ASCO 20 Virtual

Roche Analyst Event

Friday, 29 May 2020

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Welcome

Karl Mahler, Head of Investor Relations and Group Planning

Cancer immunotherapy pipeline overview

Targeting the cancer immunity cycle and tiragolumab (Anti-TIGIT) overview

Ira Mellman, Ph.D., Vice President, Cancer Immunology, Genentech Research and Early Development

ASCO 2020 Key readouts across tumor types

CITYSCAPE: Primary analysis of tiragolumab + Tecentriq in 1L NSCLC

Updated data from Alecensa, Rozlytrek and Tecentriq in lung, liver cancer & tumor-agnostic indications

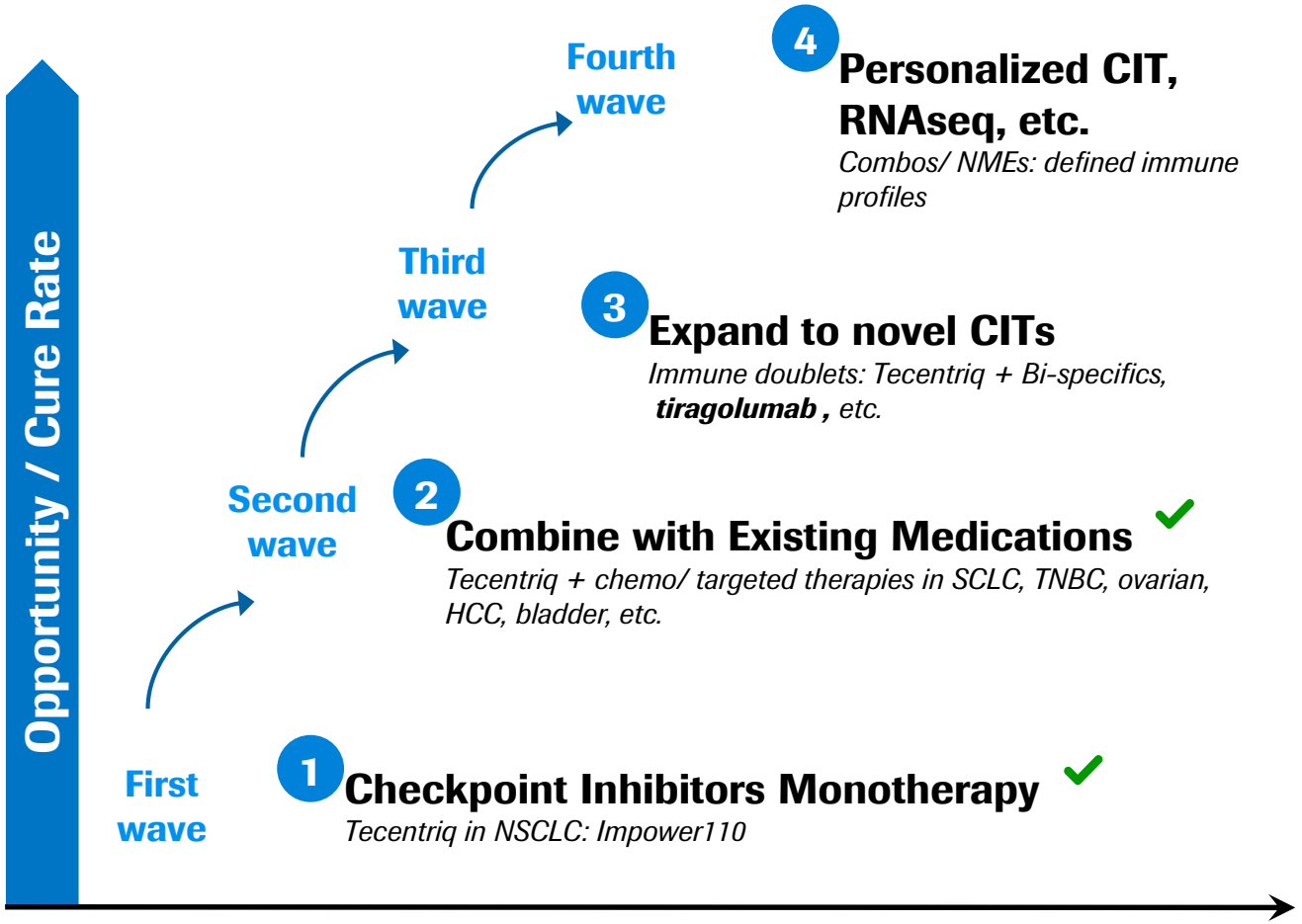
Alan Sandler, M.D., Global Head of Product Development Oncology - Solid Tumors

Q&A

Welcome

Karl Mahler | Head of Investor Relations and Group Planning

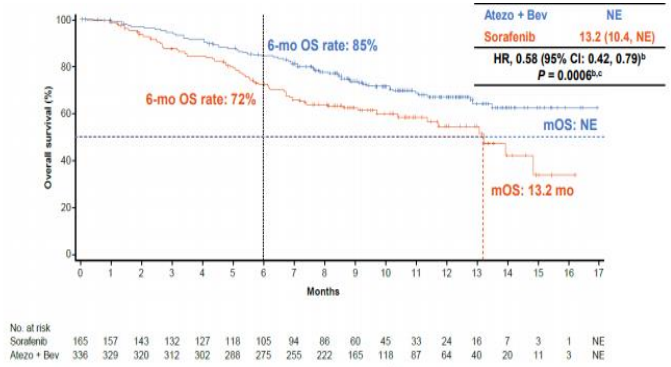
Establishing Tecentriq as standard of care in major tumor types



Wave 3 Tecentriq and tiragolumab in various cancer types have started Ph III development

- **SKYSCRAPER-01 Ph III in PD-L1+ NSCLC**
- **SKYSCRAPER-02 Ph III in ES-SCLC**
- **SKYSCRAPER-04 Ph II in PD-L1+ cervical cancer**

Wave 2 Tecentriq + Avastin in HCC
Medically meaningful improvement



NSCLC=non-small cell lung cancer; SCLC=small cell lung cancer; TNBC=triple-negative breast cancer; HCC=hepatocellular carcinoma

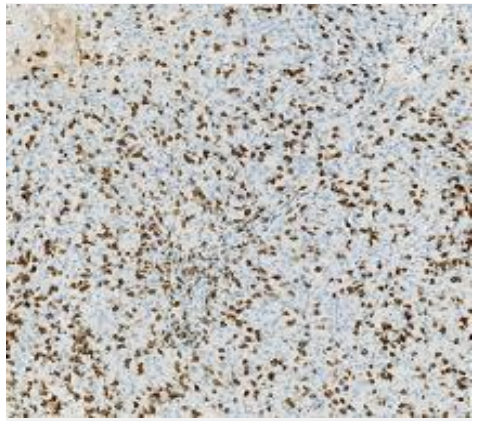
Overview of tiragolumab (Anti-TIGIT)

Ira Mellman, Ph.D. | Vice President, Cancer Immunology (gRED)

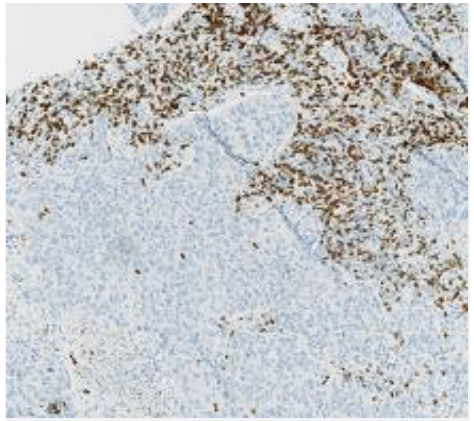
All tumors exhibit one of three basic immune phenotypes

Provides mechanistic context for response and lack of response to CIT

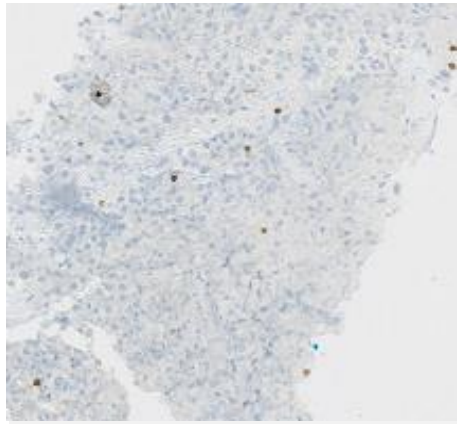
Melanoma Lung TNBC Bladder Gastric Ovarian CRC PDAC



IMMUNE INFLAMED
CD8+ T cells infiltrated, but insufficient



IMMUNE EXCLUDED
CD8+ T cells do not efficiently infiltrate out from stroma



IMMUNE DESERT
CD8+ T cells absent from tumor and periphery

Incidence	IMMUNE INFLAMED	IMMUNE EXCLUDED	IMMUNE DESERT
CRC	12%	63%	25%
NSCLC	31%	44%	25%
mUC	26%	47%	27%
TNBC	36%	47%	17%

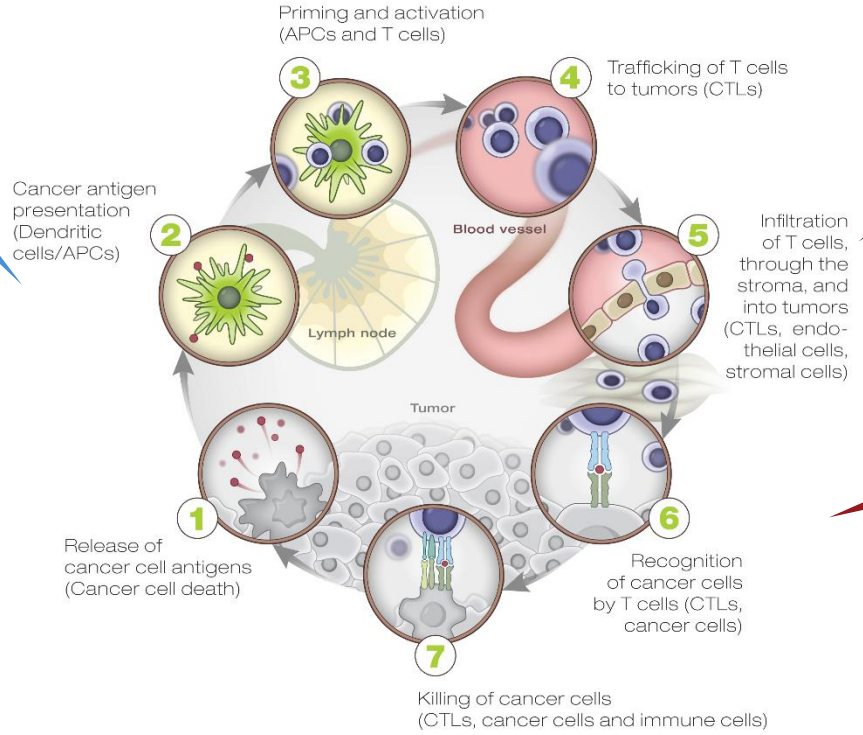
CRC: colorectal cancer, NSCLC: non small cell lung cancer; mUC metastastic urothelial carcinoma, TNBC: triple negative breast cancer, CIT: cancer immunotherapy

Strategies to promote an antitumor immune response by phenotype

Target "rate limiting steps" associated with primary and secondary resistance

IMMUNE DESERT

- Generate/release/deliver antigens
- Enhance antigen presentation and T-cell priming
- Redirect and engage T cells



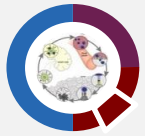
IMMUNE EXCLUDED

- Recruit T cells to tumour
- Address stromal barrier
- Redirect and engage T cells

INFLAMED

- Invigorate T cell response
- Redirect and engage T cells

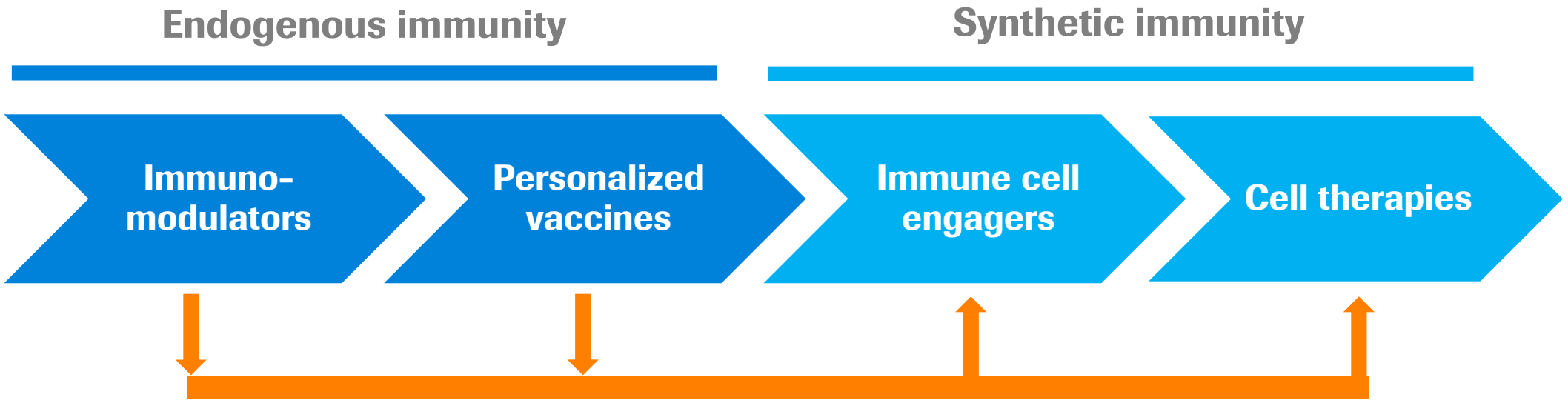
Some patients may only require targeting of negative regulator (aPD-L1 monotherapy) to enable cancer immunity



Some patients will need two or more therapies to enable cancer immunity (e.g., to drive infiltration, boost MHC expression, etc)

