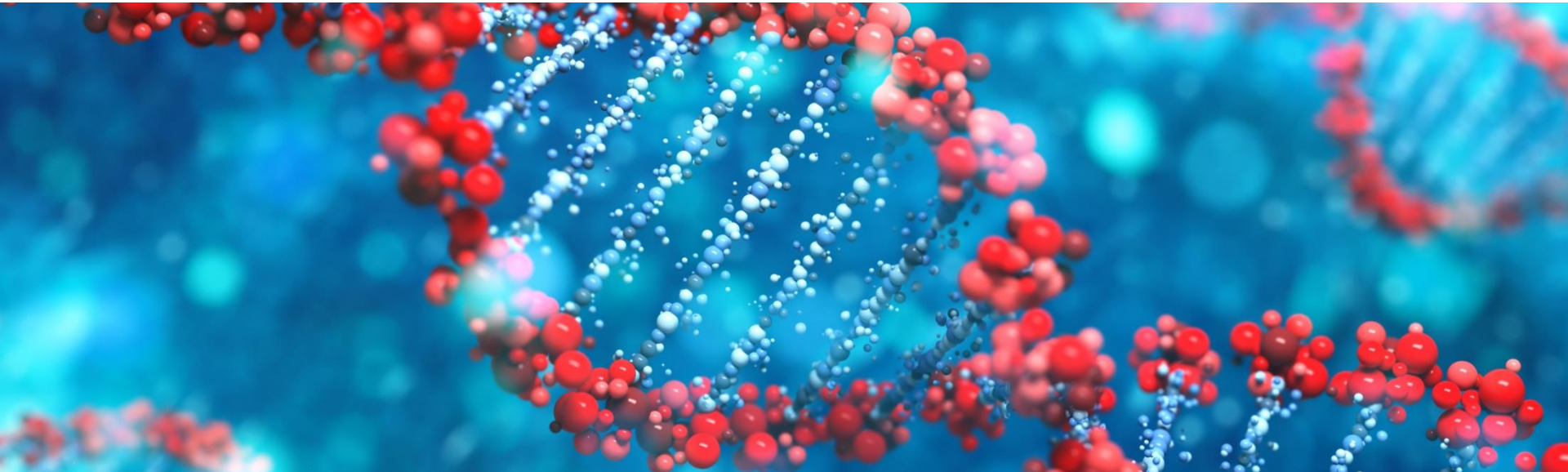

Roche

52nd ASCO Annual Meeting, Chicago

Roche Analyst Event

Sunday, 5 June 2016



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2 legislative and regulatory developments and economic conditions;
3 delay or inability in obtaining regulatory approvals or bringing products to market;
4 fluctuations in currency exchange rates and general financial market conditions;
5 uncertainties in the discovery, development or marketing of new products or new uses of existing products, including without limitation negative results of clinical trials or research projects, unexpected side-effects of pipeline or marketed products;
6 increased government pricing pressures;
7 interruptions in production;
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10 loss of key executives or other employees; and
11 adverse publicity and news coverage.

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Introduction

Karl Mahler
Head of Investor Relations

Agenda

Welcome
Karl Mahler, Head of Investor Relations

Oncology strategy and outlook
Daniel O'Day, Chief Executive Officer Roche Pharmaceuticals

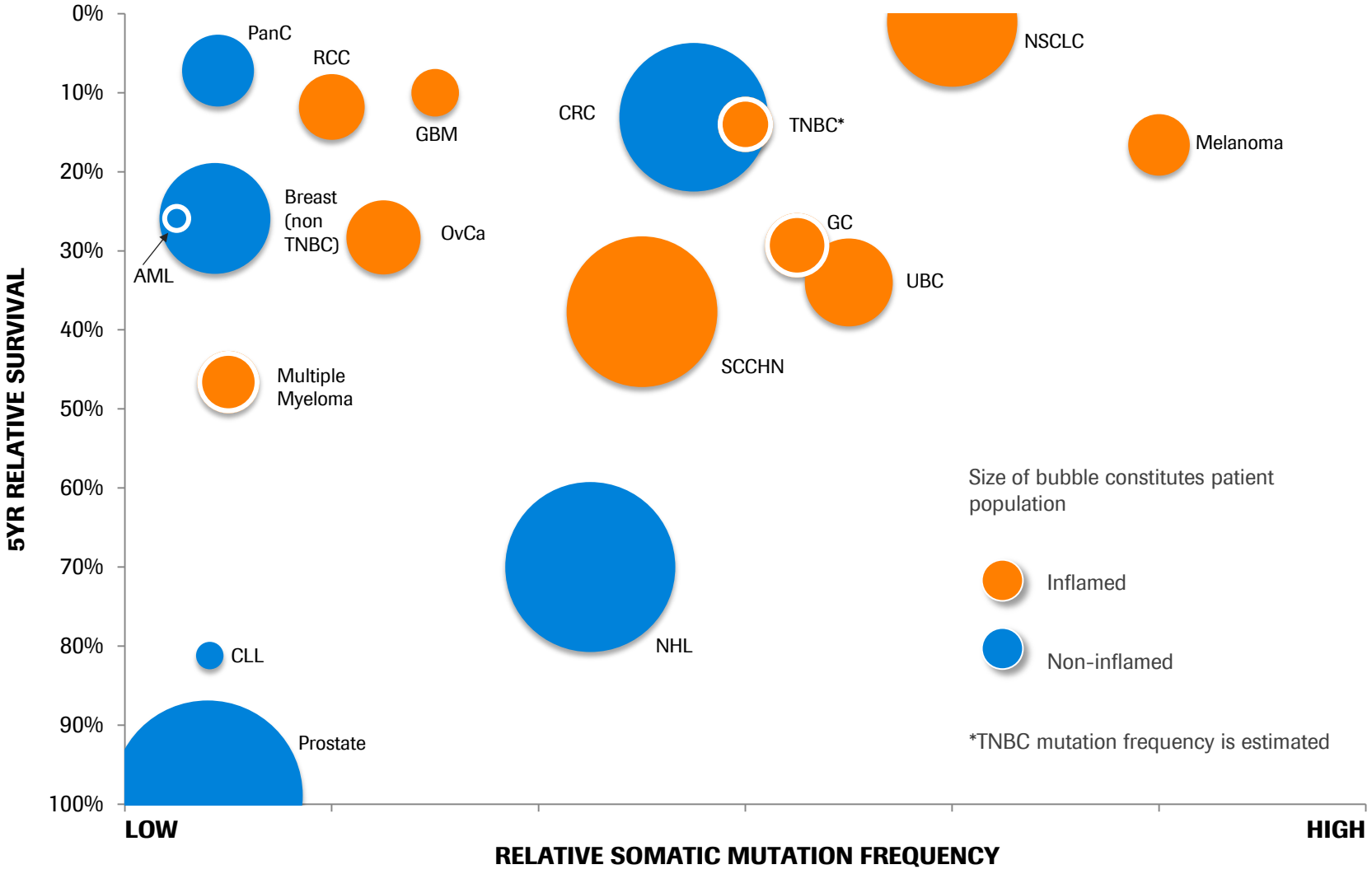
Roche highlights in cancer immunotherapy
Daniel S. Chen, M.D. , Ph.D., VP, Global Head of Cancer Immunotherapy, Global Product Development

Early pipeline update: Assets and strategies
Ira Mellman, gRED: Ph.D., VP, Cancer Immunology, Genentech
William Pao, pRED: M.D., Ph.D., Global Head Oncology Discovery and Translational Area, Roche

Targeted therapies and future combinations
Sandra Horning, M.D., Chief Medical Officer and Head Global Product Development

Q&A

Investigating tumor specific strategies



Oncology strategy and outlook

Daniel O'Day
CEO Roche Pharmaceuticals

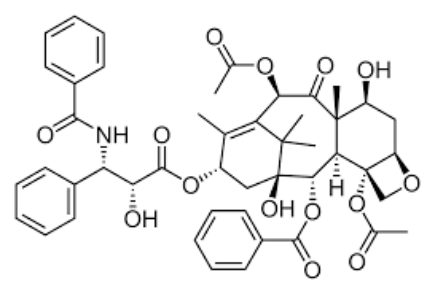
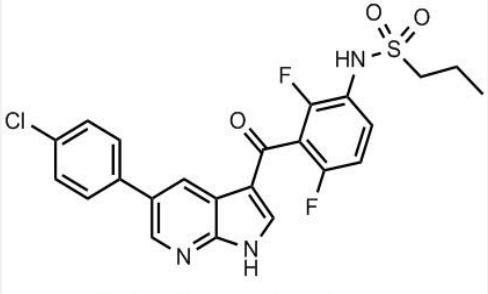
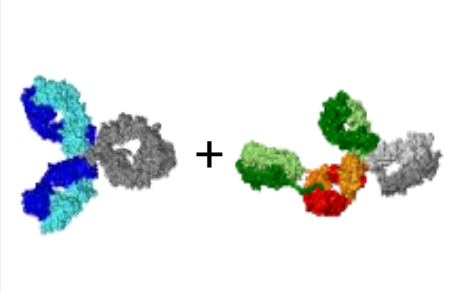
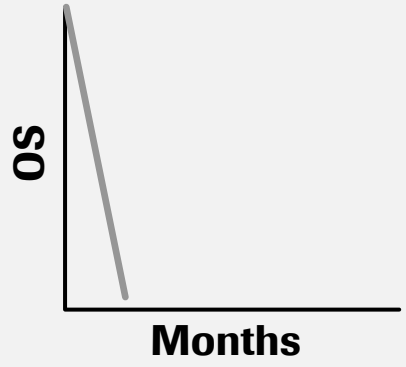
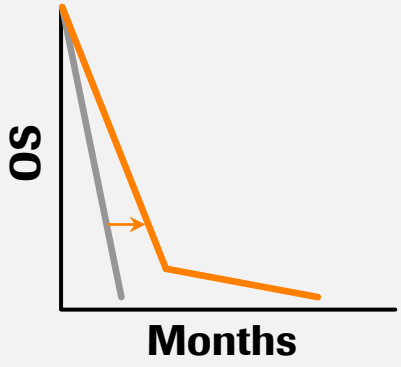
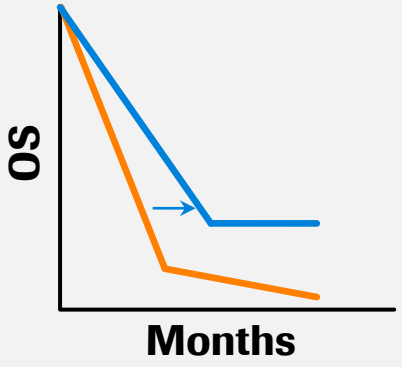
Managing increasing complexity in cancer care

Our strategy to maintain innovation leadership

Outlook

Tremendous progress made in cancer treatment

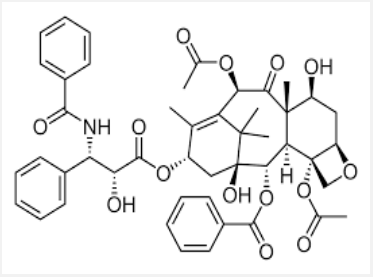
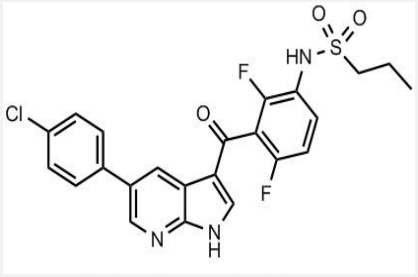
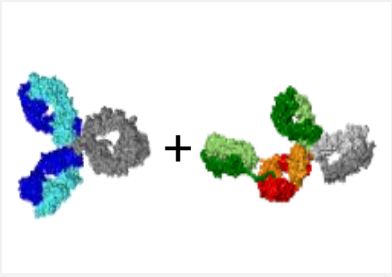
Increasing patients' chances for survival

Chemotherapy	Targeted medicines	Targeted medicines + immunotherapy
		
		

Improving SOC

With progress comes increasing complexity

Example: Implications on clinical trials

	Chemotherapy	Targeted medicines	Targeted medicines + immunotherapy
			
Clinical trial population/size	Unspecified / Large	Patient sub-groups / Medium	Individual patients / Medium - Small
Need for Dx	No diagnostics	Single disease marker	Comprehensive genomic sequencing & response monitoring
Development process	Phase I, II, III	Phase I, II, III	Phase-less basket / umbrella studies

Managing increasing complexity in cancer care

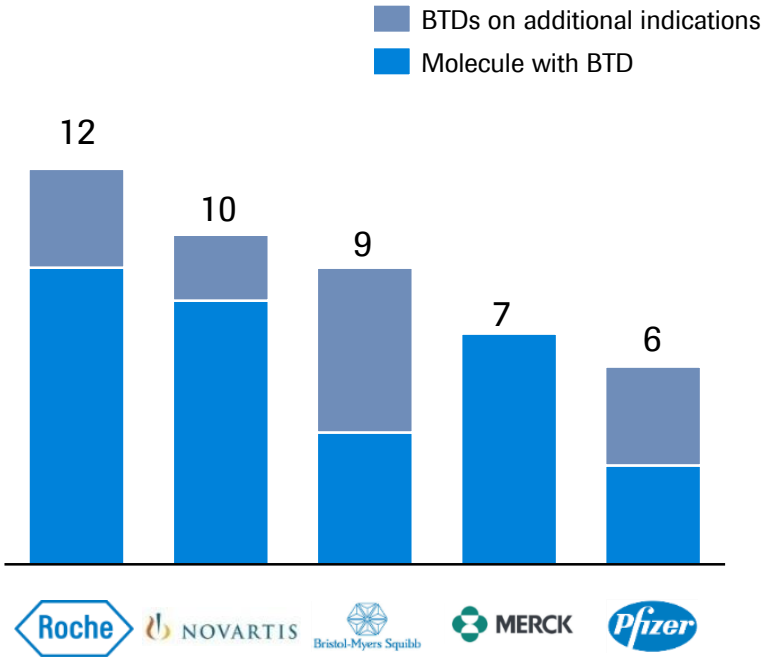
Our strategy to maintain innovation leadership

Outlook

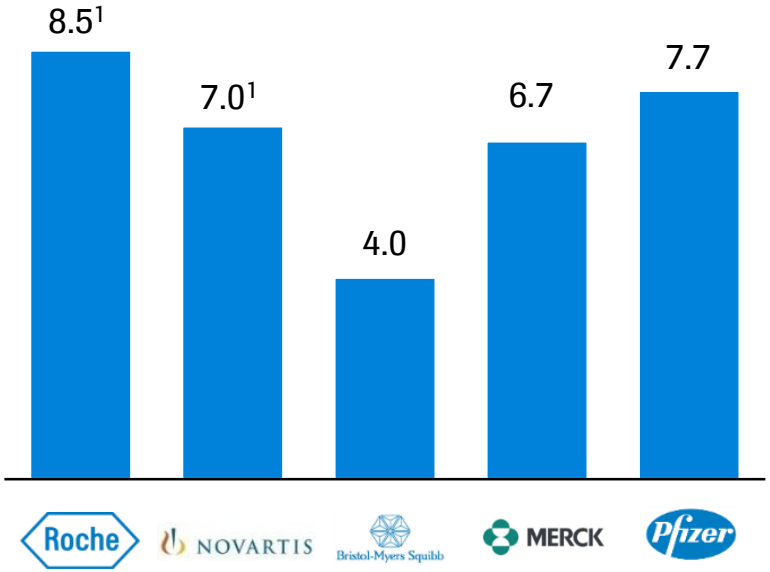
Roche: Strong history of innovation

Leading evolution of cancer treatment

Leading in breakthrough designations



Largest investment in innovation



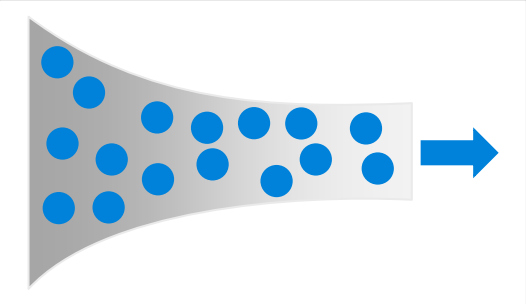
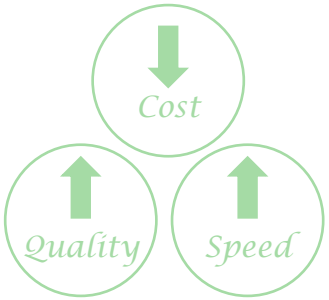
Oncology: 9 NMEs launched in 5 years, overall >30% market share

1. Pharmaceuticals, excluding generics

Source: Evaluate Pharma, companies' annual reports & investor presentations; value in USD bn

Our innovation strategy remains unchanged

Increasing focus on data analytics

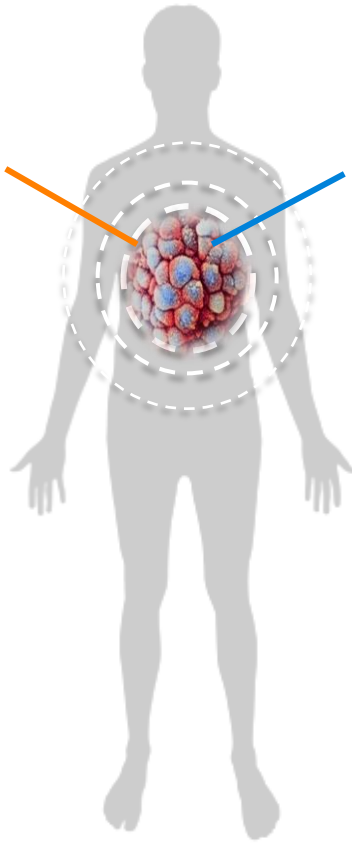
Pipeline delivery	Data & analytics	Increased productivity
		
• *Diverse, differentiated treatment approaches* • *Strategic life-cycle mgmt.*	• *Smart, more efficient R&D* • *Access & personalized patient care*	• *Innovative trial design* • *Prioritization & improved decision-making*

Outstanding talent that drives innovation & execution

Different mechanisms to target cancer

Roche investing in diverse approaches & combinations

Targeted medicines	
Oncogenes	aHER2, MEKi
Anti-angiogenesis	aAng2/VEGF
Tumor suppressors	MDM2 antagonist
Epigenetic	BETi
Apoptosis	BCL2i
Tumor specific cytotoxicity	aCD20

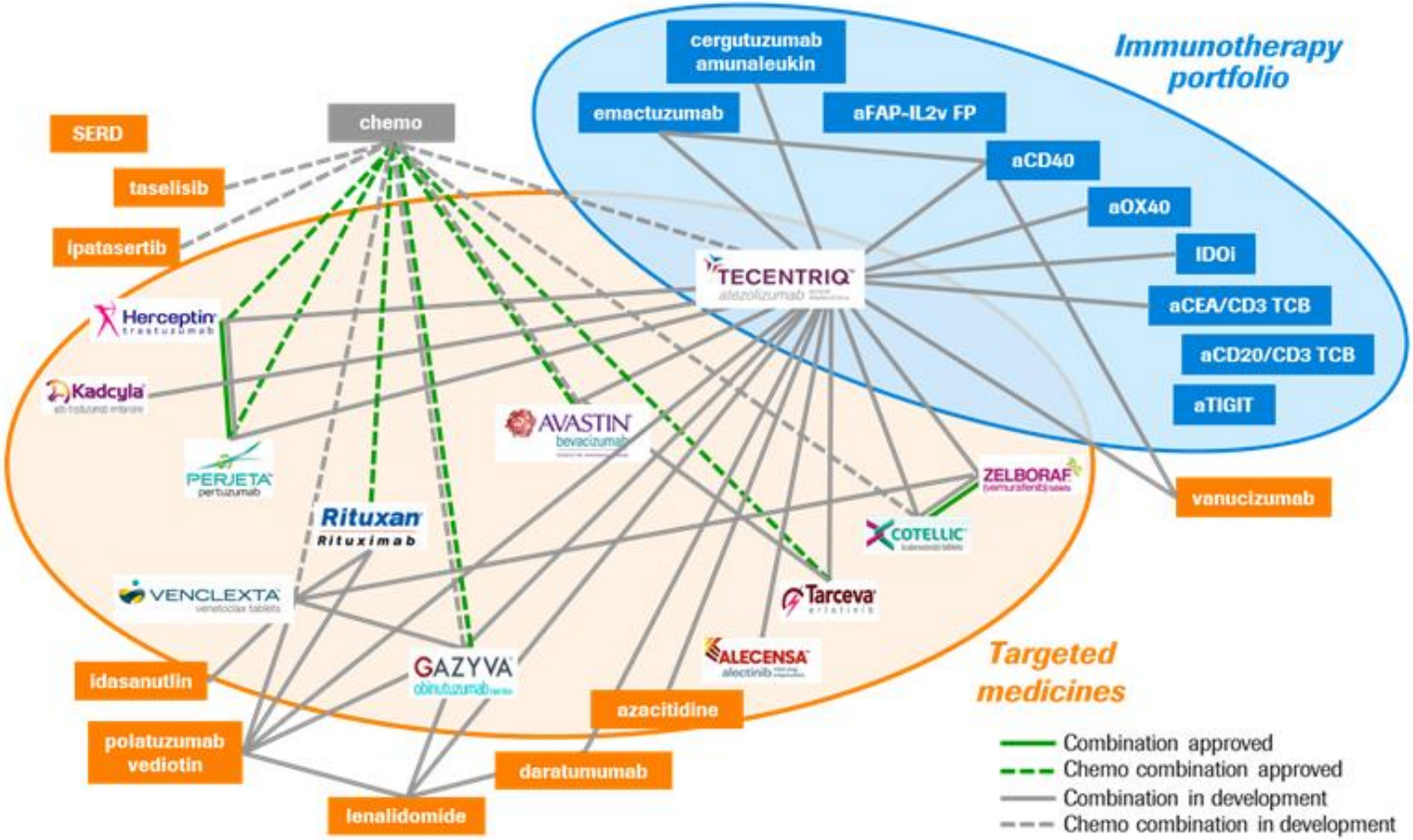


Immunotherapy	
Activate	aOX40, aCD40, aCEA-IL2v FP, aFAP-IL2v FP
Modulate	aPD-L1, aCSF-1R, IDOi aTIGIT
T cell bispecifics	aCEA/CD3 TCB, aCD20/CD3 TCB

Combinations

10 novel CIT assets in clinical development

Maximize portfolio through combinations



emactuzumab (aCSF-1R); cergutuzumab amunaleukin (aCEA-IL2v FP); vanucizumab (aAng2/VEGF); polatuzumab vediotin (aCD79b ADC); taselisib (PI3Ki); ipatasertib (AKTi); SERD (selective estrogen receptor degrader); idasanutlin (MDM2 antagonist); Venclexta in collaboration with AbbVie; Gazyva in collaboration with Biogen; Alecensa in collaboration with Chugai; Cotellic in collaboration with Exelixis; Zelboraf in collaboration with Plexxikon; polatuzumab in collaboration with Seattle Genetics; ipatasertib in collaboration with Array Biopharma; IDOi in collaboration with NewLink; daratumumab in collaboration with Janssen (J&J)

Broad coverage across approaches & tumor types

To benefit our patients

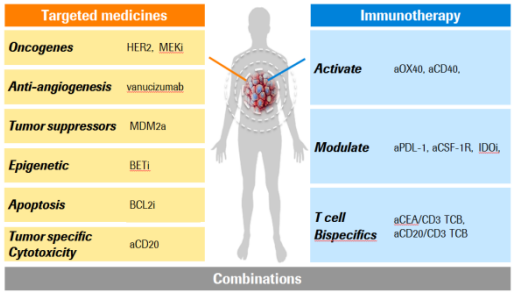
		Targeted therapies	CIT / Combos
Hematology	*CLL*	✓	✓
	aNHL	✓	✓
	iNHL	✓	✓
	AML	✓	✓
	MM	✓	✓
	MDS	✓	✓
Lung	*NSCLC*		✓
	ALK+	✓	✓
	EGFR+	✓	✓
	PDL1+		✓
Breast	*HER2+*	✓	✓
	HER2-/ER+	✓	
	TNBC		✓

		Targeted therapies	CIT / Combos
Gastric	*HER2+*	✓	✓
	GC	✓	✓
Bladder	*UBC*		✓
	MIBC PDL1+		✓
Colorectal			✓
Ovarian		✓	✓
Renal			✓
Prostate			✓
Hepatocellular			✓
Melanoma (BRAF+)		✓	

✓ Clinical studies ongoing

Substantial investments in underlying technology

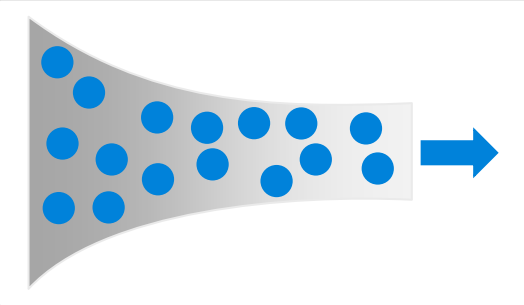
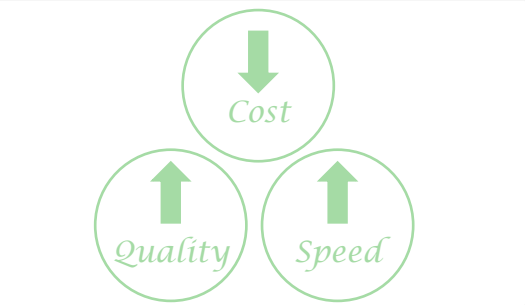
Novel antibody platforms supporting research



Monoclonal antibodies (MAb)	Antibody drug conjugates (ADC)	Glyco-engineered antibodies	Fab fragments	Antibodies with modified Fc part
Antibody cytokine fusion proteins (FP)	(1) Bispecific antibodies (biMAb)	(2) Bispecific antibodies (biMAb)	(1) T cell bispecifics	(2) T cell bispecifics

Innovation strategy remains unchanged

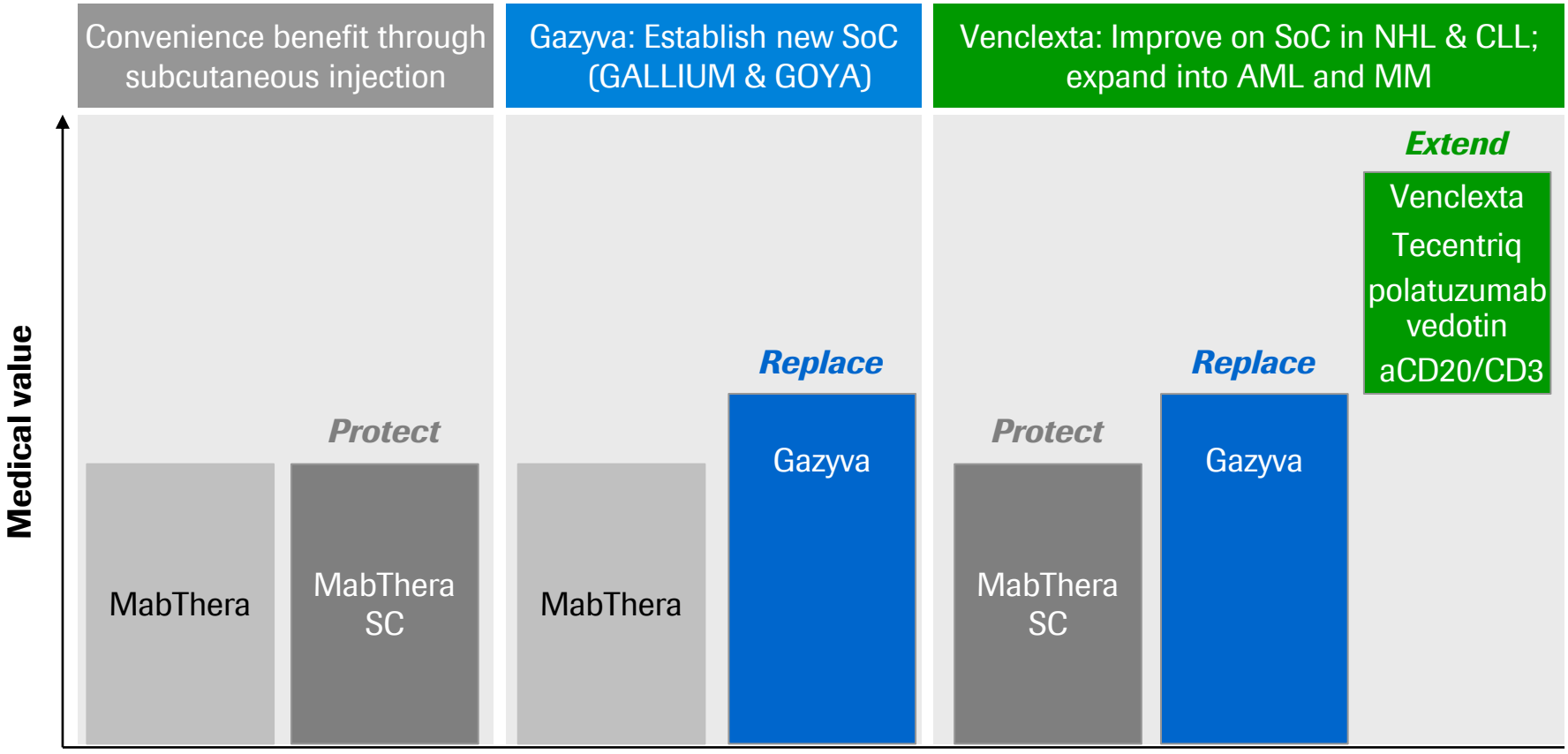
Increasing focus on data analytics

Pipeline delivery	Data & analytics	Increased productivity
		
✓ *Diverse, differentiated treatment approaches* • *Strategic life-cycle mgmt.*	• *Smart, more efficient R&D* • *Access & personalized patient care*	• *Innovative trial design* • *Prioritization & improved decision-making*

Outstanding talent that drives innovation & execution

Strategic approach to life-cycle management

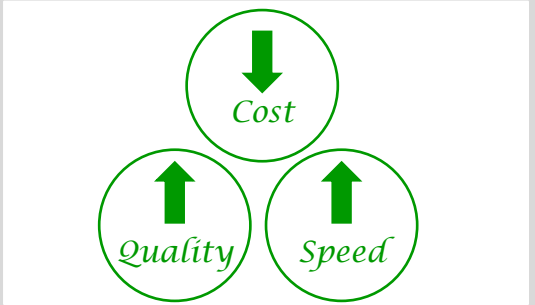
Third positive readout for Gazyva - GALLIUM in iNHL



Venclexta in collaboration with AbbVie; Gazyva in collaboration with Biogen; Polatuzumab in collaboration with Seattle Genetics;
SC=subcutaneous; CLL=chronic lymphocytic leukemia; NHL=non-hodgkin's lymphoma; AML=acute myeloid leukemia; MM=multiple myeloma

Innovation strategy remains unchanged

Increasing focus on data analytics

Pipeline delivery	Data & analytics	Increased productivity
		
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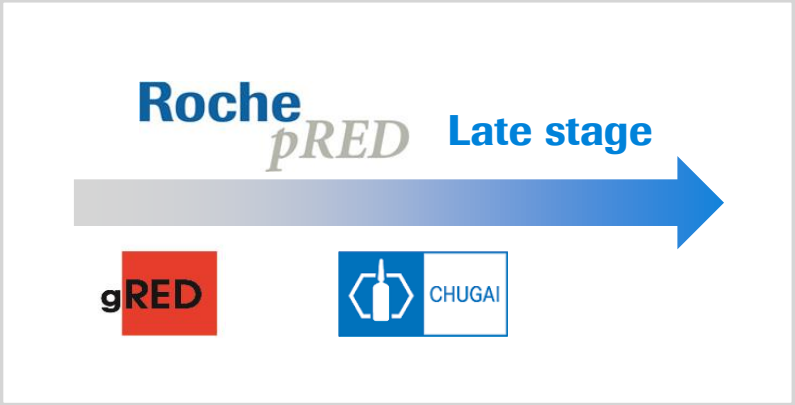
Outstanding talent that drives innovation & execution

