Roche

ASCO 2022

Virtual IR event

6 June 2022

This presentation contains certain forward-looking statements. These forward-looking statements may be identified by words such as ‘believes’, ‘expects’, ‘anticipates’, ‘projects’, ‘intends’, ‘should’, ‘seeks’, ‘estimates’, ‘future’ or similar expressions or by discussion of, among other things, strategy, goals, plans or intentions. Various factors may cause actual results to differ materially in the future from those reflected in forward-looking statements contained in this presentation, among others:

1 pricing and product initiatives of competitors;
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;
8 loss of or inability to obtain adequate protection for intellectual property rights;
9 litigation;
10 loss of key executives or other employees; and
11 adverse publicity and news coverage.

Any statements regarding earnings per share growth is not a profit forecast and should not be interpreted to mean that Roche’s earnings or earnings per share for this year or any subsequent period will necessarily match or exceed the historical published earnings or earnings per share of Roche.

For marketed products discussed in this presentation, please see full prescribing information on our website www.roche.com

All mentioned trademarks are legally protected.

Welcome

Bruno Eschli, Ph.D. |
Head of Investor Relations

Agenda

Welcome

Bruno Eschli, Ph.D., Head of Investor Relations

Oncology late-stage pipeline update

Elena Bernedo-Arzac, SVP, Oncology Therapeutic Area Head

Key data at ASCO 2022

- **Glofitamab pivotal Ph1b data in 3L+DLBCL**
- **Polivy Asian sub-population data in 1L DLBCL (POLARIX)**

Ginna Laport, VP, Global Head of Hematology NHL CLL, Product Development

Oncology early R&D update

Johanna Bendell, M.D., Global Head Oncology, Roche Pharma Research & Early Development (pRED)

Andy Chan, Ph.D., SVP, Research Biology, Genentech Research & Early Development (gRED)

Q&A

Significant key news flow remains in 2022

	Compound	Indication	Milestone	
Regulatory	**Vabysmo**	nAMD/DME	US/EU approval	✔ US
	Susvimo	nAMD	EU approval	
	mosunetuzumab	3L+ FL	US/EU approval	
	Tecentriq	Adjuvant NSCLC	EU approval	
	Hemlibra	Mild to moderate hemophilia A	EU approval	
	Polivy + R-CHP	1L DLBCL	EU/US approval	
Phase III / pivotal readouts	**glofitamab**	3L+ DLBCL	Ph Ib NP30179	✔
	Tecentriq + tiragolumab + chemo	1L ES-SCLC	Ph III SKYSCRAPER-02	✖
	Tecentriq + chemo	Adjuvant SCCHN	Ph III IMvoke010	
	Tecentriq + tiragolumab	1L PDL1+ NSCLC	Ph III SKYSCRAPER-01	Continues to next analysis
	Tecentriq	Adjuvant RCC	Ph III IMmotion010	
	giredestrant	2/3L HR+ mBC	Ph II acelERA	✖
	Tecentriq + chemo	Adjuvant HCC	Ph III IMbrave050	
	Venclexta + dexamethasone	t(11;14) MM	Ph III CANOVA	
	Tecentriq + chemo	Neoadjuvant NSCLC	Ph III IMpower030	
	Tecentriq + tiragolumab + chemo	1L esophageal cancer	Ph III SKYSCRAPER-08	
	Alecensa	Adjuvant ALK+ NSCLC	Ph III ALINA	2023
	gantenerumab	Alzheimer's disease	Ph III GRADUATE 1/2	
	Susvimo	DME	Ph III PAGODA	
	Susvimo	DR	Ph III PAVILION	

Virtual event Angiogenesis ✔	***Virtual event MDA*** ✔	***Roche ESG Day Access to Healthcare*** ✔	***Virtual event ASCO*** ✔	***Roche Pharma Day London***
Monday, 14 February 16:30 to 17:45 CEST	***Wednesday, 16 March 16:30 to 17:30 CEST***	***Monday, 16 May 15:00 to 16:30 CEST***	***Monday, 6 June 16:00 to 17:30 CEST***	***Monday, 12 September TBC***

* Outcome studies are event-driven: timelines may change

Oncology late-stage update

Elena Bernedo-Arzac |
SVP, Oncology Therapeutic Area Head

Earlier disease presents opportunity for cure

Need for high efficacy treatments that are well tolerated

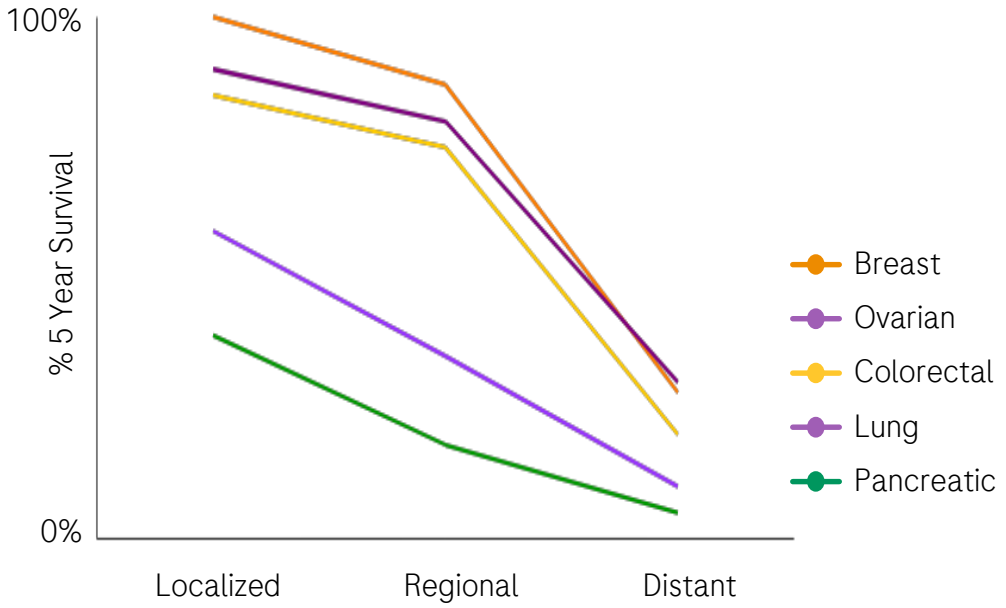
Chance for a cure: development earlier in the course of disease is critically important to improving the cure rate