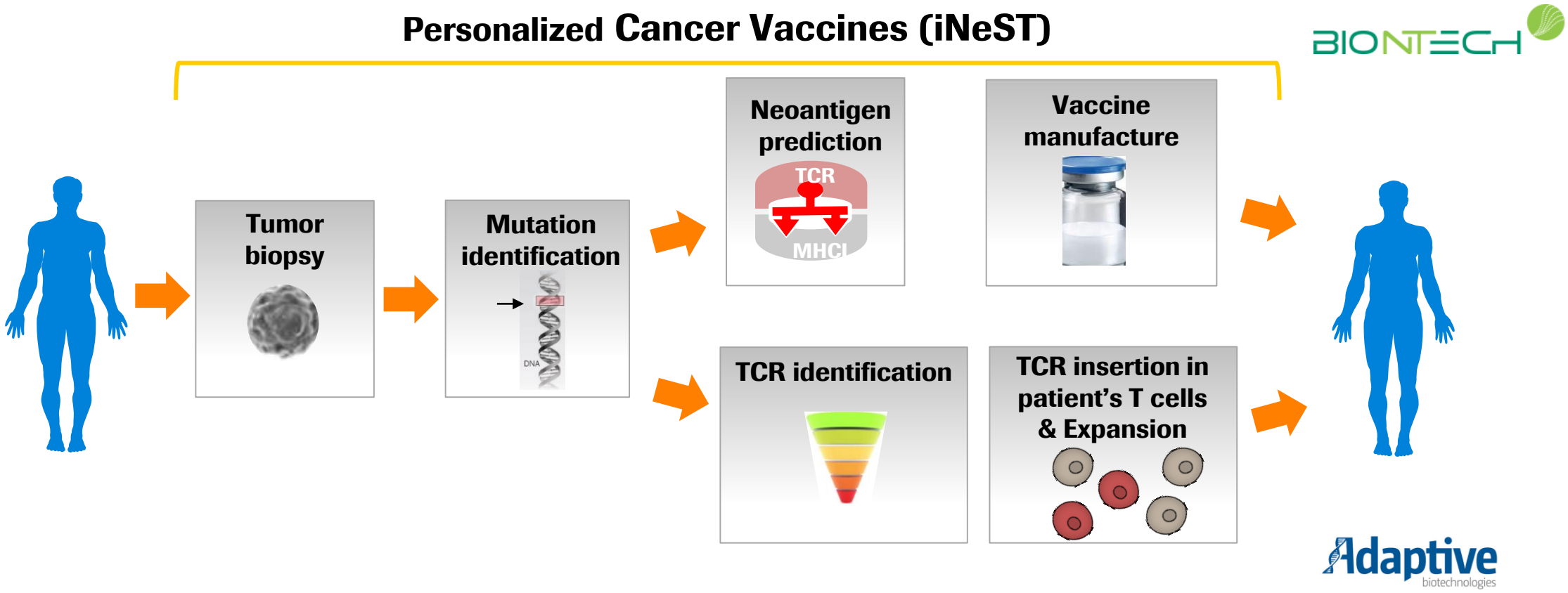
Adapted from Chen and Mellman. Immunity 2013; Hegde, et al. Clin Cancer Res 2016; Kim and Chen. Ann Oncol 2016; Chen and Mellman. Nature 2017

Targeting the cancer immunity cycle requires a methodologically coordinated approach



Immune profiles may limit the effectiveness even of synthetic approaches

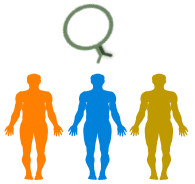
Neoantigen specific therapies: two complimentary approaches



iNEST: individualized neoantigen specific immunotherapy, TCR: T cell receptor, MHCI: major histocompatibility complex class I

Neoantigen-specific T cells can be shared or individual

Shared Neoantigens

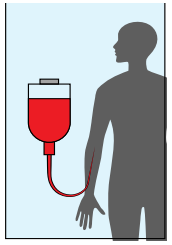


Determine patient mutation and HLA

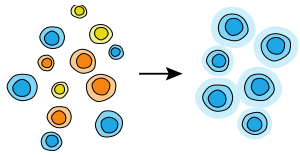
Access "warehouse" of conserved neo-AgTCRs*

Adaptive biotechnologies

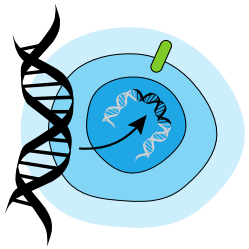
Use existing TCR encoding DNA



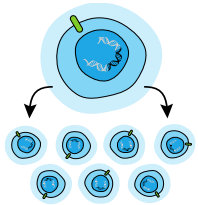
Apheresis



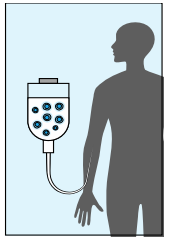
Isolate & stimulate T cells



TCR gene editing (CRISPR)



Expand T cells



Infuse

Individual Neoantigens

Patient tumor sequence

Determine patient mutation and HLA

TCR Identification/ Selection*

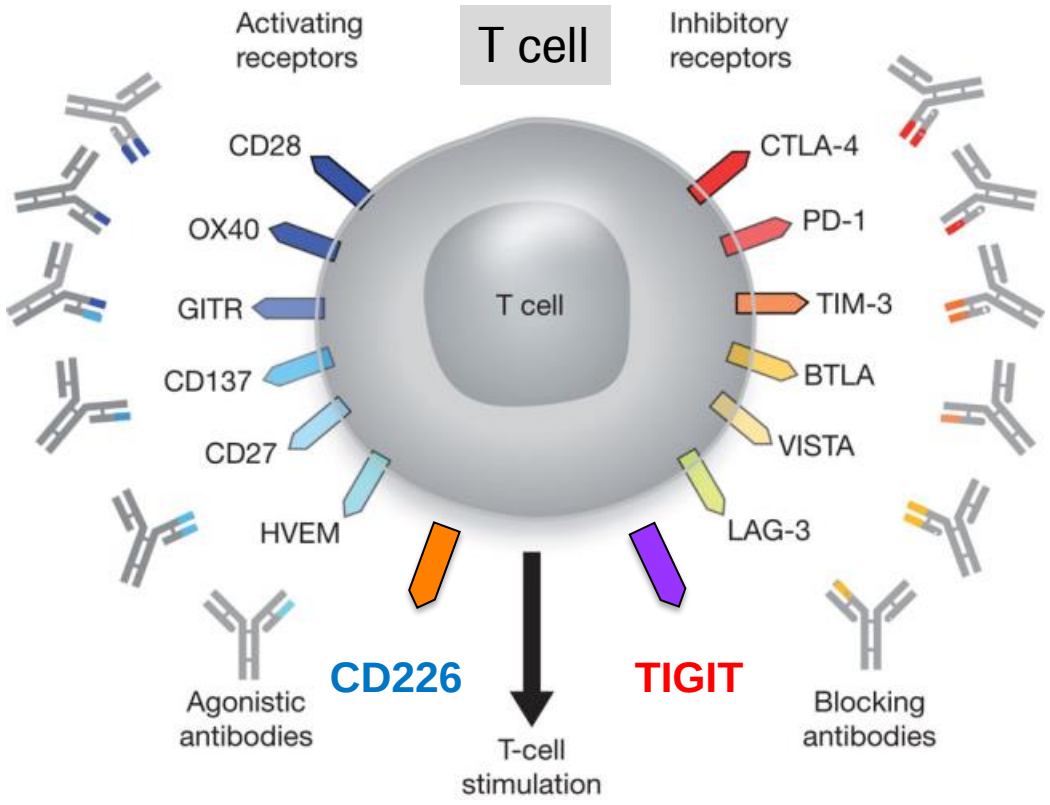
*from patient PBLs or naïve TCR library

Produce TCR encoding DNA

TCR: T cell receptor, HLA: human leukocyte antigen; PBL: peripheral blood leukocytes, neo-Ag: neoantigen

There are many T cell checkpoints, including TIGIT

T-cell regulation



About TIGIT

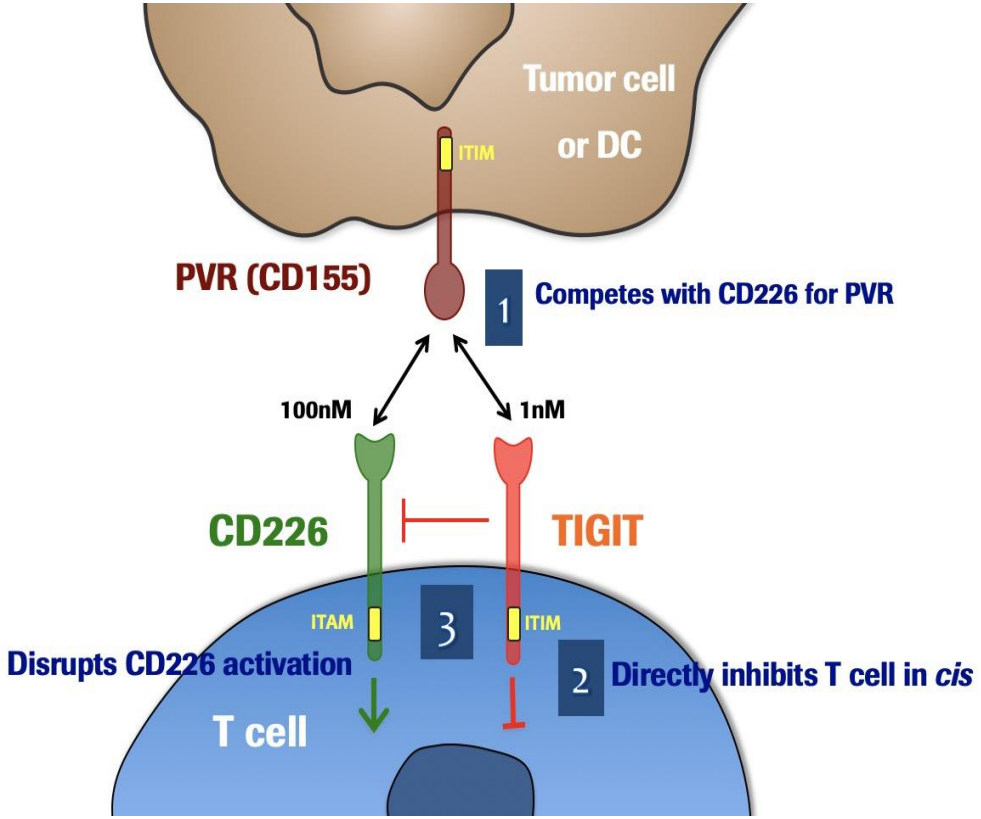
- **TIGIT** (T cell immunoreceptor with Ig and ITIM domains) is an **inhibitory receptor,** discovered at Genentech
- **TIGIT** acts as a specific negative regulator of the CD226 costimulatory receptor
- **TIGIT** is expressed on multiple immune cells, including **CD8+ T cell** (effector memory), **CD4+ T cells** (effector memory and regulatory), **Tfh cells**, and **NK cells**[2–4]
- **TIGIT** is expressed on a new population of T cells, **stem-like memory cells**, that may be the preferred targets for anti-PDx efficacy

Ig, immunoglobulin; ITIM, immunoreceptor tyrosine-based inhibition motif; Tfh, T follicular helper cell; NK, natural killer

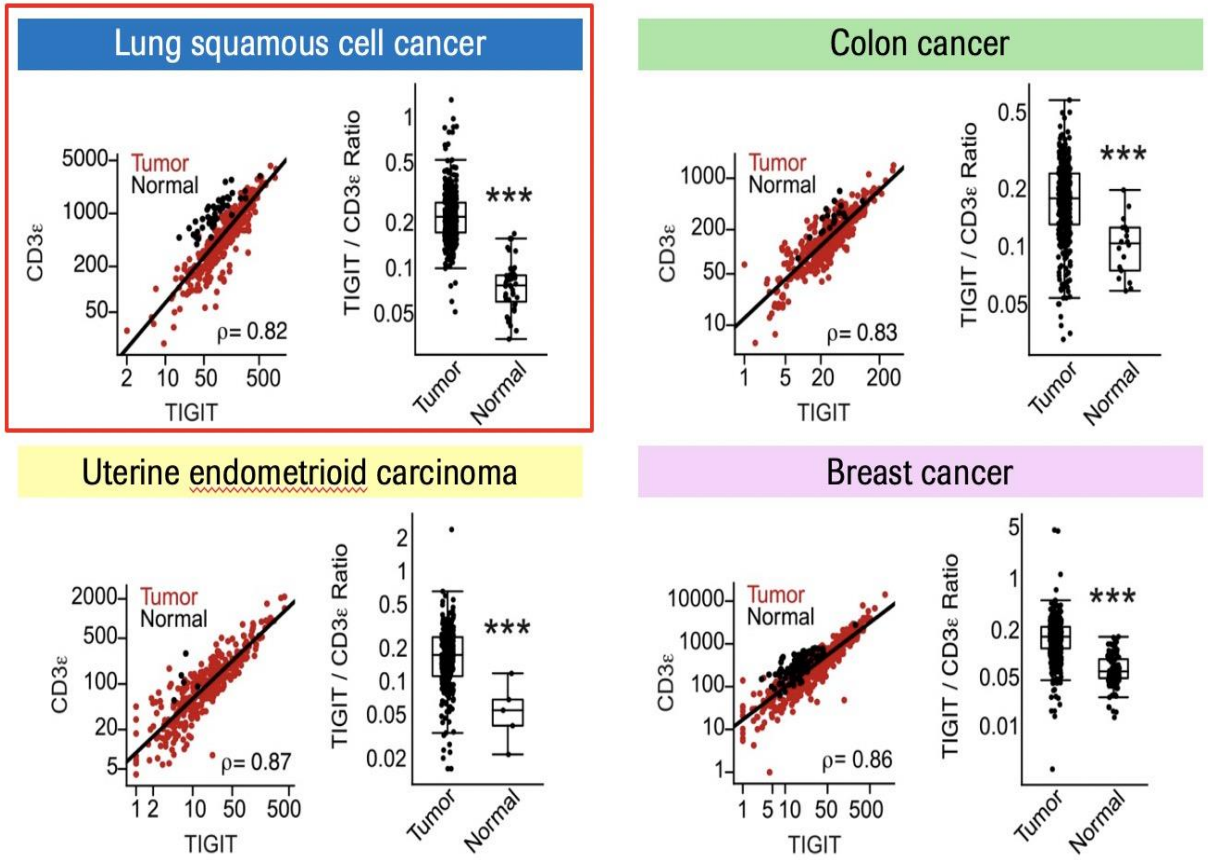
1. Figure adapted from Mellman I et al. Nature 2011; 2. Manieri NA et al. Trends Immunol 2017; 3. Rotte A et al. Annals of Oncol 2018; 4. Yu X et al. Nature Immuno 2009

