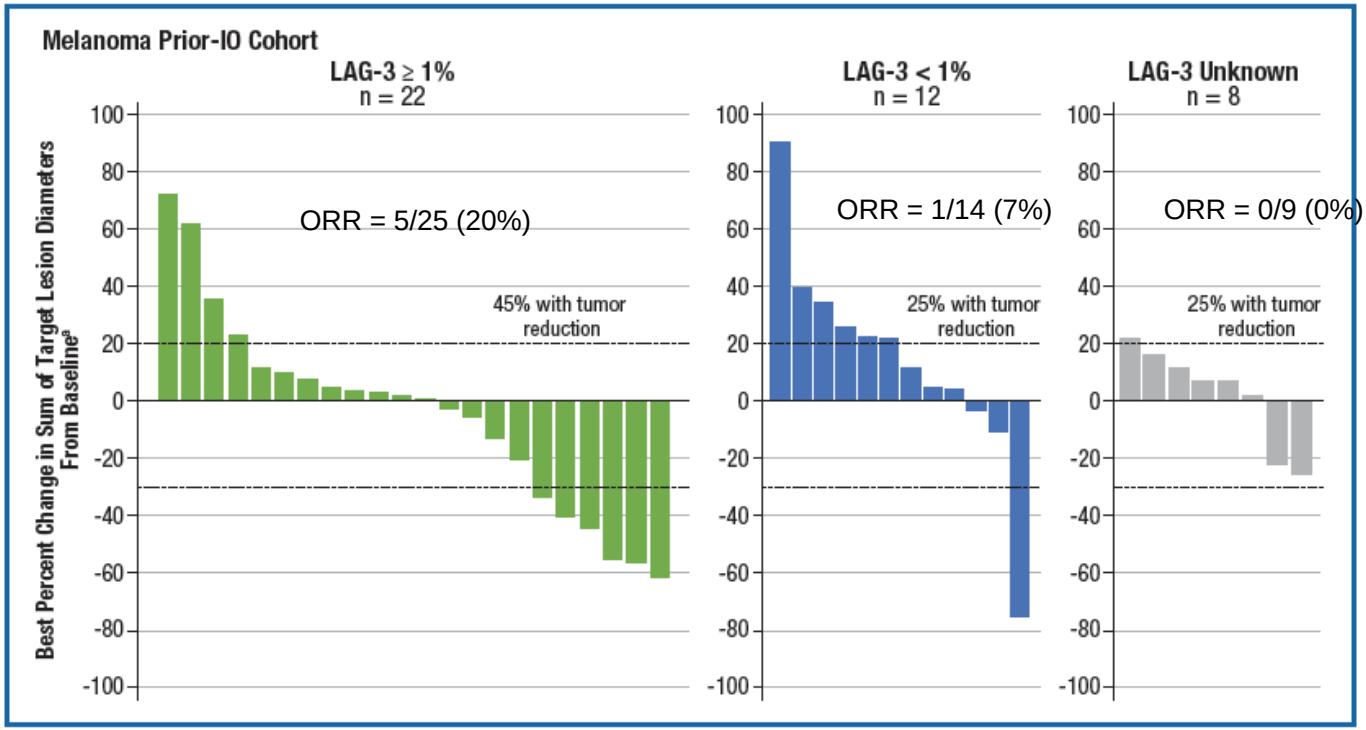
Lipson E et al ASCO 2021

Anti-LAG3 in development: Relatlimab, LAG525, MK4280, RG6139

APC, antigen-presenting cell; MHC, major histocompatibility complex; TCR, T-cell receptor.

Ph 1/2: Relatlimab + Nivolumab

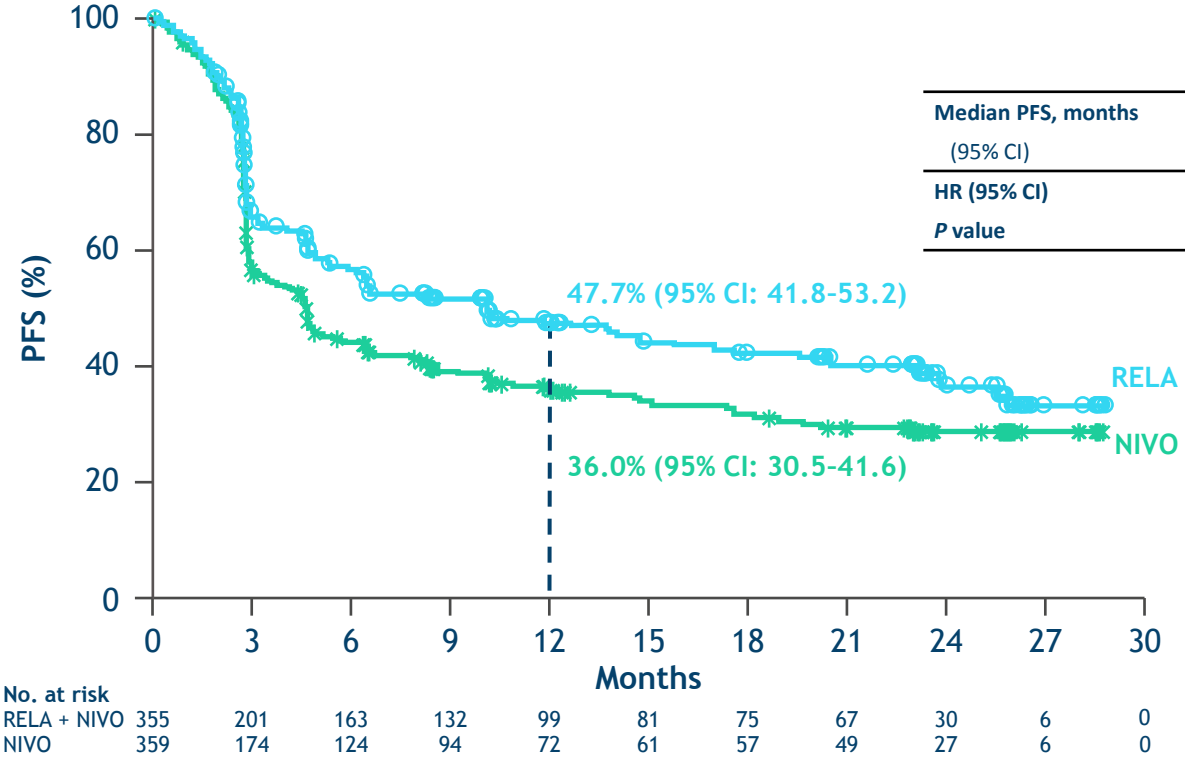
Melanoma Expansion: n=48, all PD-1/PDL-1 progressors, 15% LDH 2 xULN



6 pts not shown – progression prior to first scan

Ascierto P et el ASCO 2017

RELATIVITY 047: Ph 3 Relatlimab (anti-LAG3) + Nivolumab vs Nivolumab
Progression-Free Survival by BICR



	RELA + NIVO (n = 355)	NIVO (n = 359)
Median PFS, months	10.12	4.63
(95% CI)	(6.37–15.74)	(3.38–5.62)
HR (95% CI)	0.75 (0.62–0.92)	
P value	0.0055	