Cost to society: treatment initiated in earlier stages of cancer reduces cost vs. treatment initiated later

Unmet need: large population with continued unmet needs including opportunity to improve long-term OS

Growing population: early disease population is expected to grow with the rise of early detection technologies, increasing screening

Outcomes by cancer type and stage at diagnosis[1]



[1] National Cancer Institute, SEER database, literature review; OS=overall survival

Upcoming readouts in early disease

Potential to expand existing indications

Lung / H&N

Molecule	Indication	Ph 1	Ph 2	Ph 3	
Tecentriq	Adjuvant NSCLC	IMpower010			✓
	Neoadjuvant NSCLC	IMpower030			
	Adjuvant SCCHN	IMvoke010			
tiragolumab[1]	Stage III unres. NSCLC	SKYSCRAPER-03			
	Neoadj/Adj NSCLC	SKYSCRAPER-05			
Alecensa	Adjuvant ALK+ NSCLC	ALINA			

GI / GU

Molecule	Indication	Ph 1	Ph 2	Ph 3
Tecentriq	Adjuvant RCC	IMmotion010		
	Adjuvant HCC	IMbrave050		
	HR NMIBC	ALBAN		
	ctDNA+ HR MIBC	IMvigor011		
	MSI-H CRC	ATOMIC		
	BCG unresp. NMIBC	SWOG S1605		
tiragolumab[1]	Locally adv. ESCC	SKYSCRAPER-07		

Breast

Molecule	Indication	Ph 1	Ph 2	Ph 3	
Tecentriq	Neoadj. TNBC [2]	IMpassion031			✓
	Neoadj./Adj. TNBC	NSABP59 / GEPARDOUZE			
	Adjuvant TNBC	IMpassion030			
giredestrant	Neoadj. HR+ BC	coopERA*			✓
	Adjuvant HR+ BC	lidERA			

Heme

Molecule	Indication	Ph 1	Ph 2	Ph 3	
Polivy	1L DLBCL	POLARIX			✓
Venclexta	1L fit AML	VIALE-M			
Glofit/Mosun[3]	1L DLBCL	Ph 1b			

Readout expected in 2022 ✓ = met primary endpoint

[1] In combination with Tecentriq; [2] Positive for pCR; [3] +/- Polivy; NSCLC=non-small cell lung cancer; ESCC=esophageal squamous cell carcinoma; HCC=hepatocellular carcinoma; TNBC=triple negative breast cancer; RCC=renal cell carcinoma; NMIBC=non-muscle invasive bladder cancer; DLBCL=diffuse large b-cell lymphoma; AML=acute myeloid leukemia; CRC=colorectal carcinoma; SCCHN=Squamous cell cancer of the head and neck; HR=Hormone receptor; BC=Breast cancer; GI=Gastrointestinal; GU=Genitourinary; H&N=Head and neck; *will not be filed

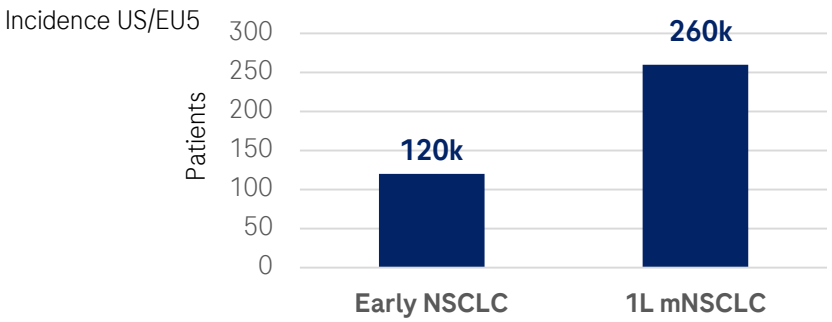
Tecentriq: First-in-class CIT in adjuvant NSCLC

*Strong US launch in PD-L1+ disease**

CT screening reduces lung-cancer mortality[2]

Low-dose CT scans can support early detection of lung cancer.[1,2]

Further growth potential in early NSCLC



25-35% of patients have resectable disease

Adjuvant NSCLC treatment still evolving

Screening: Early detection technologies expected to increase diagnosis at early stage

→ Committed to improving screening rates to support the early detection of lung cancer.[1,2]

Testing rates: Increasing with adjuvant treatment options for EGFR+, PD-L1+, ALK+ patients

→ Testing rates up from 40% to >70% in US since Tecentriq was approved in adj NSCLC

Systemic therapy: Adjuvant treatment rates expected to increase with new therapeutic options

→ Strong US launch with high oncologist awareness, approved to date in 22 countries including China, EU approval imminent