TIGIT – expressed in multiple tumor types

Model for TIGIT regulation of T cell responses



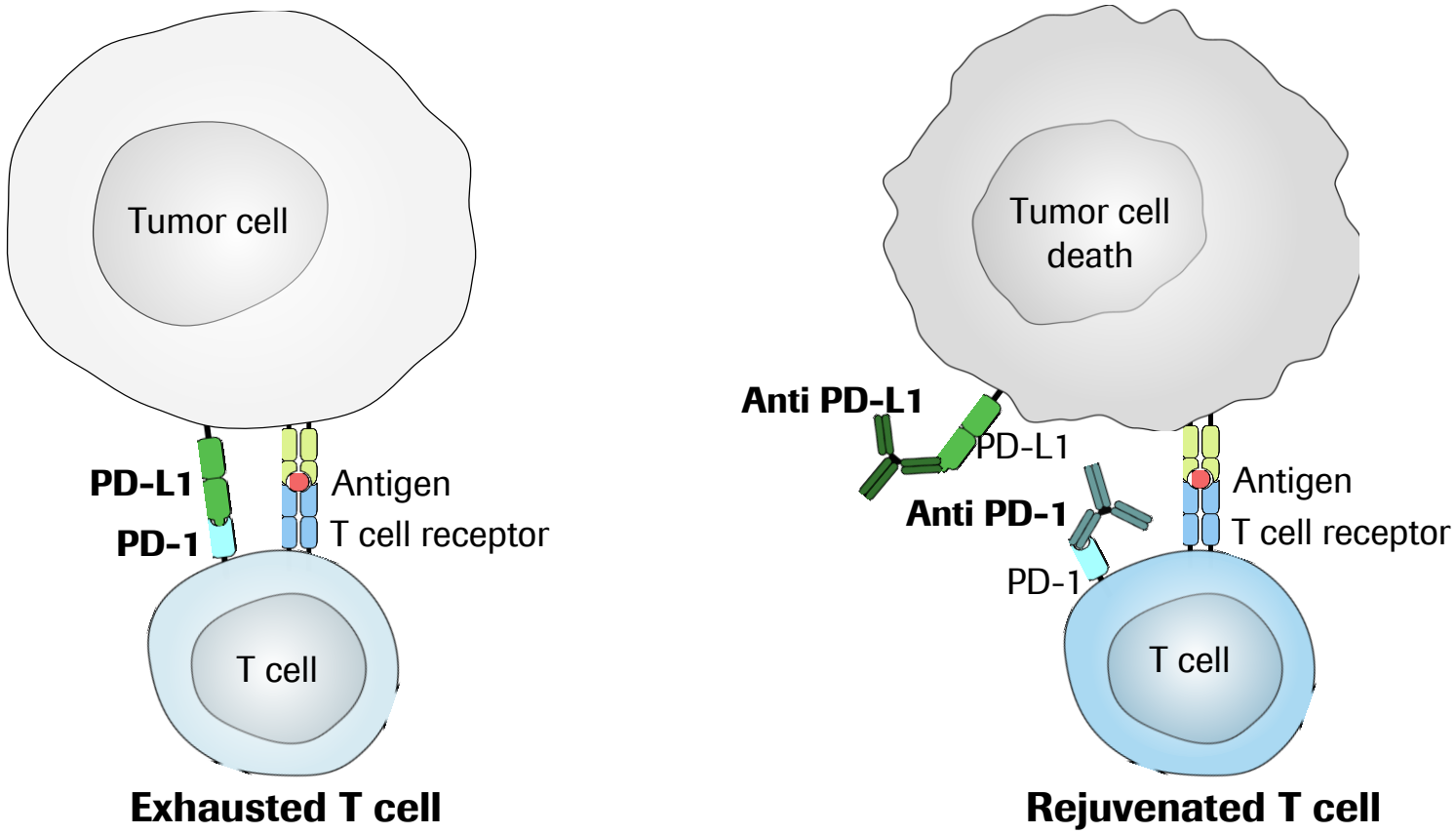
TIGIT is highly expressed in T-cell infiltrated tumors



Johnson et al. Cancer Cell 2014

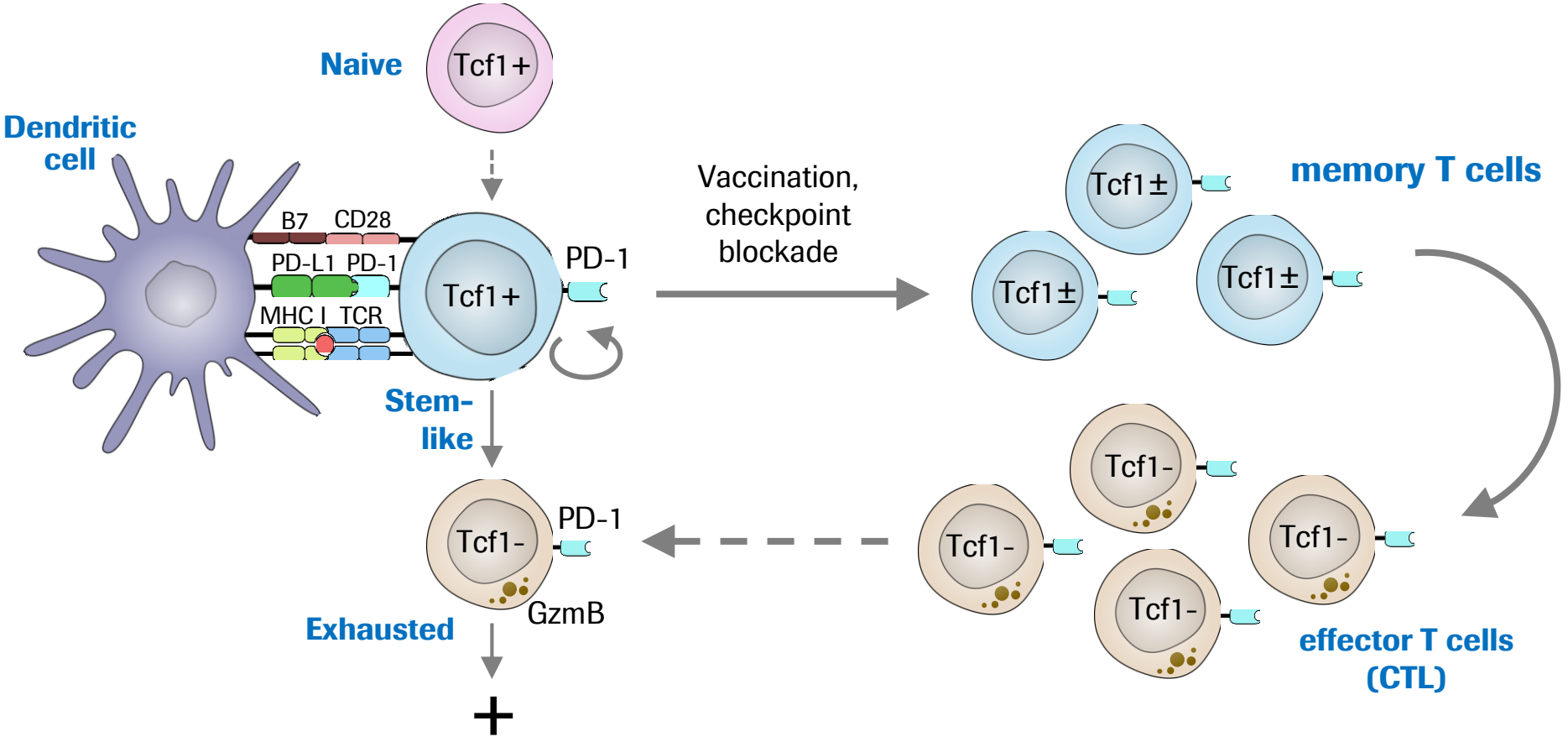
Evolving understanding of how checkpoint inhibitors work:
Reversing exhaustion vs expanding stem cell-like anti-tumor T cells

Original view: exhaustion reversal



Evolving understanding of how checkpoint inhibitors work:
Reversing exhaustion vs expanding stem cell-like anti-tumor T cells

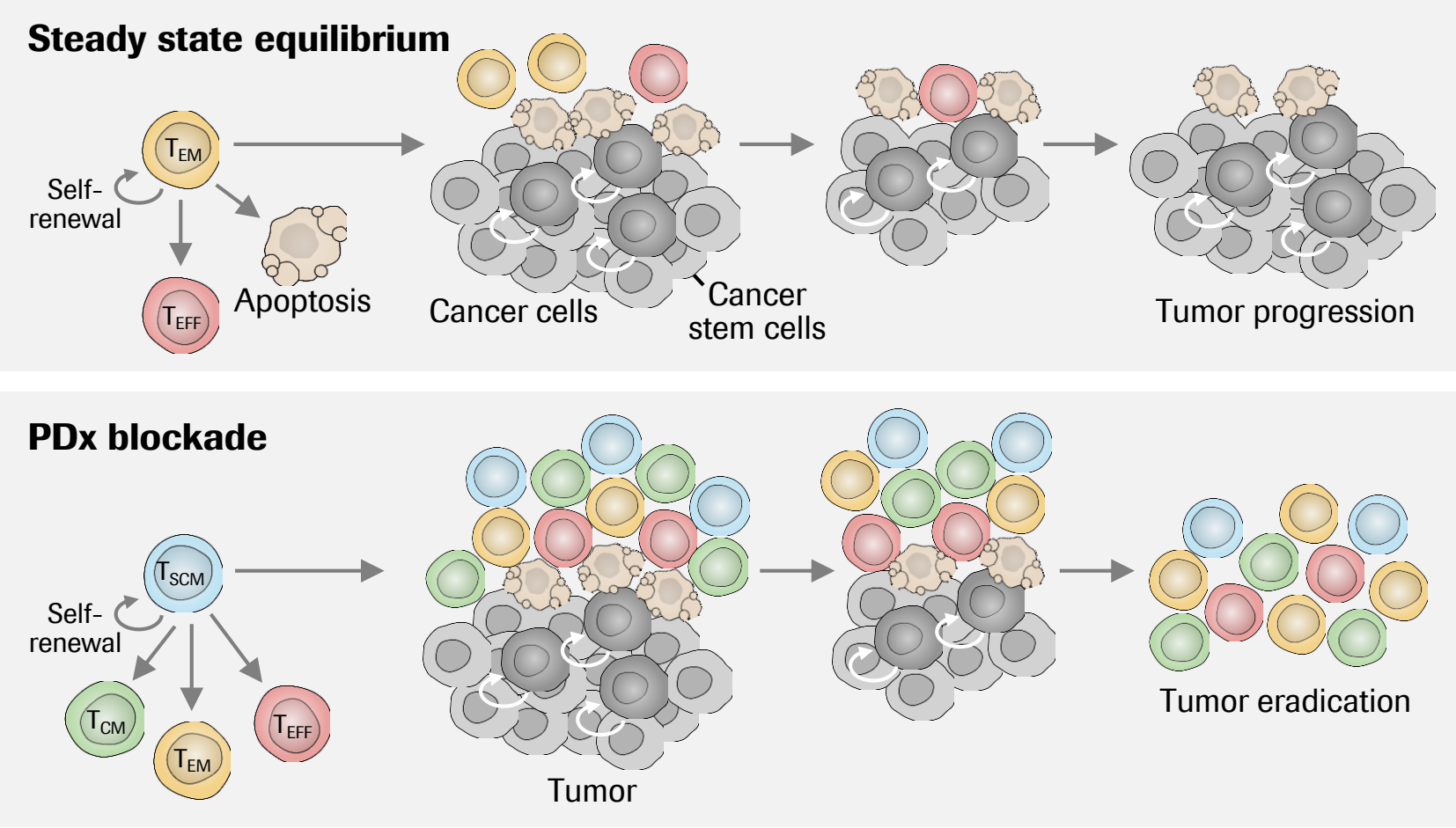
Revised view: T_{SCM} expansion



Siddiqui et al (2019) Immunity 15;50(1):195-211

- *LCMV: Im et al. 2016. PMID 27501248, Utzschneider et al 2016. PMID 27533016*
- *Cancer: Sade-Feldman et al. 2018. PMID 30388456, Kurtulus et al. 2019. PMID 30635236, Siddiqui et al. 2019. PMID 30365237, Jansen et al. 2019. PMID 31827286*

Expansion of stem cell-like anti-tumor T cells will drive the production of more tumor-specific effectors



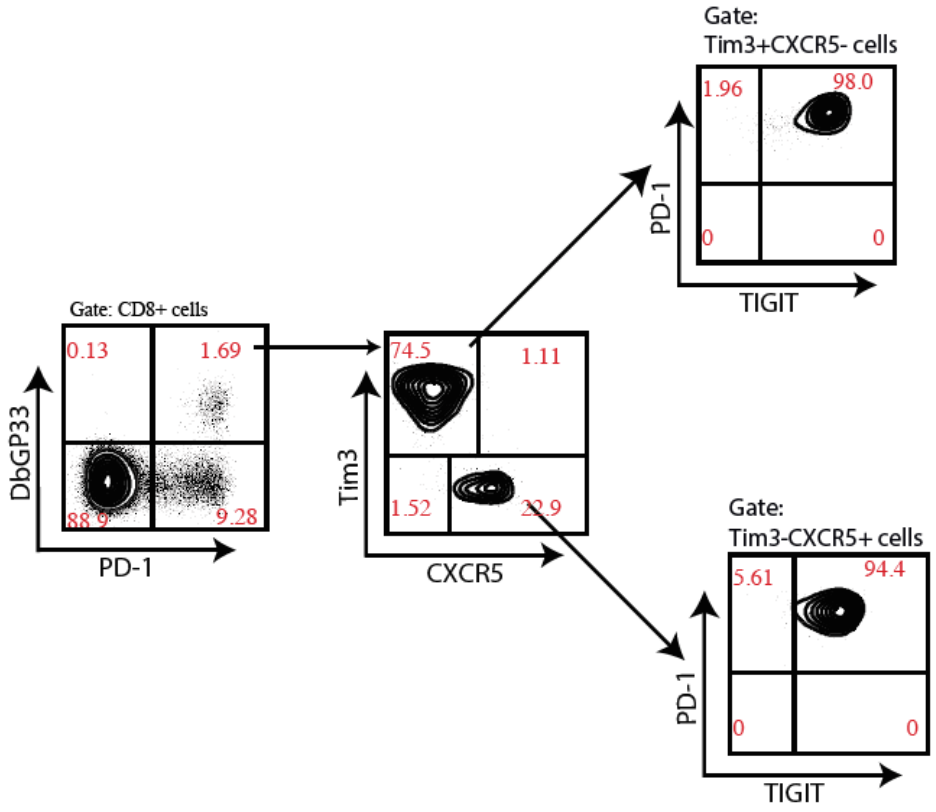
Key CIT questions

1) How do we generate more tumor reactive T_{SCM} cells?
2) How do we promote their self renewal?
3) How do we promote their differentiation and effector function?