LAG3 expression did not select for pts with PFS benefit

Gd 3/4 Treatment-Related AEs

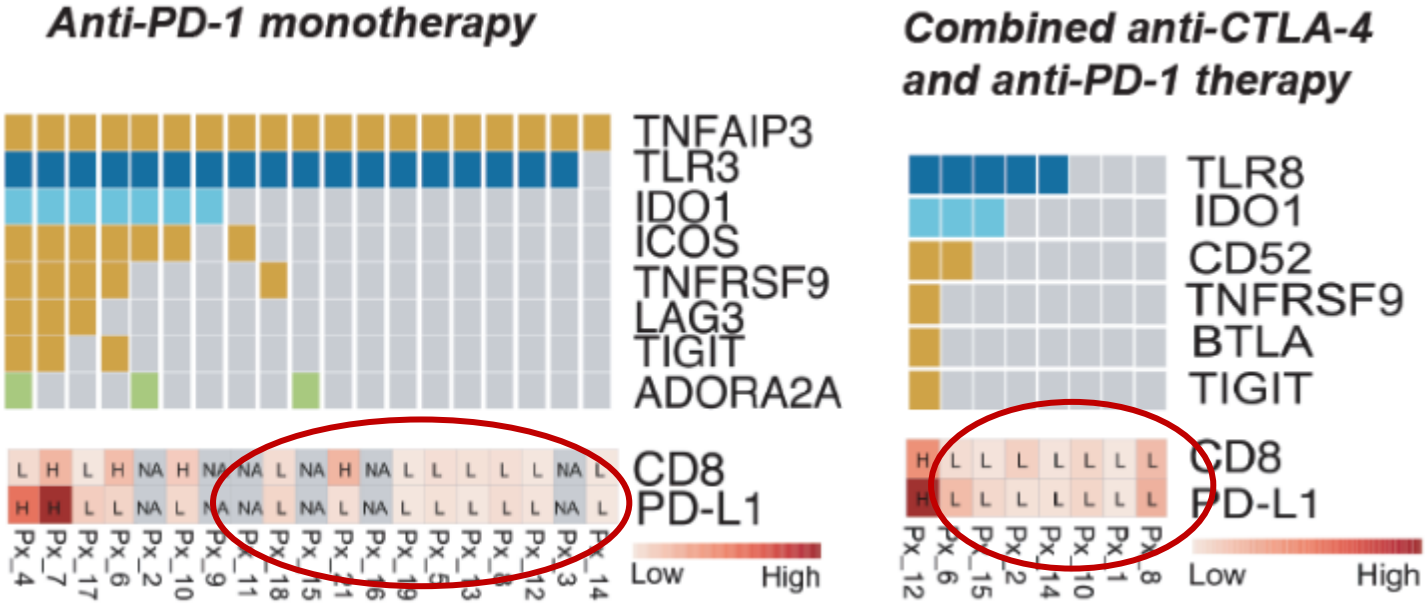
Nivo	9.7%
Nivo + Rela	18.9%
Nivo + Ipi*	55%

CI, confidence interval; HR, hazard ratio.
All randomized patients. Statistical model for HR and *P* value: stratified Cox proportional hazard model and stratified log-rank test. Stratified by LAG-3 (≥ 1% vs < 1%), *BRAF* (mutation positive vs mutation wild-type), AJCC M stage (M0/M1any[0] vs M1any[1]). PD-L1 was removed from stratification because it led to subgroups with < 10 patients.

*Larkin et al NEM 2015 CM 067 Primary Analysis

Lipson E et al ASCO 2021

RNA Expression and IHC of Baseline Melanoma Tissue Non-Responders n=34



Other T-Cell Targets:
TIGIT
TIM3
IDO

↓ TILS
↓ PDL1

IDO and Immune Microenvironment: Trying to make the tumour 'HOT'

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From Macrophages APC

IDO

↓ Tryptophan

CD8 T cell apoptosis

↑ Kynurenine

Switch to T reg

↑ **CD8**
NK Cells

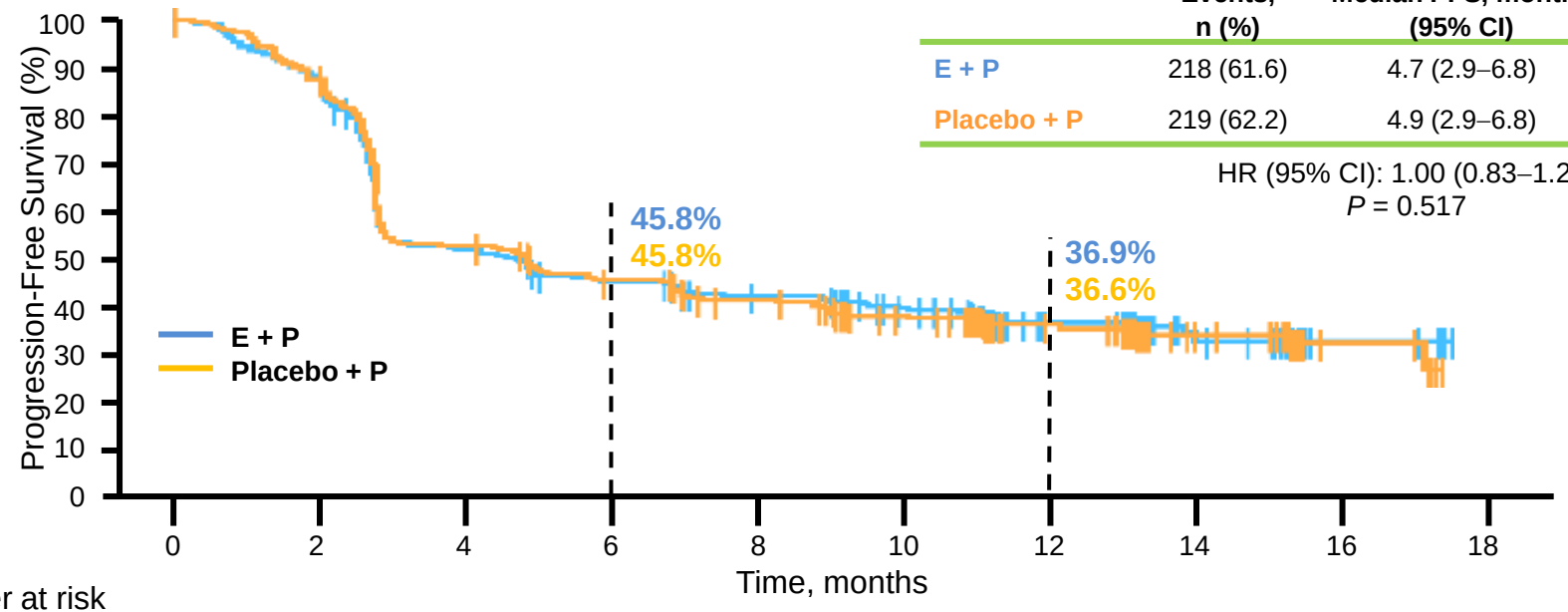
↓ **T reg**

Progression-Free Survival

Ph 3: Pembrolizumab +/- Epacadostat (IDO inhibitor)

	Events, n (%)	Median PFS, months (95% CI)
E + P	218 (61.6)	4.7 (2.9–6.8)
Placebo + P	219 (62.2)	4.9 (2.9–6.8)

HR (95% CI): 1.00 (0.83–1.21)
P = 0.517



Number at risk

E + P	354	309	181	155	137	114	57	25	5	0
Placebo + P	352	304	181	151	132	109	65	28	7	0