Continuously improving our R&D processes

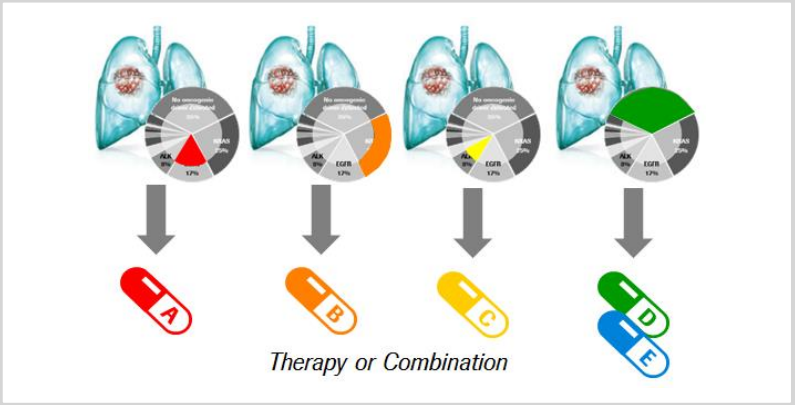
Improved decision-making and innovative trial design

Improved decision-making



- Cross-Roche strategy
- Early selection of priority candidates
- Seamless development

Innovative trial design



- Umbrella / basket studies
- Protocol design & endpoints
- Real world data

Innovation strategy remains unchanged

Increasing focus on data analytics

Pipeline delivery	Data & analytics	Increased productivity
		
• *Diverse, differentiated treatment approaches* • *Strategic life-cycle mgmt.*	• *Smart, more efficient R&D* • *Access & personalized patient care*	• *Innovative trial design* • *Prioritization & improved decision-making*

Outstanding talent that drives innovation & execution

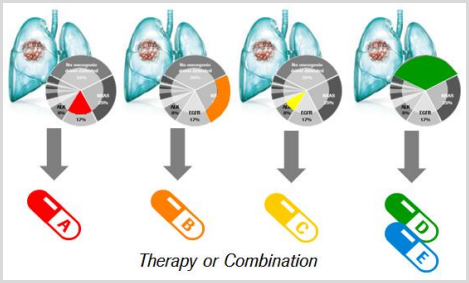
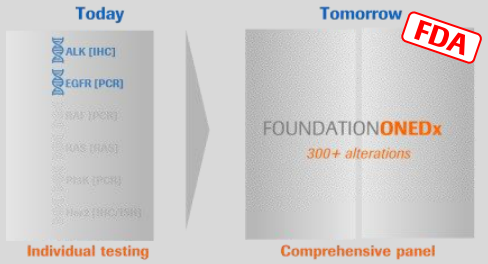
Advanced data analytics core to our strategy

Improve R&D efficiency and personalized patient care

Access meaningful data	*Create insights*	*Realise value from insights*
Diagnostic Data	Advanced analytics of integrated data	Smarter, more efficient R&D
Clinical Trial Data	FOUNDATION MEDICINE, Roche, FLATIRON	Improved access & personalised patient care
Real World Data		

Collaboration with Foundation Medicine

Next generation Dx and molecular info insights

Data analytics	Novel Dx development	Novel Dx uptake
		
Hypothesis generation and trial design	CIT Dx and blood-based monitoring	FDA approval and launch

Collaboration with Flatiron

Leveraging insights from real world data

Roche

FLATIRON

Clinical trial design and recruitment

Tecentriq NSCLC

Real world data based studies

CLL, NSCLC & mBC

Real world data based submissions

ALECENSA alectinib 150 mg capsules

Zelboraf vemurafenib

AVASTIN bevacizumab

Kadcyla ado-trastuzumab emtansine for injection

Cost-effectiveness, safety, efficacy

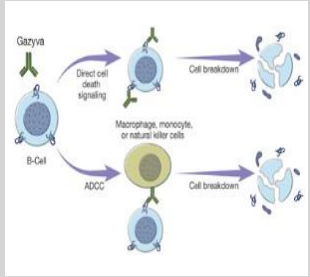
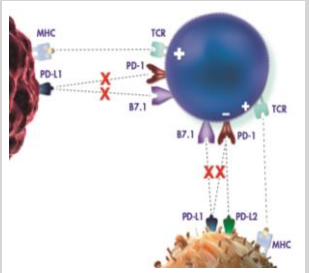
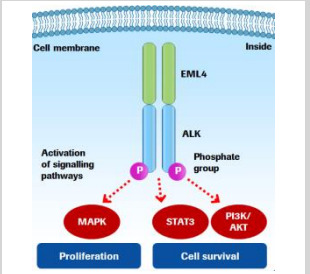
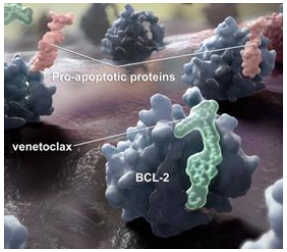
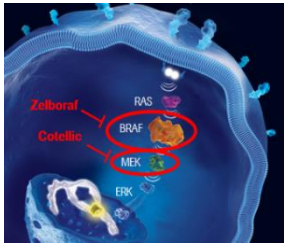
Managing increasing complexity in cancer care

Our strategy to maintain innovation leadership

Outlook

A strong start to the year

Selected pipeline highlights

Gazyva	Tecentriq	Alecensa	Venclexta	Cotellic + Zelboraf
	FDA BTD	FDA BTD	FDA BTD	
				
1L iNHL	Bladder, NSCLC	ALK+ NSCLC	AML, NHL, CLL	BRAF+ Melanoma

Continuing to improve on standard of care

Venclexta in collaboration with AbbVie; Gazyva in collaboration with Biogen; Cotellic in collaboration with Exelixis; Zelboraf in collaboration with Plexxikon

Oncology: Significant launch activities ahead

Bringing innovative medicines to our patients

2016	2017	2018
Venclexta FDA BTD R/R CLL with 17p del	**Perjeta + Herceptin** Adjuvant BC HER2+ (APHINITY)	**Tecentriq + chemo +/- Avastin** 1L NSCLC (IMpower)
Cotellic + Zelboraf BRAF+ melanoma	**Gazyva** 1L aNHL (GOYA)	**Tecentriq + Avastin** 1L RCC (IMmotion)
Alecensa FDA BTD 2L ALK+ NSCLC	**Gazyva** 1L iNHL (GALLIUM)	**Alecensa** 1L ALK+ NSCLC (ALEX)
Tecentriq FDA BTD 2L+ NSCLC and bladder cancer		
Gazyva Refractory iNHL (GADOLIN)		

NME

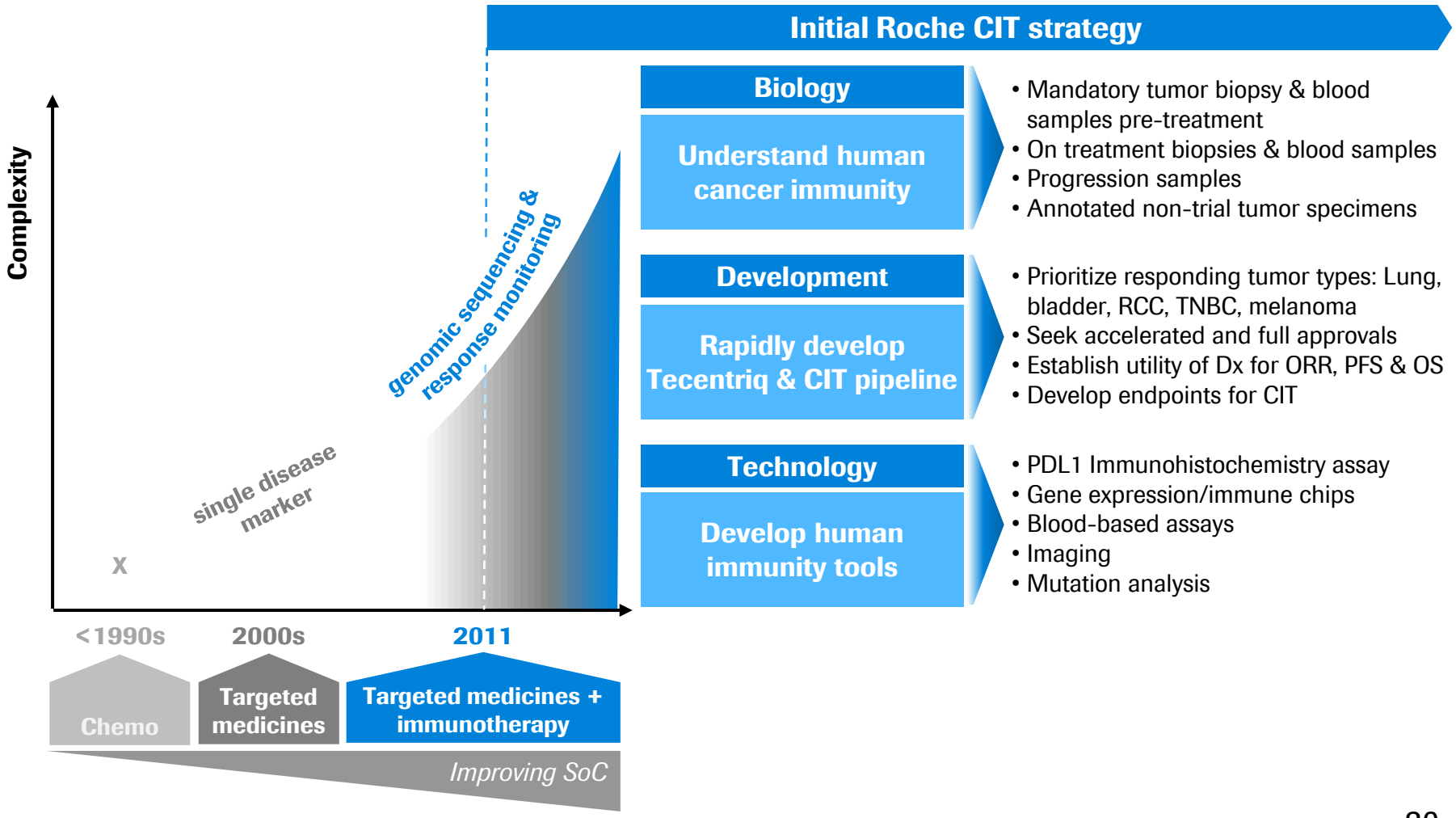
Major line extension

Venclexta in collaboration with AbbVie; Gazyva in collaboration with Biogen; Cotellic in collaboration with Exelixis; Zelboraf in collaboration with Plexxikon

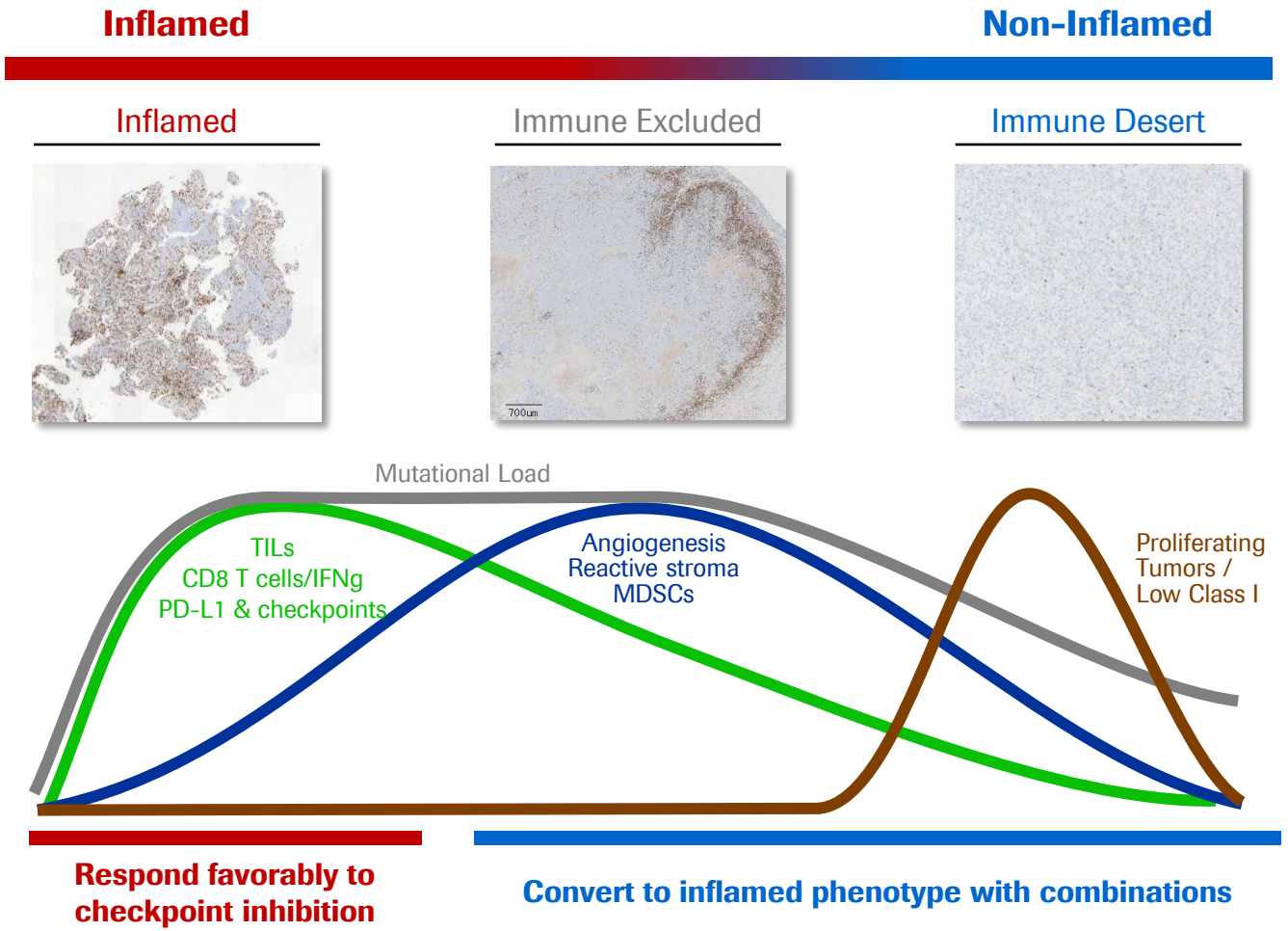
Cancer immunotherapy highlights

Daniel Chen, M.D., Ph.D.
VP, Global Head of Cancer Immunotherapy
Global Product Development

Our initial cancer immunotherapy strategy has laid the cornerstone for our programs…



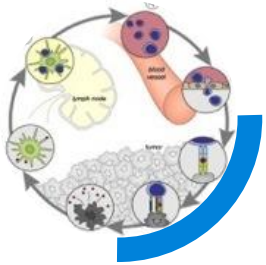
Our learnings lead to the tumor immunity continuum framework for combinations



Modified from Hegde PS et al. (2016) *Clin Canc Res*

Targeting treatment options to different patients and cancer types

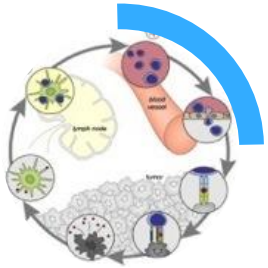
Inflamed			Immune Excluded		Immune Desert	
Melanoma	Lung	Bladder	TNBC	Colorectal	Gastric	Ovarian



CD8+ T cells infiltrated, but non-functional

Accelerate or remove brakes on T-cell response

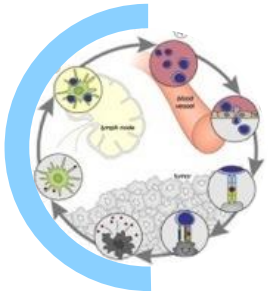
e.g. IDOi, aTIGIT, aCSF-1R



CD8+ T cells accumulated but not efficiently infiltrated

Bring T-cells in contact with cancer cells

e.g. aVEGF, chemokine agonists/antagonists, TCBs



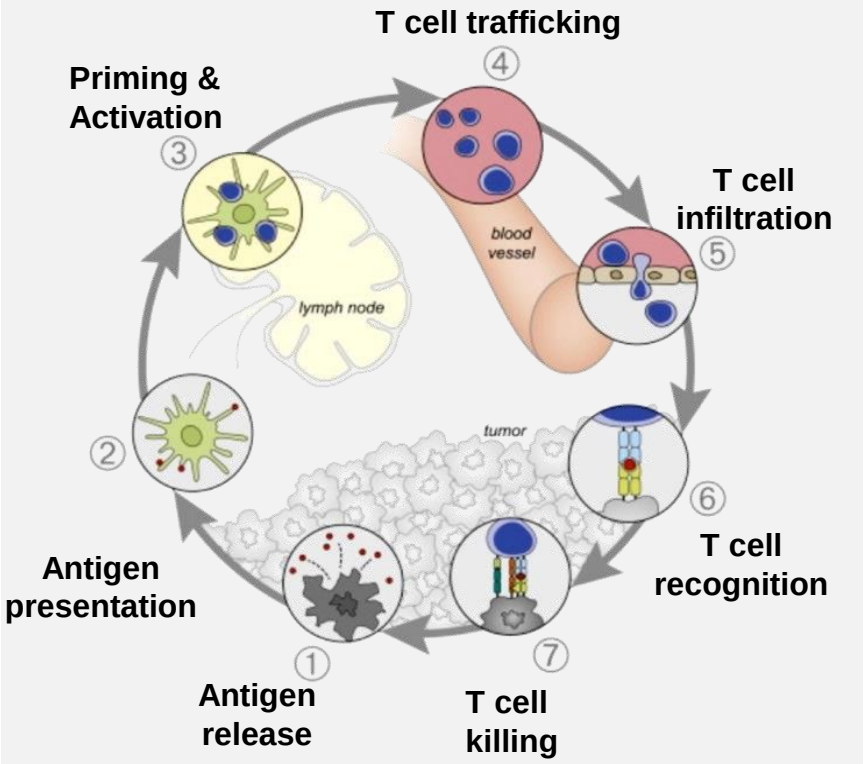
CD8+ T cells absent from tumor and periphery

Increase number of antigen-specific T-cells or increase antigen presentation

e.g. aOX40, aCD40, aCEA/FAP IL-2v, chemo, targeted therapies, vaccines

Our cancer immunotherapy strategy today

Cancer immunity cycle



Our CIT strategy

Establish Tecentriq as foundation

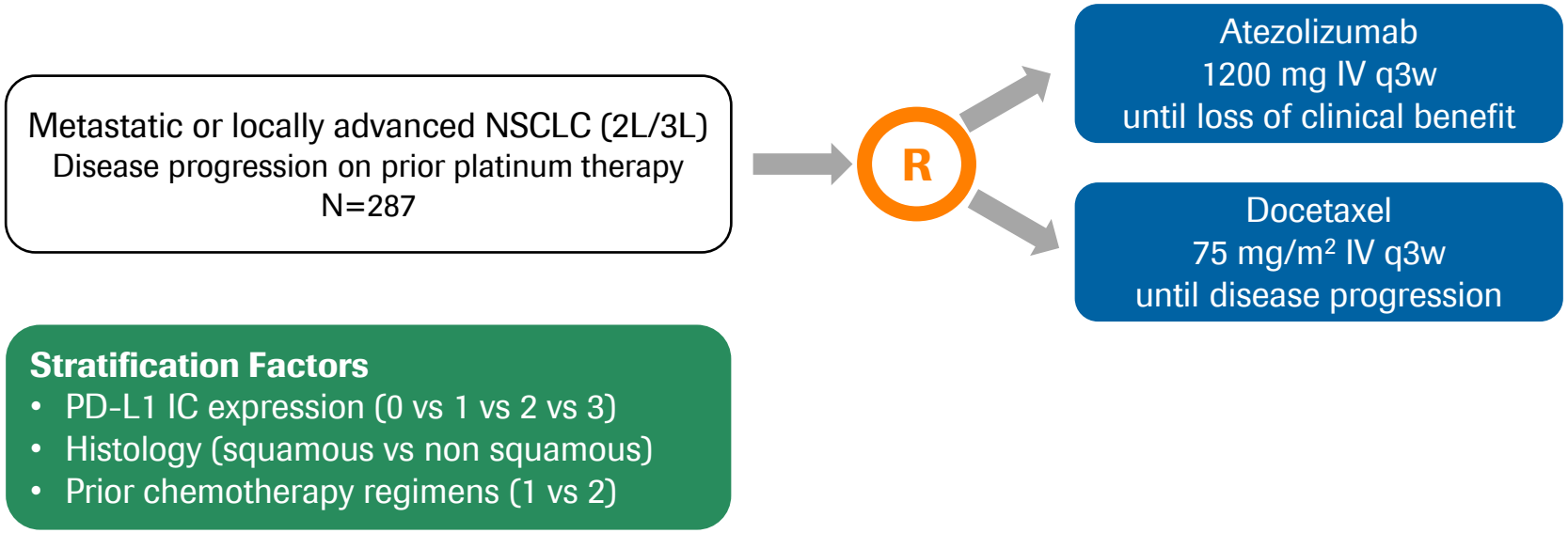
Unlock CI cycle: Tecentriq combos

Personalized cancer immunotherapy paradigm

Chen and Mellman. *Immunity* 2013

Tecentriq in NSCLC

Study Design – POPLAR randomized phase II in all-comer population



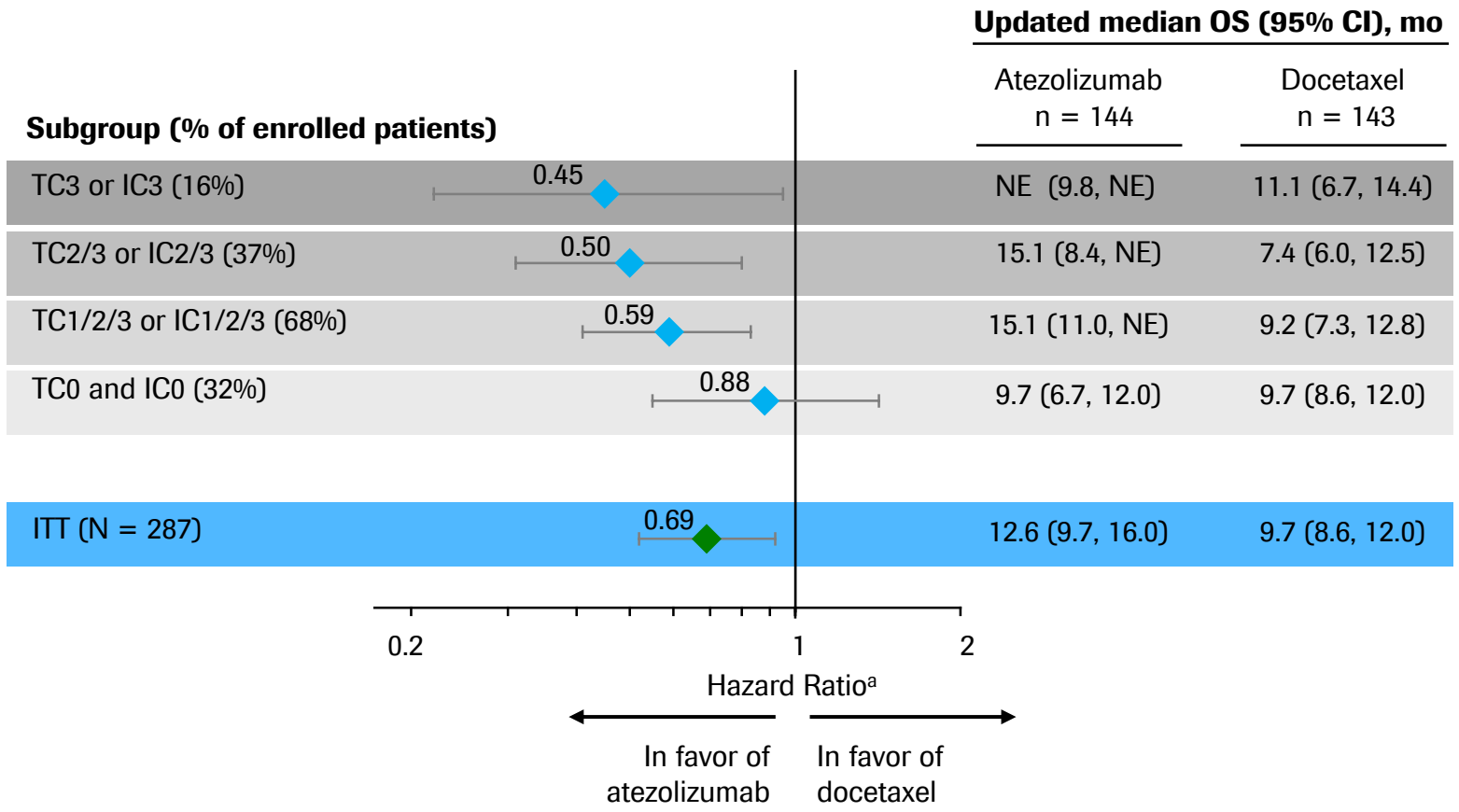
Stratification Factors

- PD-L1 IC expression (0 vs 1 vs 2 vs 3)
- Histology (squamous vs non squamous)
- Prior chemotherapy regimens (1 vs 2)

POPLAR: Updated mOS in PD-L1 subgroups

Efficacy increasing with higher PD-L1 expression

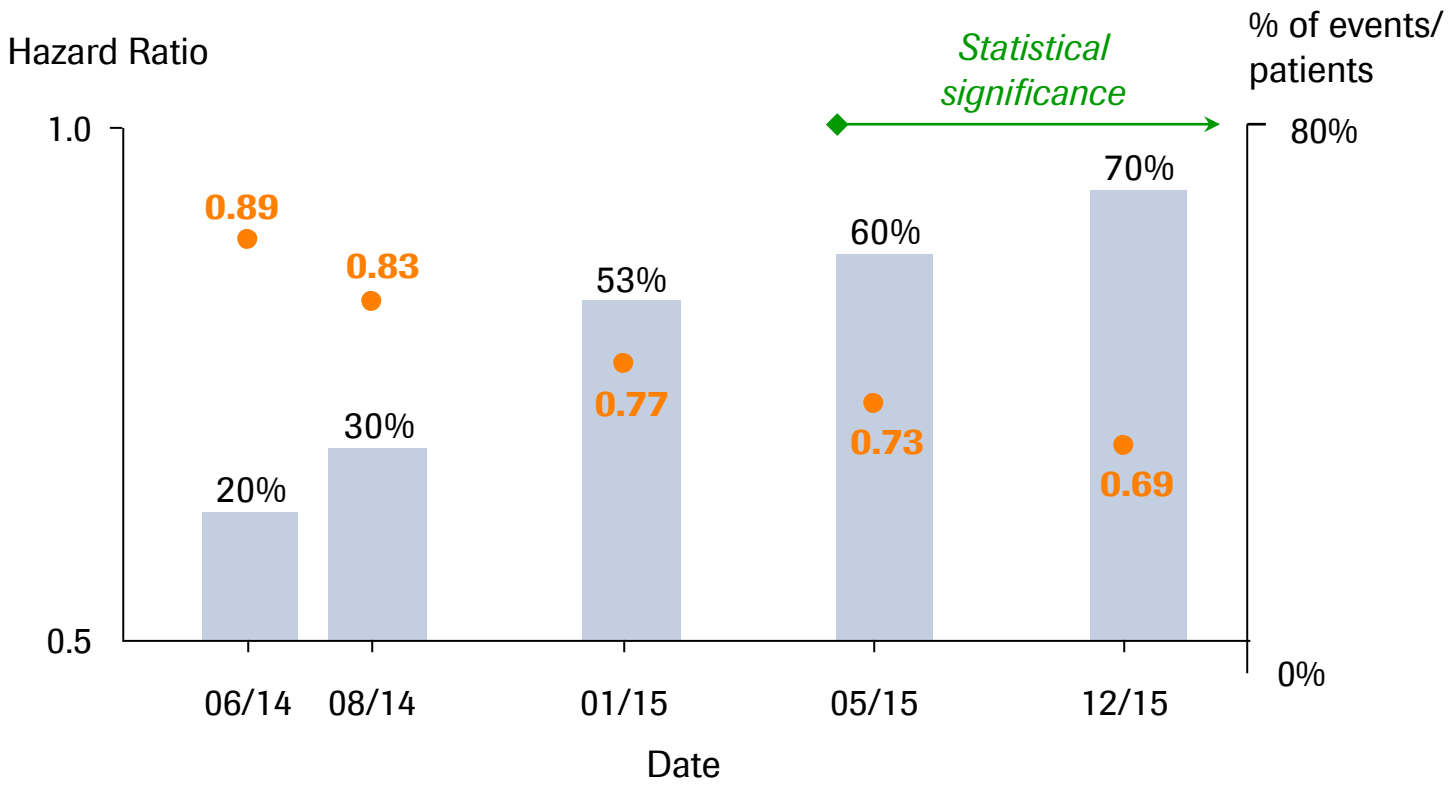
Updated analysis (Event / N=70%): Minimum follow-up 20 months



[a] Stratified HR for ITT and unstratified HRs for PD-L1 subgroups; NE, not estimable; Data cut-off: December 1, 2015

Time shows true size of the treatment effect

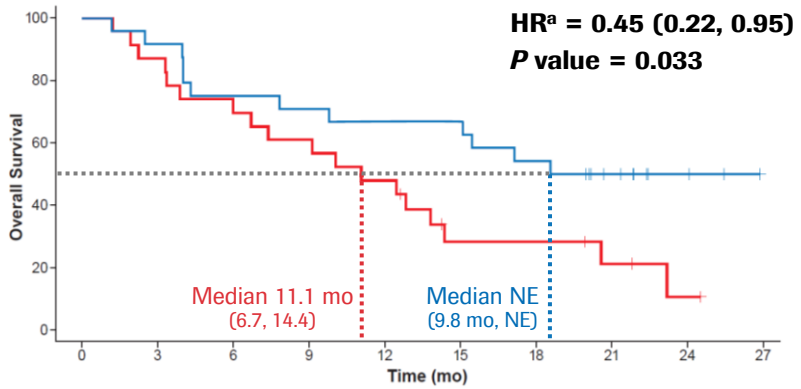
Example: Tecentriq overall survival in lung cancer



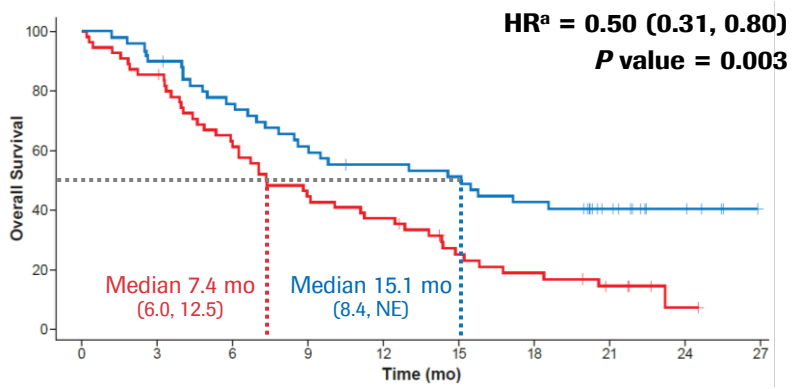
POPLAR: Updated mOS in PD-L1 subgroups

OS curves separate in all subgroups incl. TC0/IC0 over time

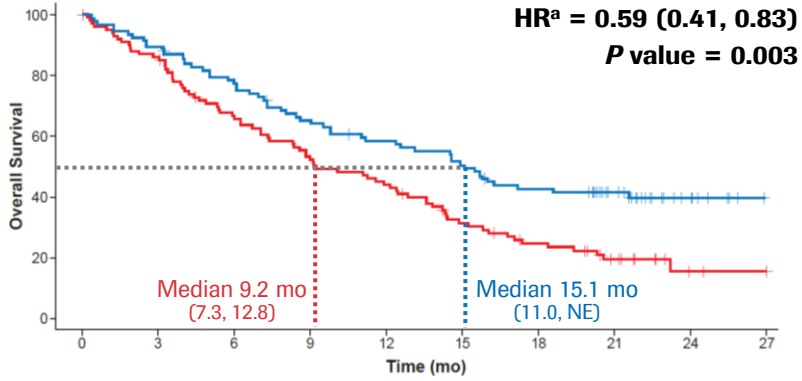
TC3 or IC3 (n = 47)