* US label: adj. treatment following resection and platinum-based chemotherapy for adult patients with Stage II to IIIA NSCLC whose tumors have PD-L1 expression on ≥ 1% of tumor cells; [1]de Koning H. J., van der Aalst C. M., de Jong P. A., et al. Reduced Lung-Cancer Mortality with Volume CT Screening in a Randomized Trial. N Engl J Med 2020; 382:503-513; [2]NLST. Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med. 2011.4;365(5):395-409; NSCLC=Non-small cell lung cancer; CT=Computerized Tomography; CIT=Cancer Immunotherapy

Tiragolumab (aTIGIT mAb)

Comprehensive development program ongoing

	Indication	Ph 1 / Ph 2 / Ph 3	
Lung cancer	1L NSCLC: PD-L1 high	SKYSCRAPER-01	Continues to next analysis
	1L ES-SCLC	SKYSCRAPER-02	✖
	Stage III unres. NSCLC	SKYSCRAPER-03	
	Neoadj / Adj NSCLC	SKYSCRAPER-05	
	1L NSq NSCLC	SKYSCRAPER-06	
Additional solid tumors	Locally advanced ESCC	SKYSCRAPER-07	
	1L ESCC	SKYSCRAPER-08	2022
	2L+ PD-L1+ Cervical Ca	SKYSCRAPER-04	2022
	1L SCCHN	SKYSCRAPER-09	
Novel combinations	HCC (+Tecentriq+Avastin)		
	Melanoma (+PD1-LAG3)		

Development strategy

1. Build on Tecentriq
2. Expand into early disease
3. Compete in new indications

- SKYSCRAPER-01 did not meet co-primary PFS endpoint, co-primary OS endpoint was immature at first IA
- Numerical improvement observed for both co-primary endpoints (PFS, OS); study will continue to next planned analysis
- Tiragolumab + Tecentriq was well-tolerated and no new safety signals were identified

SCLC=Small Cell Lung Cancer; NSCLC=Non-Small Cell Lung Cancer; SCCHN=head and neck squamous cell carcinoma; ESCC=esophageal squamous cell carcinoma; IA=Interim analysis; PFS=Progression-free survival; OS=Overall survival

Broad and diverse breast cancer portfolio

Expanding beyond HER2+ disease

Novel mechanisms and technologies

HER2 mAb

- Herceptin
- PERJETA pertuzumab
- PHESGO PERTUZUMAB-TRASTUZUMAB

HER2 ADC

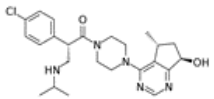
- Kadcyla ado-trastuzumab emtansine for injection

HER2 TCB mAb

- **runimotamab** (HER2xCD3)

CPI mAb

- TECENTRIQ atezolizumab



Small molecule

- **giredestrant** (SERD)
- **inavolisib** (PIK3CAi)

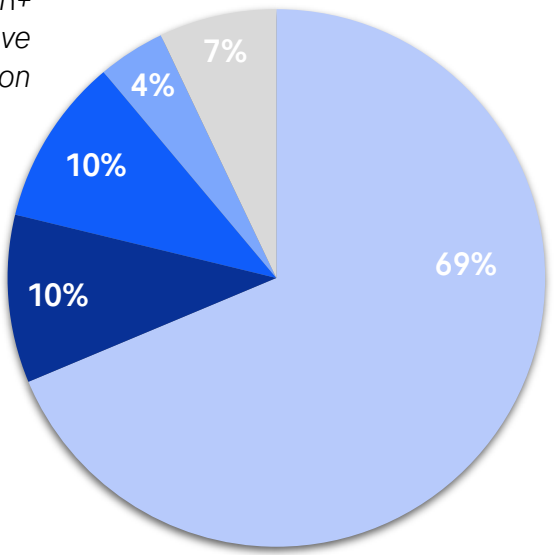
HER2+ BC

TNBC

HR+/ HER2- BC

Breast cancer cases by subtype[1]

40% of HR+ patients have PI3K mutation



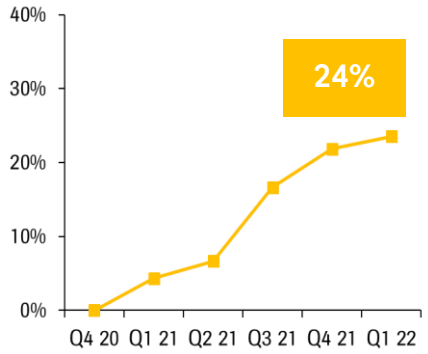
[1]Cancer Stats Facts: Female Breast Cancer Subtypes. National Cancer institute. Available at: https://seer.cancer.gov/statfacts/html/breast-subtypes.html (Access date: May 24, 2022); mAb=monoclonal antibody; ADC=antibody drug conjugate; CPI=checkpoint inhibitor; TNBC=triple negative breast cancer; TCB=T cell bispecific; HR=Hormone receptor; HER2=Human epidermal growth factor receptor; BC=breast cancer; SERD=Selective estrogen receptor degrader

HER2+ franchise: High efficacy and safety bar established in eBC

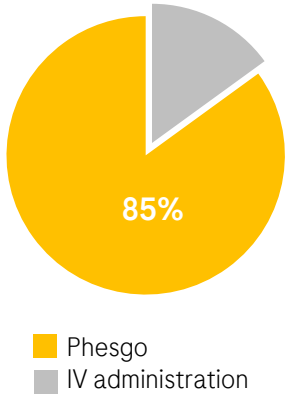
Perjeta 8-year follow-up data from landmark APHINITY study expected in 2022