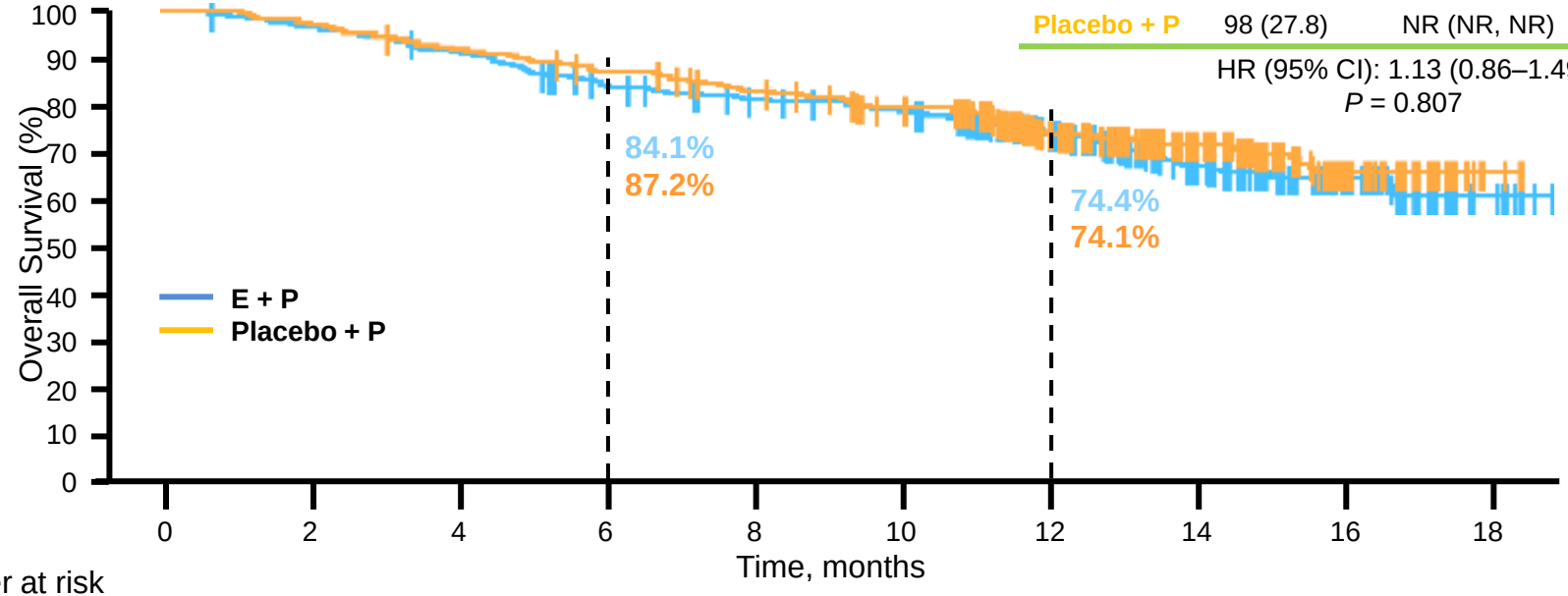
Long GV et al ASCO 2018; Lancet Onc 2019

Overall Survival

Ph 3: Pembrolizumab +/- Epacadostat (IDO inhibitor)

	Events, n (%)	Median OS, months (95% CI)
E + P	106 (29.9)	NR (NR, NR)
Placebo + P	98 (27.8)	NR (NR, NR)

HR (95% CI): 1.13 (0.86–1.49)
P = 0.807



Number at risk

E + P	354	340	322	290	274	263	183	96	42	5
Placebo + P	352	342	323	304	285	263	186	115	43	2

Long GV et al ASCO 2018; Lancet Onc 2019

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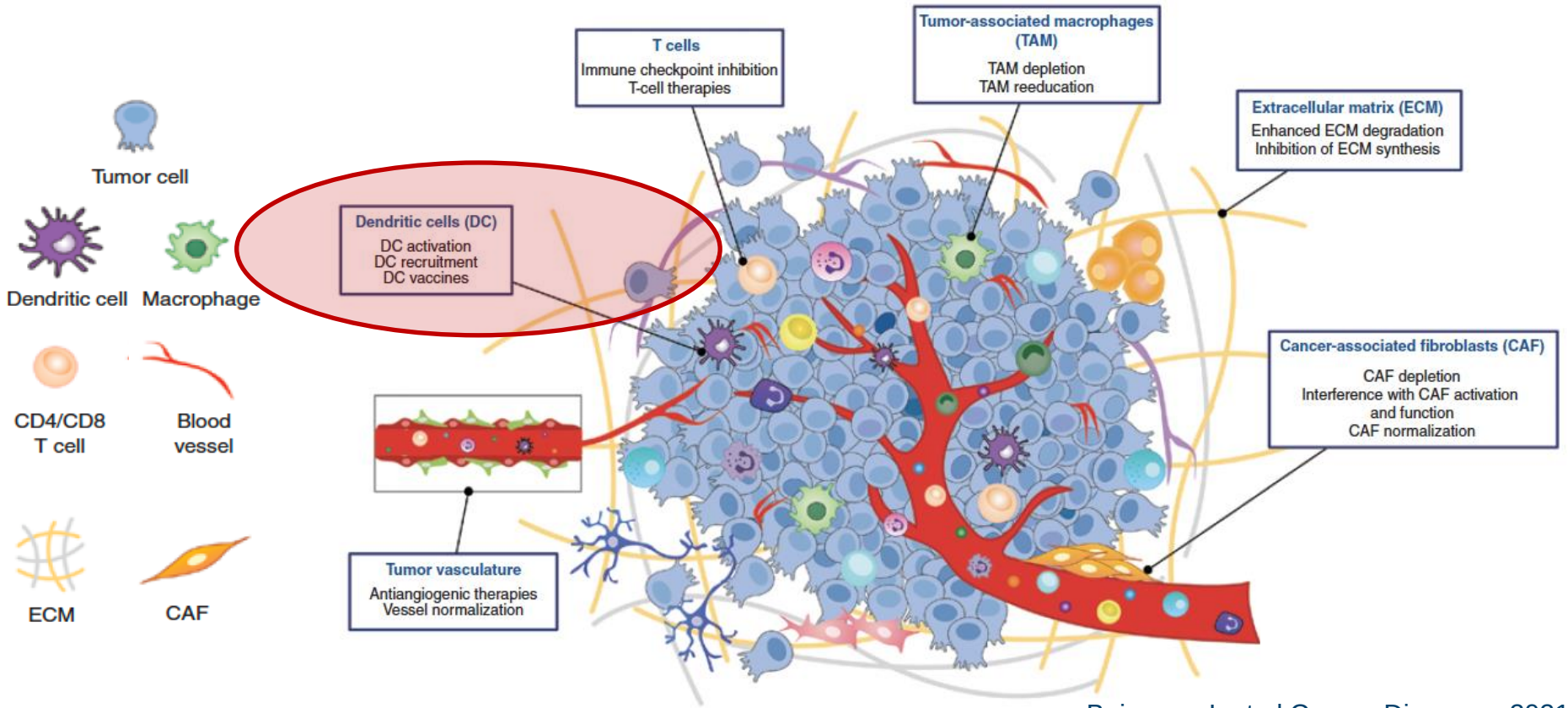
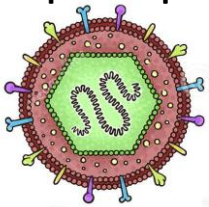
The Main Players in The Tumour Microenvironment