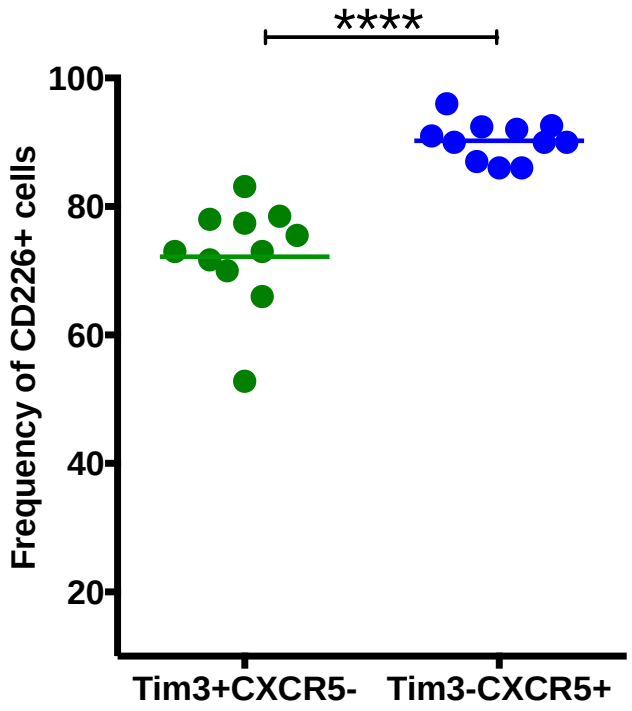
Gattinoni et al 2012 Nature Rev Cancer

T_{EM}: T effector memory cells; T_{EFF}: effector T cells; T_{CM}: central memory T cells; T_{SCM}: stem-cell like T cells

T stem like memory cells (T_{scm}) express PD-1 and TIGIT… not Tim- 3 or other negative regulators



T_{scm} are also CD226+

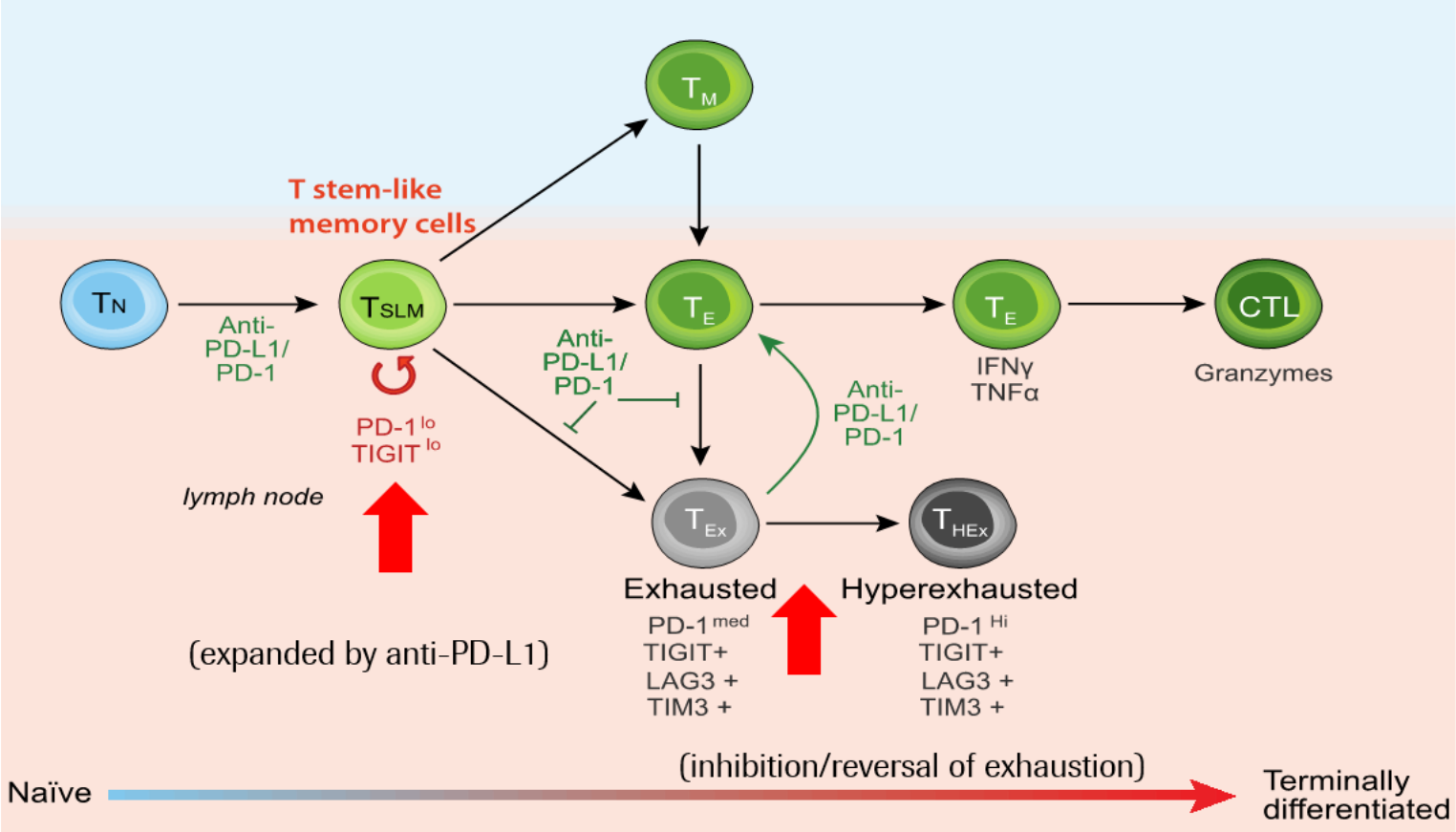


Raj Valanparambil, Eugene Chiang, Ira Mellman & Rafi Ahmed, Emory University & Genentech
T_{SCM}: stem-cell like T cells

Rationale for Tecentriq + TIGIT

PD1 and TIGIT are co-expressed on stem-like T-cells

Anti-PD-L1 expands a key population of PD-1-positive T stem-like cells, which also express TIGIT but no other negative regulator



- T-cell expansion
- Prevent/reverse T-cell exhaustion

Other potential MOA:

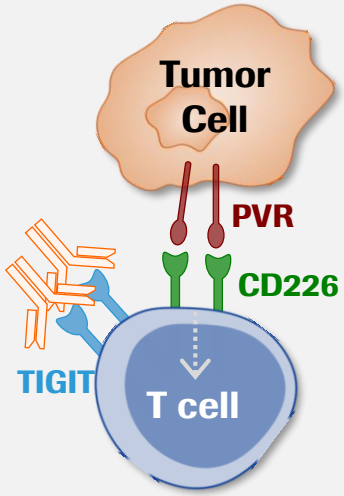
- Myeloid cell reprogramming
- T regulatory cell reprogramming
- NK effector function

Modified from Chen and Mellman Nature 2017

Additional mechanistic roles for TIGIT

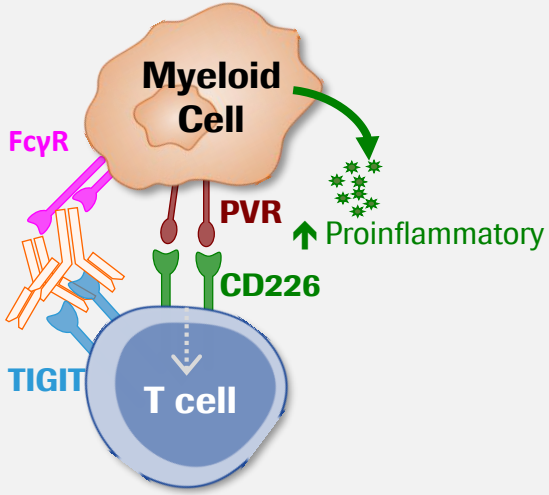
Role of specific cells, CD226, and antibody format

CD8 T cell effector function driven by CD226 signaling



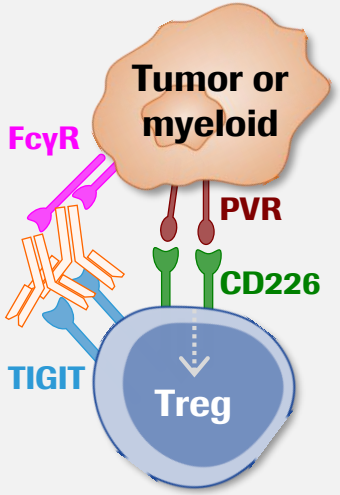
↑ Enhanced effector

Modulation of myeloid cells creates proinflammatory tumor microenvironment[1]



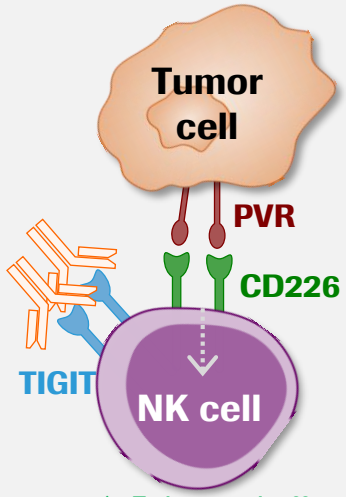
↑ Activation

CD226 signaling may dampen Treg suppression, promote effector phenotype



Reprogramming, Effector/inflammatory

TIGIT is also expressed by NK cells, unlike PD-1



↑ Enhanced effector

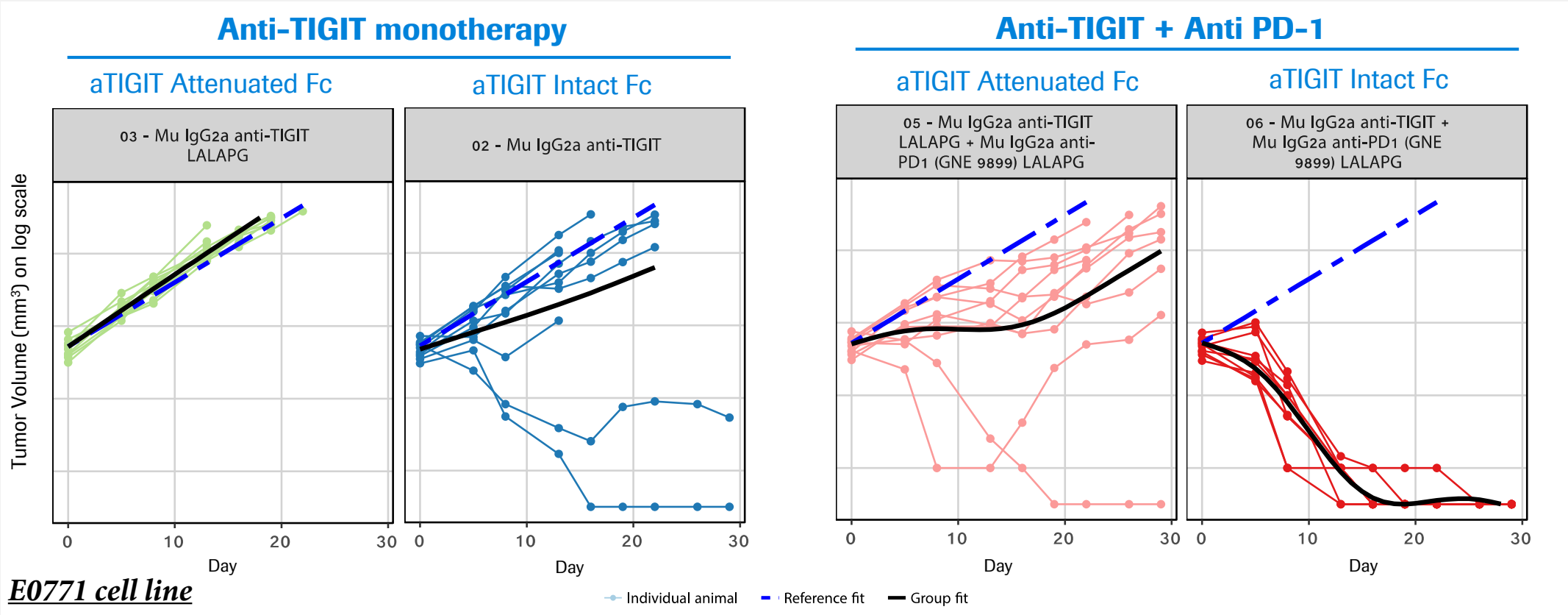
Anti-TIGIT Fc:FcγR interaction may sequester TIGIT away from the synapse, and play a role in reprogramming of myeloid cells

1. Dahan Cancer Cell 2015

NK: natural killer cell; Fc: Fragment crystallizable region

Anti-TIGIT activity may be dependent on antibody design

Preclinical data supports the hypothesis that Anti-TIGIT activity may be dependent on Fc effector function