Phesgo with strong global launch

Global Perjeta/Phesgo conversion rate



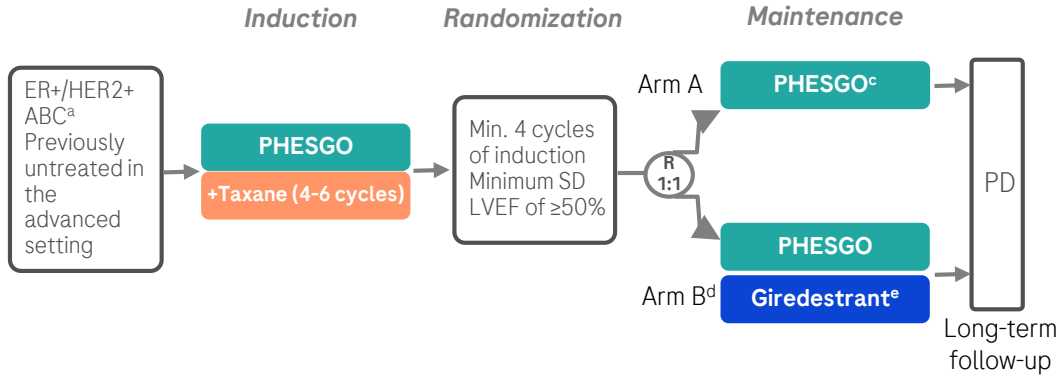
Patients preference Phesgo vs. IV administration



- Phesgo SC administration results in significantly reduced healthcare costs and resource use
- Phesgo conversion rate ~25% in early launch countries
- 85% of patients prefer Phesgo over standard IV administration
- P+H in eBC (APHINITY): Long term disease free survival at 90.6% in ITT after 6 yrs of follow-up

Continuing to build on existing standard of care

heredERA (1L HER2+/ER+ mBC)



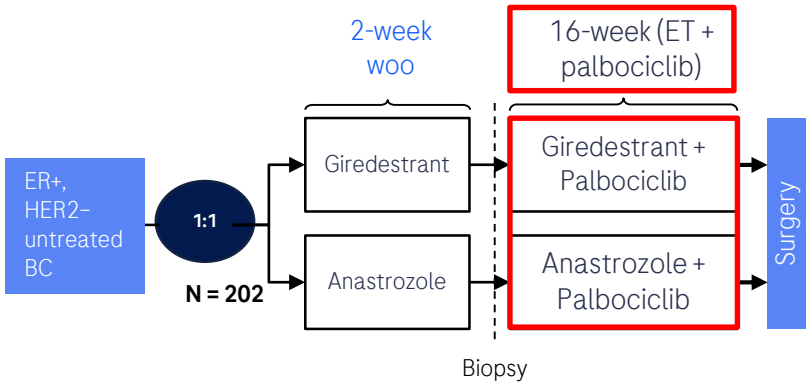
- HER2+/HR+ breast cancer has a distinctive biology with the need to address the endocrine receptor pathway
- Ph III heredERA (Phesgo + giredestrant) started enrollment in Q1 2022, and aims to improve:
  - efficacy by comprehensive blockade of both HER2 and ER pathways
  - treatment related QOL, with a patient centric regimen

HR=Hormone receptor; HER2=Human epidermal growth factor receptor 2; BC=Breast cancer; mBC=Metastatic breast cancer; ER=Estrogen receptor; IV=Intravenous; SC=Subcutaneous; QoL=Quality of life; SD=Stable disease; LVEF=Left ventricular ejection fraction; PD=Progressive disease

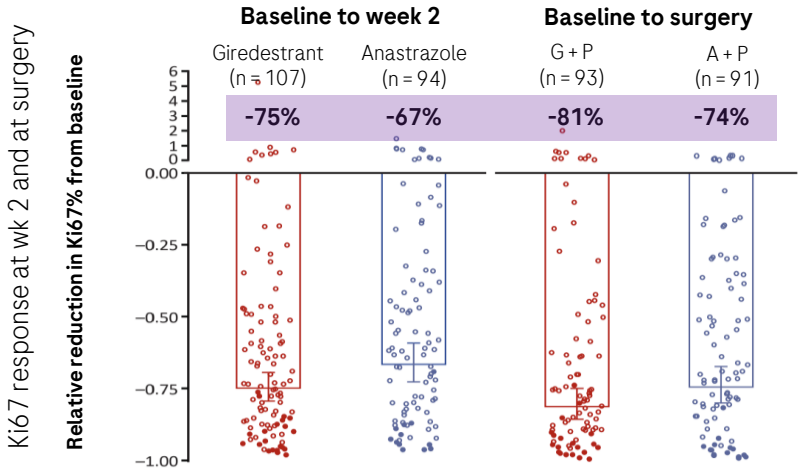
ER+/HER2– BC: Giredestrant Ph II final neoadj. results presented

Results support on-going Ph III (lidERA) development in the adjuvant setting

Ph II (coopERA) final results in neoadjuvant ER+/HER2- breast cancer at ASCO 2022



Primary endpoint: Ki67 score change from baseline to Week 2 during the window-of-opportunity phase for giredestrant vs anastrozole was met



CCCA at week 2 and at surgery

	G + P	A + P
Week 2	n=107	n=94
CCCA, %	20%	13%
Diff. arms, %	7%	
Surgery	n=93	n=91
CCCA, %	24%	16%
Diff. arms, %	7%	

G+P, Giredestrant + Palbociclib; A+P, Anastrozole + Palbociclib; CCCA, complete cell cycle arrest; Diff. arms, difference between arms