Bejarano L et al Cancer Discovery 2021

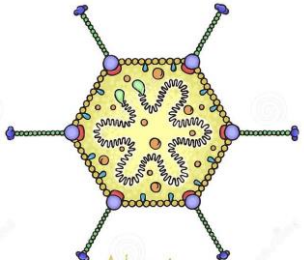
Oncolytic Viruses

Herpes Simplex



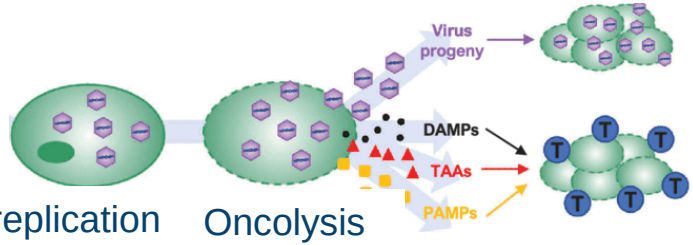
Coxsackie

Adenovirus



Insert immune stimulating genes

Remove disease-causing genes to selectively target tumour



Viral replication in cancer cells

Oncolysis

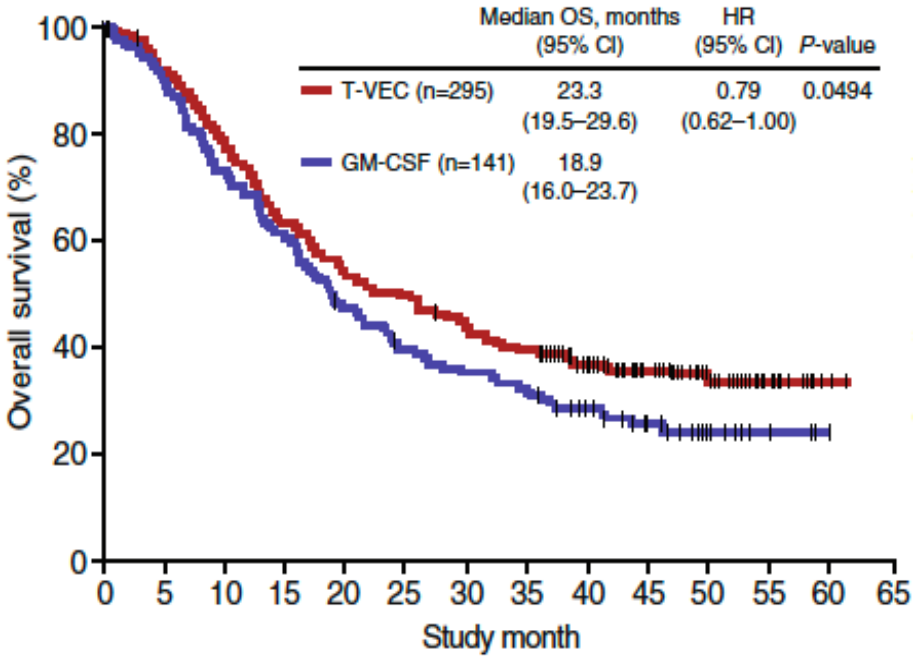
Amplification of oncolysis

Induction of anti-tumour immune response

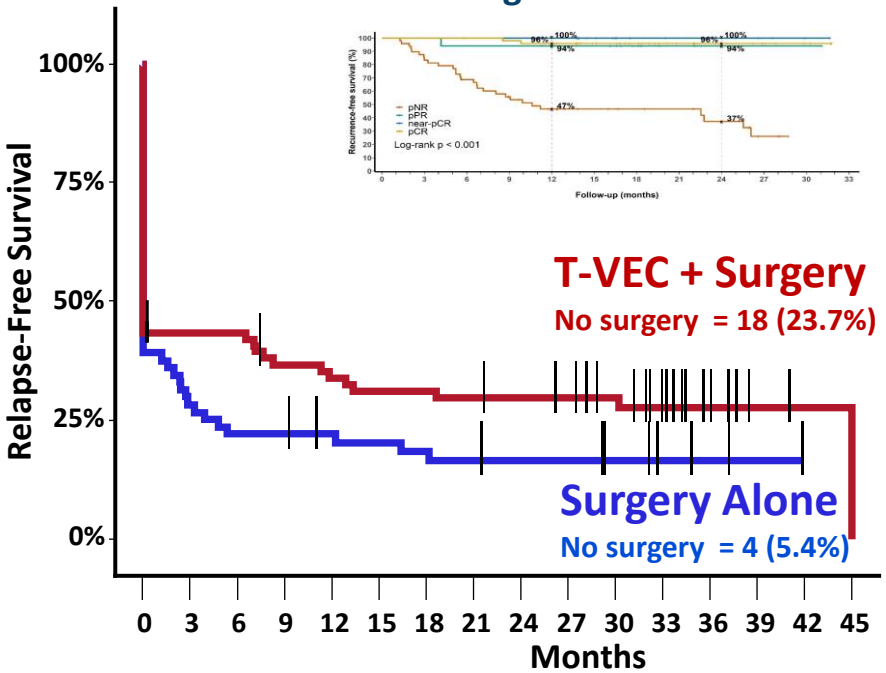
Intralesional TVEC in Melanoma

Melanoma Institute Australia

Ph 3 OPTiM: TVEC vs GM CSF in Advanced Melanoma



Ph 2: Neoadjuvant TVEC vs Upfront Surgery in Resectable stage III melanoma



TVEC + Ipilimumab vs Ipilimumab in Advanced Melanoma

ORR 39% vs 18%, p = 0.002

PFS HR 0.83 (0.56-1.23)

Andtbacka et al J Immunotherapy of Cancer 2019; Dummer et al ESMO 2019; Chesney et al JCO 2018.

Presented by Georgina V Long @ProfGLongMIA

MASTERKEY-265 Phase 3 Study

Melanoma Institute Australia

N = 660

- Unresectable stage III or IV melanoma
- Treatment-naive
- Injectable lesions
- No active brain mets
- No active herpetic skin lesions or prior complications from herpetic infection

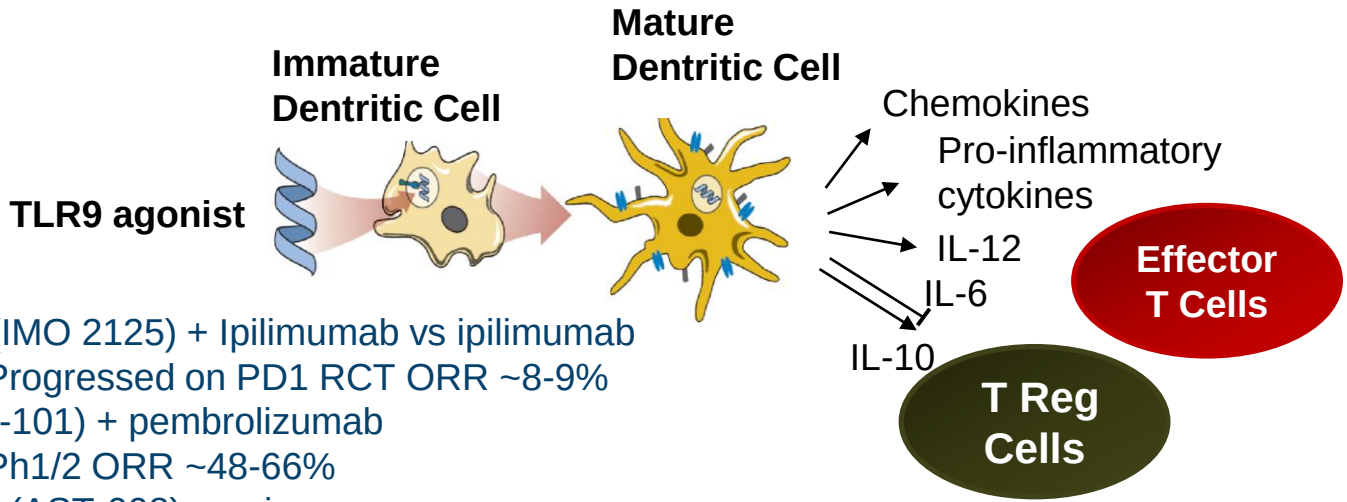
LONG-TERM FOLLOW-UP

Q12W for 5 yrs from last pt randomized

T-VEC: talimogene laherparepvec; irRC-RECIST: immune-related response criteria-response evaluation criteria in solid tumors; IV: intravenous; PFU: plaque-forming unit; Q2W: every 2 weeks; Q3W: every 3 weeks; Q12W: every 12 weeks; AEs: adverse events; OS: overall survival; PFS: progression-free survival