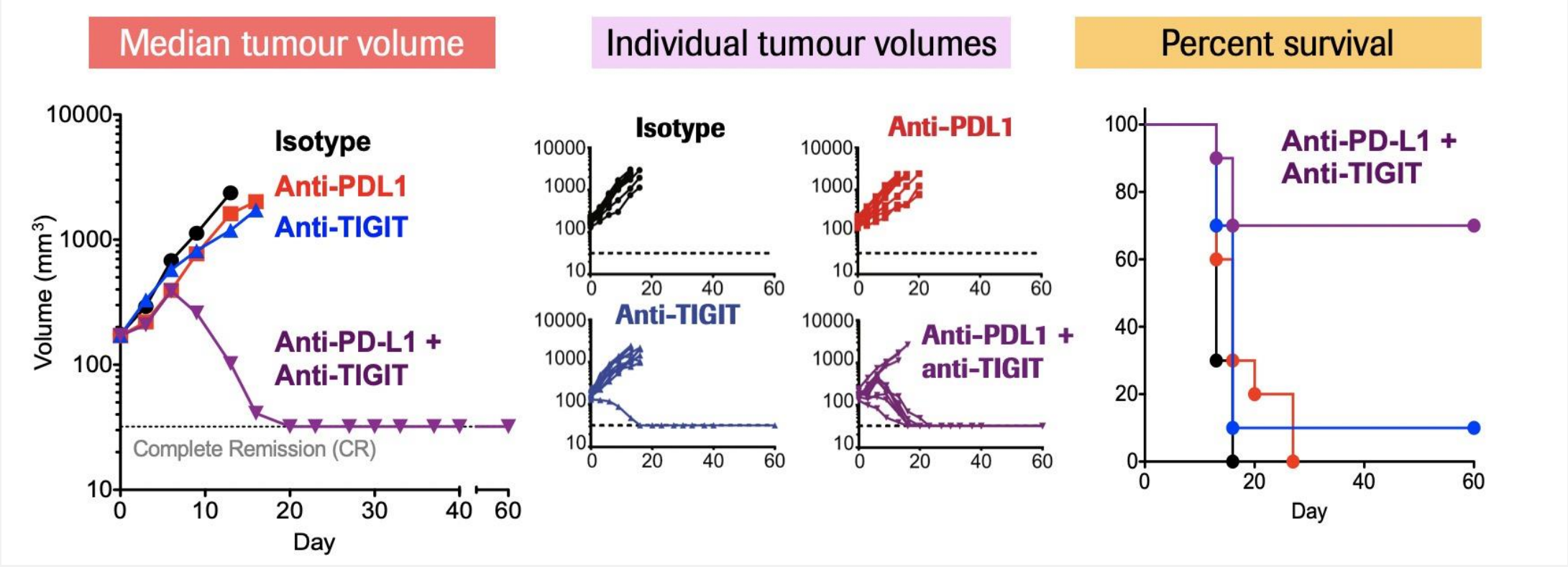


Fc: Fragment crystallizable region

TIGIT and PD-L1 blockade synergistically improves tumor control

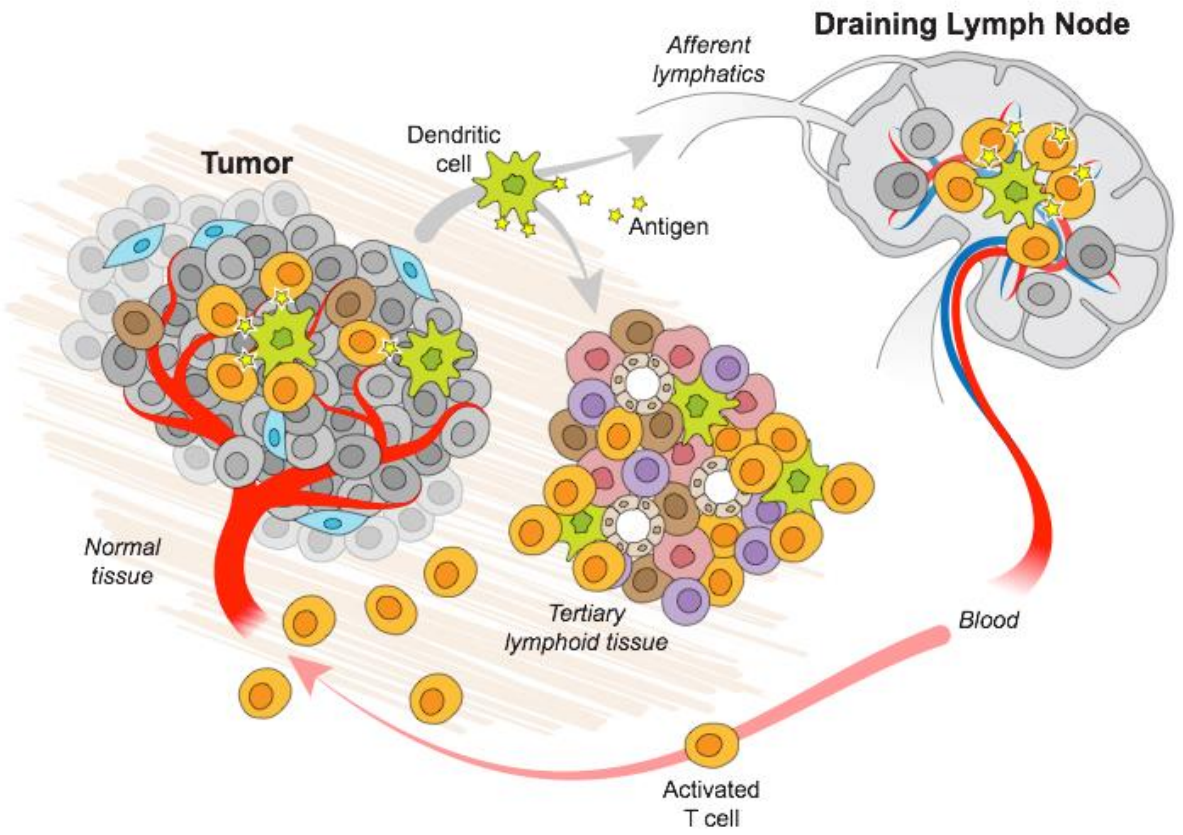
Prolongs survival in CT26 models

Blockade of TIGIT and PD-L1 showed a 75% decrease in mean tumor volume after 16 days of treatment



1. Johnston RJ et al. Cancer Cell 2014

An evolving paradigm: PD1/TIGIT blockade induce T cell expansion in dLN to achieve therapeutic anti-tumor immunity



Tom Wu, Romain Banchereau, Ira Mellman, Jane Grogan (Wu et al., 2020, Nature)
LN: lymph node

ASCO 2020 Key readouts across tumor types

Alan Sandler, M.D. | Global Head of Product Development Oncology – Solid Tumors

Lung cancer

- **CITYSCAPE: Tiragolumab + Tecentriq in 1L NSCLC**
- **ALEX: Alecensa in 1L Alk-mut. NSCLC**

Tumor agnostic indications

- **Rozlytrek updated analyses in pediatrics and adults with solid tumors**

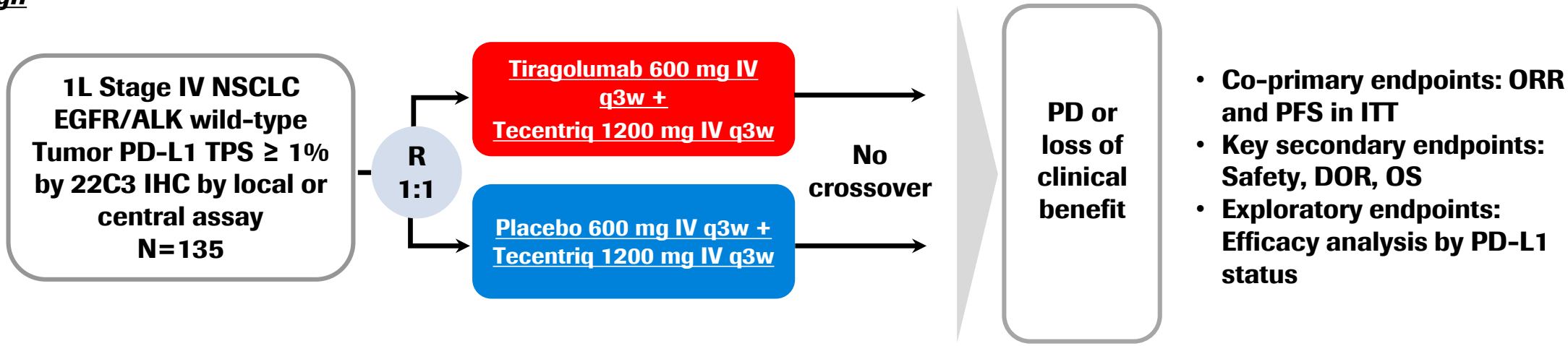
Liver cancer

- **IMbrave150: Tecentriq + Avastin in 1L HCC**

CITYSCAPE: Primary analysis of a randomized, double-blind, phase II study of the anti-TIGIT antibody tiragolumab plus Tecentriq versus placebo plus Tecentriq as 1L treatment in patients with PD-L1-selected NSCLC

CITYSCAPE rPh II: Tiragolumab plus Tecentriq in 1L NSCLC

Study design



- **Co-primary endpoints: ORR and PFS in ITT**
- **Key secondary endpoints: Safety, DOR, OS**
- **Exploratory endpoints: Efficacy analysis by PD-L1 status**

Stratification factors by baseline: ITT

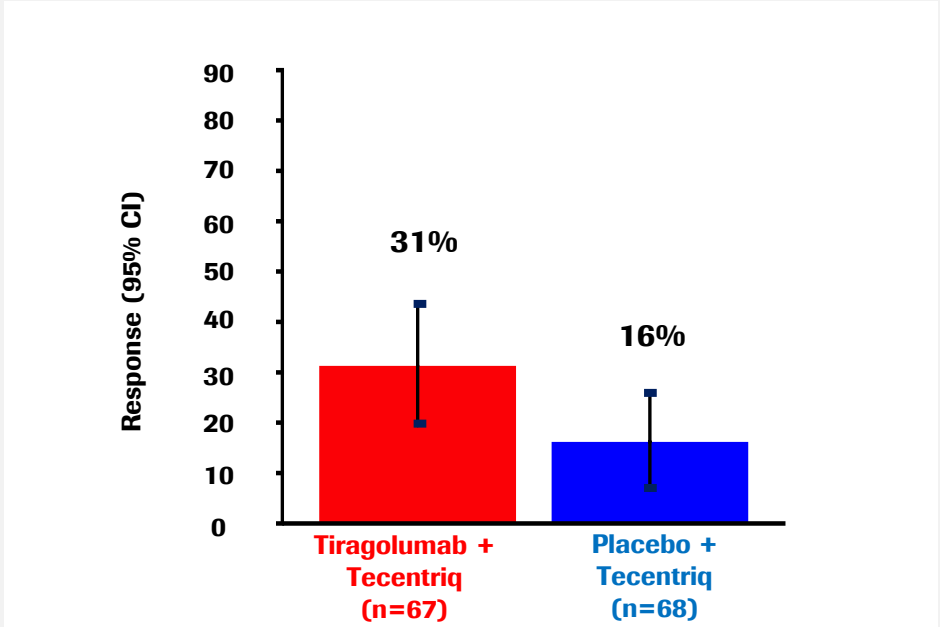
	Tiragolumab + Tecentriq (n=67)	Placebo + Tecentriq (n=68)
Never used tobacco*	7 (10%)	7 (10%)
Non-squamous histology*	40 (60%)	40 (59%)
PD-L1 TPS ≥ 50%*	29 (43%)	29 (43%)
PD-L1 TPS 1-49%*	38 (57%)	39 (57%)

Primary data cut-off: 30 June, 2019; ITT=intention-to-treat; DOR = duration of response; IHC = immunohistochemistry; ORR = confirmed overall response rate; OS = overall survival; PD = progressive disease; PFS = progression free survival; q3w = every 3 weeks; R = randomized; TPS = tumor proportion score; *stratification factors

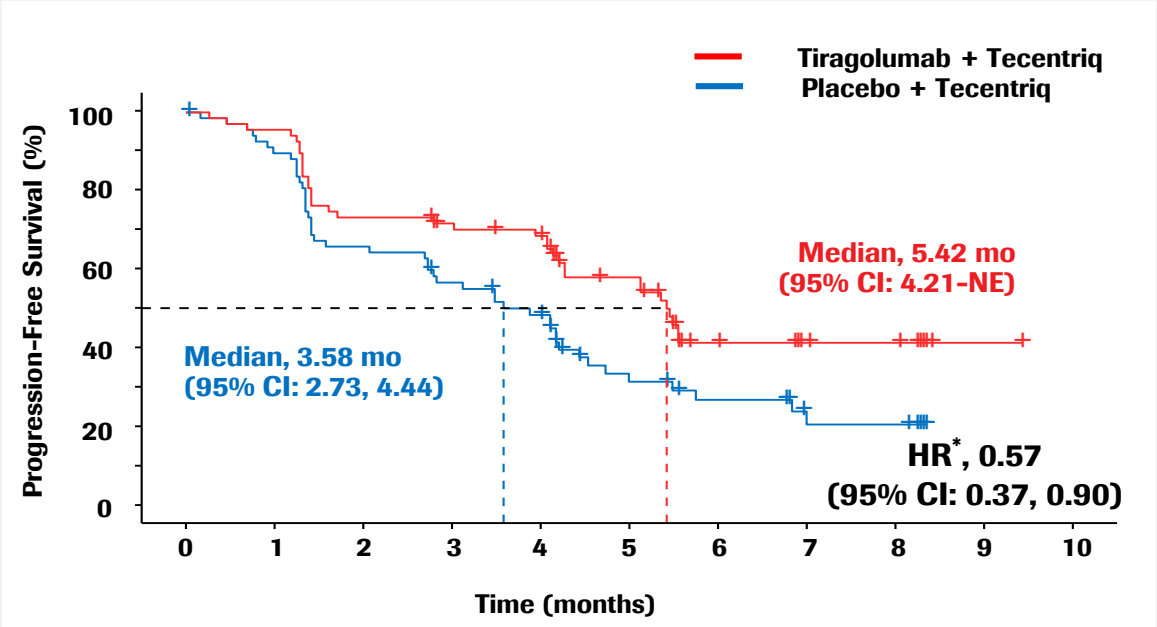
CITYSCAPE rPh II: Tiragolumab plus Tecentriq in 1L NSCLC

Primary analysis with 5.9 months median follow-up

ITT: Overall response rate



ITT: Primary Investigator-Assessed PFS after ~80 PFS events

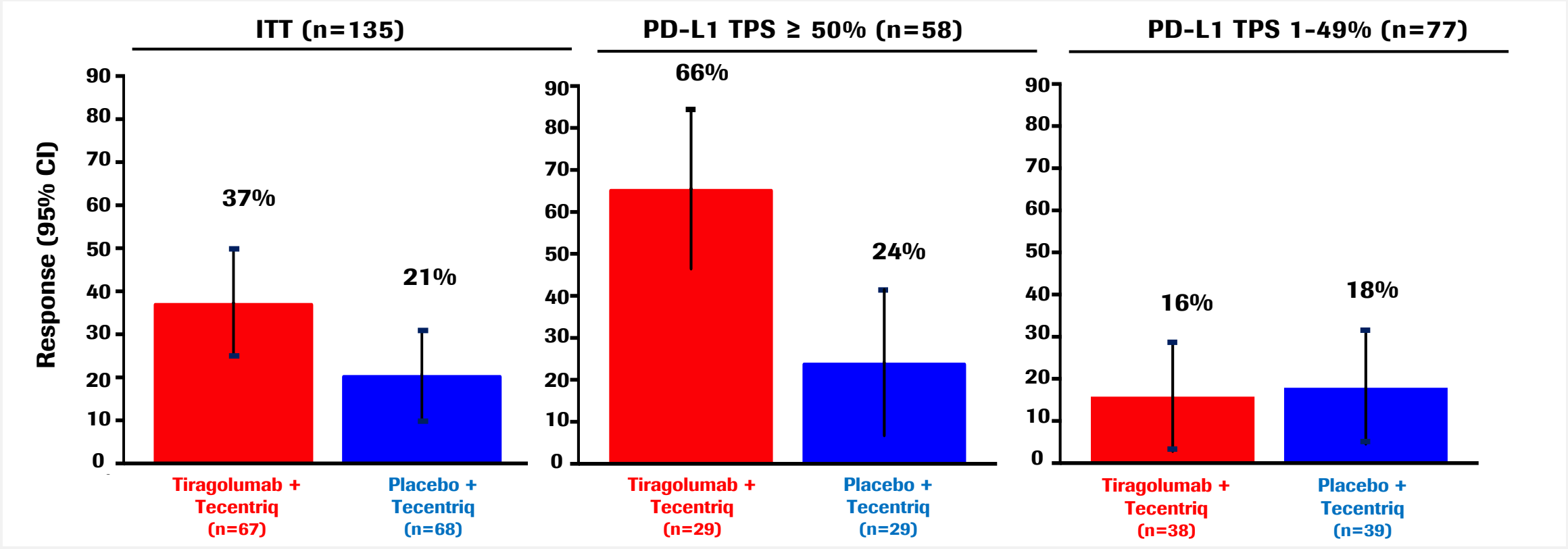


Tiragolumab plus Tecentriq met both co-primary endpoints in the ITT population, showing an improvement in ORR and PFS