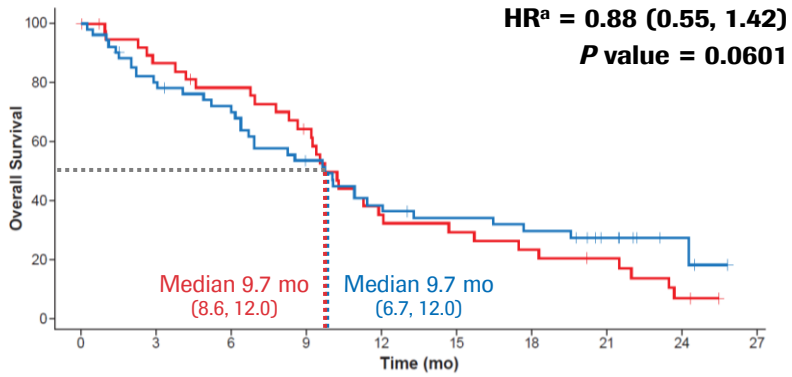
TC2/3 or IC2/3 (n = 105)



TC1/2/3 or IC1/2/3 (n = 195)



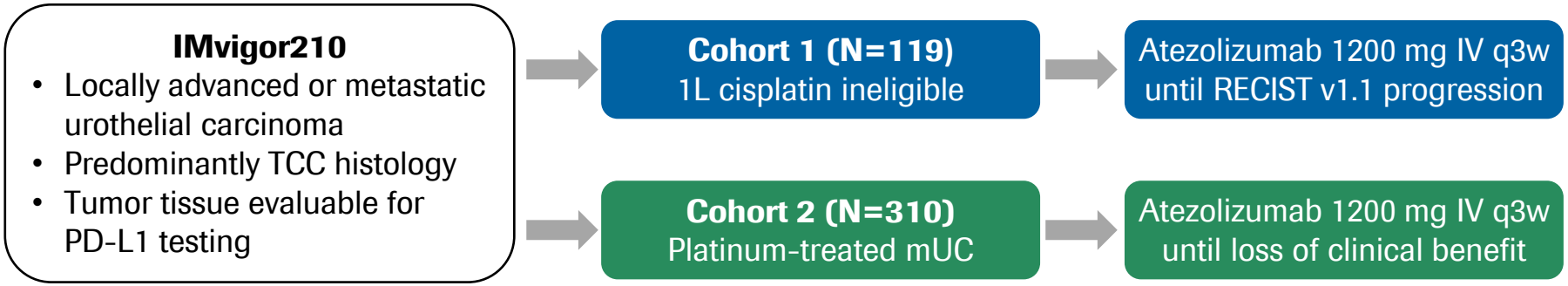
TC0 and IC0 (n = 92)



[a] Unstratified HR; Data cut-off: December 1, 2015

Tecentriq in bladder cancer

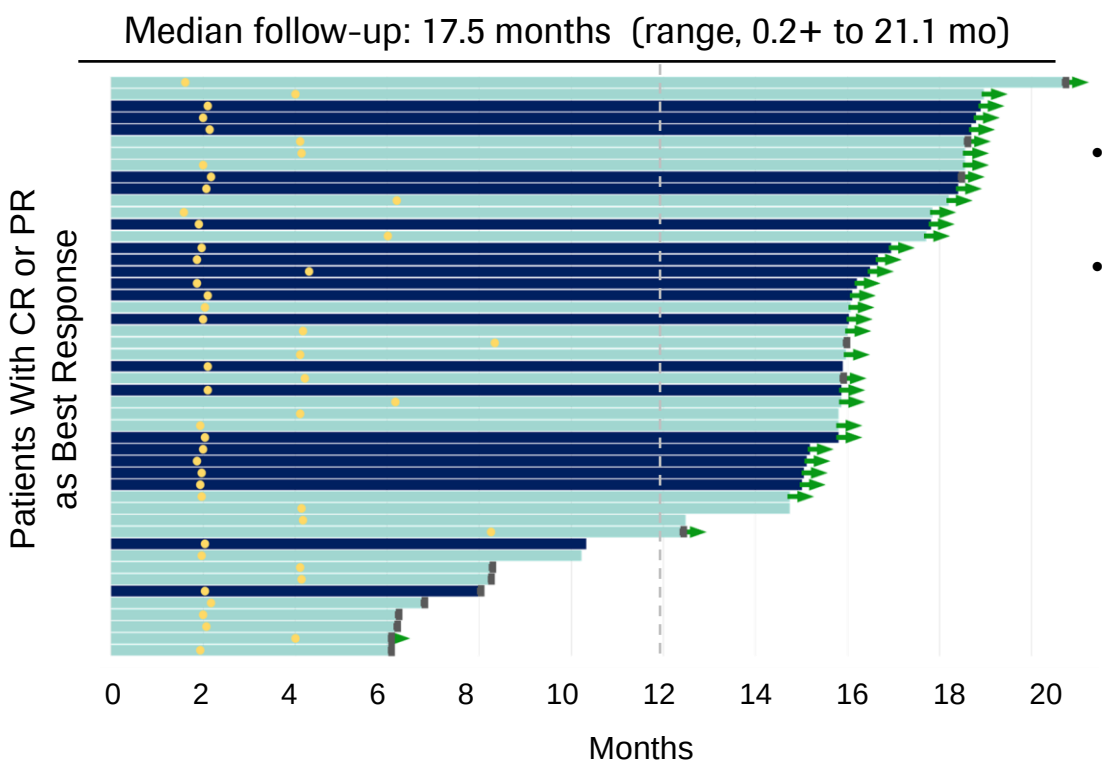
Study Design – Phase II IMvigor210



Imvigor210: Cohort 2 update

Ongoing & durable responses across all subgroups

	IC2/3 (n = 100)	IC1/2/3 (n = 207)	All[a] (N = 310)	IC1 (n = 107)	IC0 (n = 103)
ORR: confirmed IRF RECIST v1.1 (95% CI)	28% (19, 38)	19% (14, 25)	16% (12, 20)	11% (6, 19)	9% (4, 16)
CR rate: confirmed IRF RECIST v1.1 (95% CI)	15% (9, 24)	9% (6, 14)	7% (4, 10)	4% (1, 9)	2% (0, 7)



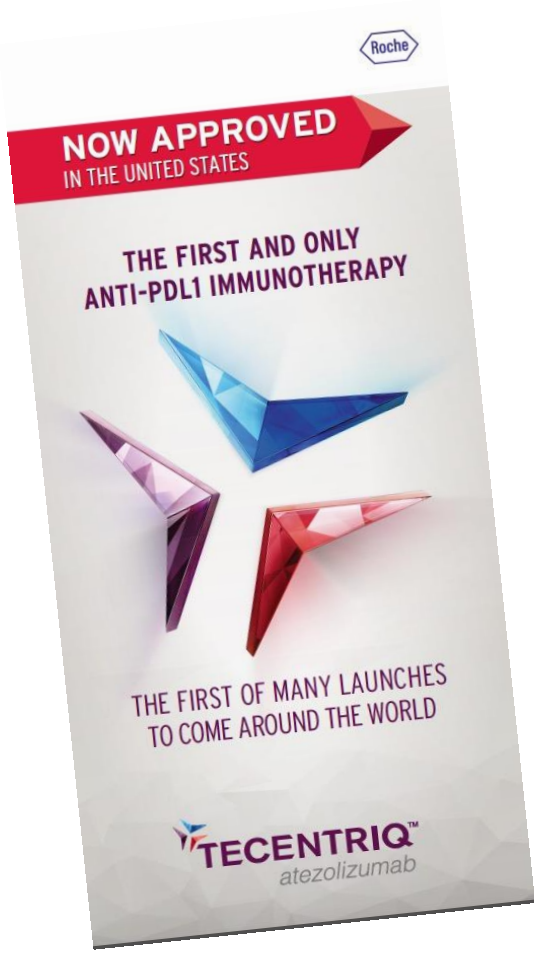
- 71% of responses (35/49) were ongoing
  - 86% of CRs ongoing
- mDOR was not yet reached in any PD-L1 IC subgroup (range, 2.1+ to 19.2+ mo)[a]

CR as best response
PR as best response
First CR/PR
Treatment discontinuation[b]
Ongoing response[c]

[a] Per IRF RECIST v1.1 [b] Discontinuation symbol does not indicating timing. [c] No PD or death only. Data cutoff: Mar. 14, 2016.

Tecentriq: First and only anti-PDL1 approved

Broad label in all-comers (no requirement for diagnostic)



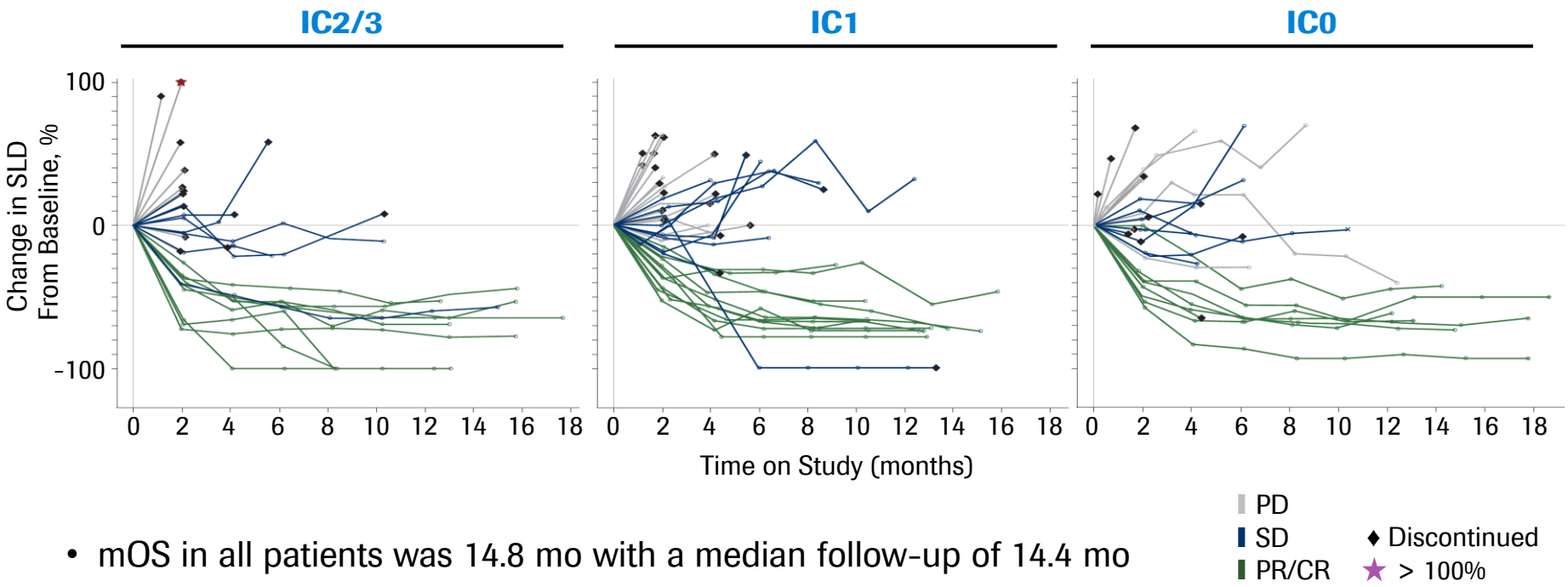
Indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma who have…

- …disease progression during or following platinum-containing chemotherapy
- …disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy

IMvigor210: Cohort 1 response rate & durability

Confirmed responses, incl. CRs observed in all subgroups

	IC2/3 (n = 32)	IC1/2/3 (n = 80)	All Patients (N = 119)	IC1 (n = 48)	IC0 (n = 39)
ORR[a] (95% CI)	28% (14, 47)	25% (16, 36)	24% (16, 32)	23% (12, 37)	21% (9, 36)
CR	6%	6%	7%	6%	8%
PR	22%	19%	17%	17%	13%

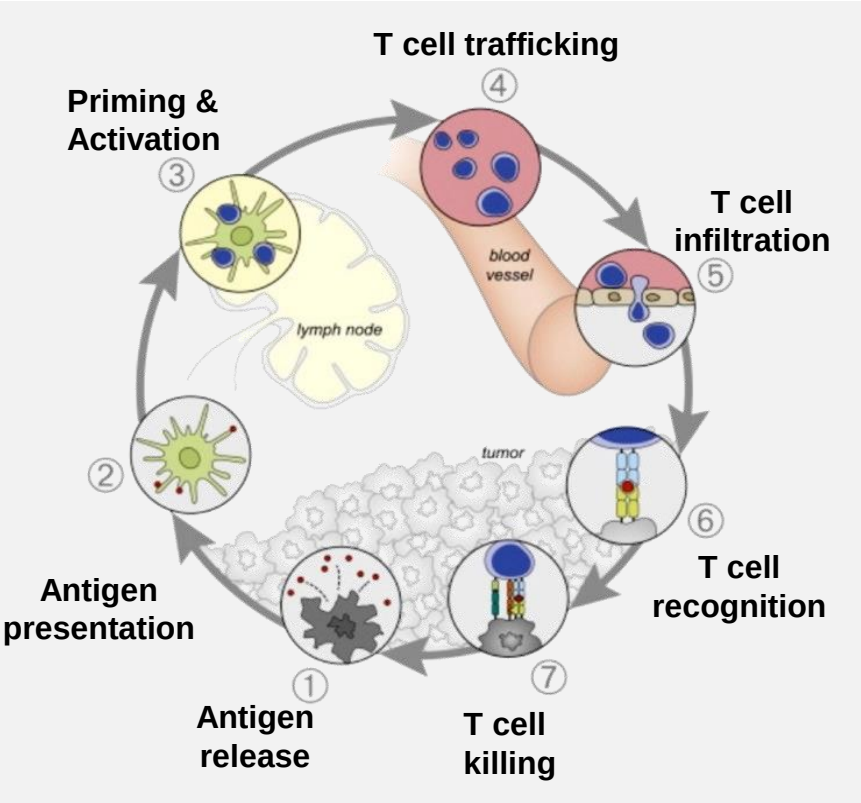


- mOS in all patients was 14.8 mo with a median follow-up of 14.4 mo

[a] Includes 19 patients with missing/unevaluable responses. All treated patients had measurable disease at baseline per investigator-assessed RECIST v1.1. PD-L1 IC status: IC2/3 (≥ 5%), IC1 (≥ 1 but < 5%), IC0 (< 1%). Data cut-off: March 14, 2016

Ways to unlock the cancer immunity cycle

Combining cancer immunotherapy assets with…



…chemotherapy

…targeted therapy

…immunotherapy

Chen and Mellman. *Immunity* 2013

Tecentriq chemo combo in TNBC

Study Design – atezolizumab + nab-paclitaxel Phase Ib (Arm F)

Phase Ib atezolizumab + nab-paclitaxel
in 1-3L+TNBC
N=32

→

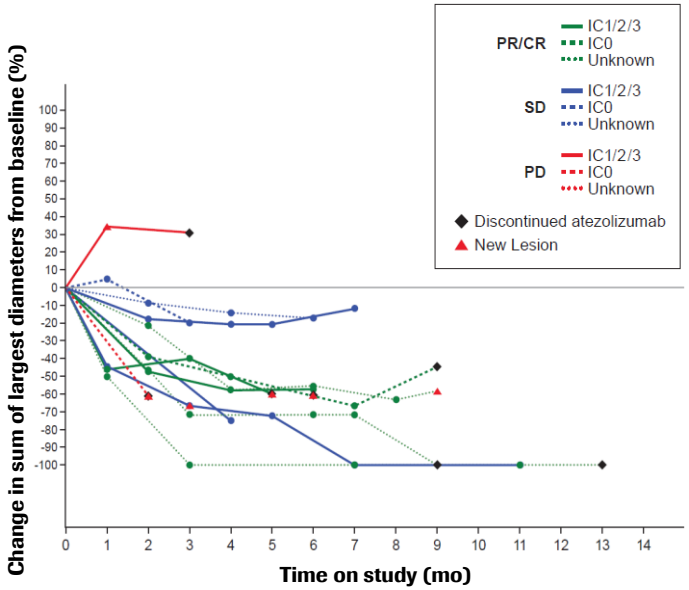
Atezolizumab 800mg/d q2w
+
Nab-paclitaxel 125mg/m2 q4w
until loss of clinical benefit

Tecentriq + Abraxane in TNBC

Response rate and duration of response

Best Overall Response	1L (n = 13)	2L (n = 9[b])	3L+ (n = 10)	All Patients (N=32)
Confirmed ORR (95% CI)[a]	46% (19, 75)	22% (3, 60)	40% (12, 74)	38% (21-56)
CR	8%	0%	0%	3%
PR	38%	22%	40%	34%
SD	38%	67%	30%	44%
PD	15%	0	30%	16%
Missing or NE	0%	11%	0%	3%

1L Patients

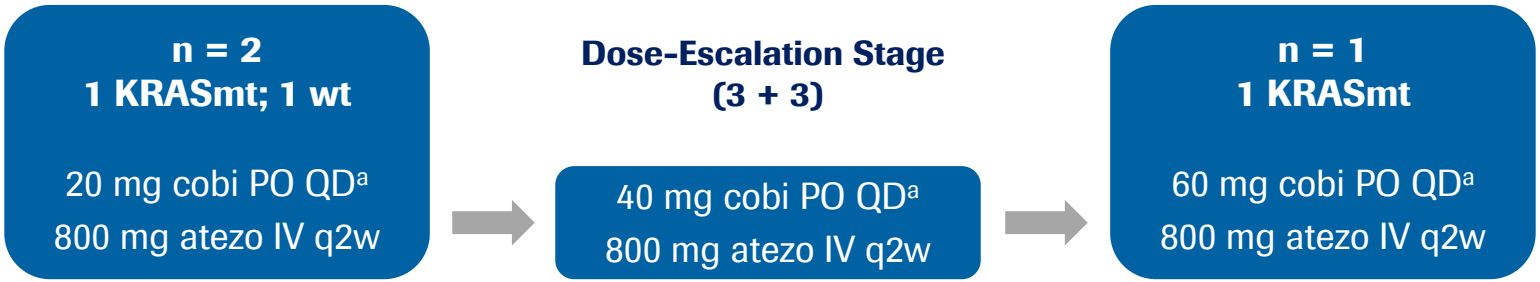


Phase 3 IMpassion 130 in 1L TNBC patients ongoing

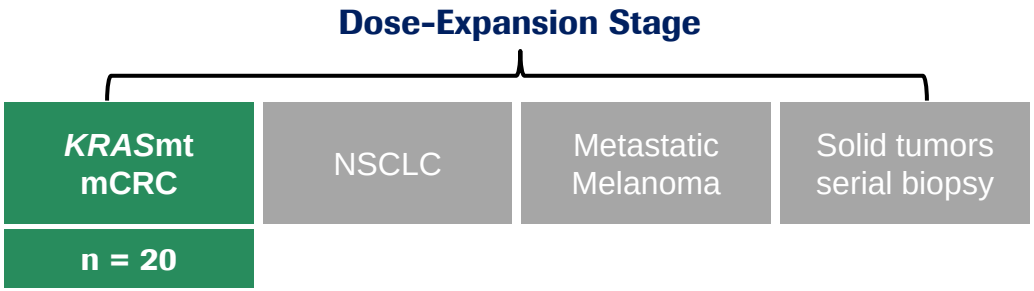
[a] Confirmed ORR defined as ≥ 2 consecutive assessments of CR or PR; [b] One patient discontinued with clinical progression before first on-treatment tumor assessment. Data cutoff date: Jan 14, 2016

Tecentriq + Cotellic in CRC

Phase Ib dose escalation and cohort expansion study

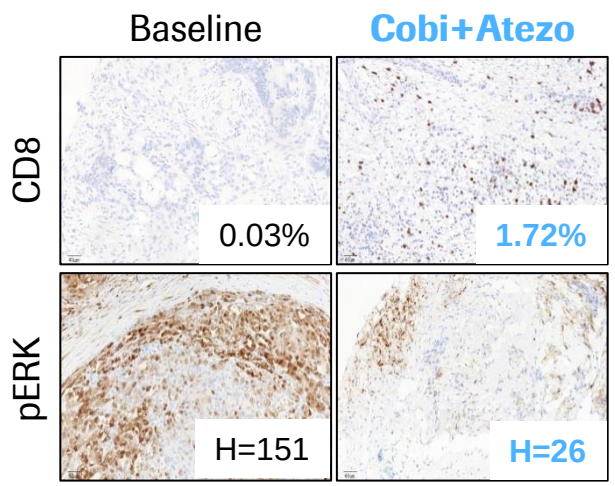


DLT window of 28 days until MTD for combination is defined

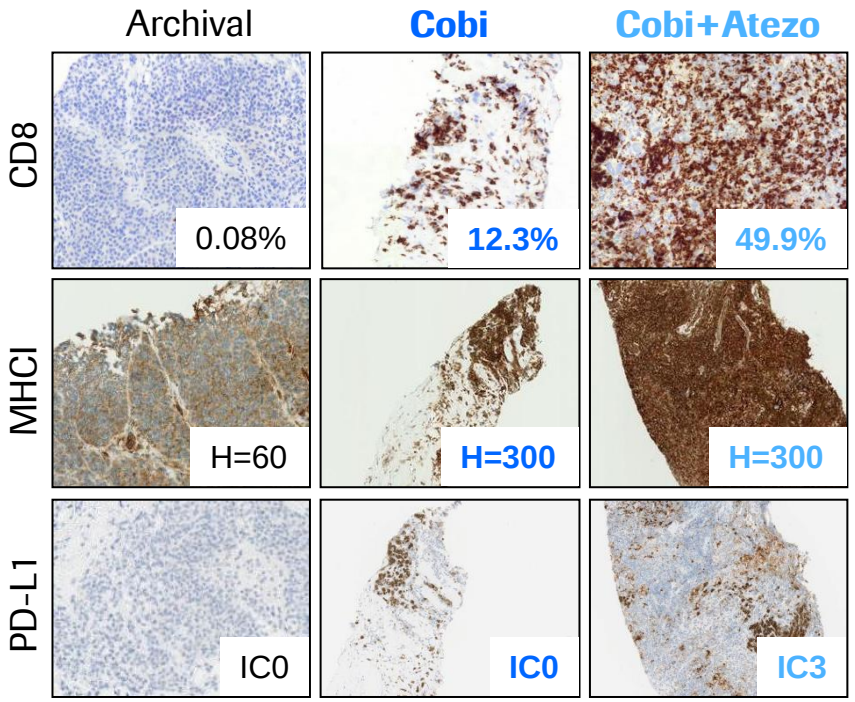


Biomarkers: CD8 T-cell accumulation and MHC I expression

KRASmt responder[a] (mCRC cohort)



Clear cell sarcoma patient[b] (Solid tumors serial biopsy cohort)



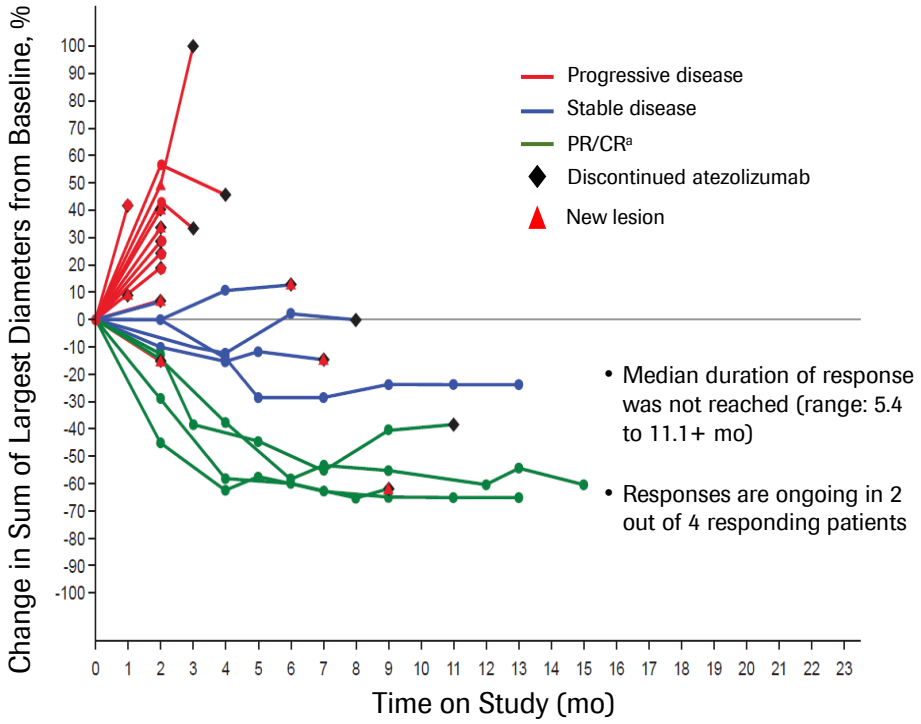
- Increased intratumoral CD8 T-cell infiltration and MHC I expression were observed with cobimetinib alone
- Further enhancement seen with cobimetinib + atezolizumab
- Similar results were seen in 75% of patients in the biopsy cohort

[a] Sarah Cannon Research Institute/Tennessee Oncology (J. Bendell)
[B] Princess Margaret Cancer Center (J. Lewin, Lillian Siu)

Tecentriq + Cotellic Phase Ib efficacy in CRC

Confirmed objective response

Confirmed response per RECIST v1.1	*KRAS* mt CRC cohort (N = 20)	All CRC patients (N = 23)
ORR (95% CI)	20% (5.7, 43.7)	17% (5.0, 38.8)
PR	20%	17%
SD	20%	22%
PD	50%	52%
NE	10%	9%



Phase 3 study in chemo-refractory mCRC is open and actively recruiting

[a] Confirmed per RECIST v1.1.

Efficacy-evaluable patients. 2 patients missing or unevaluable are not included. Data cut-off February 12, 2016

Cancer immunotherapy portfolio by tumor type

Solid tumors

Solid tumors

Tecentriq		Ph1
Tecentriq	+chemo ±Avastin	Ph1
Tecentriq	+Cotellic	Ph1
aOX40	±Tecentriq	Ph1
aCEA CD3	±Tecentriq	Ph1
IDOi	±Tecentriq	Ph1
emactuzumab	±Tecentriq	Ph1
aCEA IL2v	±Tecentriq	Ph1
aFAP IL2v		Ph1
aCD40	±Tecentriq	Ph1
emactuzumab	±aCD40	Ph1
aCD40	+vanucizumab	Ph1
Tecentriq	+vanucizumab	Ph1
aTIGIT		Ph1
Tecentriq	+daratumumab*	Ph1
Tecentriq	+IFN or Ipi*	Ph1
Tecentriq	+A2Ai*	Ph1
Tecentriq	+varlilumab (aCD27)*	Ph1
Tecentriq	+T-VEC*	Ph1

Bladder

Tecentriq (UBC)	Marketed
Tecentriq (UBC)	Ph3
Tecentriq (MIBC adj.)	Ph3

Lung (NSCLC & SCLC)

Tecentriq	2L/3L	Ph2 filed/ Ph3
Tecentriq	1L Dx+	Ph3
Tecentriq	+chemo (x3 1L trials)	Ph3
Tecentriq	+chemo ±Avastin (1L)	Ph3
Tecentriq	Adjuvant	Ph3
Tecentriq	+Tarceva or Alecensa	Ph1
Tecentriq (SCLC)	+chemo	Ph3
Tecentriq	+epacadostat*	Ph1

RCC

Tecentriq	±Avastin	Ph2
Tecentriq	±Avastin	Ph3

Breast (TNBC & HER2+)

Tecentriq (TNBC)	+chemo	Ph3
Tecentriq (HER2+)	+Kadcyla or Herceptin+Perjeta	Ph1
Tecentriq	+entinostat*	Ph2

Melanoma

Tecentriq	+Zelboraf ±Cotellic	Ph1

Ovarian

Tecentriq	+rucaparib*	Ph1

Sarcoma

Tecentriq	+CMB305 (NY-ESO-1)*	Ph2

Colon

Tecentriq	+Cotellic	Ph3

Hematological tumors

Tecentriq	+lenalidomide +daratumamab*	Ph1 (MM)
Tecentriq	±azacitidine	Ph1 (MDS)
Tecentriq	+Gazyva (lymphoma)	Ph1 (Heme)
Tecentriq	+Gazyva +polatuzumab (r/r FL / DLBCL)	Ph1/2 (Heme)
Tecentriq	+Gazyva +lenalidomide (r/r FL)	Ph1 (Heme)
Tecentriq	+Gazyva +CHOP (1L FL / DLBCL)	Ph1 (Heme)
aCD20 CD3	+Tecentriq	Ph1 (Heme)
Tecentriq	+CD19 CAR-T (refractory aNHL)*	Ph1 (Heme)

As of June 2016

Other CIT

*Collaboration

Phase 3 CIT trials: Planned data read-outs

Tumor	Trial Name		Est. Trial readout
Lung			
1L NSCLC (non-sq)	**IMpower 150**	Tecentriq + carbo/pac +/- Avastin	2017
1L NSCLC (non-sq)	**IMpower 130**	Tecentriq + carbo + Abraxane	2017
1L NSCLC (sq)	**IMpower 131**	Tecentriq + carbo + pac/Abraxane	2017
1L NSCLC (non-sq)	**IMpower 132**	Tecentriq + cis/carbo + pem	2018
1L Dx+ NSCLC (non-sq & sq)	**IMpower 110/111**	Tecentriq monotherapy	2017
Adj NSCLC	**IMpower 010**	Tecentriq monotherapy	Post 2018
1L SCLC	**IMpower 133**	Tecentriq+ carbo + etoposide	Post 2018
2L + NSCLC	**OAK**	Tecentriq monotherapy	2016
Bladder			
2L+ UBC	**IMvigor 211**	Tecentriq monotherapy	2017
Adj MIBC	**IMvigor 010**	Tecentriq monotherapy	Post 2018
RCC			
1L RCC	**IMmotion 151**	Tecentriq + Avastin	2017
Breast			
1L TNBC	**IMpassion 130**	Tecentriq + Abraxane	2018
Colon			
3L+ mCRC	**COTEZO**	Tecentriq + Cotellic	2018

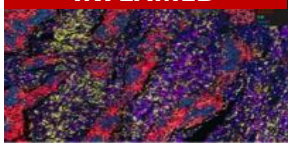
As per Q1 2016; Outcome studies are event driven, timelines may change

Towards a personalized CIT paradigm

*HYPOTHETICAL TREATMENT ALGORITHM

*EVALUATE TUMOR IMMUNOLOGY

INFLAMED



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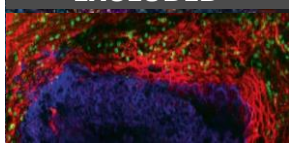
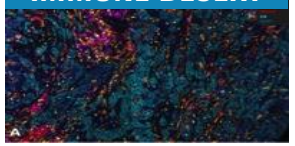


IMMUNE DESERT



Strong PD-L1 & high mutational load	Weak PD-L1 expression	No identified target	T Cells at Periphery	No Identified target	No Effectors	MHC Loss
Anti-PDL1/PD1	Anti-PDL1/PD1 + Other CIT (IDOi, aTIGIT, aCSF1R, TCBs, IL2v)	Anti-PDL1/PD1 + Chemo /targeted therapy/XRT	Anti-PDL1/PD1 +antiangiogenic + anti-stromal agents	Anti-PDL1/PD1 + Chemo /targeted therapy/XRT	Anti-PDL1/PD1 + aOX40 (or aCD40, aCTLA4, IL2v, vaccine)	Anti-PDL1/PD1 + TCBs (or IFN, CART, MEKi)