TLR Agonists

TLR9: Synthetic oligonucleotides (CpG dinucleotides)
Bind TLR9 → innate immune activation



Tilsotolimod (IMO 2125) + Ipilimumab vs ipilimumab
-Progressed on PD1 RCT ORR ~8-9%
Dynavax (SD-101) + pembrolizumab
-Ph1/2 ORR ~48-66%
Cavrotolimod (AST-008) onging

BRAFi: Induction of Tumour-Infiltrating T Cells

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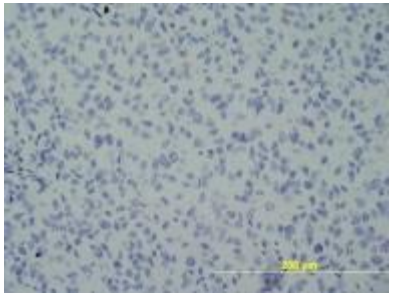
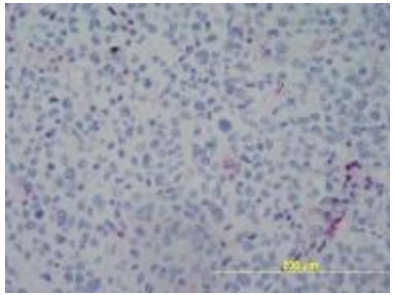
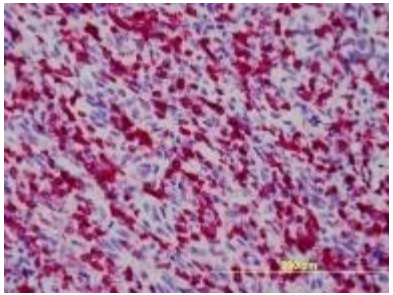
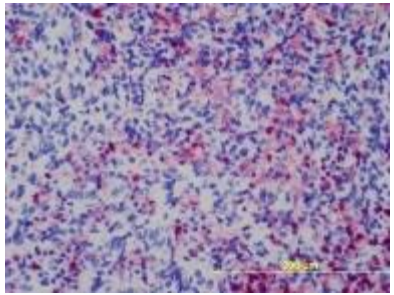
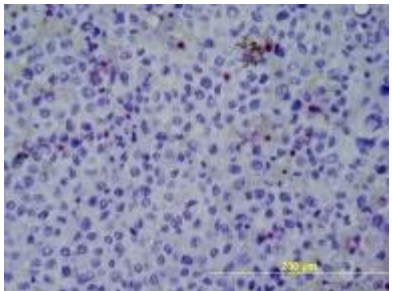
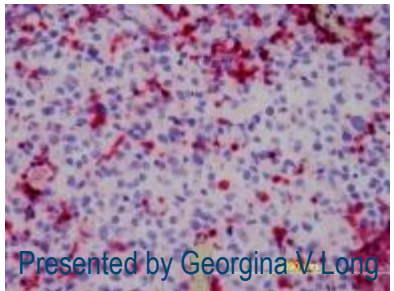
	CD8	CD4
Baseline		
Responding Day 7		
Progression		

J Wilmott, G V Long & R A Scolyer CCR 2012
Frederick-Wargo CCR 2013

Triple Therapy in Advanced Melanoma: BRAFi + MEKi + anti-PD1

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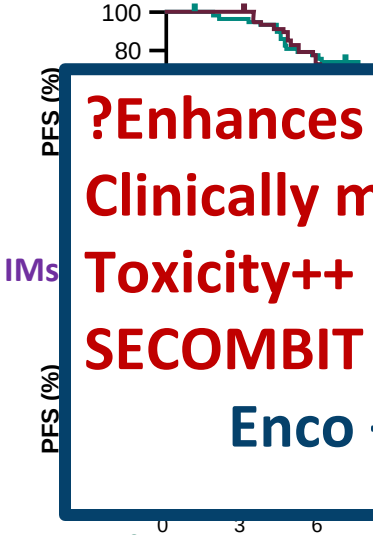
KEYNOTE 022[1]



?Enhances Anti-PD1 therapy

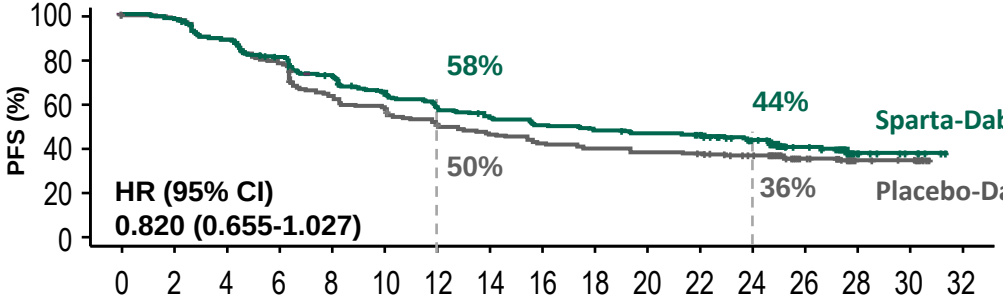
Clinically minor added benefit

Toxicity++

SECOMBIT Sandwich?[5]

Enco + Bini (8 weeks) then Ipi + Nivo until PD → Enco + Bini

COMBI-i[3]



ORR 69%
CR 20%

ORR 64%
CR 18%

Ipi + Nivo *BRAF* mut[4]