- First randomized study to show superior activity of an oral SERD (giredestrant) over an aromatase inhibitor (anastrozole) in ER+/HER2– eBC
- Final analysis confirmed that greater suppression of Ki67 as well as higher CCCA with giredestrant vs. anastrazole (first observed at week 2 in the primary analysis) was maintained at surgery despite the addition of palbociclib
- Safety data consistent with the known safety profile

SERD=Selective estrogen receptor degrader; ER=Estrogen receptor; HER2=Human epidermal growth factor receptor 2; eBC=Early breast cancer; CCCA=Complete cell cycle arrest; ORR=Overall response rate; pCR=Pathological complete response; mBC=Metastatic breast cancer; G+P=, Giredestrant + Palbociclib; A+P=Anastrozole + Palbociclib; PFS=Progression-free survival; ET=Endocrine therapy; BC=Breast cancer

HR+/HER2- BC: High unmet need remains

Large addressable population for SERD and PI3K programs

Targeting both early and metastatic disease

	eBC	1L mBC	2L/3L mBC
Endocrine Therapy Given until resistance or visceral disease present	**ET** +/- CDK4/6i	**ET** + CDK4/6i	**ET** monotherapy
SERD (giredestrant) Replace ET as SoC in all settings	**giredestrant lidERA** (adj.) **giredestrant** + palbo **coopERA** (neoadj.)	**giredestrant** + palbo **persevERA**	**giredestrant acelERA***
PI3Kαi (inavolisib)[2] Combine with SOC In Pi3Km patients		**inavolisib** + fulvestrant + palbociclib **INAVO120**	**inavolisib** Combination in planning
HR+/HER2- treated population (US/EU5)	509K	62K	44K

Giredestrant: Potential for best-in-class SERD

- **Differentiated MoA:** immobilizes on the chromosomal DNA
- **High potency:** 7-15x more potent than other SERDs in development
- **Well tolerated** alone and in combination with CDK4/6i; no drug-drug interactions observed

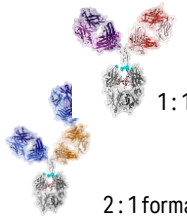
Inavolisib: Potential for best-in-class PI3Kα

- **Dual MoA:** More potent & selective for PI3Kα + degrades mutant PI3Kα
- **High potency:** greater, more durable target inhibition
- **Good safety** as single agent or combined

*acelERA (Ph2 trial) did not meet its primary endpoint of progression-free survival in people with a certain form of advanced breast cancer - however, efficacy data were encouraging with a more pronounced benefit in patients with higher dependence on estrogen receptor activity; HR=Hormone receptor; HER2=Human epidermal growth factor receptor 2; BC=Breast cancer; eBC=Early breast cancer; mBC=Metastatic breast cancer; MoA=Mode of action; ER=Estrogen receptor; SERD=Selective estrogen receptor degrader, SOC=Standard of care; Palbo=Palbociclib

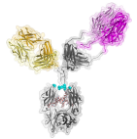
Broad and diverse portfolio in malignant hematology

Novel mechanisms and technologies



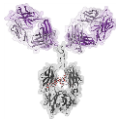
TCB mAb

mosunetuzumab
cevostamab
glofitamab
GPRC5DxCD3
HLA-A2-WT1xCD3
CD19 x CD28



Fusion Protein

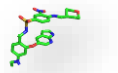
CD19 x 4-1BBL



mAb

Rituxan Rituximab

tiragolumab



Small Molecules

VENCLEXTA venetoclax tablets

ADC

POLIVY polatuzumab vedotin

Glyco-engineered mAb

GAZYVA obinutuzumab injection

- DLBCL
- FL
- MCL
- MM
- MDS
- AML
- CLL

Build on key areas of strength

- POLIVY as potential new SOC in 1L DLBCL
- Introducing CD20xCD3 bispecifics to NHL

Venture to new frontiers

- Multiple Myeloma
  - VENCLEXTA in t(11:14) Ph3 Canova data expected in 2022
  - Two bispecifics: Cevostamab and GPRC5D x CD3 TCB (RG6234) with new Ph1 data to be presented at EHA 2022

[1]Engert A, et al. Haematologica 2016;101:115-208, [2]WHO – International Agency for Research on Cancer. Available from: https://www.iarc.fr/ [Accessed on 25 May 2022]; NHL= Non-hodgkins lymphoma; DLBCL=Diffuse large B-cell lymphoma; CLL=Chronic lymphocytic leukemia; AML=Acute myeloid leukemia; FL=Follicular lymphoma; MM=Multiple myeloma; MDS=Myelodysplastic syndromes; PNH=Paroxysmal nocturnal hemoglobinuria; aHUS=atypical hemolytic uremic syndrome; SCD=Sickle cell disease; Myelofibrosis; TCB=T cell bispecifics; mAb=Monoklonal antibody; ADC=Antibody Drug Conjugate