Modified from Kim and Chen, *Annals of Oncology* 2016

Early pipeline update: The learning loop in action

Ira Mellman, Ph.D.
VP, Cancer Immunology, Genentech

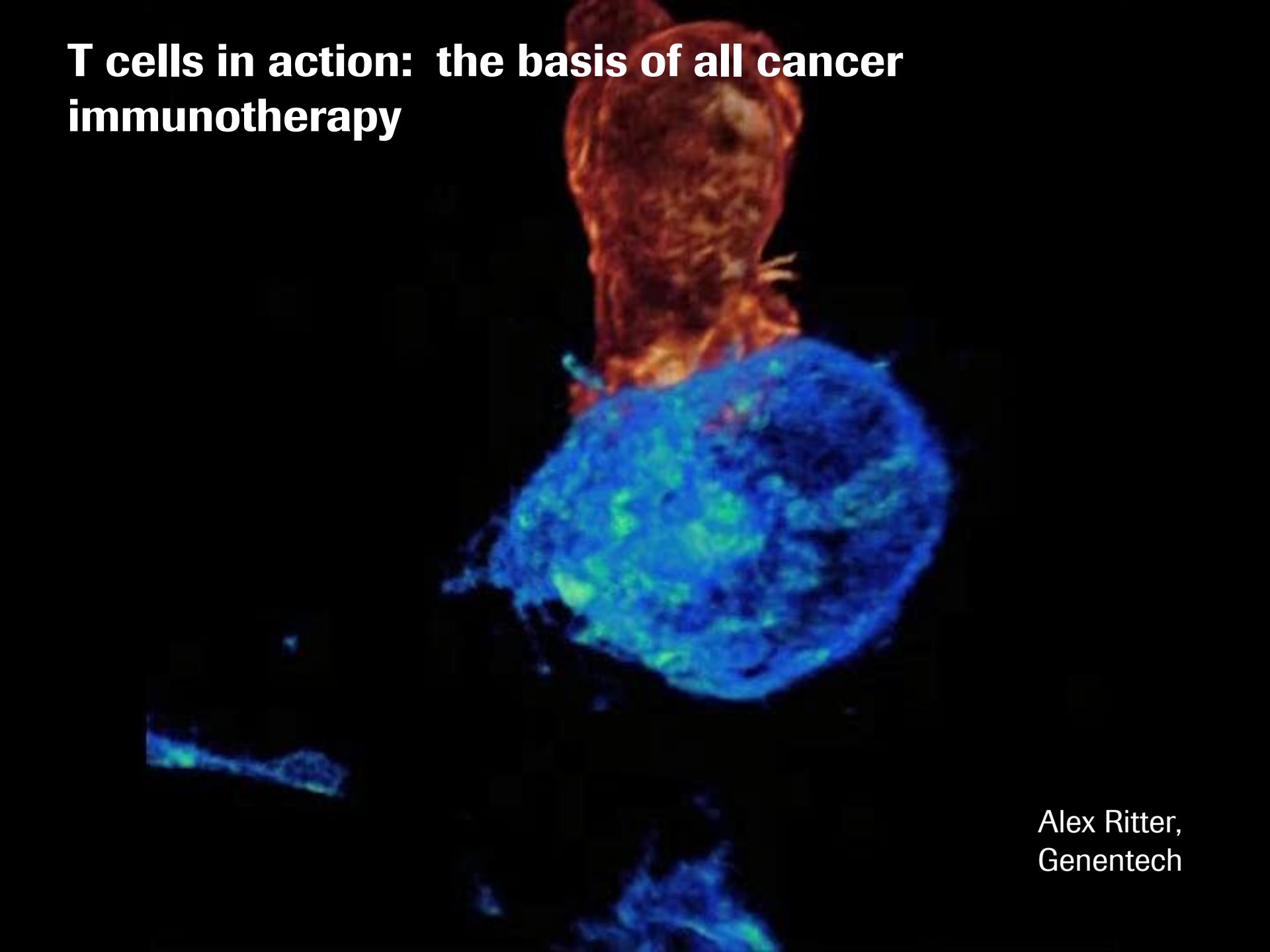
CIT has changed the oncology paradigm

Update gRED CIT portfolio

The learning loop: Clinical data informs combinations and NME selection

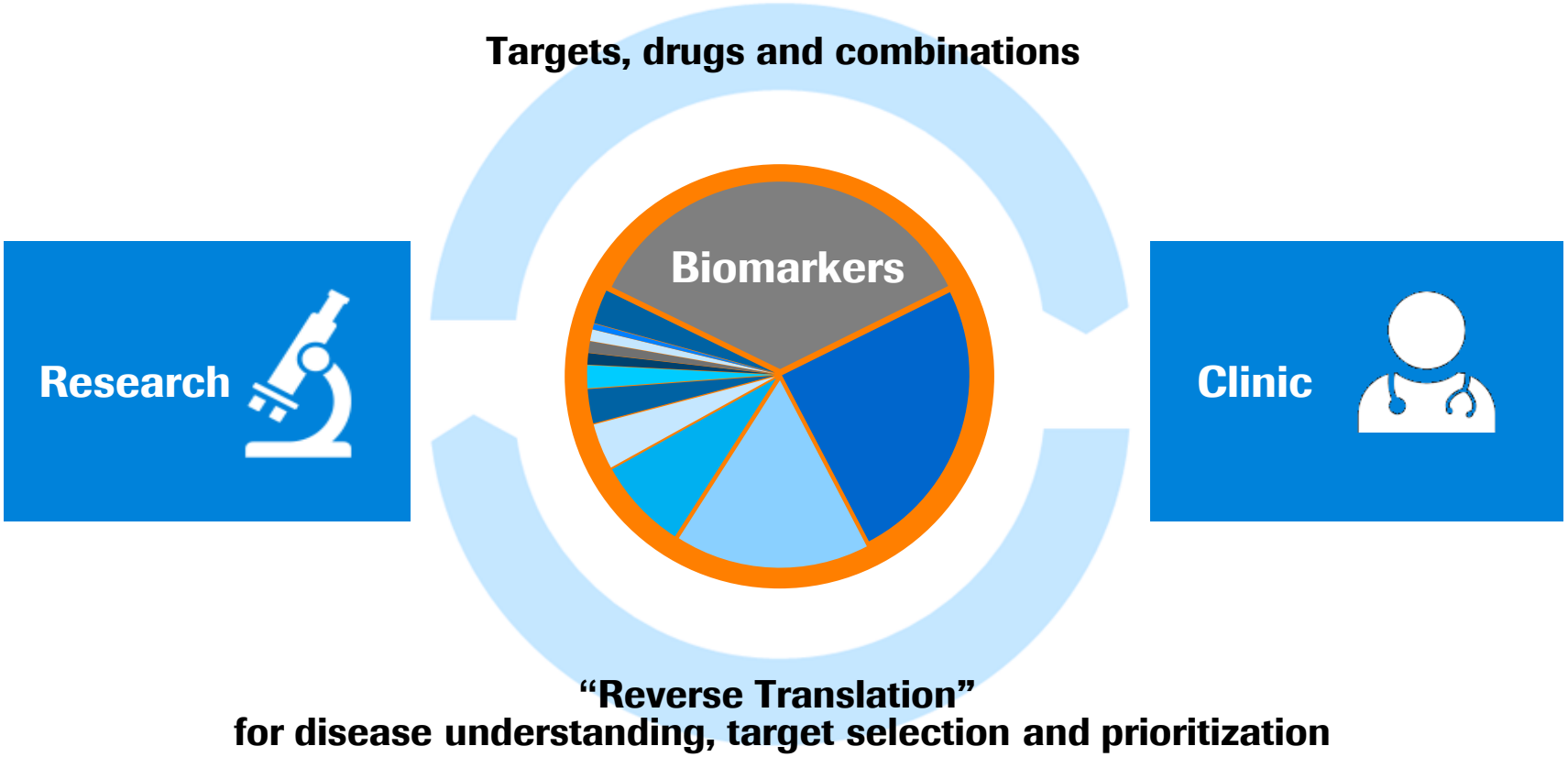
How do clinical biomarker data define next steps?

T cells in action: the basis of all cancer immunotherapy



Alex Ritter,
Genentech

Implementation of a learning loop to inform both drug discovery and clinical development



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How do clinical biomarker data define next steps?

gRED CIT portfolio is prioritized by the cancer immunity cycle

Roche

CancerImmunology

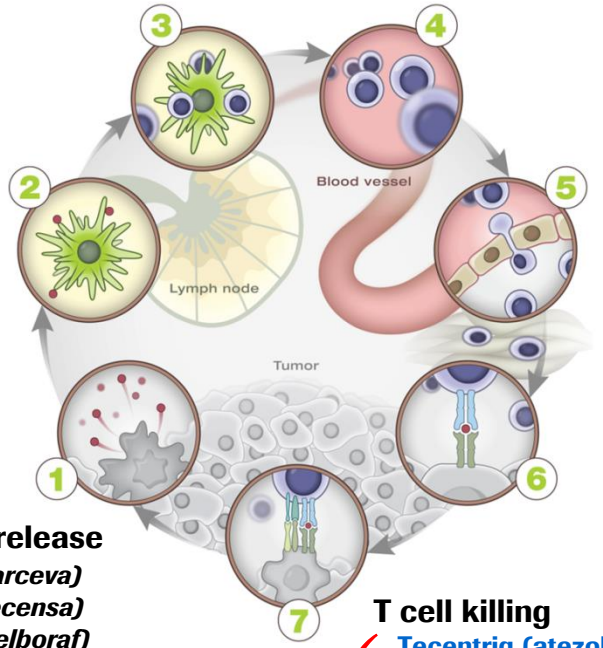
Genentech

Priming & activation
- ✓ anti-OX40
- anti-CD27* (Celldex)
- entinostat* (Syndax)

T cell Trafficking

T cell infiltration
- anti-VEGF (Avastin)

Antigen presentation
- T-Vec oncolytic virus* (Amgen)
- INFα
- CMB305 vaccine* (Immune Design)



Cancer T cell recognition
- ✓ anti-CD20/CD3 TCB
- KTE-C19* (Kite Pharma)
- ImmTAC* (Immunocore)

Antigen release
- *EGFRi (Tarceva)*
- *ALKi (Alecensa)*
- *BRAFi (Zelboraf)*
- *MEKi (Cotellic)*
- *anti-CD20 (Gazyva)*
- *anti-HER2 (Herceptin; Kadcyla; Perjeta)*
- *various chemotherapies*
- *lenalidomide* (Celgene)*
- *rucaparib* (Clovis)*
- *daratumumab* (Janssen)*

T cell killing
- ✓ Tecentriq (atezolizumab)
- ✓ IDOi (NewLink)
- ✓ anti-TIGIT
- IDOi* (Incyte)
- CPI-444* (Corvus)
- TDOi (NewLink)
- IDO1/TDOi (NewLink)

TECENTRIQ atezolizumab

- Marketed
- Clinical development
- Preclinical development
- Established therapies
- ✓ In-house CIT NMEs
- * Partnered or external

Chen and Mellman. *Immunity* 2013
CIT=cancer immunotherapy; FP=fusion protein; TCB=T-cell bispecific

gRED CIT portfolio is prioritized by the cancer immunity cycle

Roche

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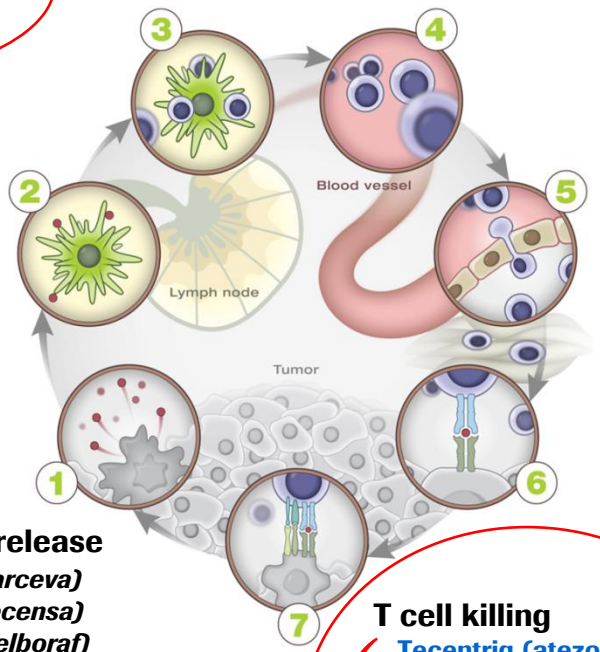

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- TDOi (NewLink)
- IDO1/TDOi (NewLink)

TECENTRIQ™ atezolizumab

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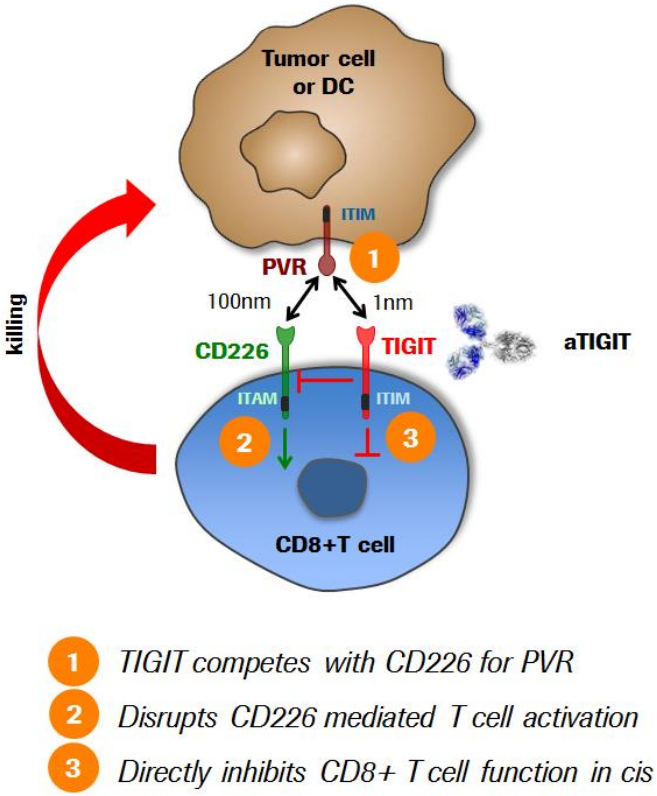
- Clinical development
- Preclinical development
- Established therapies
- ✓ In-house CIT NMEs
- * Partnered or external

Chen and Mellman. Immunity 2013
CIT=cancer immunotherapy; FP=fusion protein; TCB=T-cell bispecific

aTIGIT: A second potent negative T cell regulator

FPI achieved in May 2016



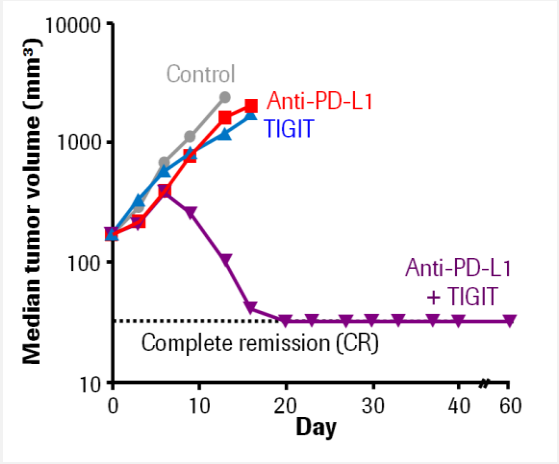
- Tumor-infiltrating CD8$^+$ T cells and NK cells express high levels of TIGIT
- Antibody co-blockade of TIGIT and PD-L1 elicits tumor rejection in preclinical models
- TIGIT limits the effector function of chronically stimulated CD8$^+$ T cells
- TIGIT restricts CD226 costimulatory signaling by competing for a common ligand (PVR); CD226 signaling is required for activity

TIGIT=T cell immunoreceptor with Ig and ITIM domains; DC=dendritic cell; CD8+ T cell=cytotoxic T lymphocyte (CTL)

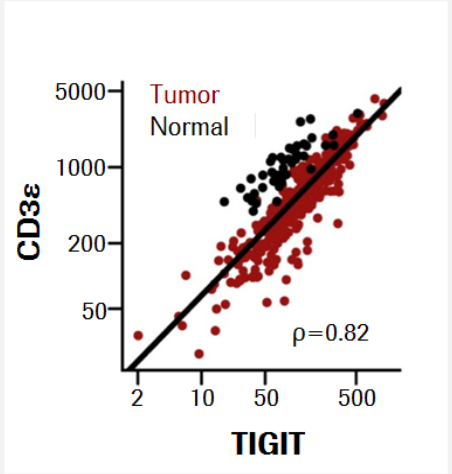
aTIGIT preclinical data

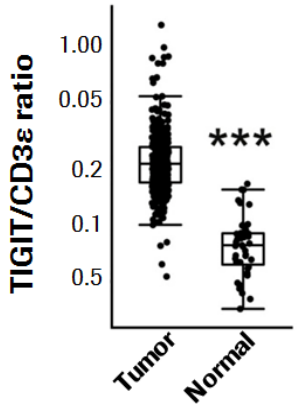
aTIGIT + aPD-L1 effective in animal model

aPD-L1 non-responsive animal model



Lung squamous cell carcinoma



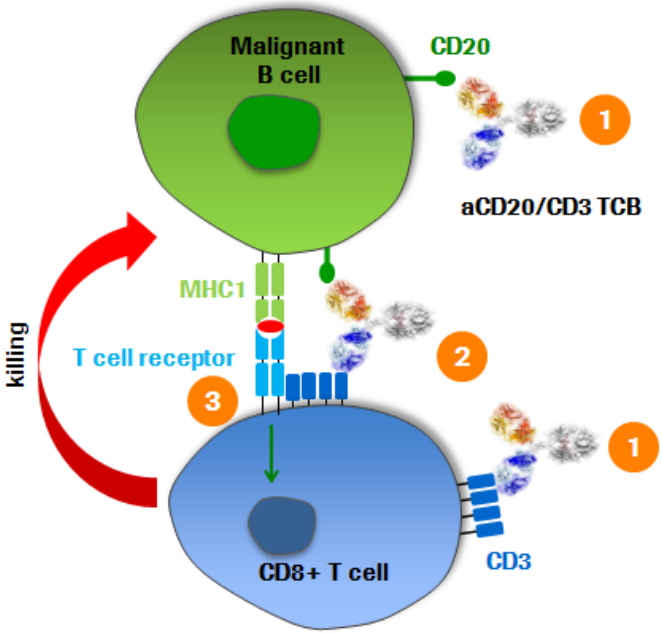


- aTIGIT + aPD-L1 combination active in a PD-L1 non-responsive model
- Elevated expression of TIGIT by T cells in human cancers
- TIGIT ligand (PVR) widely expressed by many human tumors

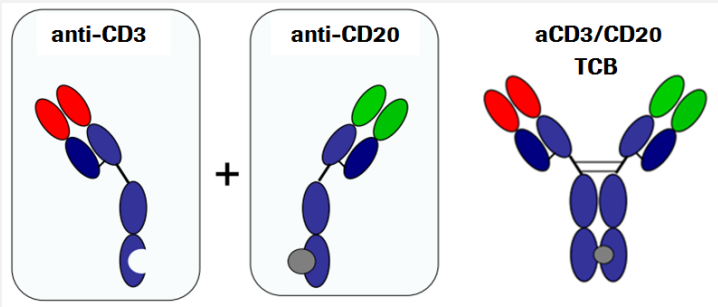
Johnson et al (2014) *Cancer Cellc;* TIGIT=T cell immunoreceptor with Ig and ITIM domains

aCD20/CD3 TCB: An alternative to CAR-Ts

Entered phase I – Combo with Tecentriq planned



1. *aCD20/CD3 TCB binds to tumor cells or CD8+ T cells*
2. *Pulls together the malignant B cell and the T cell*
3. *Enables T cell killing via CD3 stimulation*



- Fully humanized IgG1
- PK typical of conventional IgG
- No homodimers or aggregate
- Data presentation planned at ASH

Carter *et al.* 1997 J Mol Biol; Scheer *et al.* 2013 Nat Biotechnol; TCB=T cell bispecific; CAR=chimeric antigen receptor; CD8+ T cell=cytotoxic T lymphocyte (CTL)

aCD20/CD3 TCB: An alternative to CAR-Ts

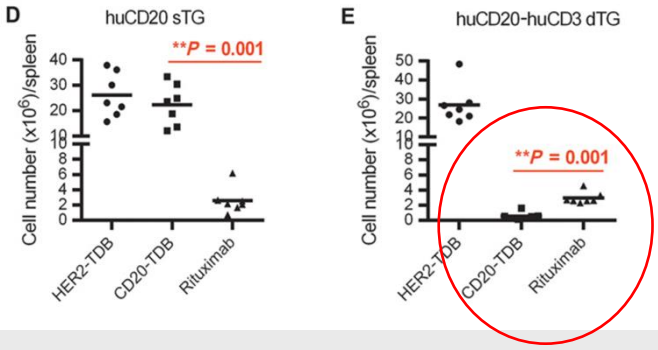
Impressive efficacy in humanized mice

Roche

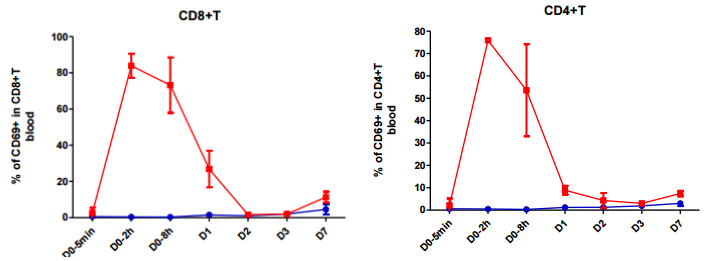
CancerImmunology

Genentech

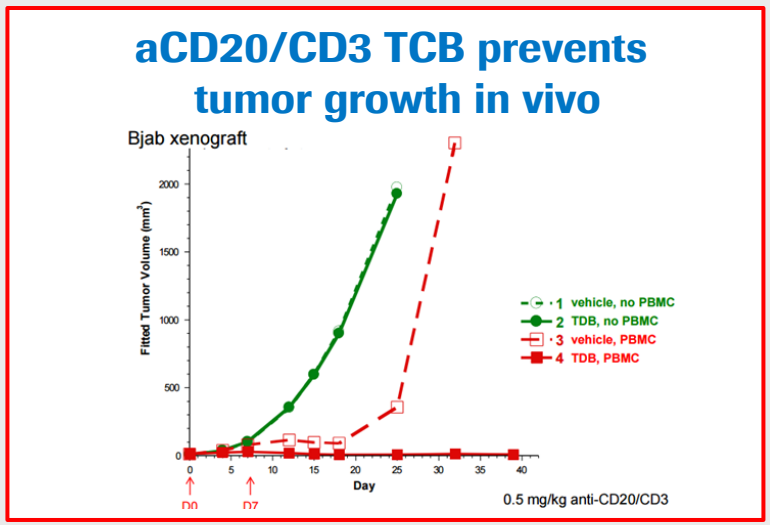
aCD20/CD3 TCB acitivity vs Rituxan



T cell activation in blood



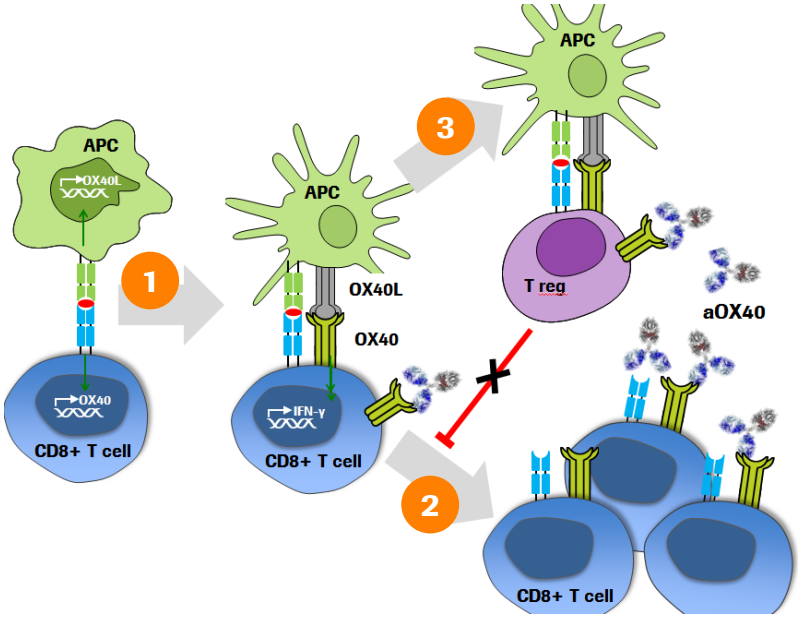
aCD20/CD3 TCB prevents tumor growth in vivo



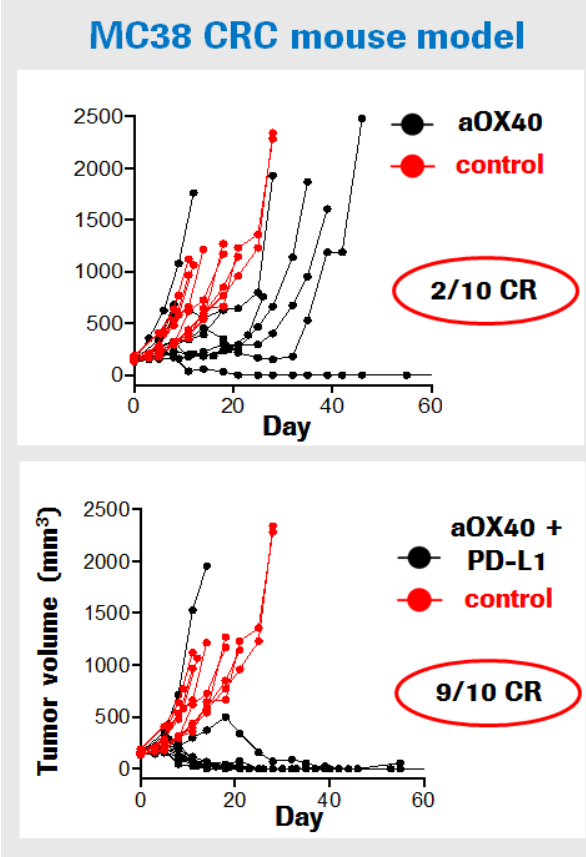
Sun L.L. et al., Science translational Medicine, May 2015; TCB=T cell bispecific; CD8+ T cell=cytotoxic T lymphocyte (CTL); CD4+ T cell=T helper cells

aOX40 exhibits a dual mechanism of action

Promote antigen dependent T cell activation and regulatory T cell inhibition



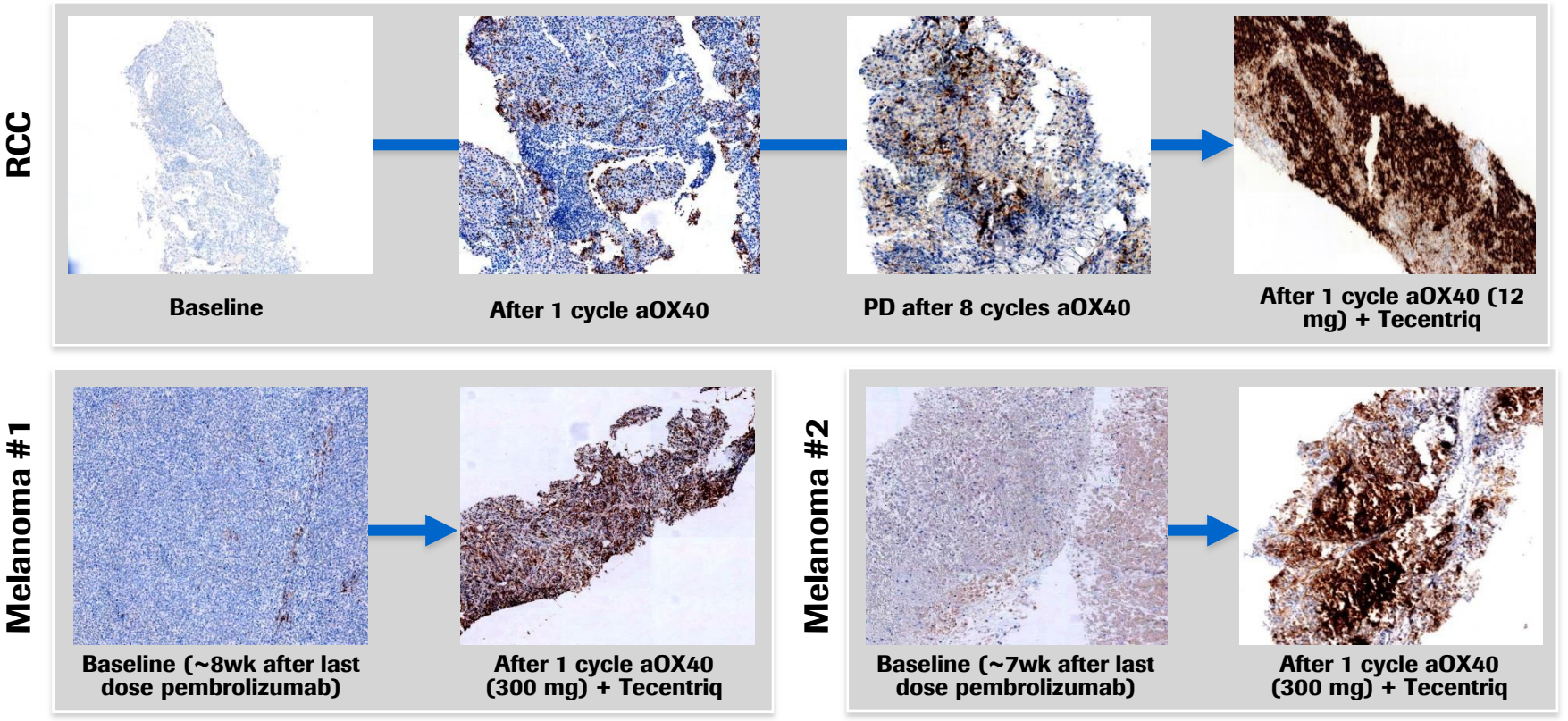
1. *Antigen dependent T cell activation*
2. *OX40L/OX40 costimulation promotes T cell activation*
3. *Inhibtion of regulatory T cells*



APC=antigen presenting cell; CD8+ T cell=cytotoxic T lymphocyte (CTL); T reg=regulatory T cell; Adapted from *Nature Rev Immunol.* 4:420 (2004); Infante J.R. et al., ASCO 2016

Early aOX40 + Tecentriq combination data

aOX40 and Tecentriq upregulates PD-L1 following aPD-1 or aOX40 monotherapy



Infante J.R. et al., ASCO 2016

CIT has changed the oncology paradigm

Update gRED CIT portfolio

The learning loop: Clinical data informs combinations and NME selection

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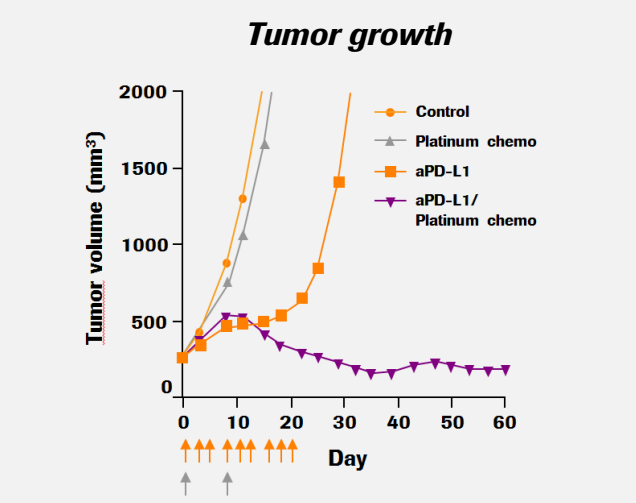
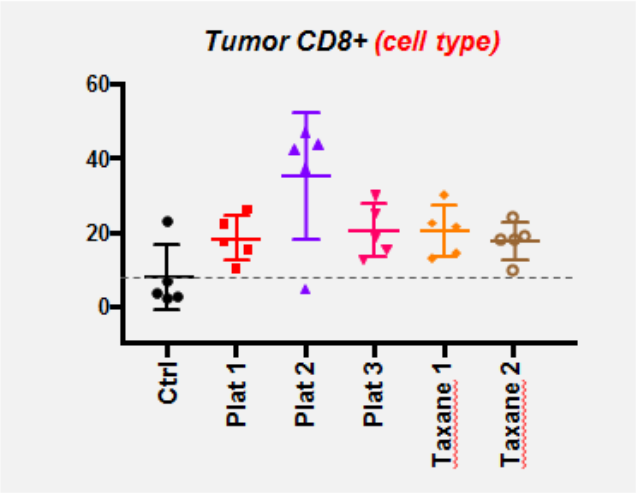
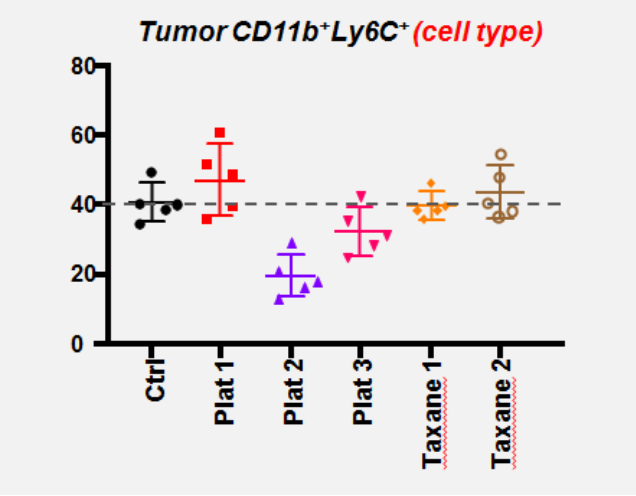
How do clinical biomarker data define next steps?