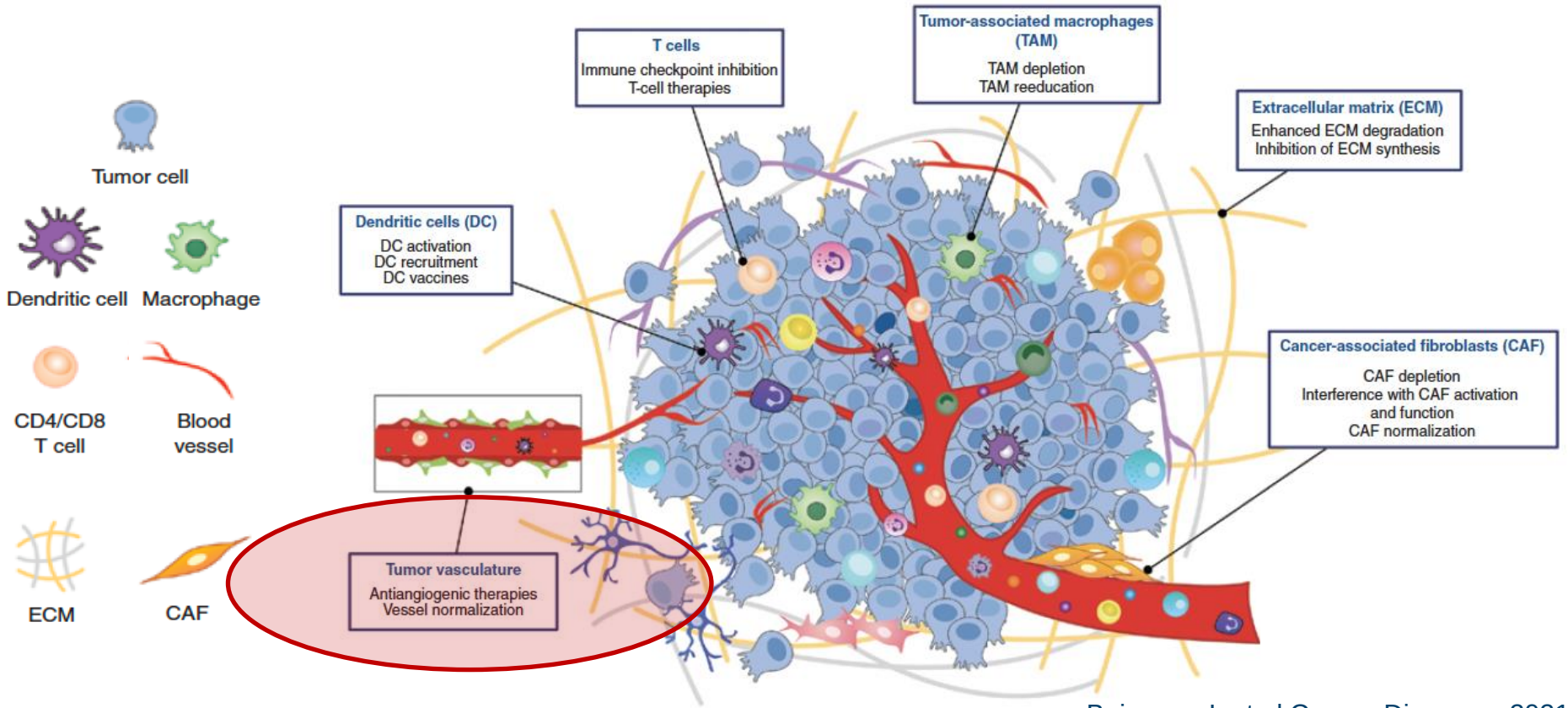
2-yr PFS 43%

1. Ferucci et al. SMR 2019. 2. Gutzmer et al Lancet 2020. 3. Nathan ESMO 2020. 4. Long GV et al. Presented at SMR 2019. 5. Ascierto PA et al. Presented at ESMO 2020; abstract LBA45.

Outline

1. What is the 'tumour microenvironment'?
2. PD1 biology → forcing a focus on the tumour microenvironment
3. **Drug Targets**
   - T cells
   - Antigen Presentation/Innate activation
   - **Vasculature**
   - Beyond PD1: Other Cells of the Microenvironment

The Main Players in The Tumour Microenvironment



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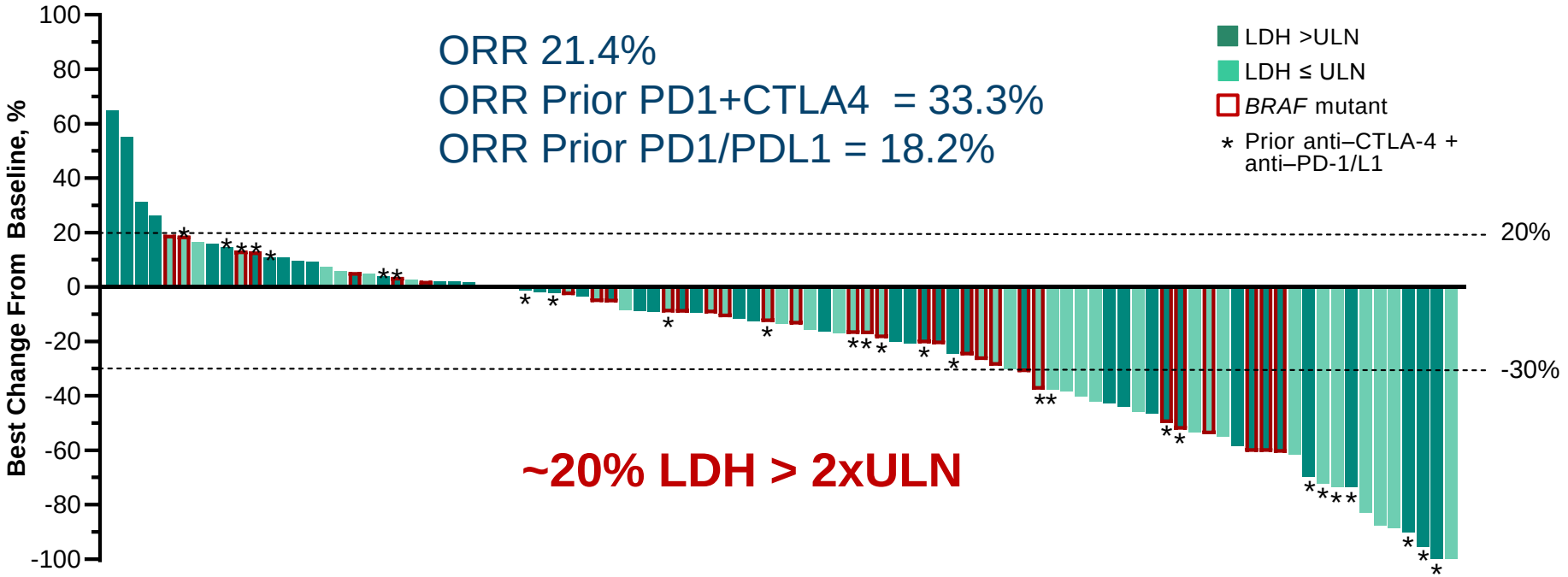
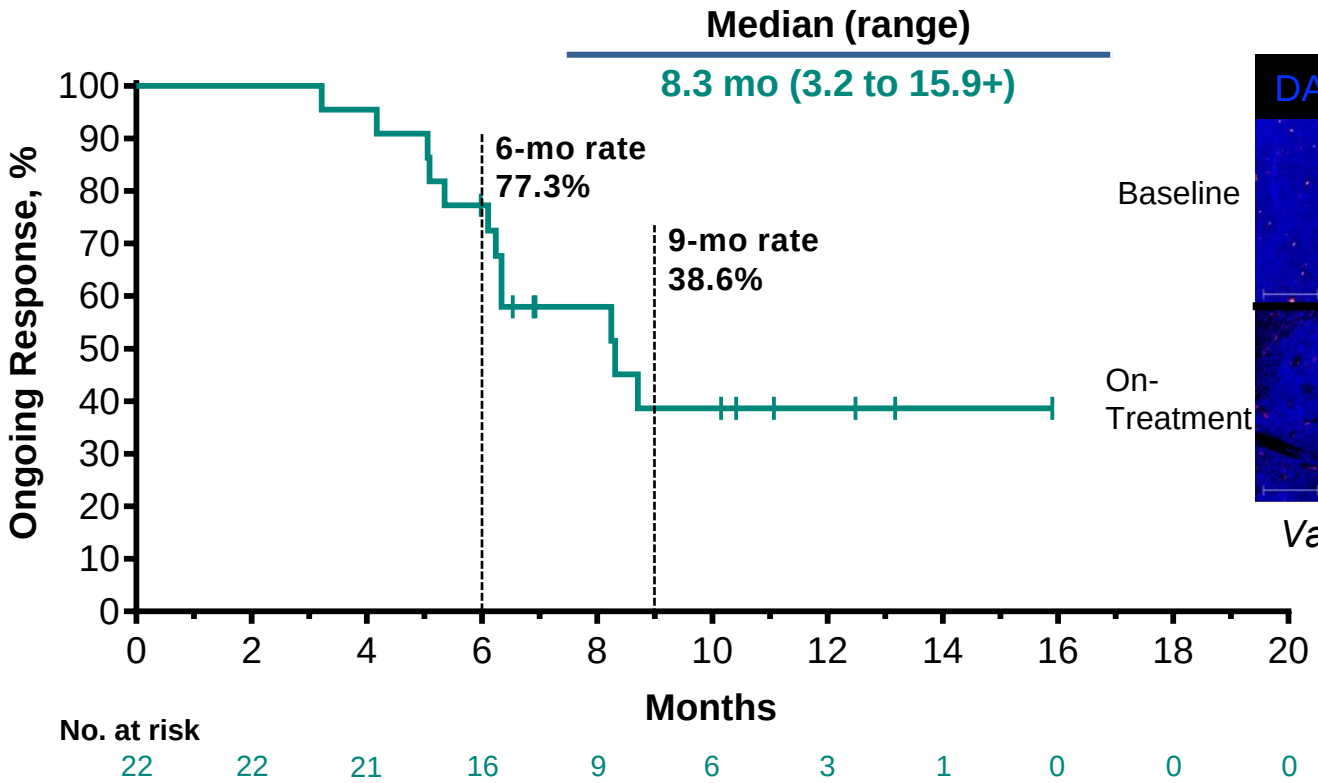
Ph 2: Pembrolizumab + Lenvatinib in Anti-PD1+/- Anti-CTLA4 Refractory Melanoma