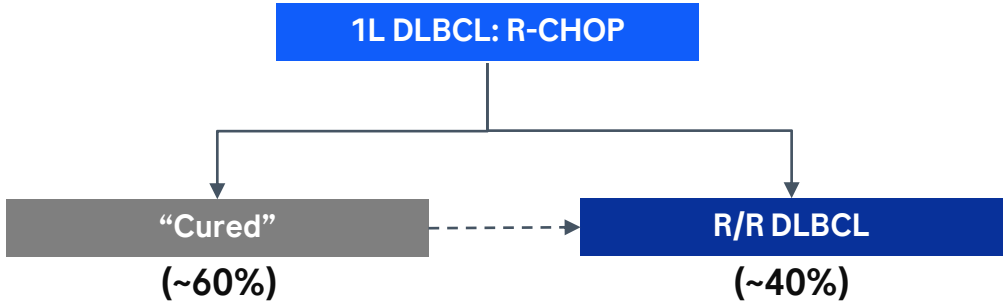
1L DLBCL: Polivy + R-CHP approved in EU

First new treatment in >20 years with clinically meaningful PFS improvement

POLIVY® polatuzumab vedotin

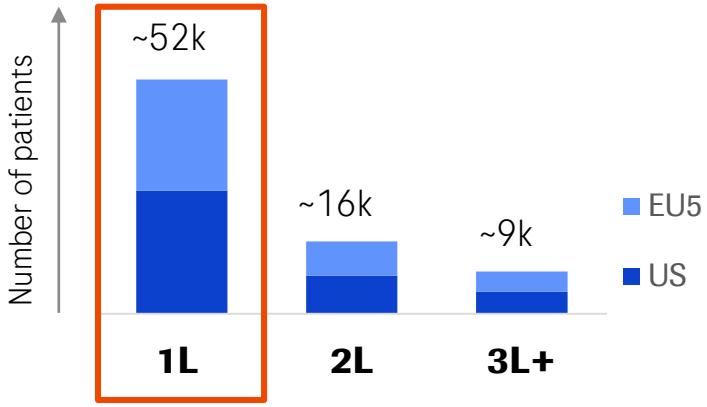
Roche

High unmet need in 1L DLBCL remains



- ~40% of patients are not cured with R-CHOP in 1L
- Patients with R/R DLBCL have poor prognosis: mOS <2yrs

Multibillion market opportunity in 1L DLBCL



- No new 1L therapies approved since R-CHOP 20 years ago
- 3x more drug treated patients in 1L than 2L DLBCL
- No further new therapies expected in 1L DLBCL for >3.5 years

Physicians already have experience using Polivy in R/R setting

- **Off the shelf and fixed duration**
  - Readily available; administered in any oncology facility
  - Administered for 6 cycles
- **Well tolerated safety profile**
  - No unique monitoring requirements
  - Safety comparable with that of R-CHOP

Polivy in collaboration with Seagen; R/R=relapsed/refractory; DLBCL=diffuse large B-cell lymphoma; R-CHOP=Rituxan + cyclophosphamide + hydroxydaunorubicin + vincristine + prednisone; mOS=median overall survival; EC=European Commission; R-CHP=R-CHOP=Rituxan + cyclophosphamide + hydroxydaunorubicin + prednisone

Mosunetuzumab and glofitamab (CD20 x CD3 bispecifics)

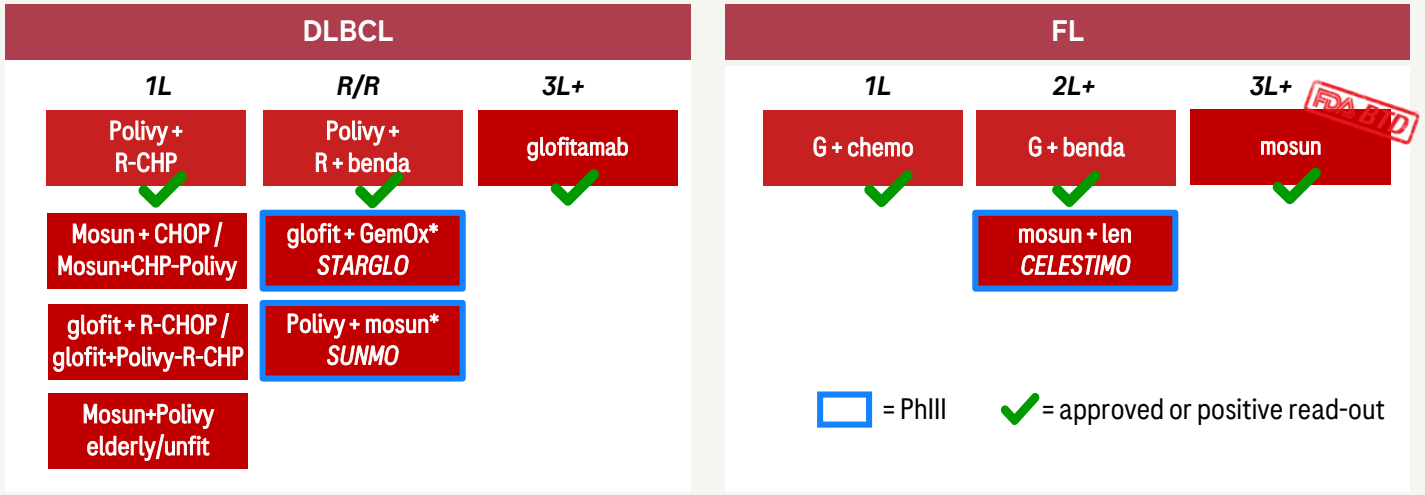
Potential to be first-in-class and best-in-class in FL and DLBCL

Tailored to address diverse patient and healthcare system needs

Off-the-shelf, fixed duration therapies

- **Mosun:** attractive profile for the outpatient setting and across a broad range of indications and settings; no required hospitalization
- **Glofit:** best in class efficacy potential with high CR rates, durable responses and manageable CRS with a fixed treatment duration

Most advanced clinical development plan



- **Regulatory status:** Mosun positive CHMP opinion for r/r 3L+ FL April 22, glofit pivotal cohort for r/r 3L+ DLBCL filed April 2022 in EU
- **New combinations:** Glofit in combination with CD19 4-1BBL and with CD19xCD28 ongoing in r/r NHL (both combinations in PhI); **New indications:** Mosun PhI in R/R CLL started Q1 2022
- **Growing Ph III program in NHL:** Glofit+ GemOx (STARGLO) in 2L+ DLBCL started Q1 21; mosun + lenalidomide (CELESTIMO) in 2L+ FL started Q4 21; Polivy + mosun (SUNMO) in 2L+ DLBCL initiated in Q4 21