Primary data cut-off: 30 June, 2019; ITT=intention-to-treat; ORR = confirmed overall response rate; PFS = progression free survival; NE = non-evaluable; *stratified HR

CITYSCAPE rPh II: Tiragolumab plus Tecentriq in 1L NSCLC

Updated ORR analysis with 10.9 months median follow-up



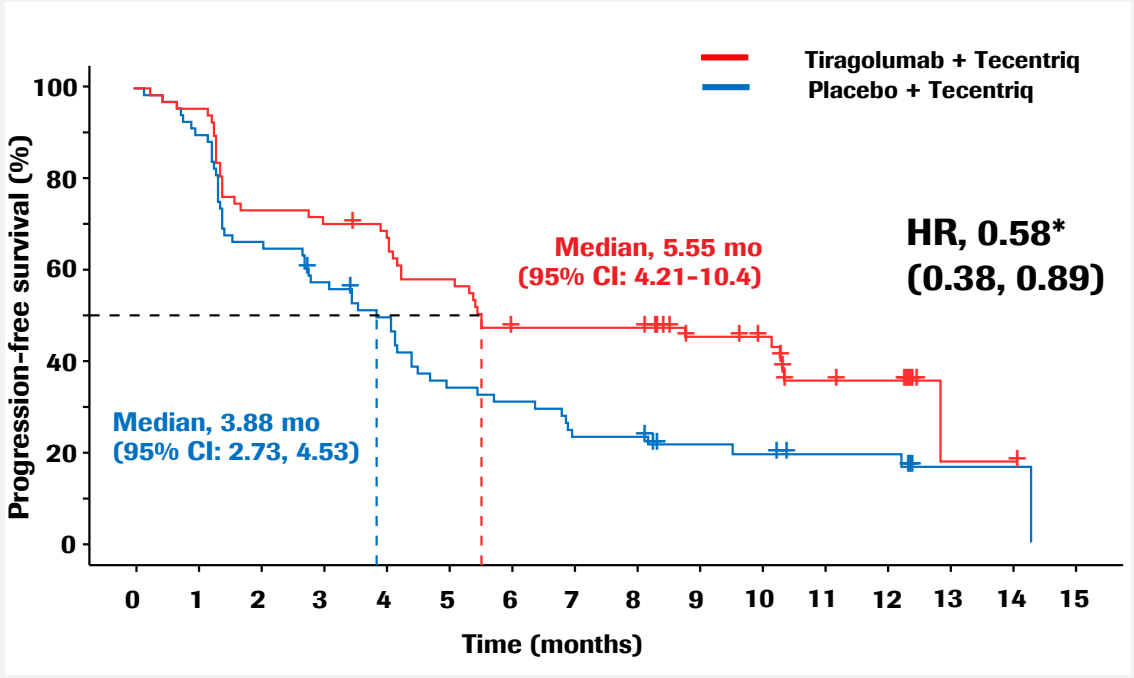
Consistent and clinically meaningful overall response rate (ORR), mainly driven by the PD-L1 high population (TPS>50%)

Follow-up data cut-off: 02 December, 2019; ITT=intention-to-treat; TPS=tumor proportion score

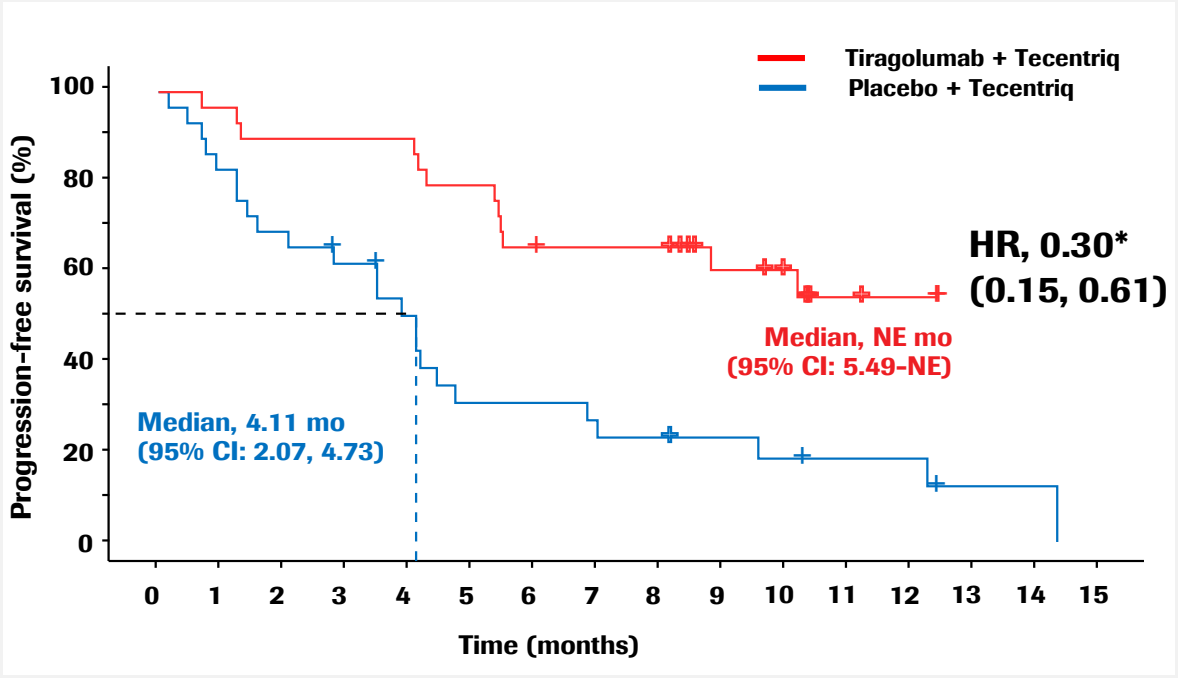
CITYSCAPE rPh II: Tiragolumab plus Tecentriq in 1L NSCLC

Updated PFS analysis with 10.9 months median follow-up

Updated investigator-assessed PFS: ITT



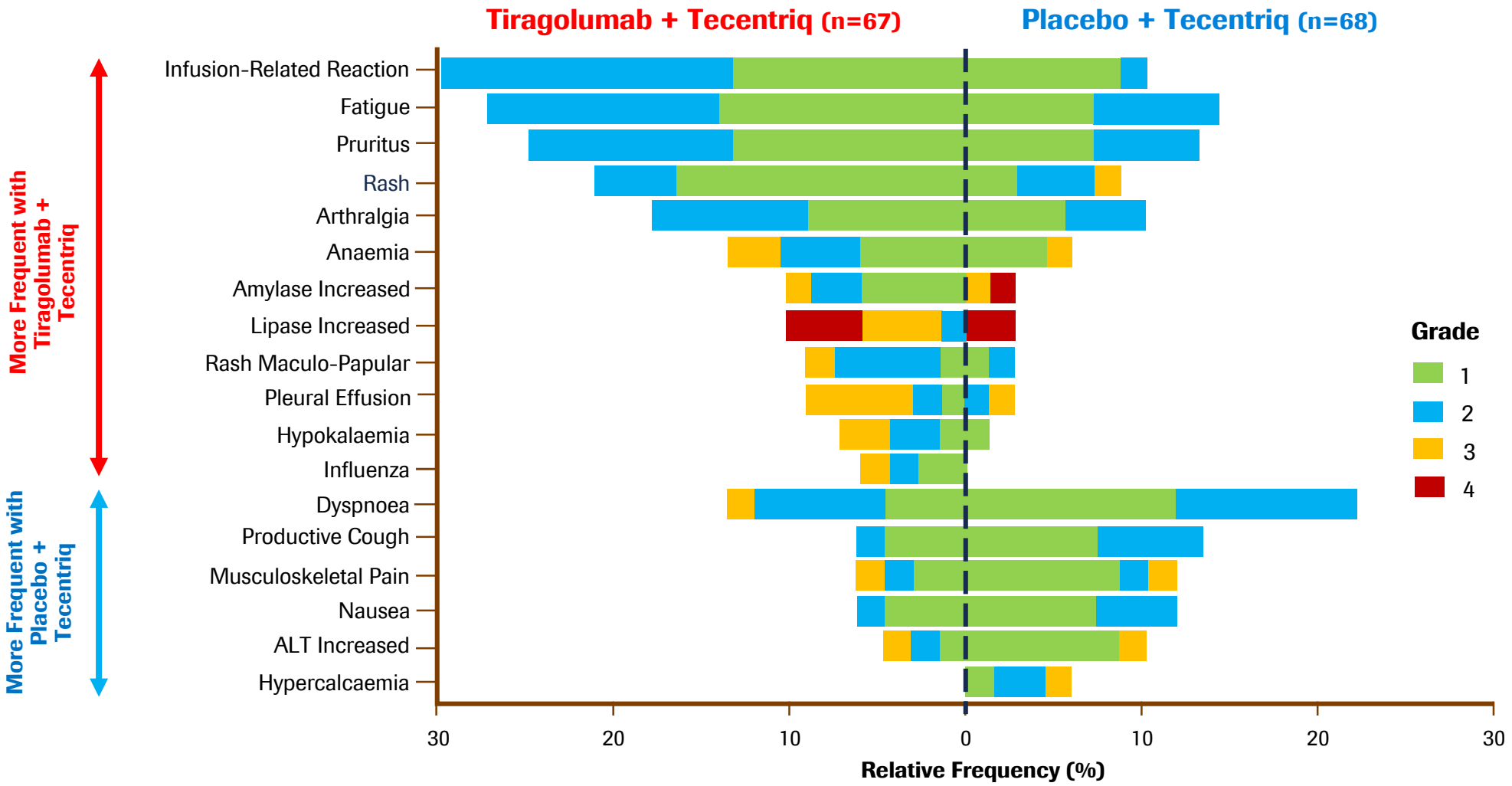
Updated Investigator-Assessed PFS: PD-L1 TPS ≥ 50%



Consistent and clinically meaningful PFS at longer follow-up with greater magnitude of improvement in the PD-L1 high population

Follow-up data cut-off: 02 December, 2019; NE = non-evaluable; PFS = progression free survival; ITT=intention-to-treat; TPS = tumor proportion score *unstratified HR

CITYSCAPE: All-cause adverse events (updated analysis)



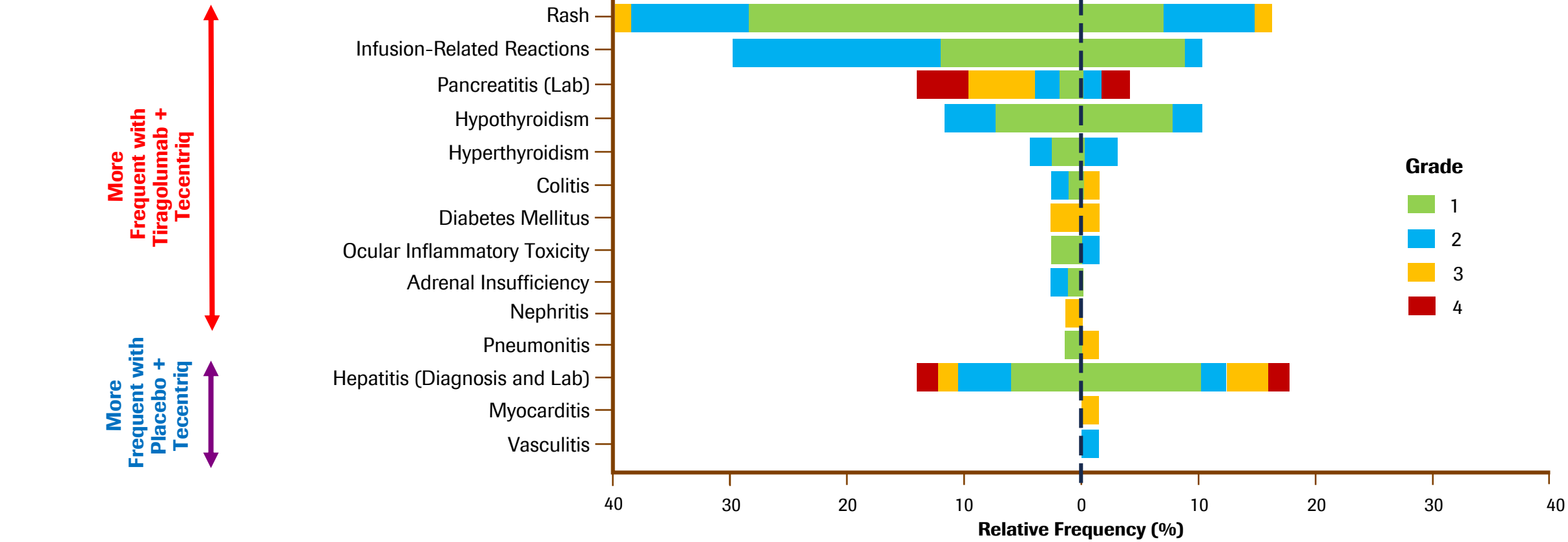
Combining tiragolumab and Tecentriq was well-tolerated with similar rates of all Grade 3+ AEs compared with Tecentriq alone

ALT, alanine aminotransferase

Updated data cutoff: 2 Dec 2019

CITYSCAPE: Immune-mediated adverse events (updated analysis)

	Tiragolumab + Tecentriq (n=67)	Placebo + Tecentriq (n=68)
Immune-Mediated Adverse Event*, n (%)	46 (69%)	32 (47%)
Grade 3-4	12 (18%)	9 (13%)



More frequent immune-related AEs with the combination of tiragolumab and Tecentriq, but primarily Grade 1-2 IRR and rash

*imAE's captured using Atezo AESI basket strategy to identify possibly immune related PT's

Updated data cutoff: 2 Dec 2019

CITYSCAPE: Conclusions

- Tiragolumab + Tecentriq showed clinically meaningful improvement in ORR and PFS in the ITT population compared to placebo + Tecentriq
- With longer follow-up, the treatment benefit of tiragolumab + Tecentriq remained consistent, with a greater magnitude of improvement seen in the PD-L1 TPS ≥ 50% subgroup
- Tiragolumab + Tecentriq was well-tolerated, with a safety profile similar to placebo + Tecentriq
    - Immune-mediated adverse events (imAEs) were more frequent with tiragolumab + Tecentriq but were primarily Grade 1-2 imAEs (mostly IRR and rash) and were manageable
- The observed activity and safety of tiragolumab + Tecentriq is to be confirmed in an ongoing Phase III study (SKYSCRAPER-01) in first-line PD-L1 TPS ≥ 50% NSCLC (NCT04294810)