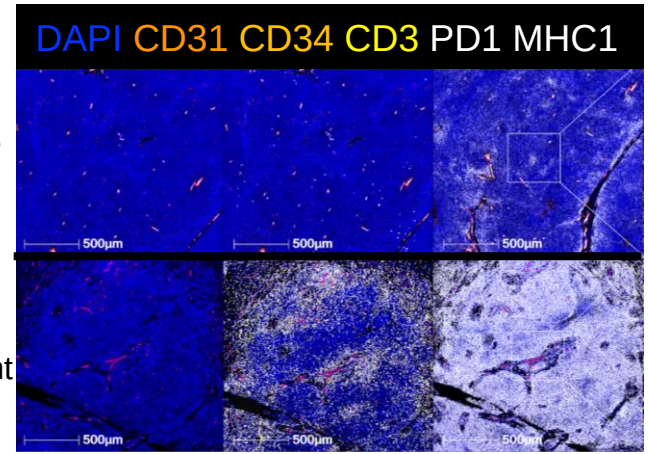


[a]The 8 participants who did not have ≥1 post-baseline imaging assessment evaluable for change from baseline in target lesions are excluded from the graph.
Data cutoff date: Sep 18, 2020.

Arance A et al ASCO 2021

Duration of Response





Vasculature change, ↑ PD1, ↑MHC1

Data cutoff date: Sep 18, 2020.

Arance A et al ASCO 2021

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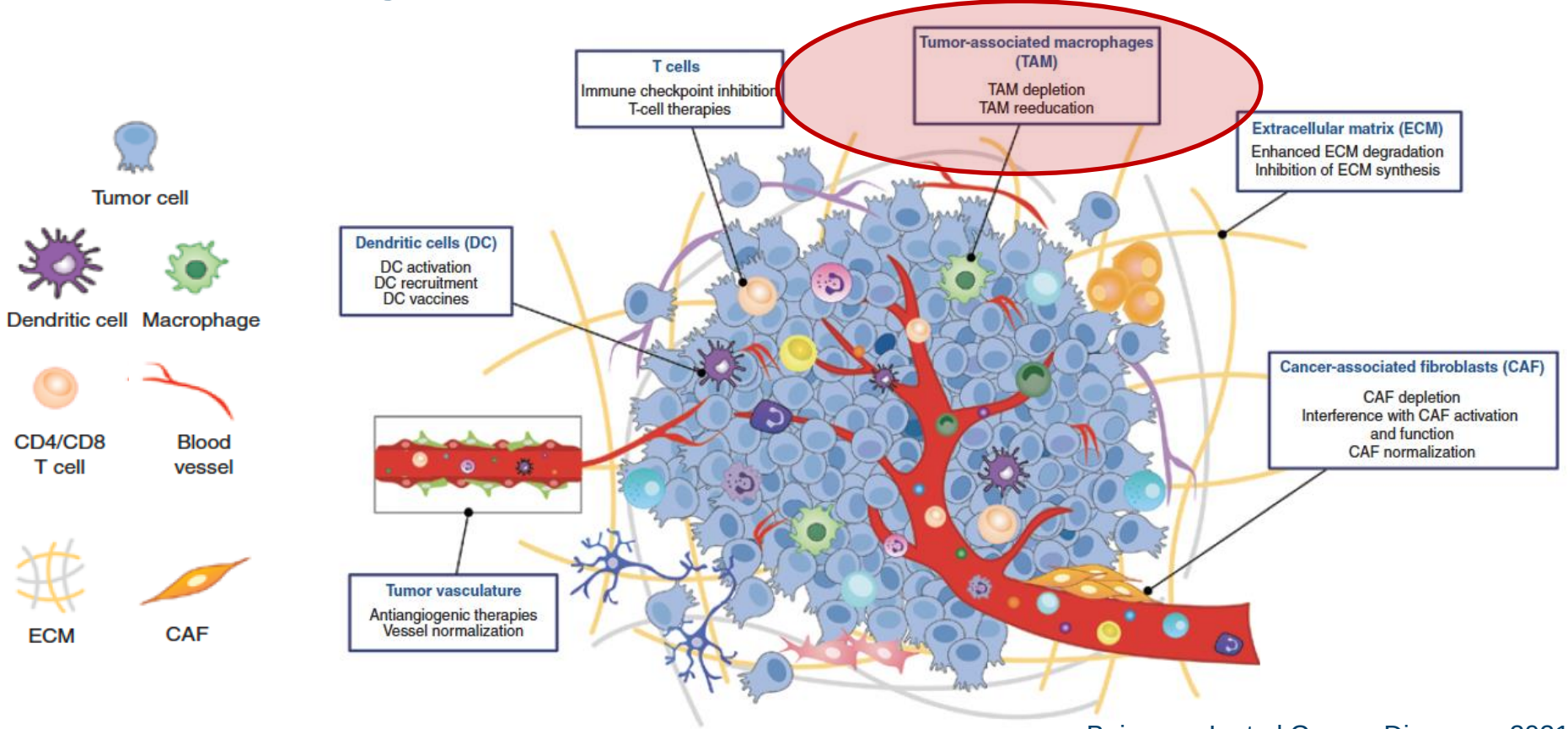
Georgina V Long, Melanoma Institute Australia