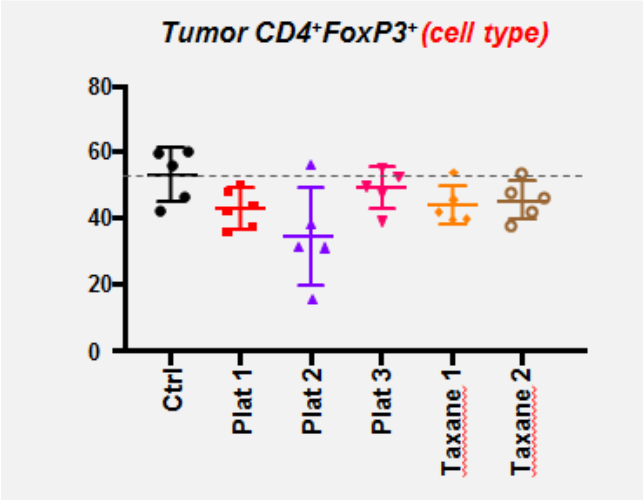
Learning loop story 1: Chemo as immunotherapy

Platins effect preclinical efficacy and immunobiology









Camidge et al., WLCL 2015

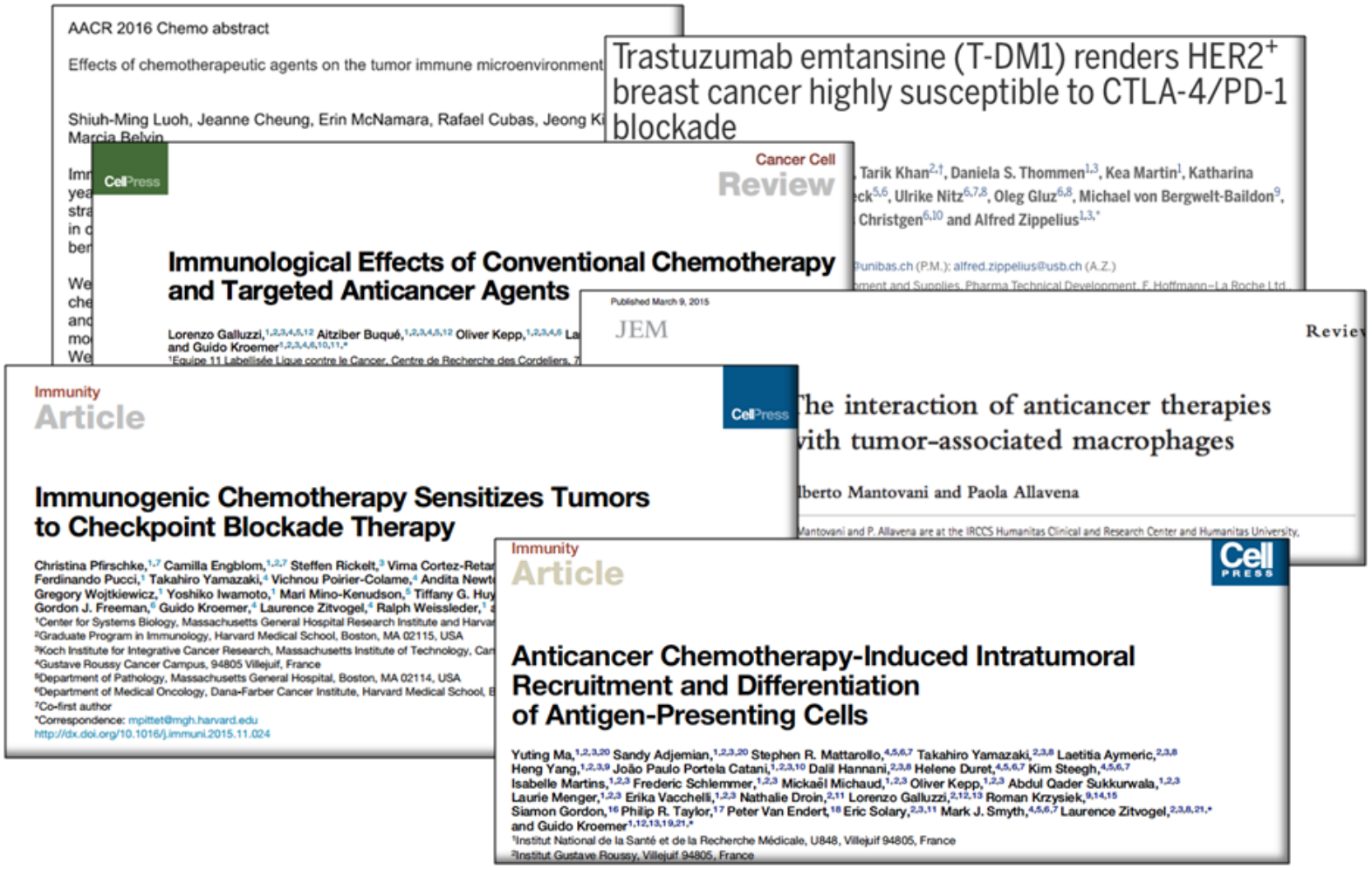
Chemo combinations in immunotherapy

The field is confirming in house findings

Roche

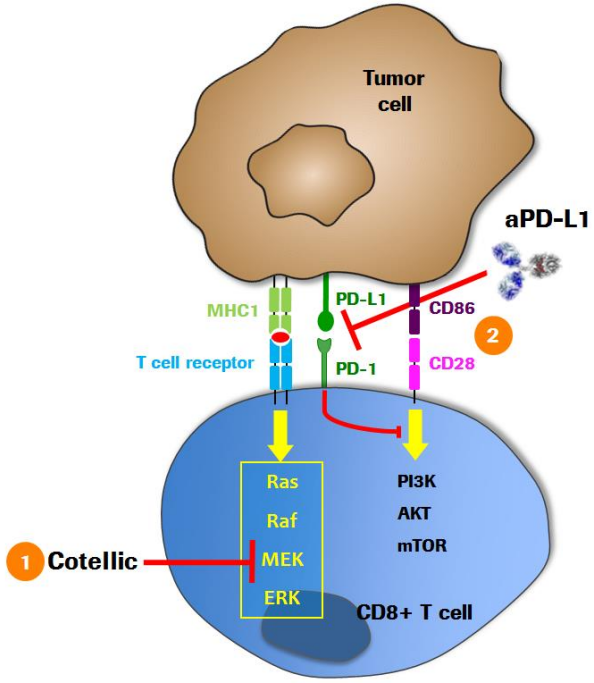
CancerImmunology

Genentech

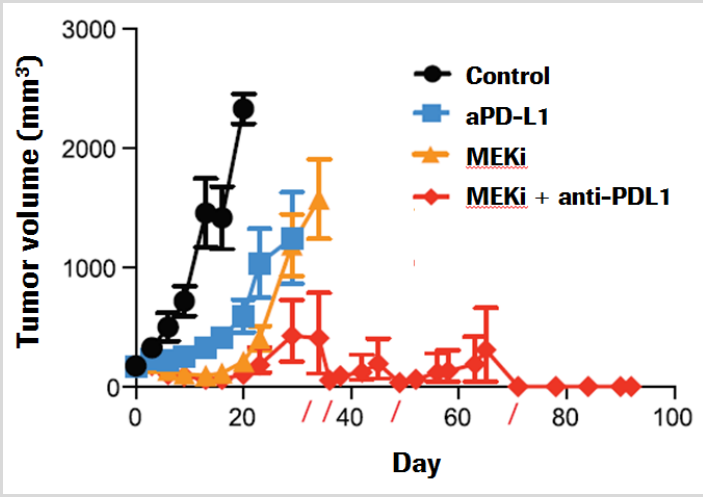


Learning loop story 2: MEKi+Tecentriq

Although MEK inhibition should block T cell function
MEKi + aPD-L1 combo shows preclinical efficacy



Primary tumor challenge of aPD-L1 + MEKi (BT26 model)



1. *MEK inhibition should block T cell function*
2. *PD-L1/PD-1 regulates signaling by costimulatory molecules via the PI3 kinase pathway*

Ebert et al. *Immunity* 2016; BT26 (KRASmt) colorectal mouse model

MEKi combines with aPD-L1 preclinically

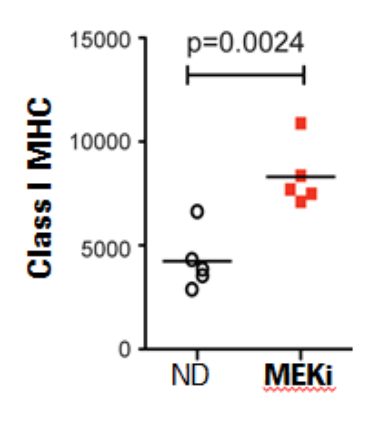
Positive impact on tumor antigen presentation and accumulation of intra-tumoral T cell effectors

Roche

CancerImmunology

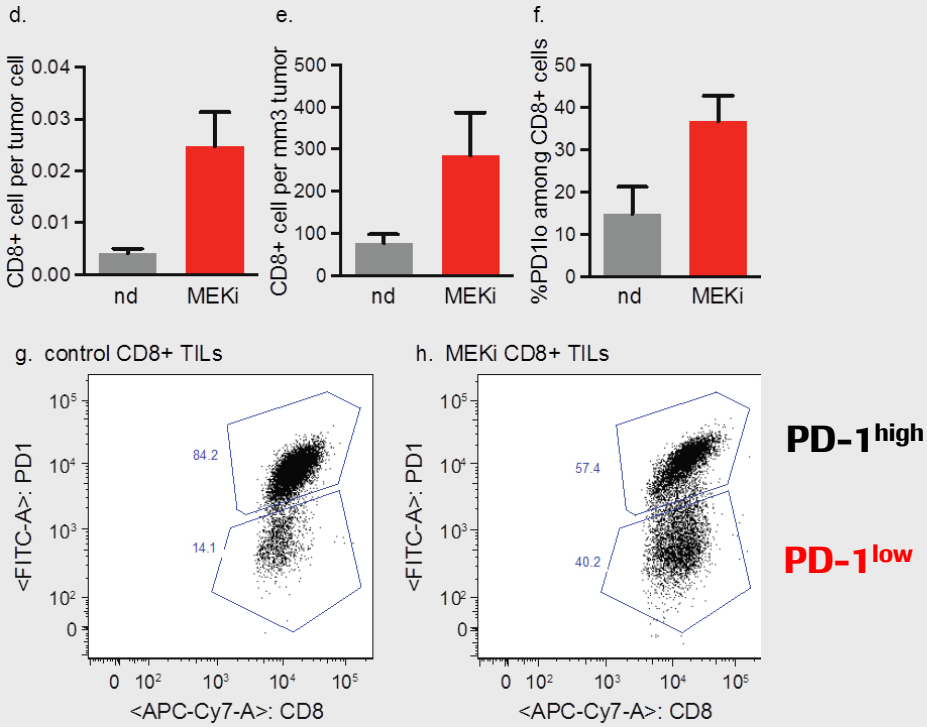
Genentech

Upregulation of tumor MHC class I and antigen presentation



Ras/MAPK pathway activation down regulates MHC class I; MEKi reverses

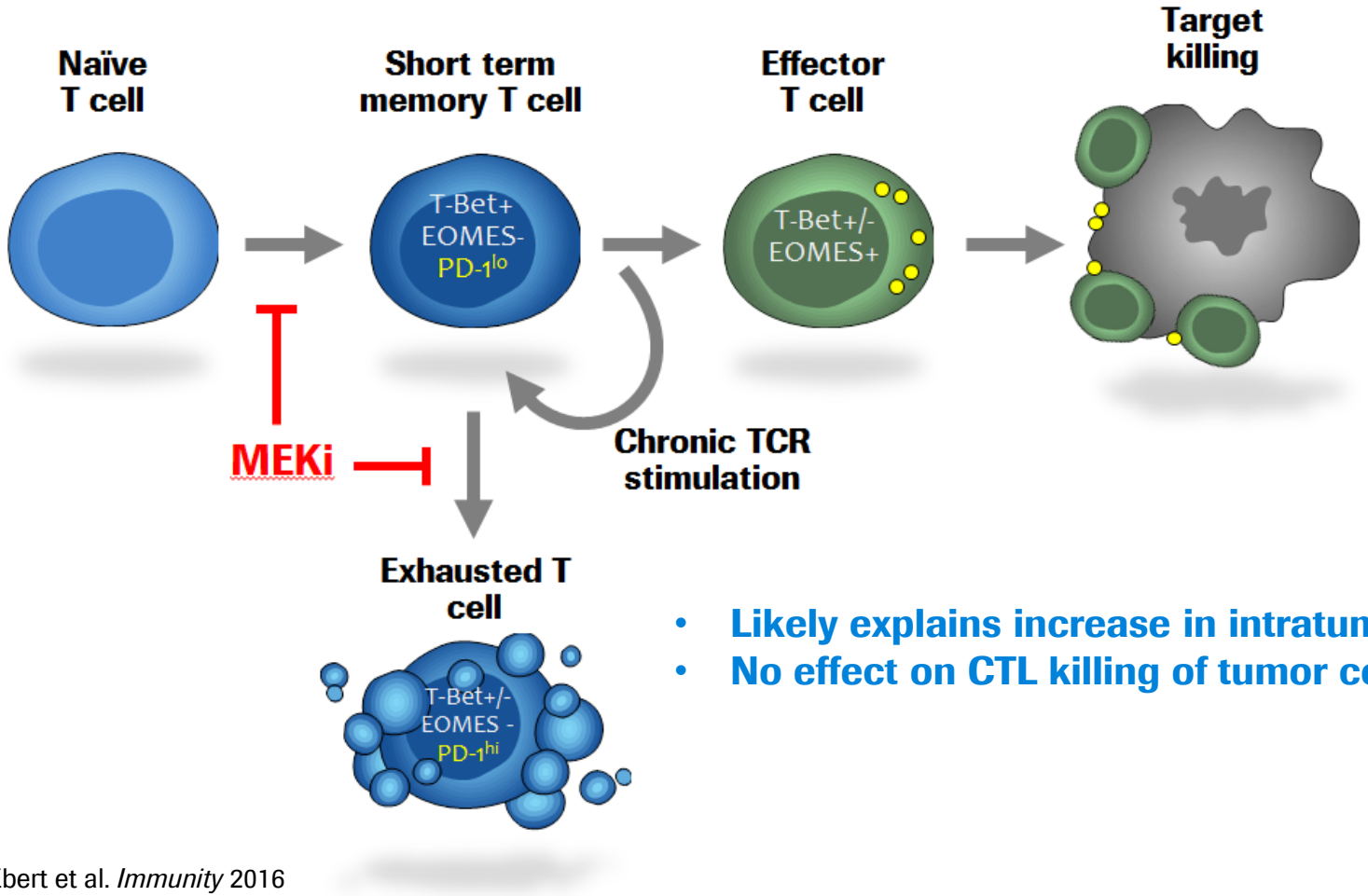
MEK inhibition causes an increase in incompletely exhausted PD-1^{low} CD8+ T cells in tumors



Ebert et al. *Immunity* 2016

MEKi is an unexpected combo partner for aPD-L1

Blocks naive T cell priming but inhibits T cell exhaustion



- **Likely explains increase in intratumoral T cells**
- **No effect on CTL killing of tumor cells**

Ebert et al. *Immunity* 2016

CIT has changed the oncology paradigm

Update gRED CIT portfolio

The learning loop: Clinical data informs combinations and NME selection

---

How do clinical biomarker data define next steps?

Human tumors can be classified according to three generalized “immune profiles”

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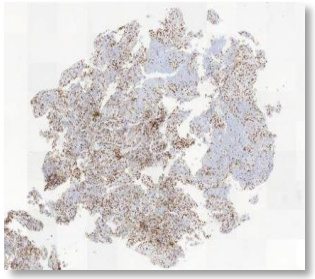
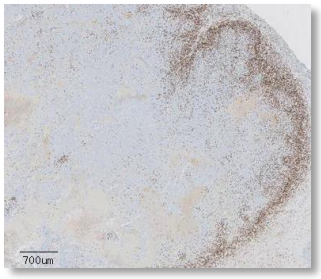
Inflamed



CD8+ T cells infiltrated, but non-functional

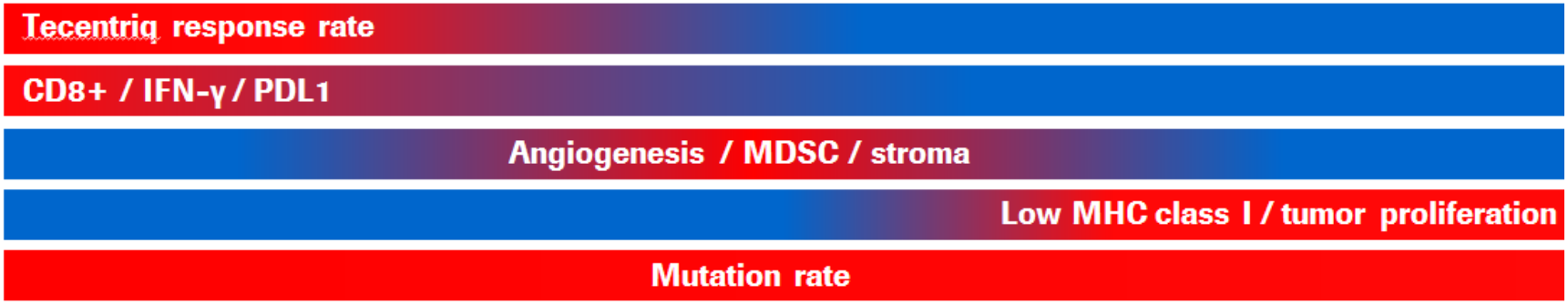
Immune Excluded



CD8+ T cells accumulated but have not efficiently infiltrated

Immune Desert

CD8+ T cells absent from tumor and its periphery



MDSC=myeloid-derived suppressor cells

Clinical findings define the rate limiting steps on the Cancer Immunity Cycle, and what to do next

Roche

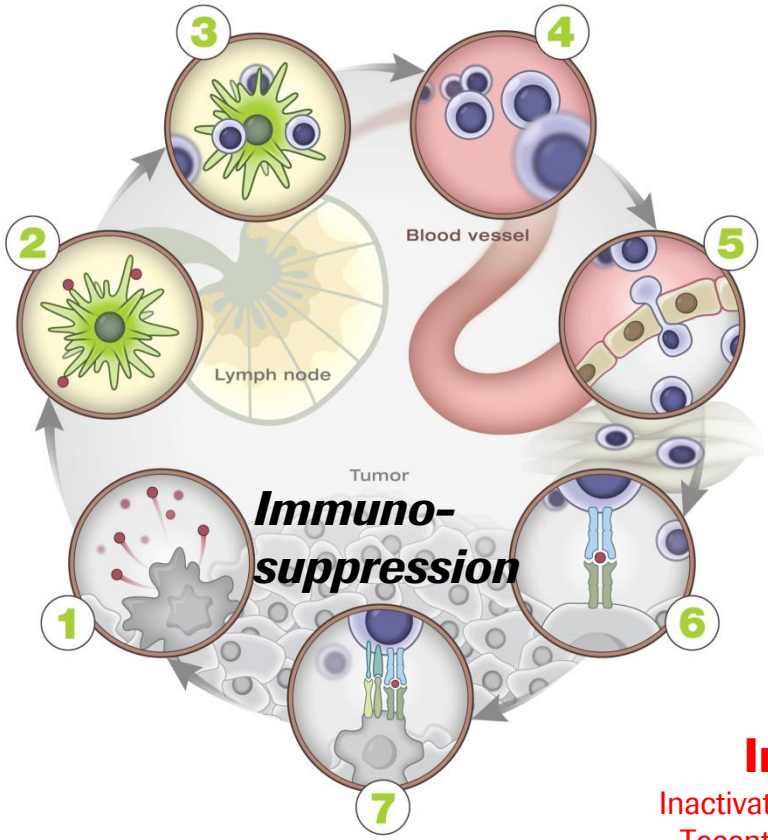
CancerImmunology

Genentech

Immune desert

Insufficient T cell response

- Vaccines
- Chemo
- Pro-inflammatory strategies
- TCB's



Excluded infiltrate

Inadequate T cell homing

- Anti-angiogenics
- Stromal targets
- Chemokines
- Vaccines

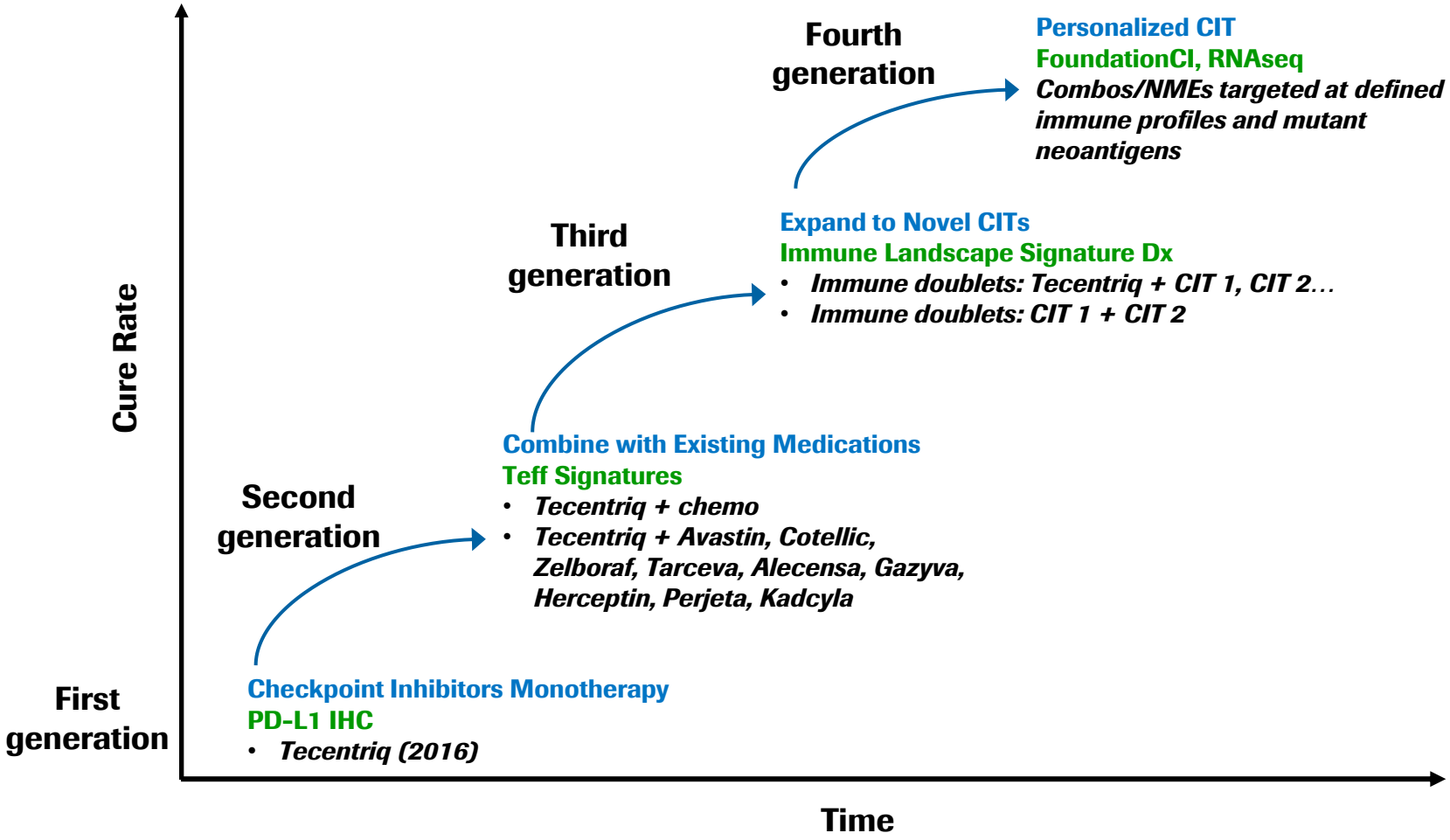
Inflamed

Inactivated T cell response: Tecentriq most effective

- Negative regulators
- Vaccines

Realizing the potential of cancer immunotherapy

The learning loop will guide CIT progress



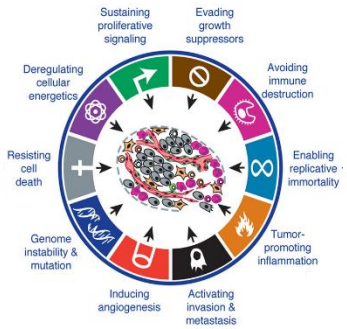
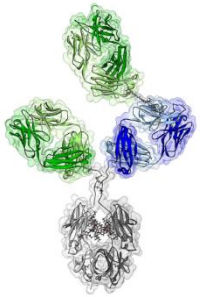
NME=new molecular entity

Early pipeline update: Assets and strategies

William Pao, M.D., Ph.D.
Global Head Oncology Discovery and Translational Area, Roche pRED

Foundation for pRED oncology drug development

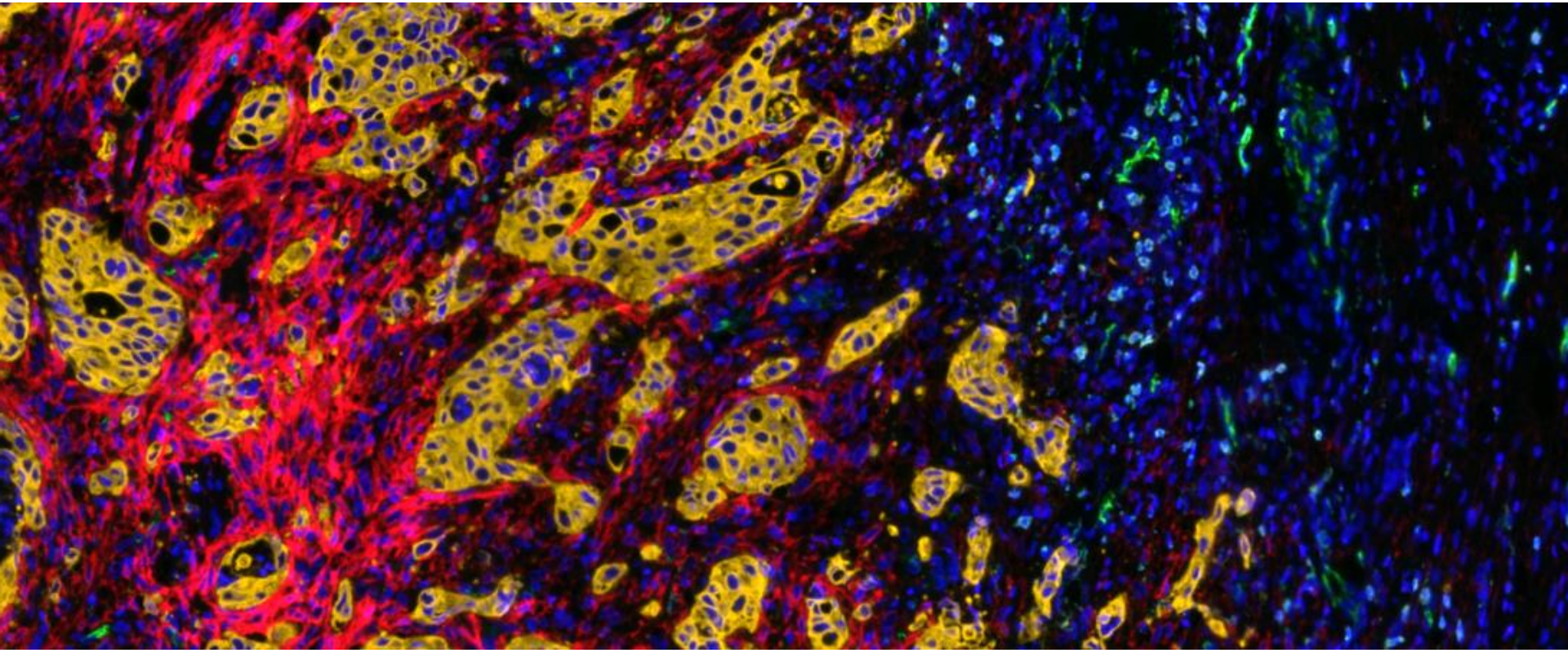
Developing medicines of the future

Deep understanding of disease biology	Fit for purpose molecules	Personalized healthcare
		
Identify tractable and druggable targets within the hallmarks of cancer	Develop the right drug with the right format against the right target	Develop the right drug for the right patient at the right time

Hanahan and Weinberg, *Cell* '11

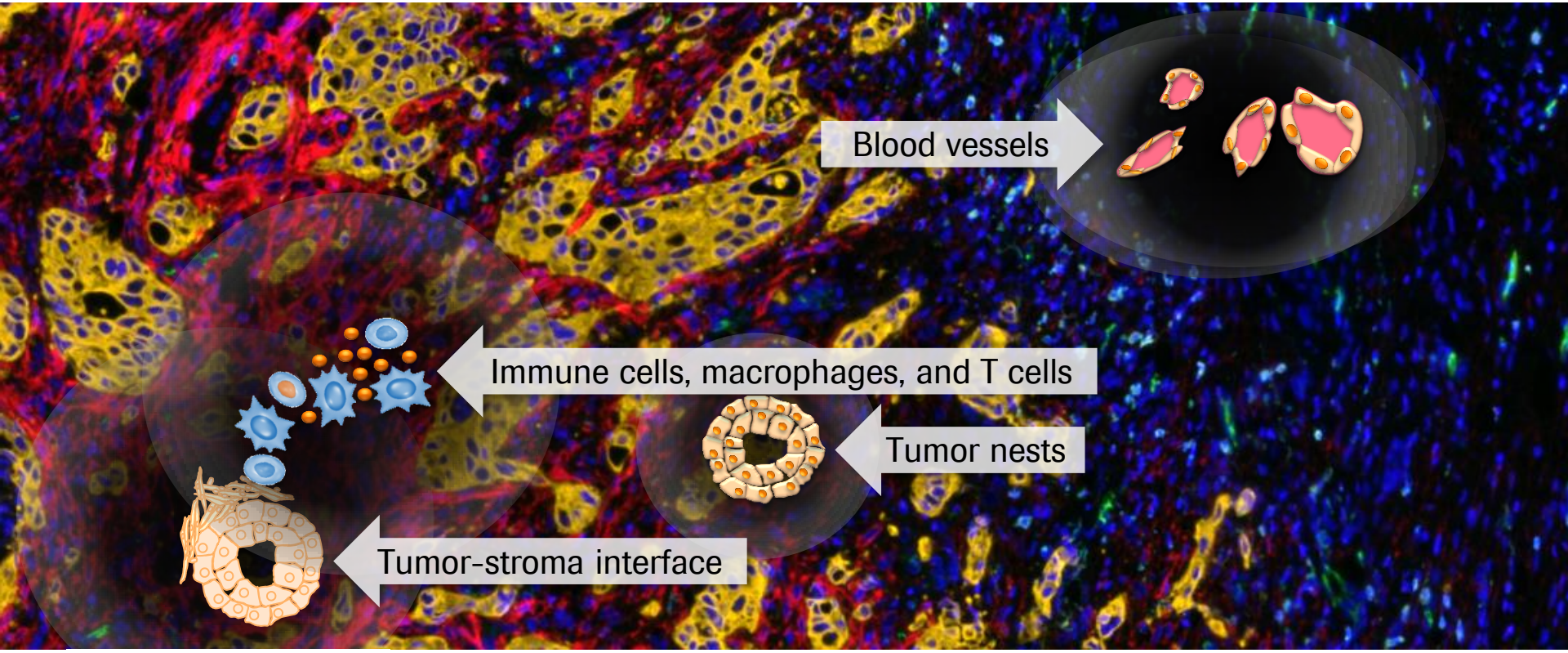
Following the science

Understanding patient, tumor and immune context are key to developing new molecules