Tiragolumab: Broad clinical development program

Further studies to be started over the course of next 12 months

Phase 1 GO30103	Solid tumors	Ongoing
Phase 1 GO41036	R/R Multiple myeloma or NHL	Ongoing
Phase 2 CITYSCAPE	Non-small cell lung cancer PD-L1 TPS ≥ 1%	Ongoing
Phase 3 SKYSCRAPER-01	Non-small cell lung cancer PD-L1 TPS>50%	FPI Q1 '20
Phase 3 SKYSCRAPER-02	Extensive stage small-cell lung cancer	FPI Q1 '20
Phase 2 SKYSCRAPER-04	Cervical cancer PD-L1-selected	FPI exp. Q2 '20
Phase 1b/2 YO39609	MORPHEUS GI cancer	Ongoing
Phase 1b/2 WO39608	MORPHEUS pancreatic cancer	Ongoing
Phase 1b/2 WO39613	MORPHEUS urothelial carcinoma	Ongoing

Data from NSCLC cohort at AACR 2020

Data at ASCO 2020

Signal-seeking in various tumor types ongoing; four additional phase 3 studies including chemo-free immune doublets to be initiated in 2020

Lung cancer

- **CITYSCAPE: Tiragolumab + Tecentriq in 1L NSCLC**
- **ALEX: Alecensa in 1L Alk-mut. NSCLC**

Tumor agnostic indications

- **Rozlytrek updated analyses in pediatrics and adults with solid tumors**

Liver cancer

- **IMbrave150: Tecentriq + Avastin in 1L HCC**

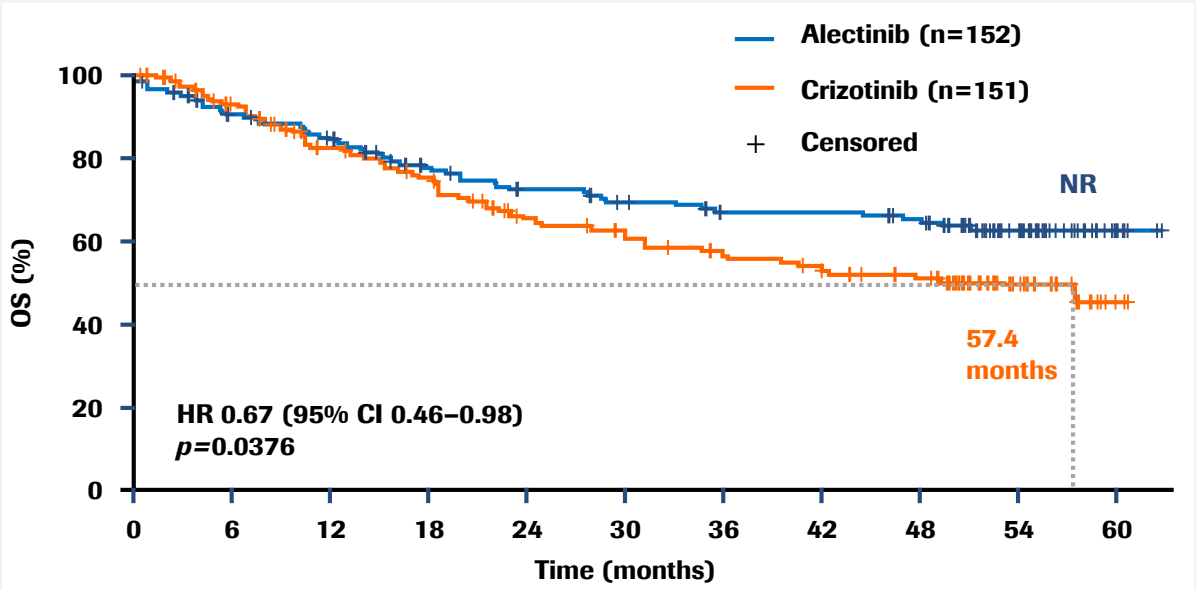
Alecensa in 1L *ALK+* NSCLC (ALEX): Greater than 60% of patients alive after 5 years

Stage IIIB/IV *ALK*+ NSCLC
- Treatment naive
- ECOG PS 0–2
- Central *ALK* testing by IHC

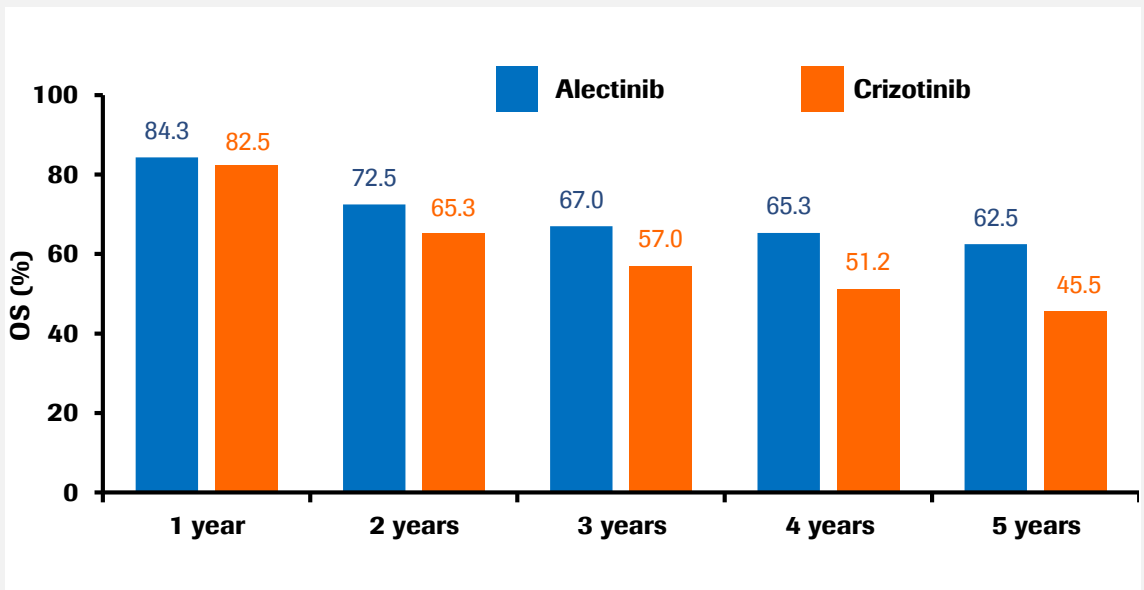
R 1:1

- **Alectinib 600 mg twice daily**
- **Crizotinib 250 mg twice daily**

5-year OS rate (ITT) of 62.5% independent of CNS metastases at BL



ALEX tx comparison: Increasing Δ of OS-event free rate (ITT) over 5 yrs



The updated analysis confirms the superior OS efficacy and tolerability of Alecensa in comparison to crizotinib

*Data cut-off 29 Nov 2019; ECOG = Eastern Cooperative Oncology Group; PS = performance status; IHC = immunohistochemistry; ITT=intention-to-treat; OS = overall survival; NR = not reached

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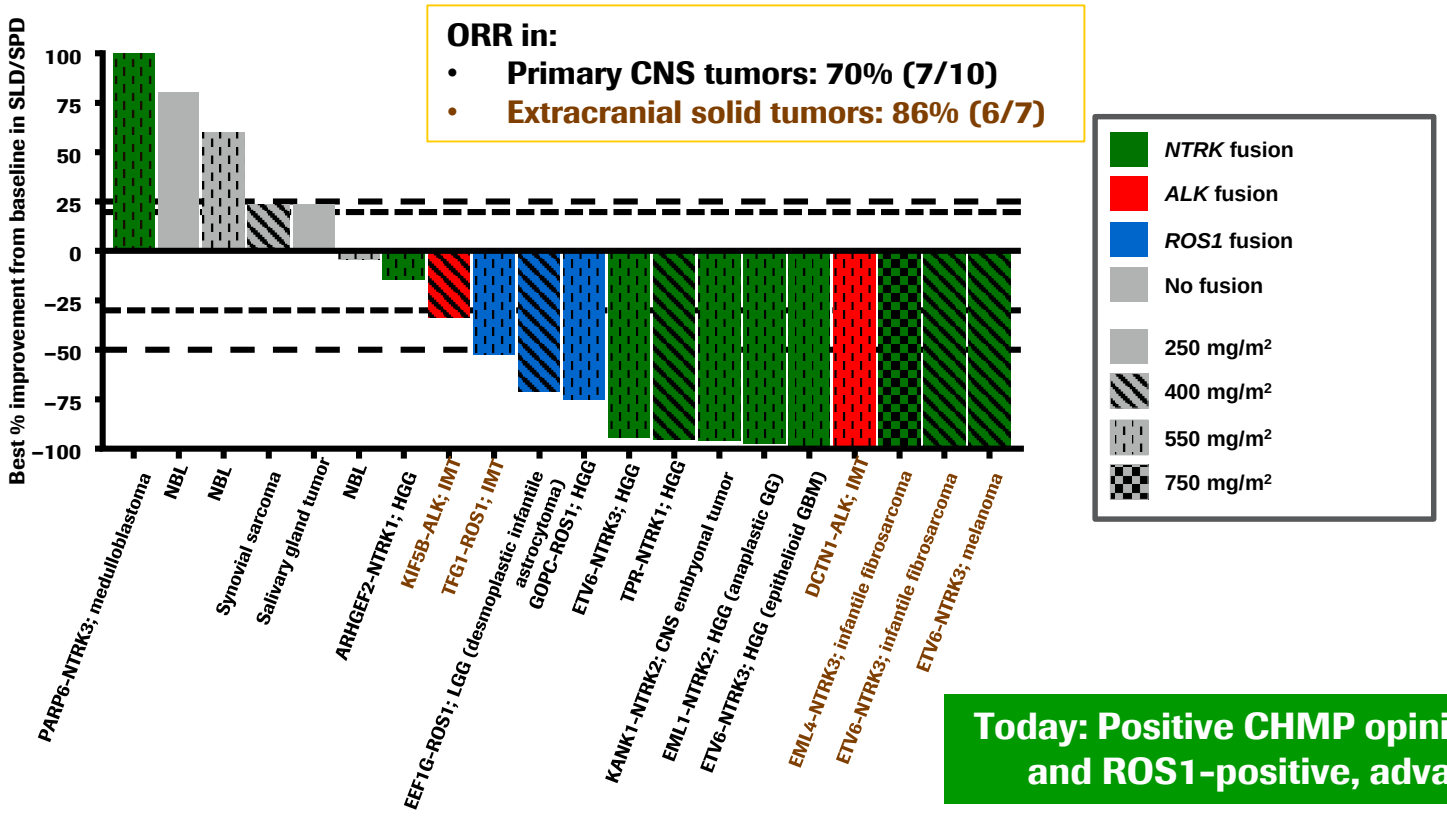
Rozlytrek activity in children and adolescents in tumors with and without NTRK1/2/3, ROS1 or ALK fusions: STARTRK-NG update

Response rate in pediatric solid tumors
- ORR in fusion-positive tumors: 76% (13/17)



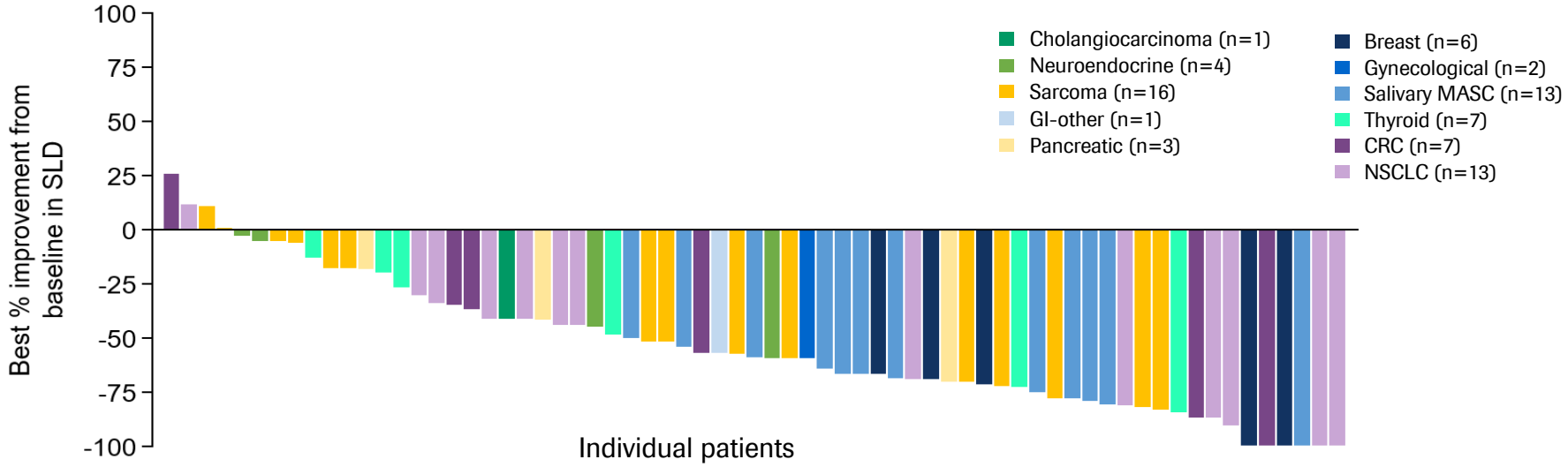
- Efficacy data, with longer follow-up, confirm the rapid and durable objective responses seen in both high-grade CNS tumors and extracranial solid tumors
- Median confirmed DoR not reached: (95% CI 14.3mo, NE)
- Safety profile was consistent with prior reports

Today: Positive CHMP opinion for Rozlytrek in NTRK fusion-positive solid tumors and ROS1-positive, advanced NSCLC in patients 12 years of age and older

Data cut-off: 1 July 2019. Investigator assessed. HGG, high-grade glioma; IMT, inflammatory myofibroblastic tumor; LGG, low-grade glioma; NBL, neuroblastoma; SLD, sum of longest diameter; SPD, sum of product diameters; 2 fusion-positive patients are not depicted as they had non-measurable disease

Rozlytrek in adult patients with *NTRK* fusion-positive solid tumors: Updated integrated analysis[1]

Best individual response per BICR, by tumor type; N=74



Clinically meaningful responses and survival outcomes in *NTRK*-fp solid tumors

ORR 63.5%
mPFS 11.2 mo
mOS 23.9 mo

Systemic efficacy irrespective of presence or absence of CNS metastases at baseline