The Main Players in The Tumour Microenvironment



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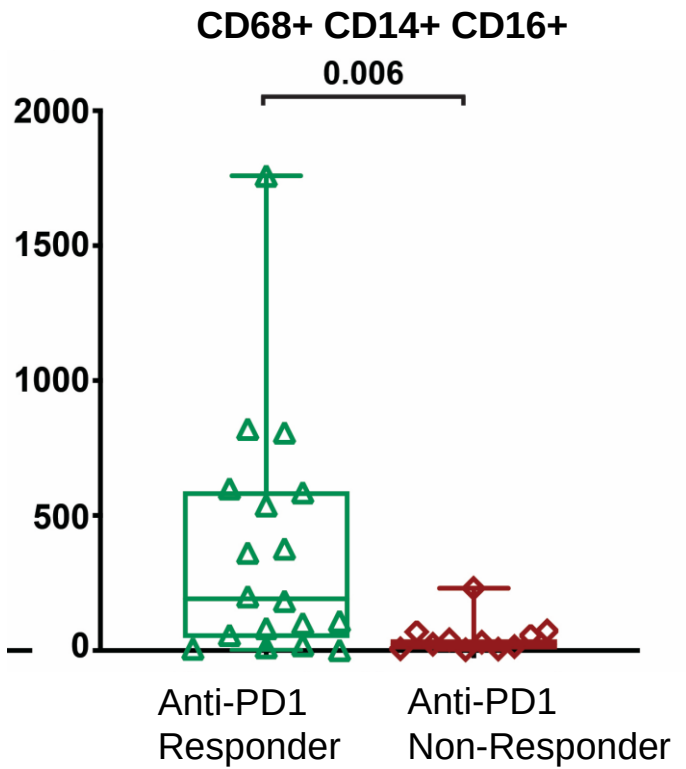
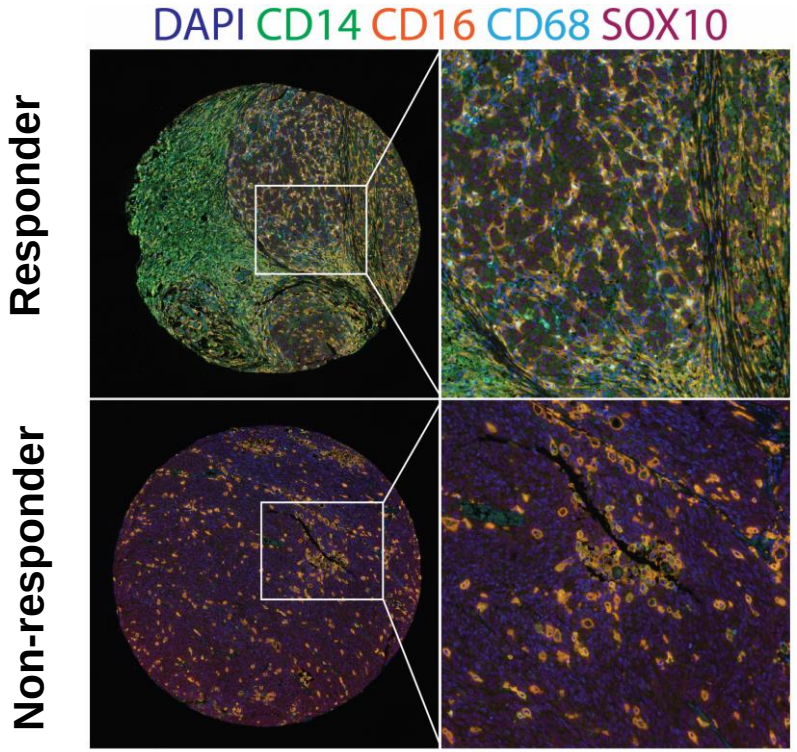
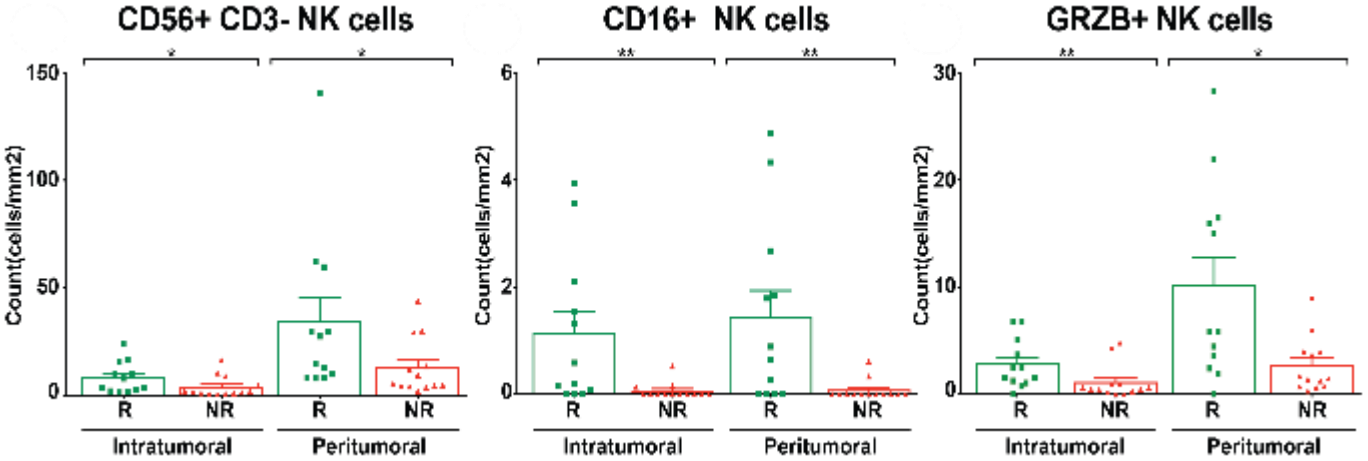
There are GOOD Macrophage Subsets

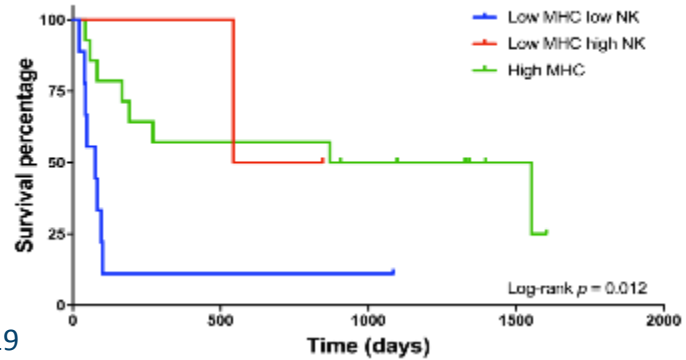




Anti-PD-1 Responders have higher activated & differentiated intratumoural + peritumoural NK cell densities



Responders with MHC Class I loss have high NK cells



Lee H et al OncoImmunology 2019

Presented by Georgina V Long @ProfGLongMIA

Outline

1. What is the 'tumour microenvironment'?
2. PD1 biology → forcing a focus on the tumour microenvironment
3. Drug Targets
   - T cells — **LAG3, IDO**
   - Antigen Presentation/Innate activation — **TVEC, TLR, Targeted Therapies**
   - Vasculature — **VEGFi**
   - Beyond PD1: Other Cells of the Microenvironment — **Macrophages NK Cells**

Acknowledgements

- Patients and Families
- National and International Colleagues and Scientists in Cancer
- Melanoma Institute Australia and Trials Team

Melanoma Institute Australia

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