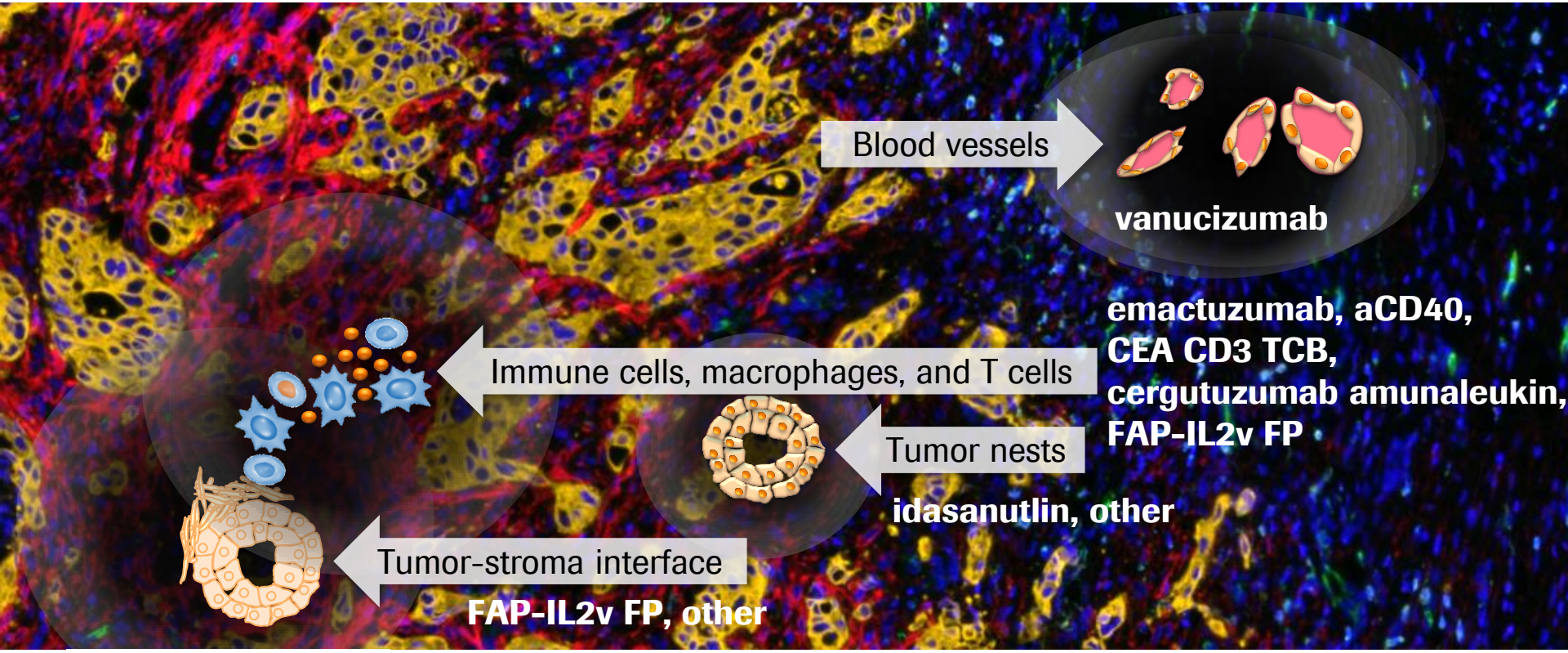
Following the science

Understanding patient, tumor and immune context are key to developing new molecules



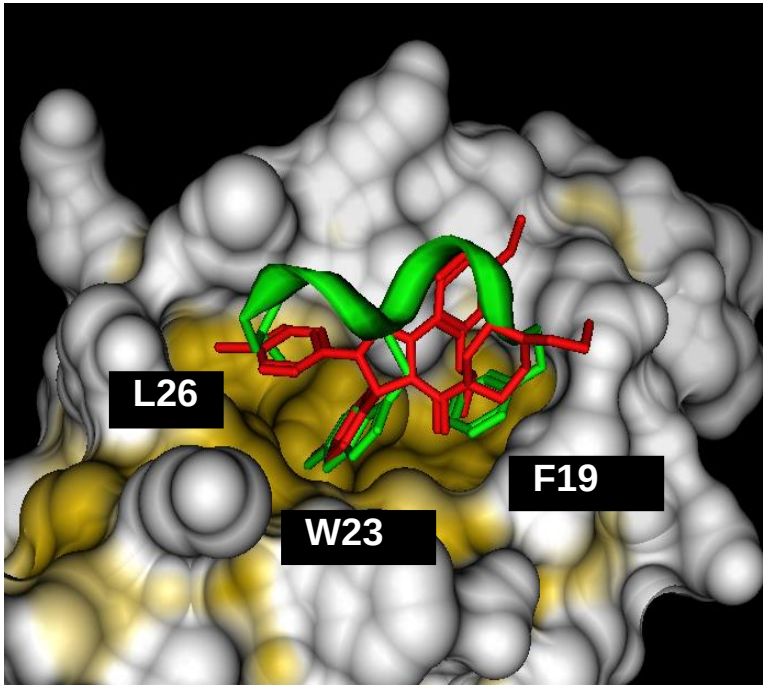
Following the science

Understanding patient, tumor and immune context are key to developing new molecules



Idasanutlin

Novel MDM2 antagonist for activating tumor suppressor p53



Mechanism of action

- **First-in-class**, oral, selective, MDM2 antagonist inhibiting binding to p53. Blocking the MDM2-p53 interaction **stabilizes p53**, activates p53-mediated apoptosis, and inhibits tumor cell growth
- Among first small molecules to disrupt a non-enzyme **protein:protein interaction** (Vassilev et al., *Science* 2004)

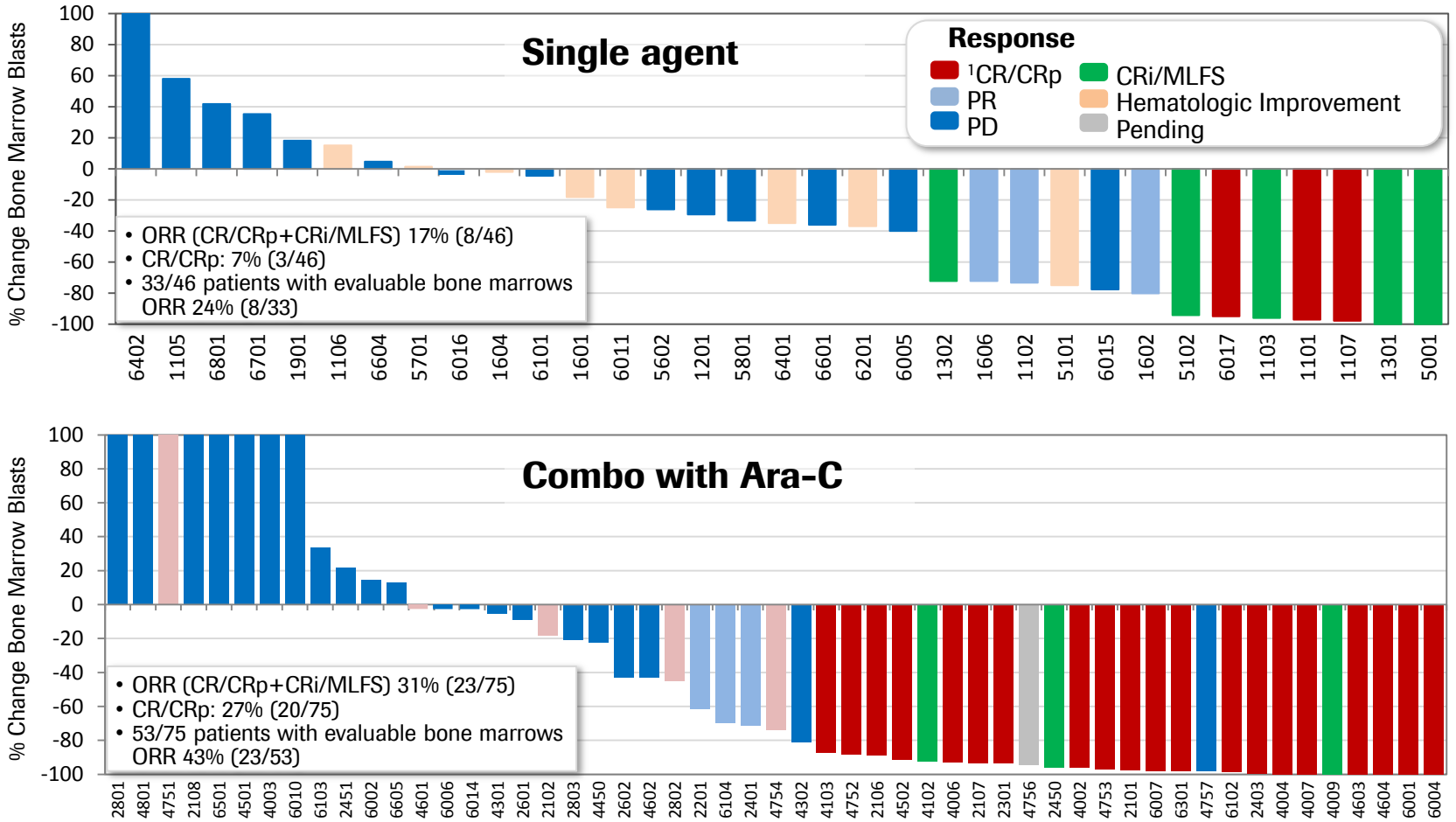
Status of idasanutlin

- Ph Ib study in **relapsed/refractory AML** showed promising activity as monotherapy and with cytarabine
- **Phase III** (MIRROS) study in AML started Jan 2016
- Additional **combination** studies ongoing in myeloproliferative neoplasms (with PEG-IFN), elderly unfit AML (with Venclexta), and NHL (with Gazyva)

Venclexta in collaboration with AbbVie

Update of idasanutlin responses in AML (Ph1/1b)

Median duration of response > 7 months

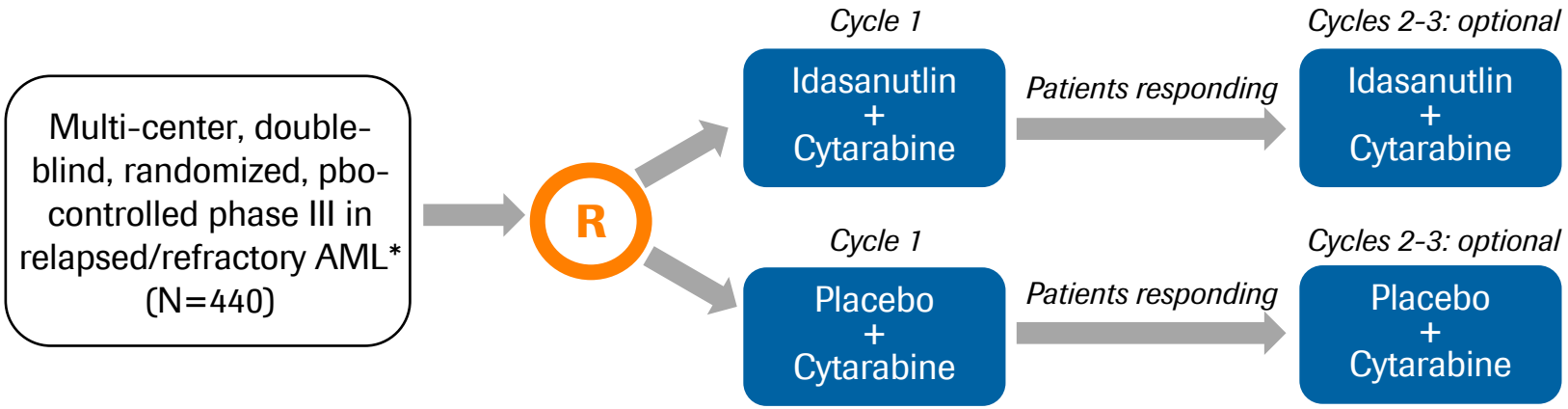


[1]CR defined as marrow assessment after cycle 1 with a second marrow assessment > 28 d after initial assessment

Response definitions:
CR: < 5% marrow blasts with complete recovery of peripheral counts; CRp – CR with incomplete platelet recovery; CRi / MLFS: < 5% marrow blasts with incomplete / no recovery of peripheral counts, morphologic leukemia free state; PR: > 50% decrease in marrow blasts

Idasanutlin: Phase 3 MIRROS study in R/R AML

- **Study design**



Primary outcome measures

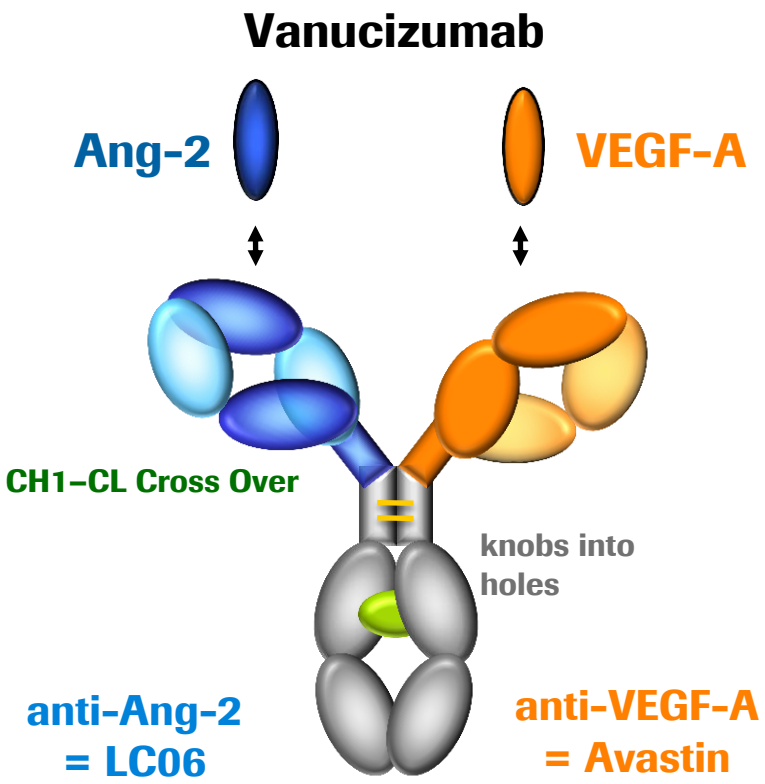
- OS in TP53 wild-type population

Key secondary outcome measures

- OS in overall population, CRi, ORR, including CR, CRp and CRi, EFS

R/R AML – relapsed/refractory acute myeloid leukemia; *Non-US trial

Vanucizumab
Bispecific antibody against Ang-2 and VEGF-A



Mechanism of action

- Binds to **both** angiopoetin-2 and VEGF-A, neutralizing two complementary angiogenic factors
- Additional potential **immunomodulatory** effects through inhibition of Ang-2 and VEGF-A
- First Roche antibody to use **CrossMab technology**

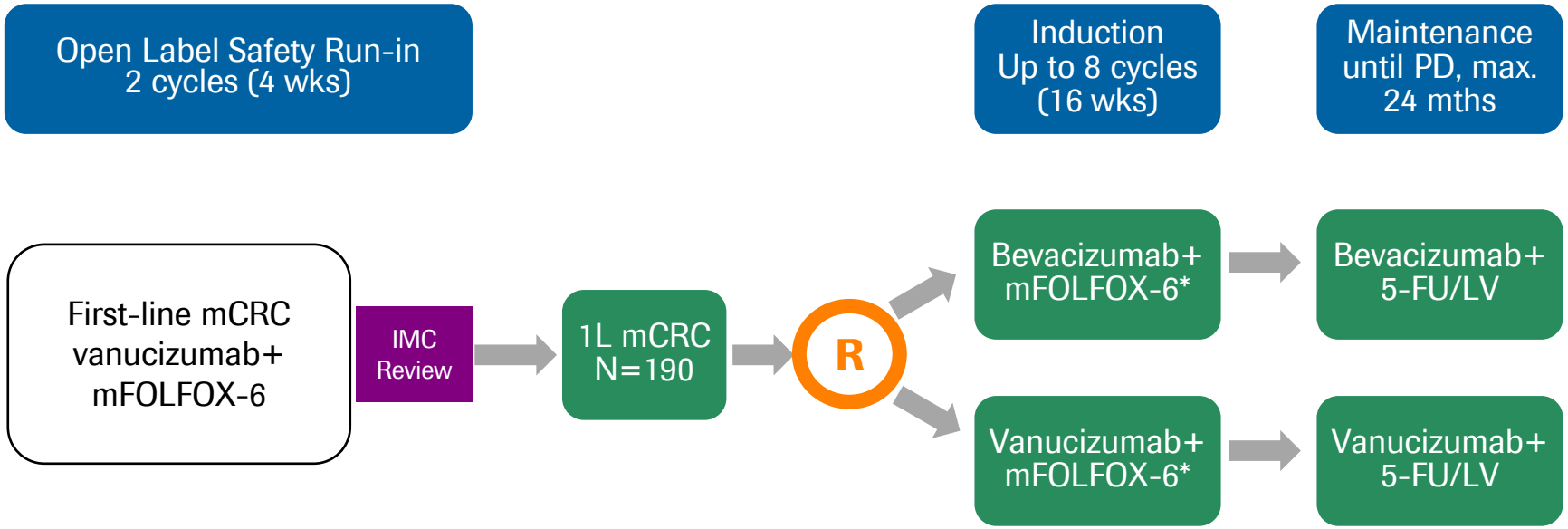
Status of vanucizumab

- **Ph II** (McCave) study in **1L CRC** H2H against Avastin ongoing
- **Phase Ib** in platinum-resistant **ovarian** cancer showed 29% RR*
- **Ph Ib** with **CD40** in solid tumors ongoing
- **Ph Ib** with **Tecentriq** in solid tumors ongoing

Kienast et al., *CCR* 2013; *Oaknin et al., *PASCO* '15

Vanucizumab: 1L CRC, McCAVE Phase 2 Study

Data expected in late 2016



Primary outcome measures

- PFS

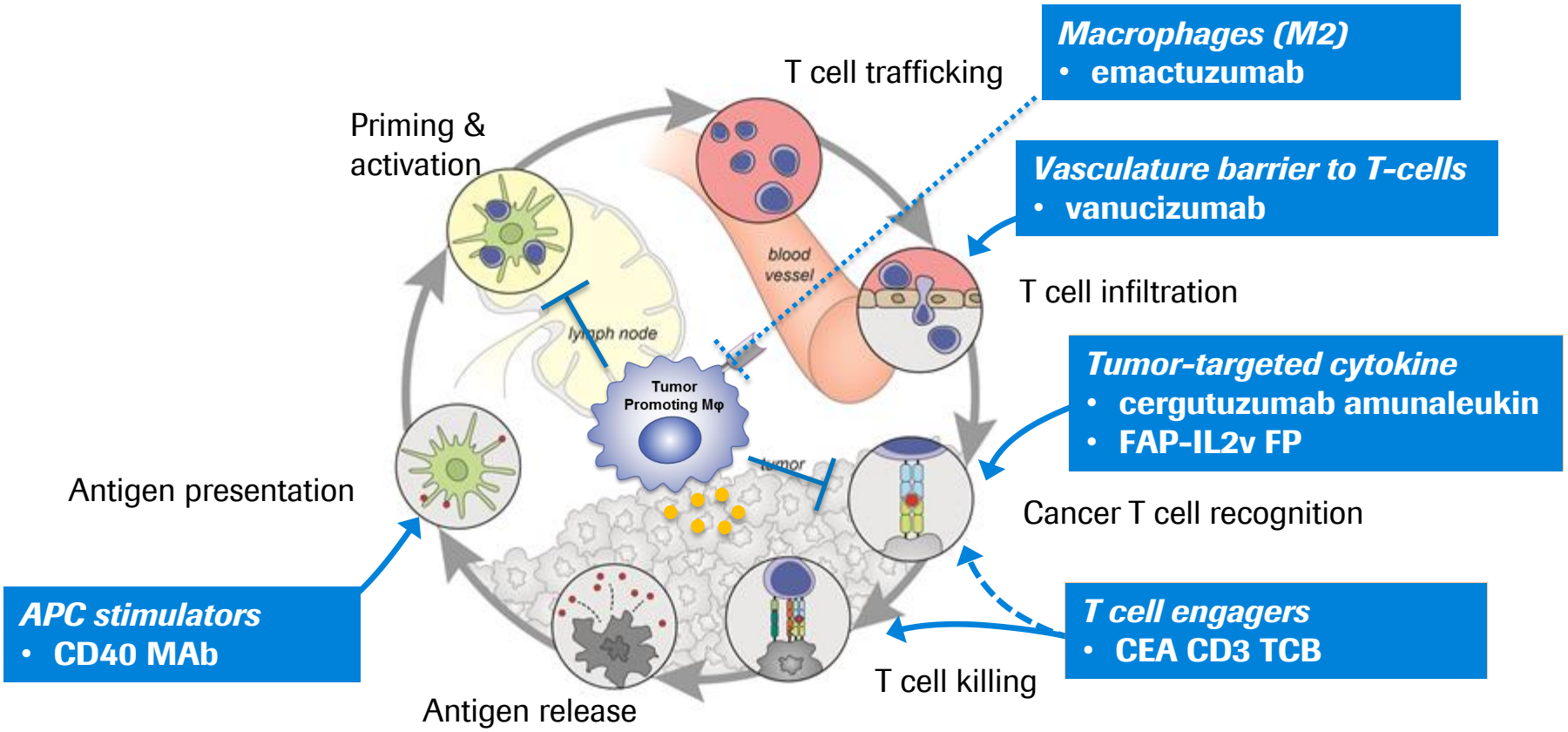
Key secondary outcome measures

- Safety and tolerability, RECIST ORR, OS and duration of response, PK

*mFOLFOX-6: 85 mg/m^2 Oxaliplatin; 400 mg folinic acid i.v. over 2 hrs; 400 mg/m^2 5-FU as bolus, 2.400 mg/m^2 5-FU as 46-hrs permanent infusion

Roche pRED CIT molecules in the clinic

Targeting multiple steps of the cancer-immune cycle



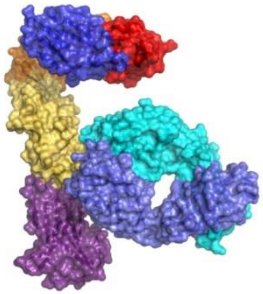
Adapted from Chen & Mellman, *Immunity* '13

APC=antigen presenting cell; CD=classification determinant; CEA=carcinoembryonic antigen; CIT=cancer immune therapy; FAP=fibroblast activation protein; TCB=T cell bispecific

Ongoing or planned pRED immune doublets

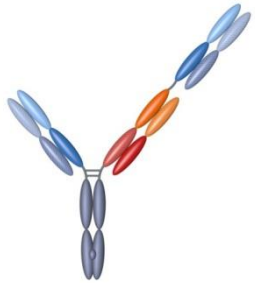
Seven novel combinations in the clinic

aCSF-1R

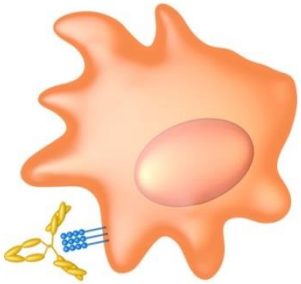


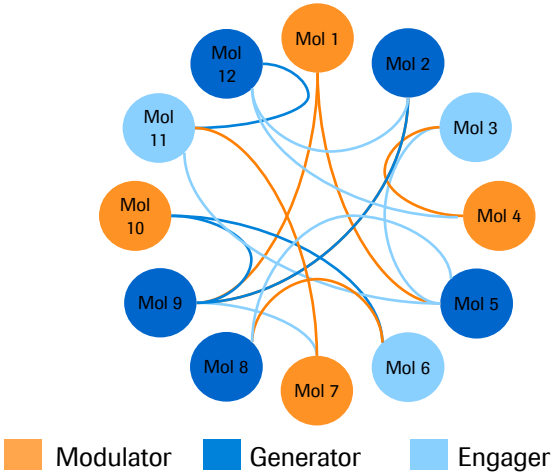
CEA-IL2v FP
FAP-IL2v FP

CEA CD3 TCB



aCD40

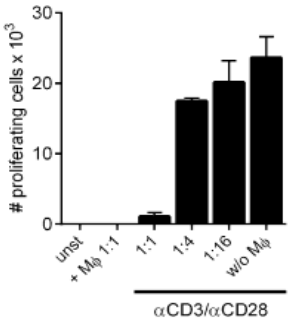


Combinations	***With Tecentriq***	***Other***
	✓ • aCSF-1R	✓ • aCD40/aCSF-1R
	✓ • aCD40	✓ • aCD40/Ang2-VEGF biMAb
	✓ • CEA-IL2v FP	• aCSF-1R/Avastin (IST)
	✓ • CEA CD3 TCB	• aFAP-IL2v/cetuximab
	✓ • Ang2-VEGF biMAb	
	• FAP-IL2v FP	

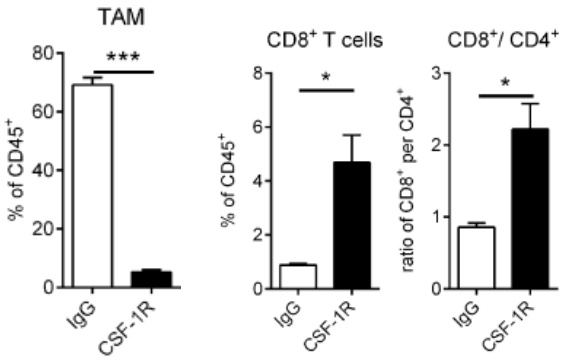
✓ Phase I ongoing

Emactuzumab eliminates T cell suppressive macrophages and enhances anti-tumor immunity

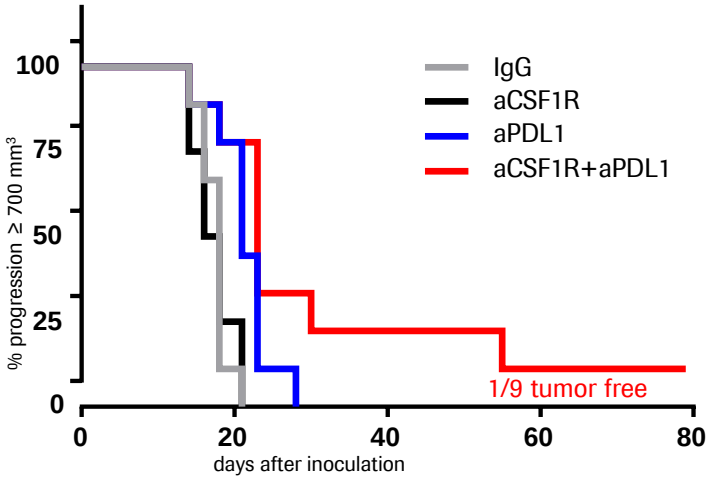
Tumor-derived macrophages suppress T cell proliferation



aCSF-1R antibody treatment increases lymphocyte infiltration in colon cancer mouse model



aCSF1R + aPD-L1 combination in colon cancer mouse model



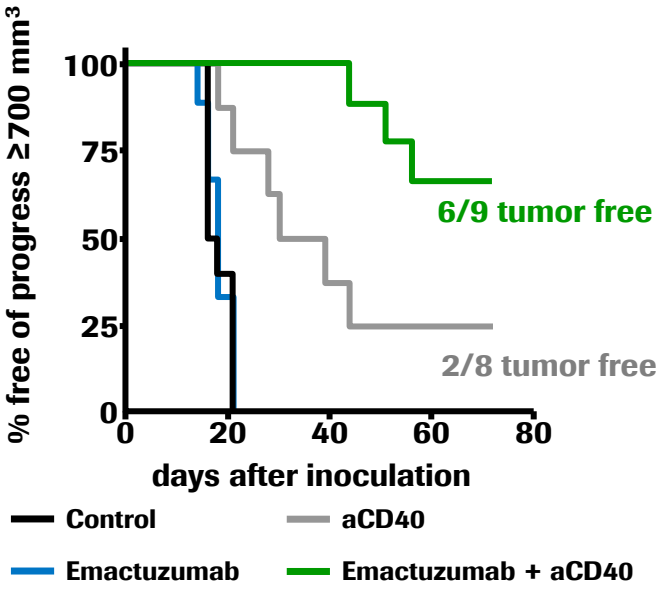
Phase Ib study combining emactuzumab and atezolizumab in solid tumors ongoing

Ries et al., *Cancer Cell* '14

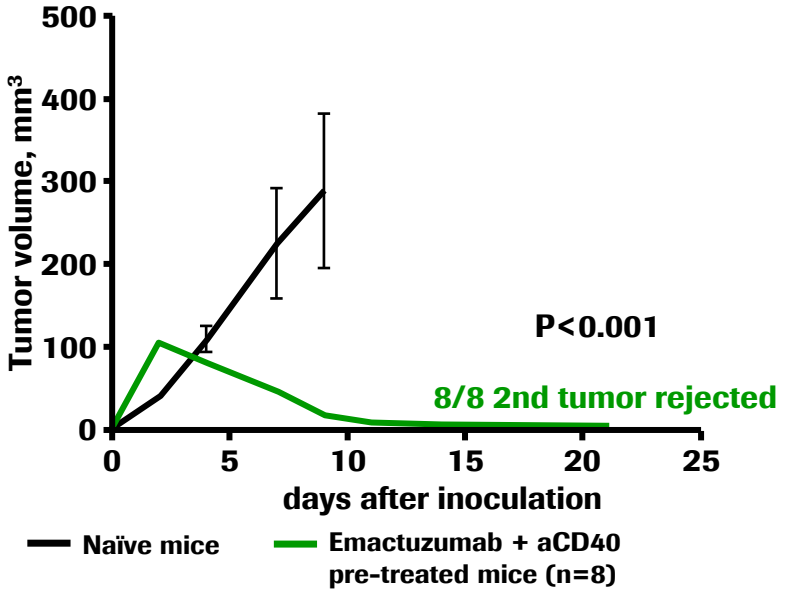
CIT combos may yield long-term benefits

aCSF1R + aCD40 doublet induces immunologic "memory" in mice – tumors rejected on re-challenge

Emactuzumab + aCD40 in colon cancer mouse model



100% second tumor rejection in combo pre-treated vs. naïve mice



Phase Ib study combining emactuzumab and aCD40 in solid tumors ongoing

C. Wolter, K. Wartha, S. Hoves, C. Ries, Roche Innovation Center Munich

IL2v fusion protein platform

Two targeted molecules in development

Advantages over proleukin

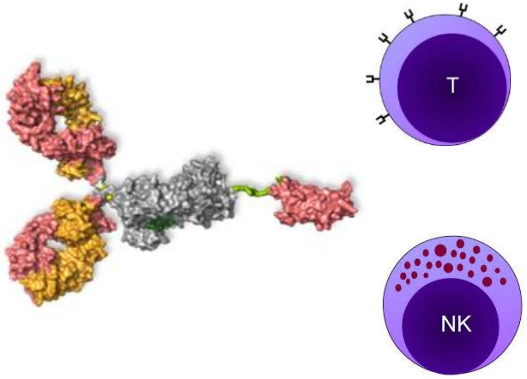
- **Higher** exposure
- More **favorable PD** effects: NK / immune-effector > suppressor-cells
- Clinical evidence for **tumor targeting**
- Better **safety** profile