*2L+ SCT ineligible DLBCL; R/R=relapsed/refractory; DLBCL=diffuse large B-cell lymphoma; FL=follicular lymphoma; len=lenalidomide; gemOx=gemcitabine + oxaliplatin; CR=complete response; CRS=cytokine release syndrome; Glofit=Glofitamab; Mosun=Mosunetuzumab

Glofitamab clinical data

Ginna Laport |
VP Global Head of Hematology NHL CLL,
Product Development

Glofitamab in patients with R/R diffuse large B-cell lymphoma (DLBCL) and ≥2 prior therapies: pivotal Phase II expansion results

Single-arm pivotal Phase II expansion cohort in patients with R/R DLBCL and ≥2 prior therapies

Key inclusion criteria

- DLBCL NOS, HGBCL, transformed FL or PMBCL
- ECOG PS 0–1
- ≥2 prior therapies, including: anti-CD20 antibody and anthracycline

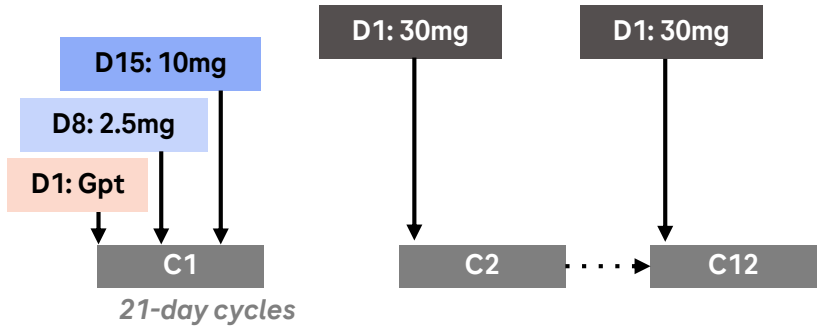
Glofitamab IV administration

Fixed-duration treatment

- max. 12 cycles

CRS mitigation:

- obinutuzumab pretreatment (1 x 1000mg)
- C1 step-up dosing
- monitoring after first dose (2.5mg)



Endpoints

- **Primary: CR (best response) rate by IRC***
- **Key secondary:** ORR rate,† DoR, DoCR,† PFS, and OS

*by PET-CT (Lugano criteria)[1]; †by IRC and investigator. BCL, B-cell lymphoma; FL, follicular lymphoma; Gpt, obinutuzumab pretreatment; HGBCL, high-grade BCL; IRC, Independent Review Committee; NOS, not otherwise specified; PMBCL, primary mediastinal large BCL ;Cheson, et al. J Clin Oncol 2014.

Baseline characteristics

Heavily pre-treated, highly refractory population

n (%)*		N=154†
Median age, years (range)		66.0 (21–90)
Male		100 (64.9)
ECOG PS‡	0	69 (44.8)
	1	84 (54.5)
Ann Arbor stage	I	10 (6.5)
	II	25 (16.2)
	III	31 (20.1)
	IV	85 (55.2)
NHL subtype	DLBCL	110 (71.4)
	trFL	27 (17.5)
	HGBCL	11 (7.1)
	PMBCL	6 (3.9)
Bulky disease	>6cm	64 (41.6)
	>10cm	18 (11.7)

n (%)*	N=154
Median no. of prior lines, n (range)	3 (2–7)
2 prior lines	62 (40.3)
≥3 prior lines	92 (59.7)
Prior anti-CD20 Ab	154 (100.0)
Prior anthracycline	149 (96.8)
Prior CAR-T	51 (33.1)
Prior ASCT	28 (18.2)
Refractory to any prior therapy	139 (90.3)
Refractory to last prior therapy	132 (85.7)
Primary refractory	90 (58.4)
Refractory to prior CAR-T	46 (29.9)
Refractory to any prior anti-CD20	128 (83.1)

Clinical cut-off date: March 14, 2022; *unless otherwise specified; †safety-evaluable population (all treated patients); ‡ECOG PS 2, n=1 (0.6%); Ab, antibody; ASCT, autologous stem cell transplant; trFL, transformed follicular lymphoma.

Response rates – primary endpoint met

High CR/ORR rate at recommended phase II dose (RP2D)

Efficacy endpoint[1]	Glofitamab 2.5/10/30mg (n=155)
CR rate*	**61 (39.4%)** [95% CI: 31.6%, 47.5%]
ORR*	**80 (51.6%)** [95% CI: 43.5%, 59.7%]

- Median duration of follow-up: 12.6 months (range: 0–22)
- Responses were achieved early: median time to first CR was 42 days (95% CI: 42, 44)

- At time of primary analysis, primary endpoint met in the primary efficacy population (n=108)†: 35.2% CR rate by IRC significantly greater (p<0.0001) than 20% historical control CR rate‡