ORR
with 62.5%
without 63.8%

Strong intracranial efficacy in patients with CNS metastases at baseline

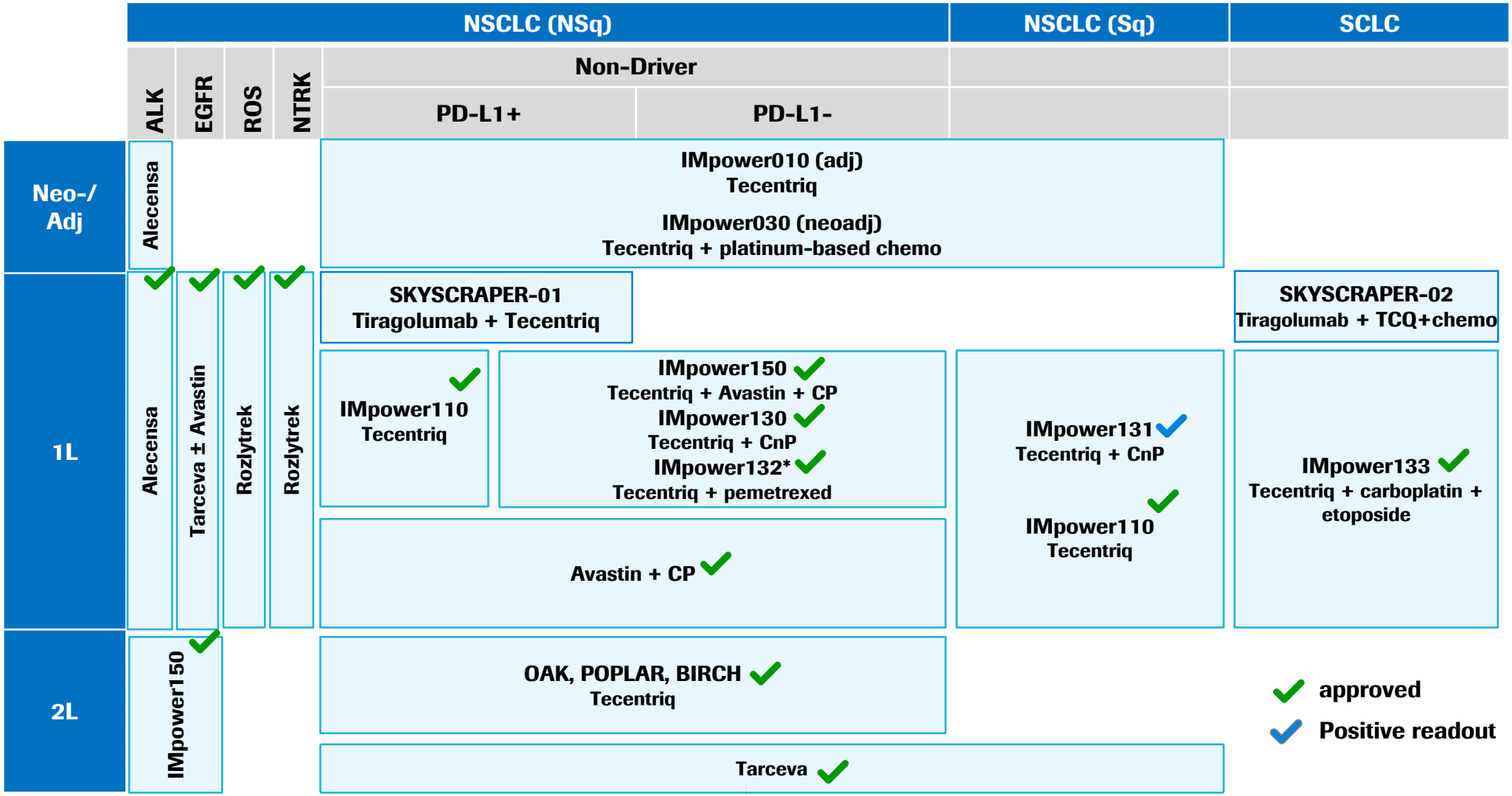
Intracranial ORR 50.0%

Durable disease control
DoR 12.9 months vs previous 10.4

1.Integrated analysis of phase 1/2 studies (ALKA-372-001, STARTRK-1, STARTRK-2; EudraCT 2012-000148-88; NCT02097810; NCT02568267)
Patients with missing SLD percent change are excluded from the plot. SLD, sum of longest diameters. GI, gastrointestinal. CRC, colorectal cancer. NSCLC, non-small-cell lung cancer. MASC, mammary analogue secretory carcinoma.

Broadest NSCLC portfolio with the potential for chemo-free combos

Newly added tiragolumab complements activity of Tecentriq



*IMpower132 approved in Japan

Lung cancer

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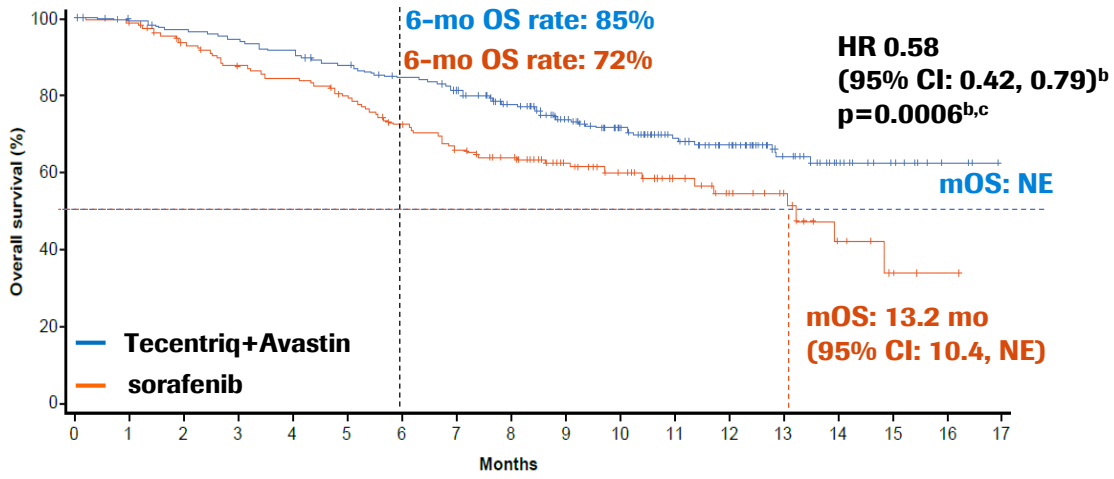
- **IMbrave150: Tecentriq + Avastin in 1L HCC**

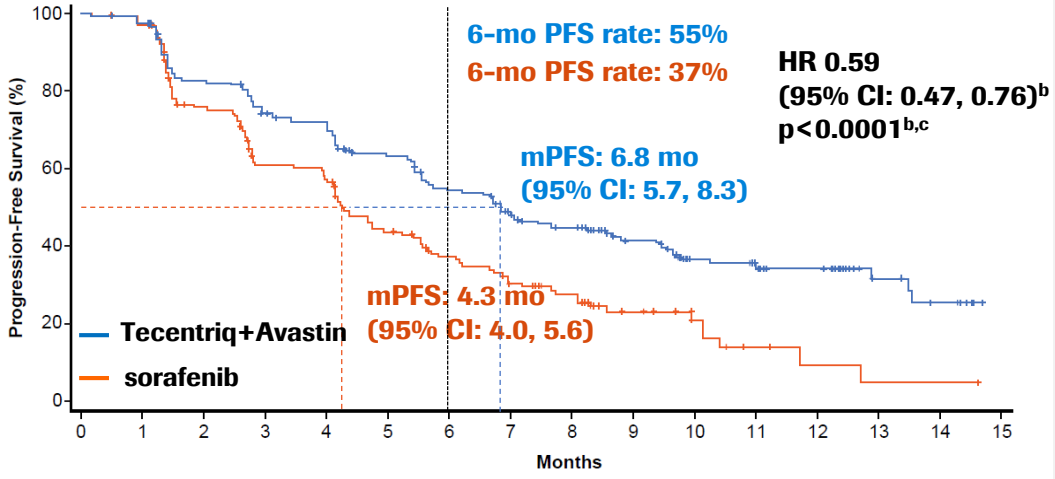
Tecentriq + Avastin in 1L HCC

A new standard of care in unresectable HCC

IMbrave150: Overall survival primary analysis



IMbrave150: Confirmed progression-free survival[a]



- Statistically significant and clinically meaningful improvement in both OS and PFS with Tecentriq + Avastin vs sorafenib in patients with unresectable HCC who had not received prior systemic therapy
- Tecentriq + Avastin may be a practice-changing treatment for patients with unresectable HCC who have not received prior systemic treatment

NE, not estimable; [a]assessed by IRF per RECIST 1.1.; [b] HR and *P* value were from Cox model and log-rank test and were stratified by geographic region (Asia vs rest of world, including Japan), AFP level (< 400 vs ≥ 400 ng/mL) at baseline and MVI and/or EHS (yes vs no) per IxRS. [c] The 2-sided *P* value boundary based on 161 events is 0.0033. Data cutoff, 29 Aug 2019; median survival follow-up, 8.6 mo.

Tecentriq + Avastin in 1L unresectable HCC: Complete responses regardless of poorer prognostic factors or HCC etiology

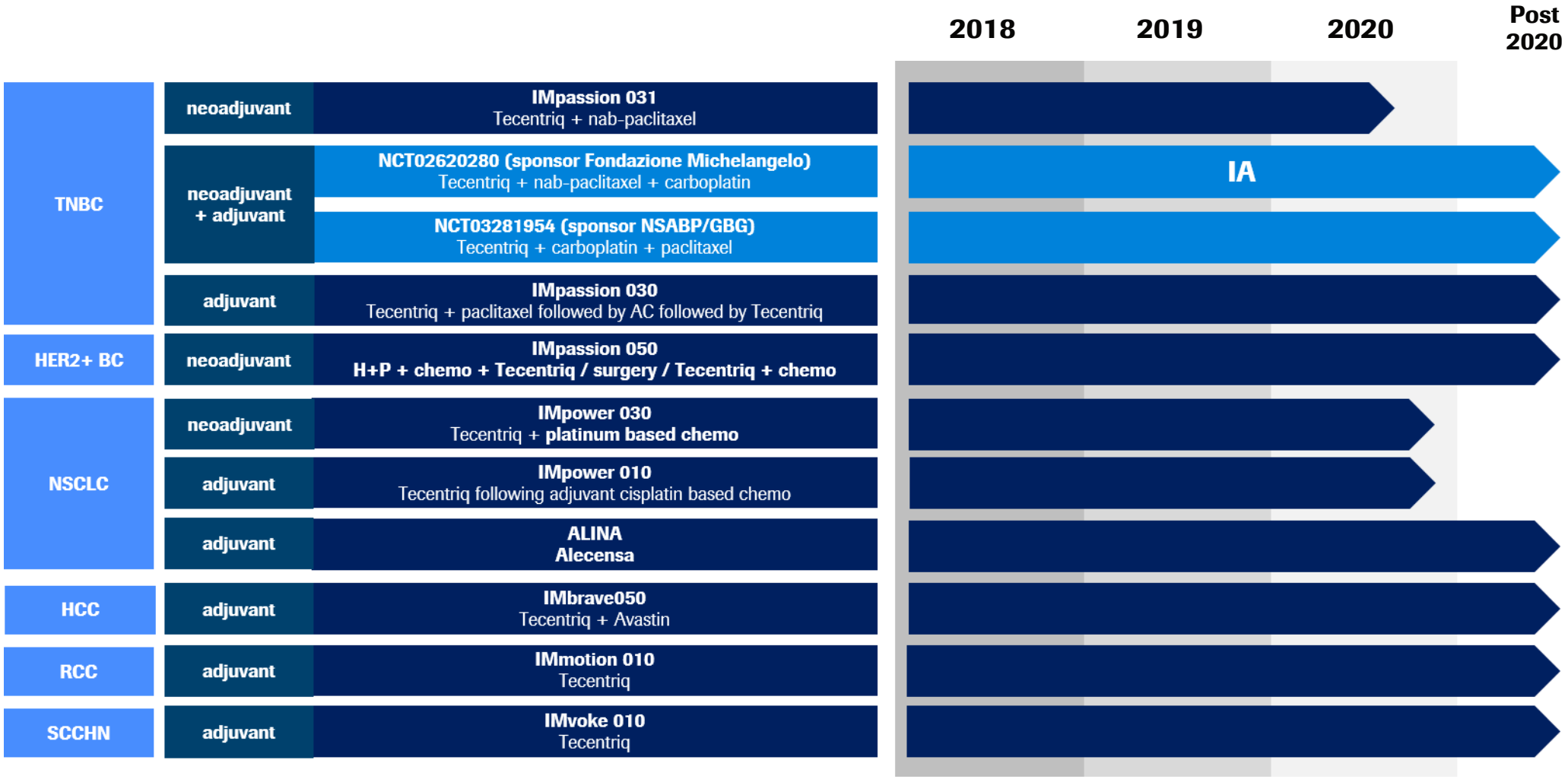
	IRF RECIST 1.1		IRF HCC mRECIST	
	Atezo + Bev (n = 326)	Sorafenib (n = 159)	Atezo + Bev (n = 325)[a]	Sorafenib (n = 158)
Confirmed ORR, n **(%)**	89 **(27)**	19 **(12)**	108 **(33)**	21 **(13)**
(95% CI)	(23, 33)	(7, 18)	(28, 39)	(8, 20)
CR	**18 (6)**	**0**	**33 (10)**	**3 (2)**
PR	71 (22)	19 (12)	75 (23)	18 (11)
Stratified *P* value[b]	**< 0.0001**		**< 0.0001**	
SD, n (%)	151 (46)	69 (43)	127 (39)	66 (42)
PD, n (%)	64 (20)	39 (25)	66 (20)	40 (25)
DCR, n (%)	240 (74)	88 (55)	235 (72)	87 (55)
Ongoing response, n (%)[c]	77 (87)	13 (68)	84 (78)	13 (62)
Median DOR, months (95% CI)	NE	6.3 (4.7, NE)	NE	6.3 (4.9, NE)
Event-free rate at 6 months, n (%)	**88**	**59**	**82**	**63**

- Six % of patients achieved a CR per RECIST1.1 with Tecentriq+Avastin vs 0% with sorafenib despite historically low CR rates
- Significantly higher ORR with Tecentriq+Avastin (although similar TTR as sorafenib): median TTR per RECIST1.1 of 2.8 months with 27% of patients responding, compared with TTR of 2.7 months for sorafenib with 12% of patients responding
- In the vast majority of patients, CR was still ongoing at 6 months and a median duration of CR has not yet been reached

[a] IRF HCC mRECIST–evaluable population was based on patients who presented with measurable disease at baseline per HCC mRECIST criteria.
[b] Stratification factors included geographic region (Asia vs rest of world, including Japan), AFP level (< 400 vs ≥ 400 ng/mL) at baseline and MVI and/or EHS (yes vs no) per IxRS.
[c] Denominator is patients with confirmed CR/PR. Data cutoff, 29 Aug 2019; median survival follow-up, 8.6 mo.

Overview CIT adjuvant program

Liver cancer added, lung and breast studies starting to read out in 2020



Doing now what patients need next