CEA vs FAP targeting

CEA – tumor cells

FAP – stromal cells

Mechanisms of action

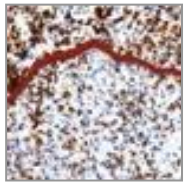
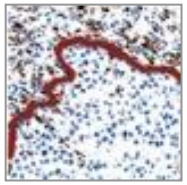
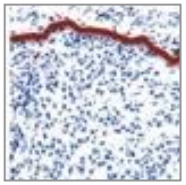


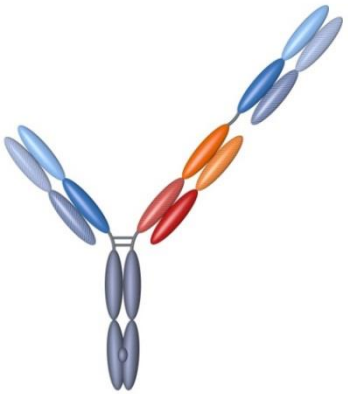
- **Phase Ib study combining cergutuzumab amunaleukin and atezolizumab ongoing**
- **Phase I with FAP-IL2v FP ongoing; combination of FAP-IL2v FP and atezolizumab planned**

Tabernero et al., ECC '15; Nicolini et al., AACR '16

CEA CD3 T cell bispecific for solid tumors

Using innovative engineering from pRED to develop best-in-class platform

Tumor histology	***Inflamed***	***Immune Excluded***	***Immune Desert***
			
CEA CD3 TCB	**Mono/combo potential**		



Binding simultaneously to tumor and T cells by CEA CD3 TCB results in:

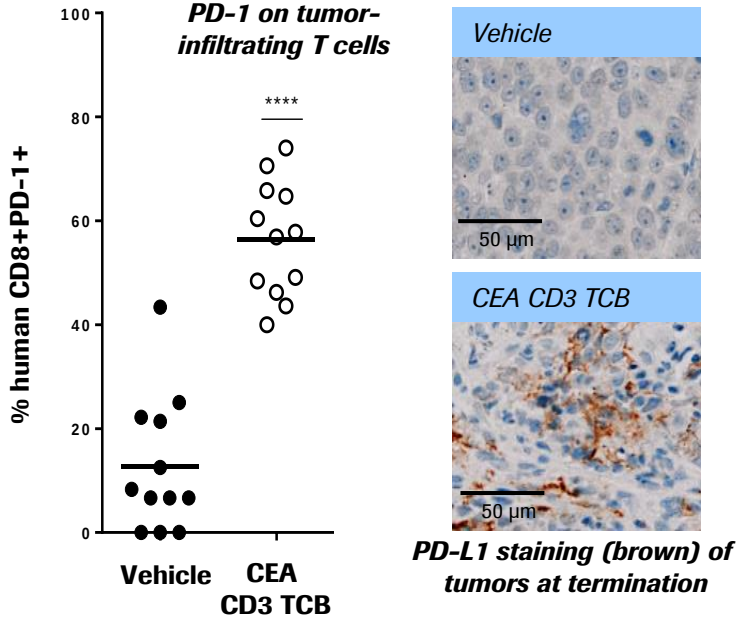
- T cell engagement, activation and **killing of tumor cells** by delivery of cytotoxic granules
- **T cell proliferation** (expansion) selectively at site of activation

CIT=cancer immune therapy; TCB=T cell bispecific antibody; Hegde et al., *CCR* '16; Bacac et al., *CCR '16*

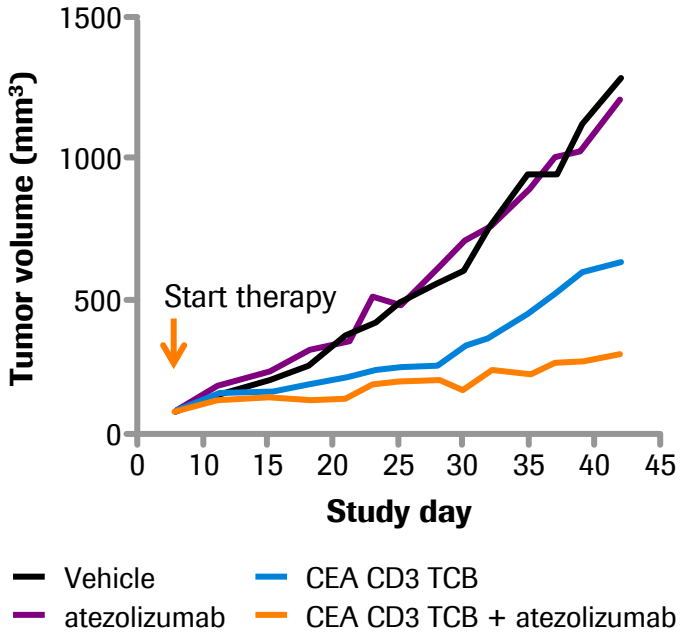
Combination of CEA CD3 TCB + atezolizumab elicits superior anti-tumor activity

Upregulation of PD-L1 and PD-1 by TCB consistent with MoA

CEA CD3 TCB: induces PD-1 on T cells and PD-L1 on tumor cells in preclinical models



CEA CD3 TCB + aPD-L1 in fully humanized PD-L1-resistant xenograft model



Phase Ib study combining CEA CD3 TCB and atezolizumab ongoing in CEA+ tumors

CEA=carcinoembryonic antigen; MoA=mode of action; PD-1=programmed death 1; PD-L1=Programmed death ligand 1; TCB=T cell bispecific antibody; Bacac et al., AACR '16

pRED: Rich newsflow ahead for immune combos

Study	Molecule	Primary endpoint	Status	*Expected readout
Tecentriq combination studies				
Phase I N=110	emactuzumab (aCSF-1R)	Safety	FPI Q1 2015	2017
Phase I N=160	CD40 MAb	Safety, PD, efficacy	FPI Q4 2014	2017
Phase I N=100	CEA CD3 TCB	Safety, PK, PD, imaging, biomarkers	FPI Q1 2016	2017
Phase I N=75	cergutuzumab amunaleukin (CEA-IL2v)	Safety, efficacy, PK, PD	FPI Q2 2015	2017
Phase I N~40	vanucizumab	Safety, efficacy	FPI Q2 2016	2017
aCD40 combination studies				
Phase I N~120	emactuzumab	Safety, PK, PD	FPI Q2 2016	2017
Phase I N=170	vanucizumab	Safety, PD, efficacy	FPI Q1 2016	2017

*Event-driven, timelines may change

Targeted therapies and future combinations

Sandra Horning, M.D.
Executive VP
Chief Medical Officer and Head Global Product Development

Introduction: Portfolio progress

Lung: Alecensa (J-ALEX)

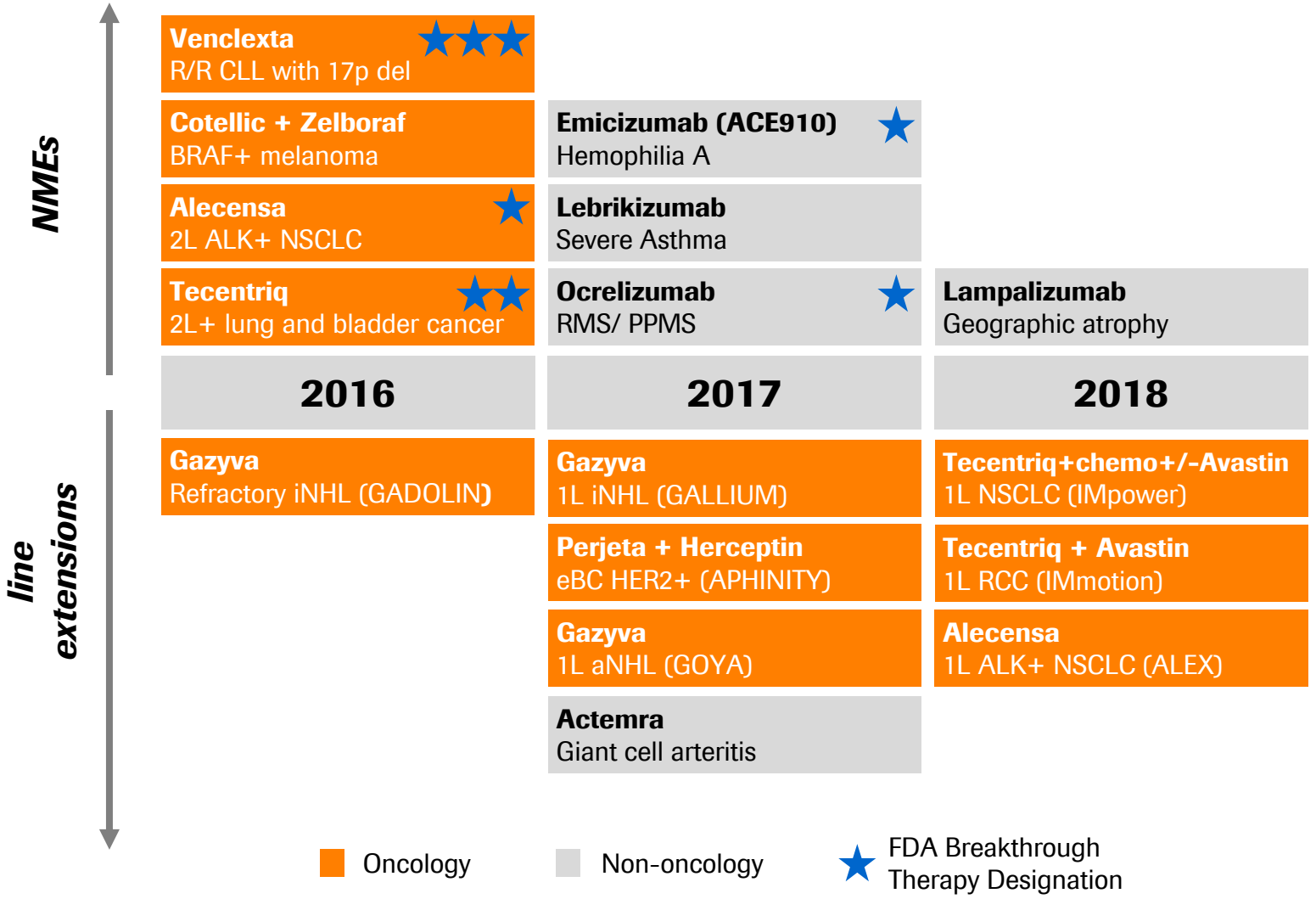
Melanoma: Cotellic + Zelboraf

Breast: Cotellic, Perjeta (PHEREXA)

Hematology: Gazyva, Venclexta

Summary

2016 onwards: Significant launch activities



Outcome studies are event-driven: timelines may change. Standard approval timelines of 1 year assumed; Alecensa and emicizumab in collaboration with Chugai; Venclexta in collaboration with AbbVie; Cotellic in collabortion with Exelixis; Gazyva in collaboration with Biogen

Roche significantly advancing patient care

Recognition for innovation 2013-present

12 *Breakthrough Therapy Designations*

Rank	Company	#
1	**Roche**	**12**
2	Novartis	10
3	BMS	9
4	Merck	7
5	Pfizer	6
6	GSK	5

Year	Molecule
2016	***Ocrelizumab*** *(PPMS)*
	Venclexta *(AML)*
	Venclexta + Rituxan *(R/R CLL)*
2015	***Actemra*** *(Systemic sclerosis)*
	Tecentriq *(NSCLC)*
	Venclexta *(R/R CLL 17p del)*
	Emicizumab*/ACE 910 (Hemophilia A)*
2014	***Esbriet*** *(IPF)*
	Lucentis *(Diabetic retinopathy)*
	Tecentriq *(Bladder)*
2013	***Alecensa*** *(2L ALK+ NSCLC)*
	Gazyva *(1L CLL)*

Source: http://www.focr.org/breakthrough-therapies as at June 2016; PPMS=Primary Progressive Multiple Sclerosis; CLL=Chronic Lymphocytic Leukemia; NSCLC=Non-Small Cell Lung Cancer; IPF=Idiopathic Pulmonary Fibrosis

Introduction: Portfolio progress

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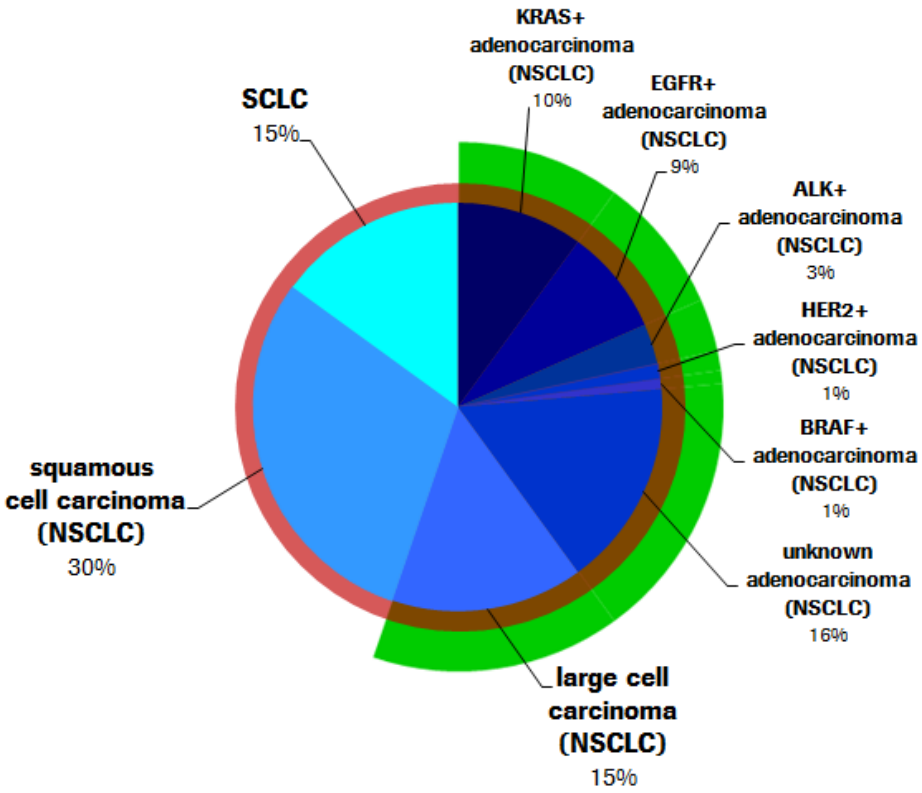
Summary

Lung cancer: Still high unmet medical need

Incidence cases reach 560,000 pts[1]



= Roche marketed

= Roche in development

ALECENSA alectinib 150 mg capsules

Tarceva erlotinib

AVASTIN bevacizumab

TECENTRIQ atezolizumab

COTELLIC (cobimetinib) tablets

Kadcyla ado-trastuzumab emtansine

taselisib
(PI3K inhibitor)

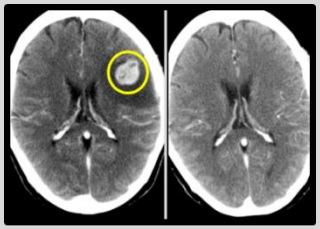
[1] Datamonitor; incidence rates includes the 7 major markets (US, Japan, France, Germany, Italy, Spain, UK); NSCLC=non-small cell lung cancer; SCLC=small cell lung cancer; Alecensa in collaboartion with Chugai; Cotellic in collaboration with Exelixis

Alecensa: ALKi with excellent CNS disease control

Outstanding head-to-head data in 1L ALK+ NSCLC

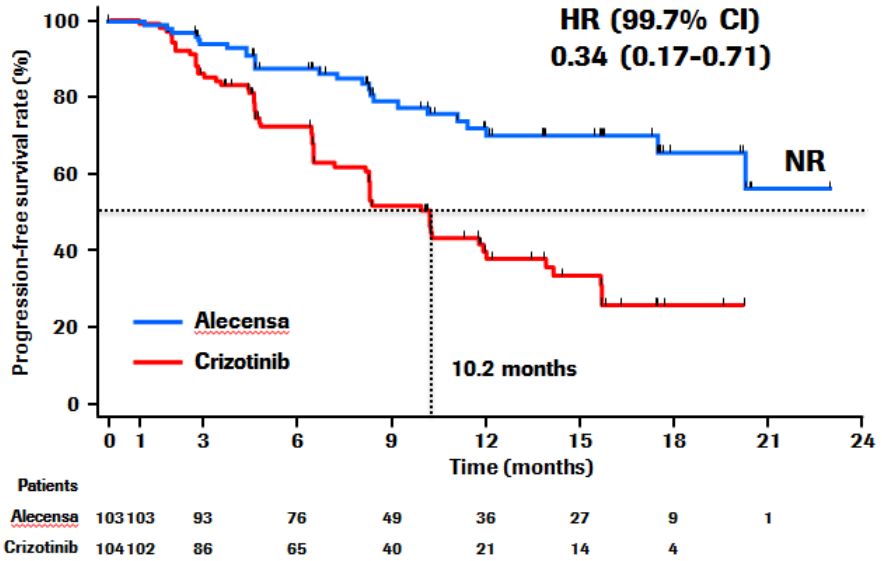
	Alecensa	crizotinib
ORR by IRF* (%)	91.6 (n=83)	78.9 (n=90)
Median PFS (95% CI) by IRF in ITT	NR (20.3-NR) (n=103)	10.2 (8.2-12.0) (n=104)

* In measurable lesions at baseline by IRF



Day 6 Day 87

Progression free survival



Japanese Phase III results (J-ALEX)

- PFS HR of 0.34 versus crizotinib exceeds targeted HR of 0.64 (mPFS was not reached)
- Favorable safety profile compared to crizotinib
- US launch in 2L off to a strong start with 19% share of new patients
- H2H 1L data from global study (ALEX) expected beginning 2017

Nokihara H. *et al,* ASCO 2016; Alecensa (alectinib) in collaboration with Chugai

Introduction: Portfolio progress

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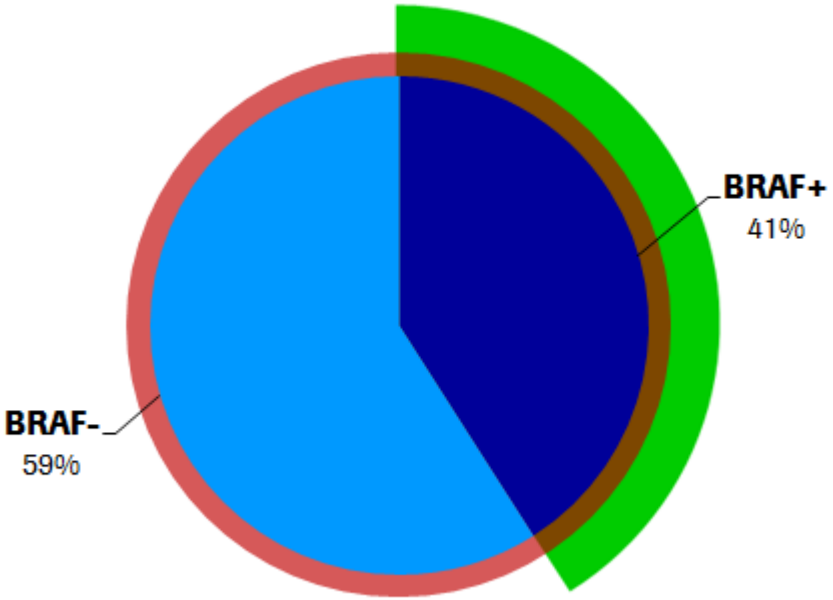
Breast: Cotellic, Perjeta (PHEREXA)

Hematology: Gazyva, Venclexta

Summary

Melanoma: Still high unmet medical need

Incidence cases reach 125,000 pts[1]



ZELBORAF (vemurafenib) tablets

COTELLIC (cobimetinib) tablets

TECENTRIQ atezolizumab

= Roche marketed

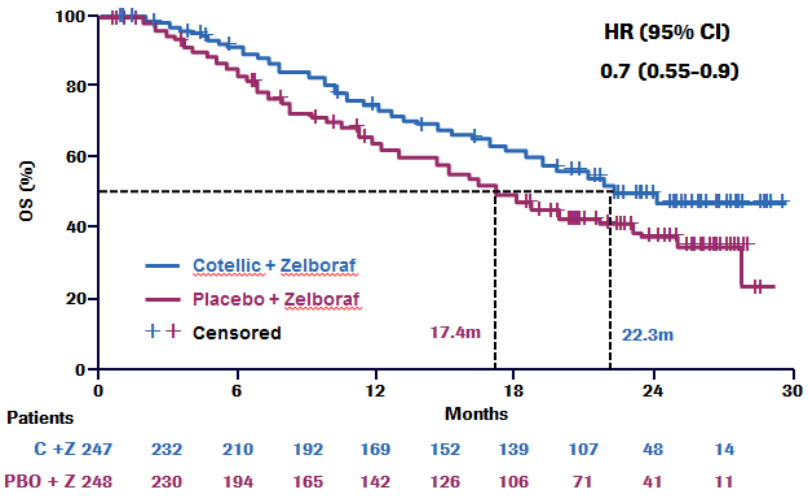
= Roche in development

[1] Datamonitor; incidence rates includes the 7 major markets (US, Japan, France, Germany, Italy, Spain, UK); Cotellic in collaboration with Exelixis; Zelboraf in collaboration with Plexxikon

Cotellic+Zelboraf in BRAF+ melanoma

PFS and OS subgroup analysis

Overall survival



	n		Median OS (months) (95% CI)	
	PBO+Z	C+Z	PBO+Z	C+Z
ITT	**248**	**247**	**17.4 (15.0-19.8)**	**22.3 (20.3-NR)**
LDH level: <0.8 ULN	84	76	25	**NR**
LDH level: >2x ULN	38	31	6.3	**9.2**
Stage M1c+LDH<ULN	68	58	18.0	**NR**
Stage M1c+LDH>ULN	82	86	8.3	**14.5**
No liver metastases	170	164	19.8	**NR**
With liver metastases	78	83	12.7	**18.5**
Baseline SLD <median	127	121	24.9	**NR**
Basellne SLD >median	119	125	13.5	**18.6**

Phase III coBRIM subgroup analysis

- ITT population: mOS of 22.3 months (HR=0.7)
- Across all subsets, Cotellic+Zelboraf showed mPFS and mOS benefit
- US: +6% share of new patients achieved in 1L and 2L after launch

Phase Ib BRIM7 OS update

- BRIM7 update (single arm Ph1b): mOS in BRAFi naive patients exceeded 2.5 years

Atkinson V. *et al,* SMR 2015; McArthur G. *et al*, ASCO 2016; Cotellic in collaboration with Exelixis; Zelboraf in collaboration with Plexxikon; PBO=placebo; M1c (disease stage); LDH=lactate dehydrogenase; ULN=upper limit of normal; SLD=sum of longest diameters

Introduction: Portfolio progress

Lung: Alecensa (J-ALEX)

Melanoma: Cotellic + Zelboraf

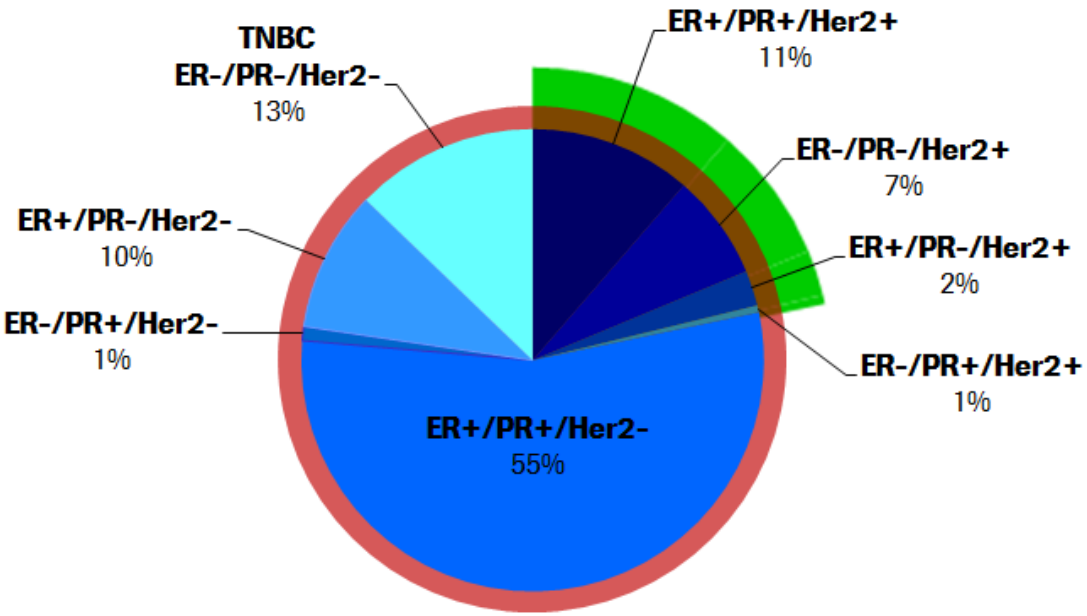
Breast: Cotellic, Perjeta (PHEREXA)

Hematology: Gazyva, Venclexta

Summary

Breast cancer: Still high unmet medical need

Incidence cases reach 490,000 pts[1]



= Roche marketed

= Roche in development

Herceptin trastuzumab

PERJETA pertuzumab

Kadcyla ado-trastuzumab emtansine

AVASTIN bevacizumab

TECENTRIQ atezolizumab

COTELLIC (cobimetinib) tablets

ipatasertib
(AKT inhibitor)

SERD
(Selective estrogen receptor degrader)

taselisib
(PI3K inhibitor)

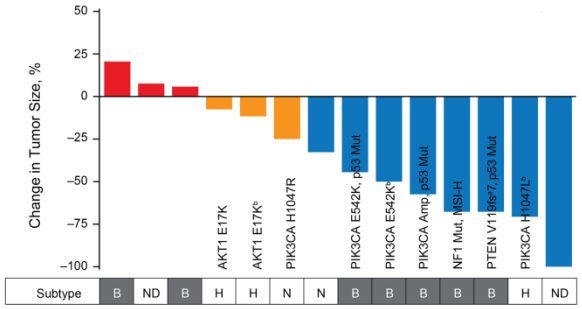
[1] Datamonitor; incidence rates includes the 7 major markets (US, Japan, France, Germany, Italy, Spain, UK); ER=estrogen receptor; PR=progesterone receptor; TNBC=triple negative breast cancer; Ipatasertib in collaboration with Array BioPharma

Cotellic + paclitaxel in 1L TNBC

Overcoming potential resistance mechanism

Response, n (%)	Cotellic + paclitaxel (n=16)
ORR	8 (50)
CR	0 (0)
PR	8 (50)
SD	3 (19)
PD	3 (19)
Not done	2 (13)

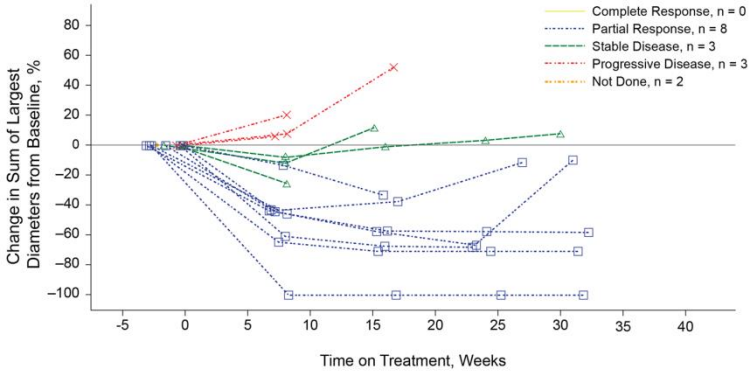
Change in tumor size



Phase II (COLET); Safety run-in results

- Resistance to 1L taxane therapy is thought to be caused by MAPK pathway upregulation
- ORR of 50%
- Responses were durable up to 30 weeks
- Manageable safety-profile
- Randomized P2 (COLET) ongoing (n=100)

Change in tumor size over time



Brufsky A. *et al*., ASCO 2016; Cotellic in collaboartion with Exelixis; MAPK=mitogen-activated protein kinase

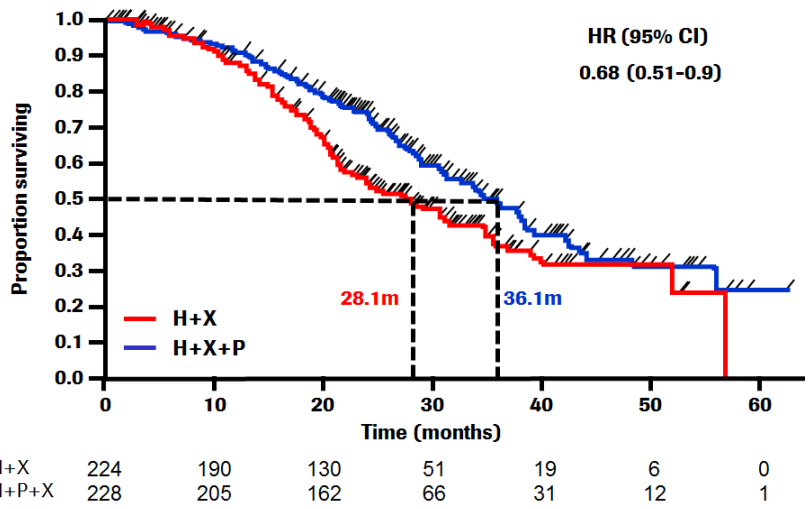
Perjeta + Herceptin in 2L HER2+ mBC

PHEREXA phase III results

Response, n (%)	Herceptin + Xeloda (n=224)	Herceptin + Perjeta + Xeloda (n=228)
PFS by IRF	9.0	11.1
HR (95% CI)	0.82 (0.65-1.02) p=0.07	
PFS by investigator	9.0	11.8
HR (95% CI)	0.81 (0.66-1.00) *	
OS	28.1	36.1
HR (95% CI)	0.68 (0.51-0.90) *	

* Statistical significance cannot be claimed due to the hierarchical testing of OS after the primary IRF PFS endpoint

Overall survival



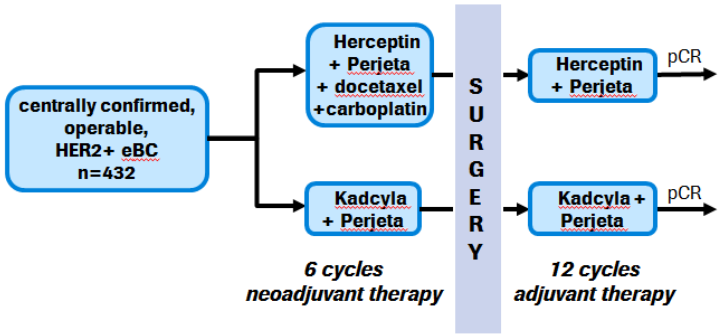
Phase III PHEREXA results

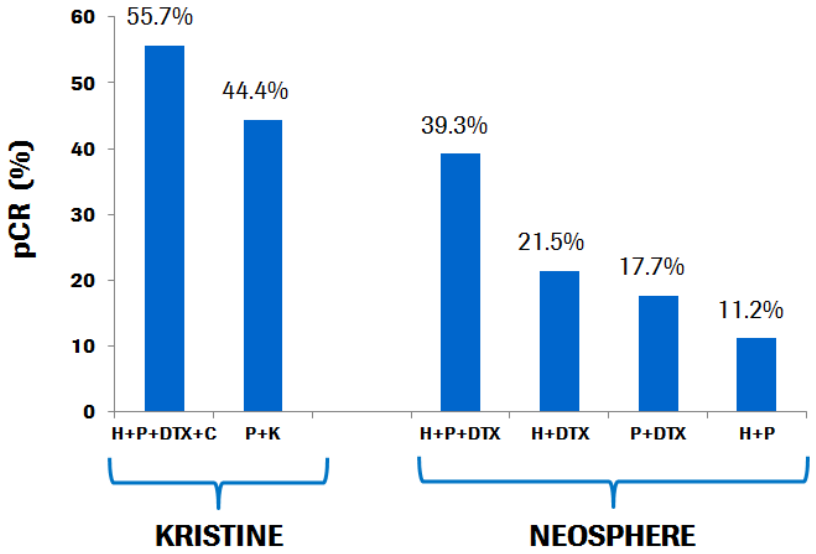
- Primary endpoint: Independent review facility assessed mPFS was not statistically significant
- 8-month increase in mOS to 36.1 months was observed
- Magnitude of the OS benefit is in line with prior experience of Perjeta in mBC

Urruticoechea *et al*., ASCO 2016; H=Herceptin; P=Perjeta; X=xeloda; IRF=independent review facility

Perjeta in neoadjuvant HER2+ eBC
KRISTINE results support NEOSPHERE

KRISTINE study design





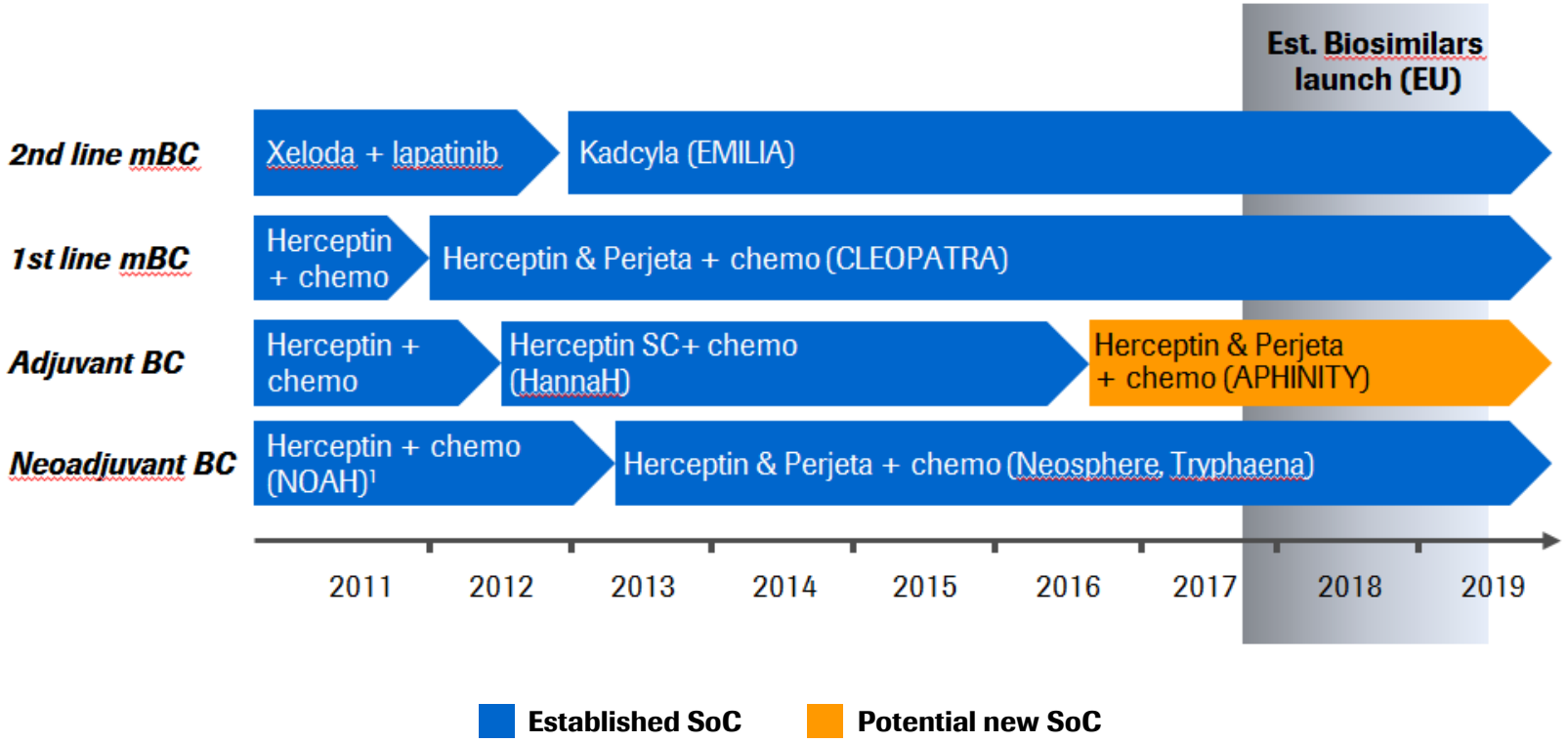
Phase III KRISTINE results

- Herceptin + Perjeta + docetaxel + carboplatin was superior to Perjeta + Kadcyla
- Herceptin + Perjeta + docetaxel + carboplatin achieved higher breast conservation rate (52.6% vs 41.7%)

Hurvitz *et al*., ASCO 2016; H=Herceptin; P=Perjeta; DTX=docetaxel; C=carboplatin; pCR=pathologic complete response

HER2 franchise evolution

Further improving the standard of care



- Phase III results (APHINITY) for Perjeta + Herceptin in the adjuvant setting expected end of 2016

mBC=metastatic breast cancer; SC=subcutaneous; SoC=standard of care

Introduction: Portfolio progress

Lung: Alecensa (J-ALEX)

Melanoma: Cotellic + Zelboraf

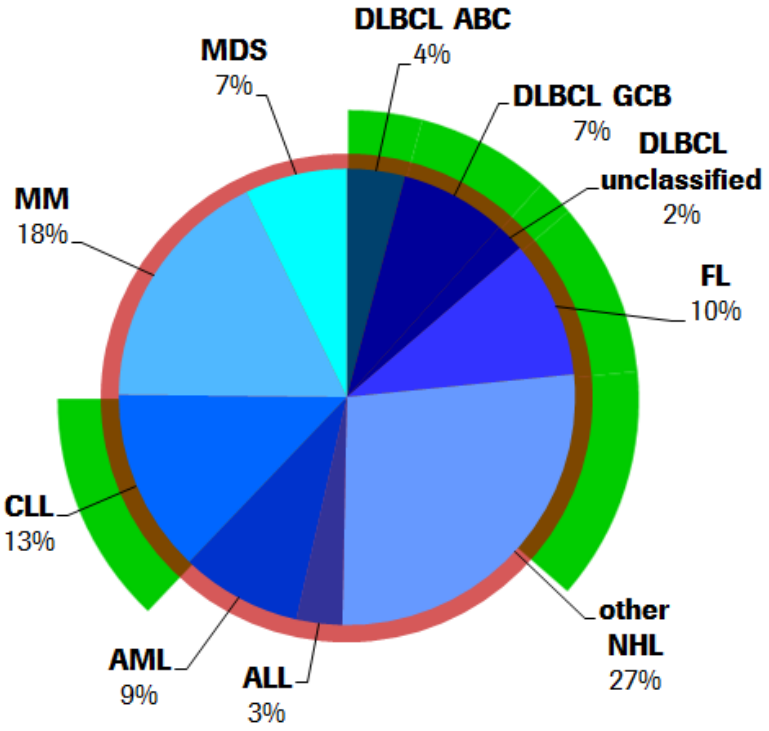
Breast: Cotellic, Perjeta (PHEREXA)

Hematology: Gazyva, Venclexta

Summary

Blood cancer: Still high unmet medical need

Incidence cases reach 330,000 pts[1]



GAZYVA obinutuzumab injection

Rituxan Rituximab

VENCLEXTA venetoclax tablets

TECENTRIQ atezolizumab

COTELLIC (cobimetinib) tablets

aCD20/CD3 TCB

polatuzumab vedotin
(anti-CD79b ADC)

idasanutlin
(MDM2 antagonist)

LSD1 inhibitor

= Roche marketed

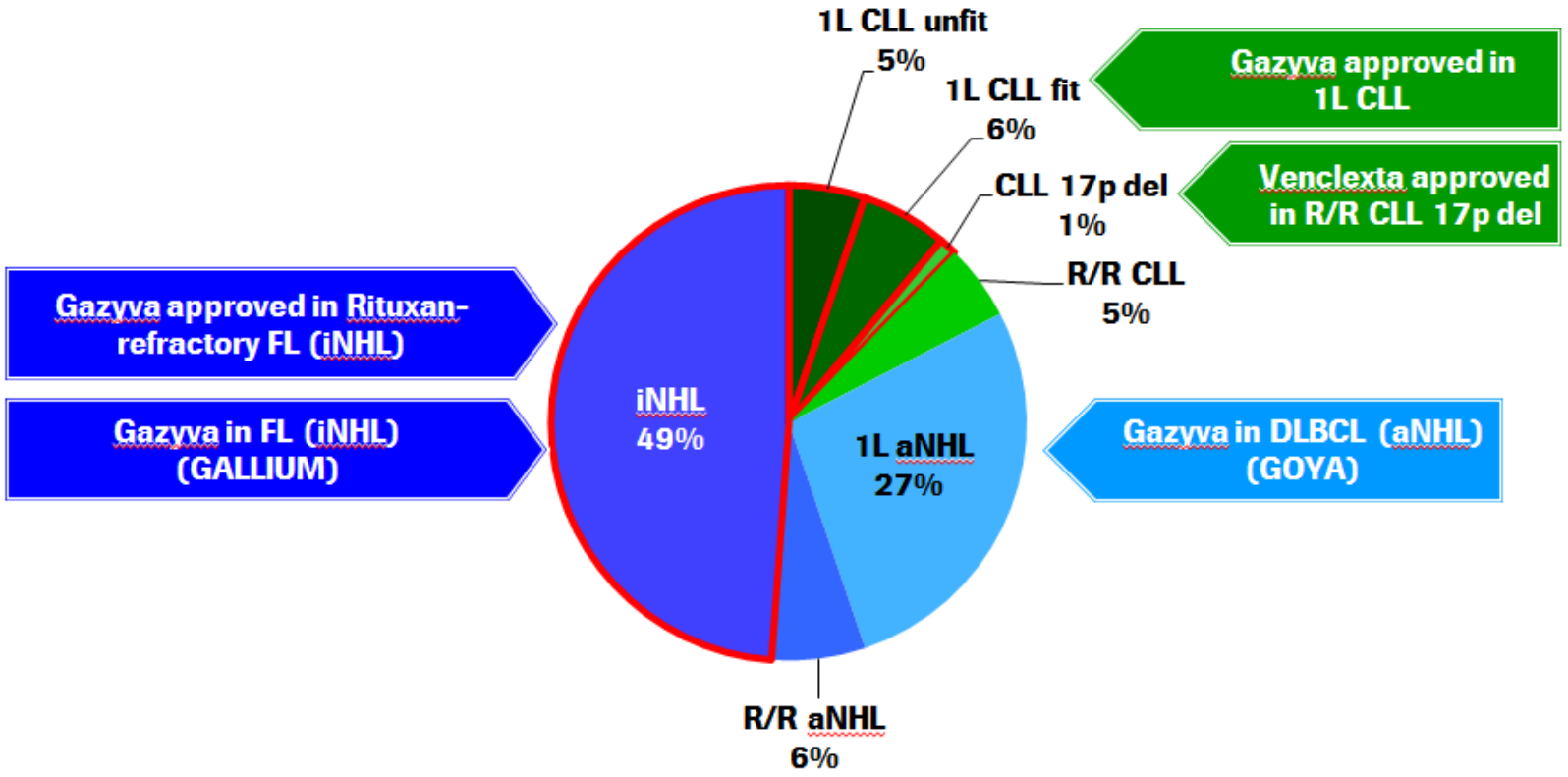
= Roche in development

[1] Datamonitor; incidence rates includes the 7 major markets (US, Japan, France, Germany, Italy, Spain, UK); NHL=non-hodgkin`s lymphoma; DLBCL (aNHL)=diffuse large B-cell lymphoma; FL (iNHL)=follicular lymphoma; ALL=acute lymphoblastic leukemia; AML=acute myeloid leukemia; CLL=chronic lymphoid leukemia; MM= multiple myeloma; MDS=myelodysplastic syndrome; Venclexta in collaboration with AbbVie; Cotellic in collaboration with Exelixis; Gazyva in collaboration with Biogen; polatuzumab vediotin in collaboration with Seattle Genetics; LSD1inhibitor in collaboration with Oryzon Genomics

Establishing Gazyva as the new CD20 backbone

From good to great

Rituxan sales split by indication

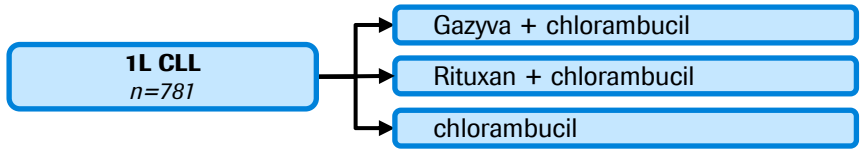


CLL=chronic lymphocytic leukemia; iNHL=indolent non-hodgkin's lymphoma; FL=follicular lymphoma; aNHL=aggressive NHL; DLBCL=diffuse large B cell lymphoma; Gazyva in collaboration with Biogen; Venclexta in collaboration with AbbVie

Third positive readout for Gazyva
GALLIUM in 1L iNHL

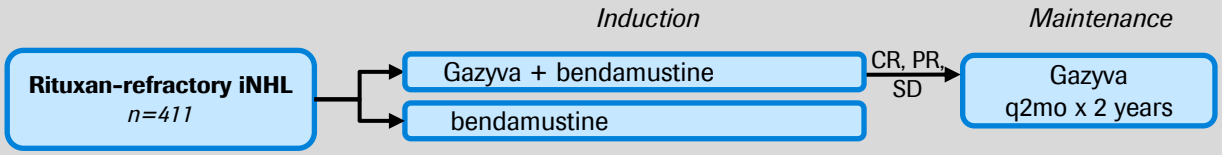
Primary end-point:

CLL11: Ph III Chronic Lymphocytic Leukemia (CLL)



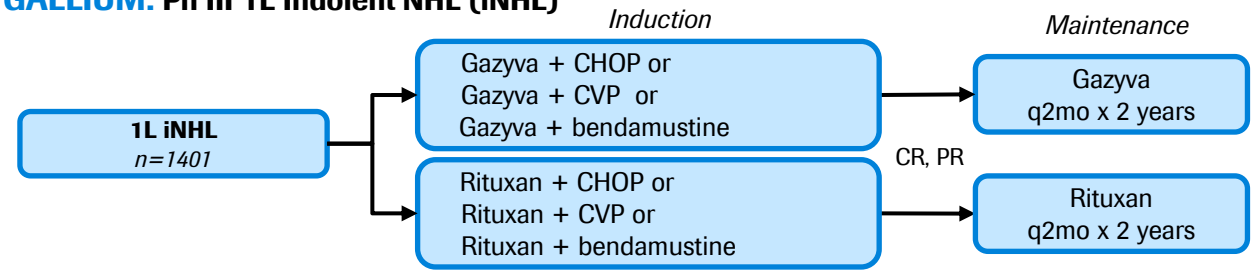
PFS
Approved in Q4 2013 ✓

GADOLIN: Ph III Recurrent Indolent NHL (iNHL)



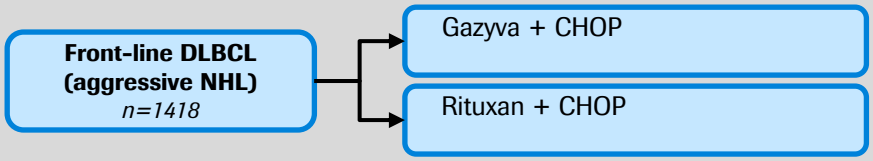
PFS
Approved in Q1 2016 ✓

GALLIUM: Ph III 1L Indolent NHL (iNHL)



PFS ✓
Stopped at interim analysis

GOYA: Ph III 1L Diffuse Large B-cell Lymphoma (DLBCL)



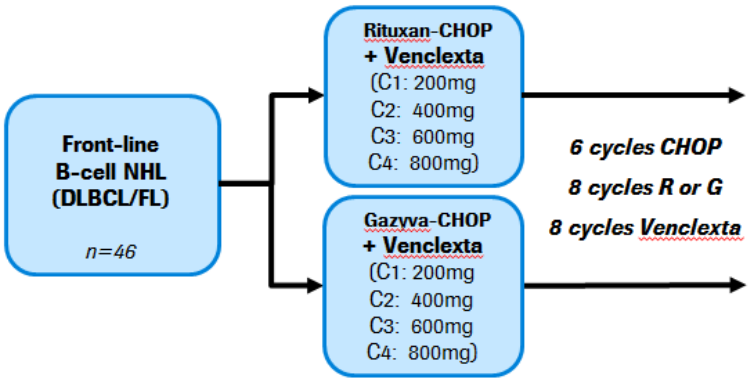
PFS
Data expected in H2 2016

Gazyva in collaboration with Biogen; CHOP=Cyclophosphamide, Doxorubicin, Vincristine and Prednisone; CVP=Cyclophosphamide, Vincristine and Prednisolone

Venclexta* + R/G-CHOP in 1L NHL

First efficacy data in combination with CD20 backbone

Phase Ib dose escalation



Response, n (%)	Venclexta + R-CHOP (n=19)	Venclexta + G-CHOP (n=15)
ORR	16 (84)	15 (100)
CR	13 (68)	12 (80)
PR	3 (16)	3 (20)
PD	3 (16)	0 (0)

Phase Ib results (CAVALLI)

- Venclexta + R/G-CHOP was tolerable with discontinuous Venclexta dosing
- Both combinations showed strong ORR, especially CR
- Ph2 study for Venclexta + R-CHOP at 800mg Venclexta (recommended dose) has been initiated
- Dose-finding on-going for Venclexta + G-CHOP

Zelenetz A. *et al*., ASCO 2016; *Venclexta (venetoclax) in collaboration with AbbVie; R=Rituxan; G=Gazyva; CHOP=cyclophosphamide, doxorubicin, vincristine and prednisone

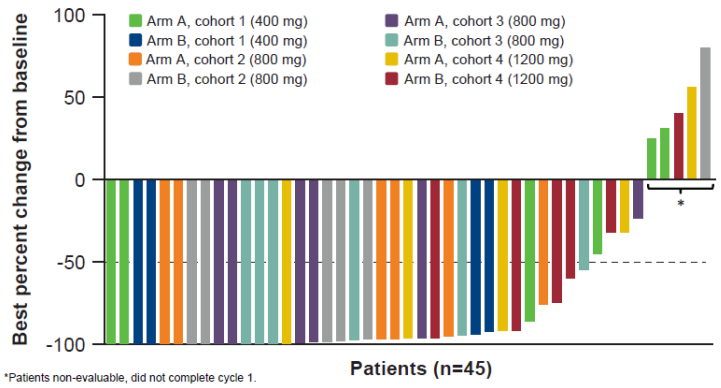
Venclexta* + hypomethylating agents in 1L AML

New options for chemo-unfit elderly

FDA BTD

Response, n (%)	Venclexta + decitabine (n=23)	Venclexta + azacitidine (n=22)	Total (n=45)
ORR	16 (70)	12 (55)	28 (62)
CR/CRi	15 (65)	12 (55)	27 (60)
CR	5 (22)	7 (32)	12 (27)
CRi	10 (44)	5 (23)	15 (33)
PR	1 (4)	0 (0)	1 (2)

Bone marrow blast count



Phase Ib results

- 90% of patients achieved significant reduction in bone marrow blast counts
- ORR of 62% taking both hypomethylating agent combinations together
- Tolerable safety profile for treatment-naive chemo-unfit patients aged ≥65y
- Safety expansion with both hypomethylating agents at 2 Venclexta doses ongoing (n=100)

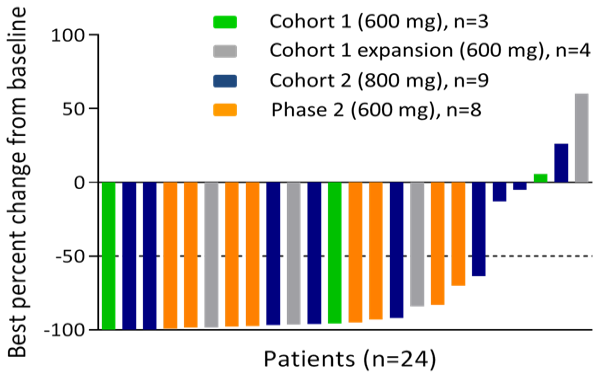
Pollyea D. *et al*., ASCO 2016; *Venclexta (venetoclax) in collaboration with AbbVie; CRi=complete remission with incomplete marrow recovery

Venclexta* + LDAC in 1L AML

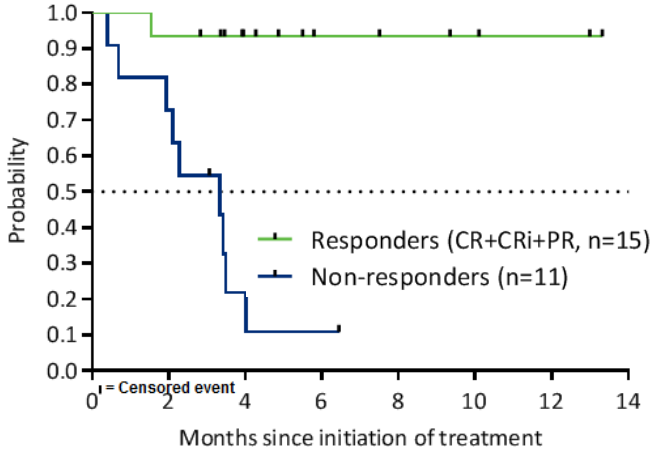
ORR of 68% achieved in patients with no prior MPN

Response, n (%)	Venclexta + LDAC All patients (n=26)	Venclexta + LDAC Patients with no prior MPN (n=22)	Venclexta + LDAC Patients with no prior HMA (n=21)
ORR	15 (58)	15 (68)	13 (62)
CR/CRi	14 (54)	14 (64)	12 (57)
CR	6 (23)		
CRi	8 (31)		
PR	1 (4)		
BM blast count <5%	21 (81)		

Bone marrow blast count



Overall survival



Phase Ib results

- Majority of patients achieved significant reduction in BM and peripheral blast counts
- ORR of 68% in patients with not prior MPN
- Combination demonstrates a tolerable safety profile for treatment-naive chemo-unfit patients aged ≥65y
- Ph2 expansion on-going (n=50)

Lin T. *et al*., ASCO 2016; *Venclexta (venetoclax) in collaboration with AbbVie; LDAC=low dose cytarabine; MPN=myeloproliferative neoplasm; HMA=hypomethylating agent; CRi=complete remission with incomplete marrow recovery; BM=bone marrow

Development plan I: Hematology franchise

8 novel molecules in the clinic

✓ = approved/ positive data

	Compound	Combination	Study name	Indication	Ph1 Ph2 Ph3	
NHL	**Gazyva**	+bendamustine	GADOLIN	FL (iNHL) (Rituxan refractory)		✓
	Gazyva	+CHOP	GOYA	DLBCL (aNHL)		
	Gazyva	+chemo	GALLIUM	1L FL (iNHL)		✓
CLL	**Gazyva**	+chemo	CLL11	CLL		✓
	Gazyva	+FC/bendamustin/Clb	GREEN	CLL and R/R CLL		
NHL	**Venclexta***	**+Rituxan/+Rituxan**+bendamustine	CONTRALTO	R/R FL (iNHL)		
	Venclexta	**+Rituxan**+CHOP**/Gazyva**+CHOP	CAVALLI	1L aNHL		ASCO
	Venclexta	**+Rituxan**+bendamustine		R/R NHL		
	Venclexta			R/R CLL and R/R NHL		ASCO
	Venclexta	**+Gazyva+polatuzumab vedotin**		aNHL and iNHL		
	Venclexta	**+Gazyva+polatuzumab vedotin**		R/R aNHL and R/R iNHL		
CLL	**Venclexta**	**+Rituxan**		R/R CLL and SLL		
	Venclexta	**+Gazyva**	CLL14	CLL		
	Venclexta	**+Rituxan**	MURANO	R/R CLL		
	Venclexta			R/R CLL 17p		✓
	Venclexta			R/R CLL after ibru/idel		ASCO
	Venclexta	**+Rituxan**+bendamustine		R/R CLL and CLL		
	Venclexta	**+Gazyva**		R/R CLL and CLL		
MM	**Venclexta**			R/R MM		ASCO
	Venclexta	+bortezomib+dexamethasone		R/R MM		ASCO
AML	**Venclexta**			AML		
	Venclexta	+decitabine/+azacitidine/+LdAraC		AML		ASCO
	Venclexta	**+Cotellic**		R/R AML		

iNHL=indolent non-hodgkin`s lymphoma; aNHL=agressive NHL; CLL=chronic lymphoid leukemia; R/R CLL=relapsed/refractory CLL; MM=multiple myeloma; AML=acute myeloid leukemia; CHOP=cyclophosphamide, doxorubicin, vincristine and prednisone; FC=fludarabine, cyclophosphamide; LDAC=low dose cytarabine; * Venclexta in collaboration with AbbVie; Gazyva in collaboration with Biogen; Cotellic in collaboration with Exelixis; polatuzumab in collaboration with Seattle Genetics

Development plan hematology franchise II

8 novel molecules in the clinic

	Compound	Combination	Study name	Indication	Ph1 Ph2 Ph3
NHL	***polatuzumab***	***+Rituxan/Gazyva***	*ROMULUS*	R/R FL and aNHL	
	polatuzumab	***+Gazyva+benda/Rituxan+benda***		R/R FL (iNHL) and aNHL	
	polatuzumab	***+Gazyva+CHP/Rituxan+CHP***		1L aNHL	
	polatuzumab	***+Gazyva****+lenalidomide*		R/R FL and aNHL	
	polatuzumab	***+Gazyva+Venclexta***		R/R FL and aNHL	
NHL	***Tecentriq***	***+Gazyva***		R/R FL (iNHL) and aNHL	
	Tecentriq	***+Gazyva****+lenalidomide*		R/R FL and aNHL	
	Tecentriq	*+CHOP*		aNHL	
	Tecentriq	*+bendamustine*		R/R FL and aNHL	
	Tecentriq	***+Gazyva+polatuzumab***		R/R FL and aNHL	
MM	***Tecentriq***	*+lenalidomide*		MM	
	Tecentriq	*+daratumumab+/-lenalidomide or +/-pomalidomide*		R/R MM	
MDS	***Tecentriq***	*+azacitidine*		MDS	
	aCD20/CD3 biMab			Heme tumors	
AML	***LSD1 inhibitor***			AML	
NHL	***idasanutlin***	***+Gazyva***		R/R FL (iNHL) and aNHL	
AML	***idasanutlin***	***+Venclexta***		Chemo unfit R/R AML	
	idasanutlin	*+cytarabine*		R/R AML	
NHL	***undisclosed ADC***			R/R NHL	

Venclexta in collaboration with AbbVie; Polatuzumab vediotin in collaboration with Seattle Genetics; LSD1inhibitor in collaboration with Oryzon Genomics; daratumumab in collaboration with Janssen (J&J); iNHL=indolent non-hodgkin`s lymphoma; R/R FL=relapsed/refractory follicular lymphoma; aNHL=agressive NHL (DLBCL); MM=multiple myeloma; MDS=myelodysplastic syndrom; AML=acute myeloid leukemia;

Introduction: Portfolio progress

Lung: Alecensa (J-ALEX)

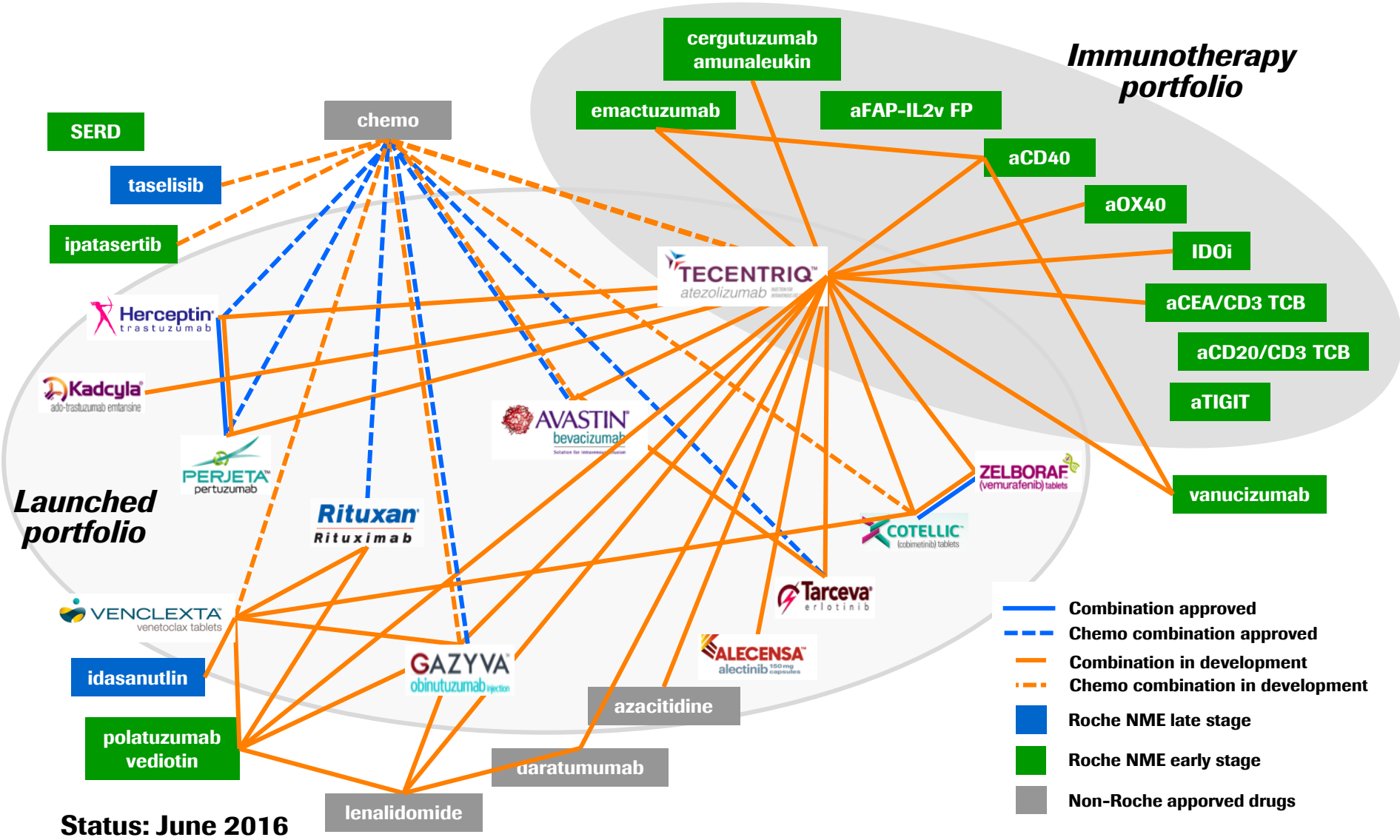
Melanoma: Cotellic + Zelboraf

Breast: Cotellic, Perjeta (PHEREXA)

Hematology: Gazyva, Venclexta

Summary

Maximizing value: Novel assets and combinations



Status: June 2016

emactuzumab (aCSF-1R); cergutuzumab amunaleukin (aCEA-IL2v FP); vanucizumab (aAng2/VEGF); polatuzumab vediotin (aCD79b ADC); taselisib (PI3Ki); ipatasertib (AKTi); SERD (selective estrogen receptor degrader); idasanutlin (MDM2 antagonist); Venclexta in collaboration with AbbVie; Gazyva in collaboration with Biogen; Alecensa in collaboration with Chugai; Cotellic in collaboration with Exelixis; Zelboraf in collaboration with Plexxikon; polatuzumab in collaboration with Seattle Genetics; ipatasertib in collaboration with Array Biopharma; IDOi in collaboration with NewLink; daratumumab in collaboration with Janssen (J&J)

Doing now what patients need next