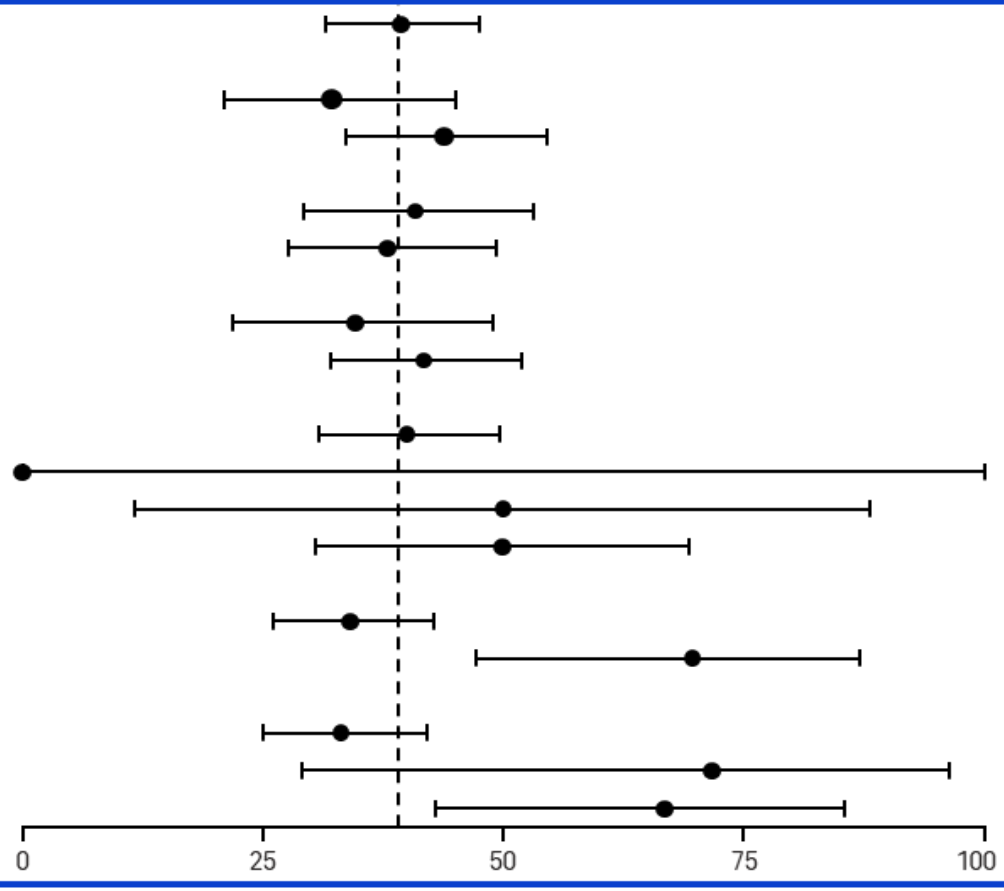
*best response by intent-to-treat population; †the pivotal expansion cohort population; ‡the historical control CR rate was pre-specified based on a meta-analysis in patients with R/R DLBCL (where most [≥50%] had received ≥2 prior therapies) and compared with the CR rate in the primary efficacy-evaluable population using an exact binomial test (2-sided alpha level: 5%).

1. Cheson, et al. J Clin Oncol 2014.

Complete response rates by IRC in pre-specified subgroups

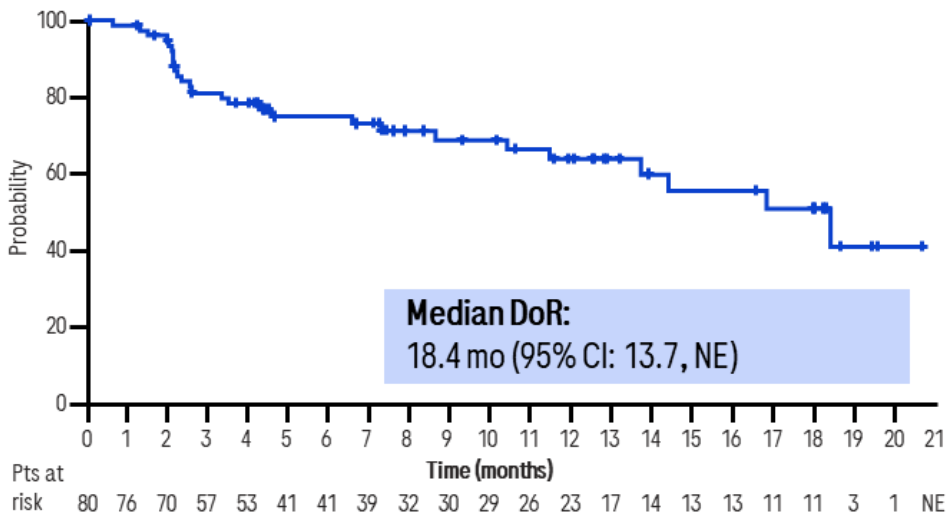
Consistent CR rates in patients with prior CAR-T therapy; CR rates higher in relapsed patients

Subgroups	No. of patients	CR (95% CI) by IRC
Overall	155 (100%)	39% (32%, 48%)
Number of prior line of therapies		
2	62 (40%)	32% (21%, 45%)
≥3	93 (60%)	44% (34%, 55%)
Age group		
<65	71 (46%)	41% (29%, 53%)
≥65	84 (54%)	38% (28%, 49%)
Prior CAR-T therapy		
Yes	52 (34%)	35% (22%, 49%)
No	103 (66%)	42% (32%, 52%)
NHL subtype at study entry		
DLBCL	110 (71%)	40% (31%, 50%)
HGBCL	11 (7%)	0%
PMBCL	6 (4%)	50% (12%, 88%)
trFL	28 (18%)	50% (31%, 69%)
R/R to last prior therapy		
Refractory	132 (85%)	34% (26%, 43%)
Relapsed	23 (15%)	70% (47%, 87%)
Post ASCT		
No	127 (82%)	33% (25%, 42%)
Refractory	7 (5%)	71% (29%, 96%)
Relapsed	21 (14%)	67% (43%, 85%)



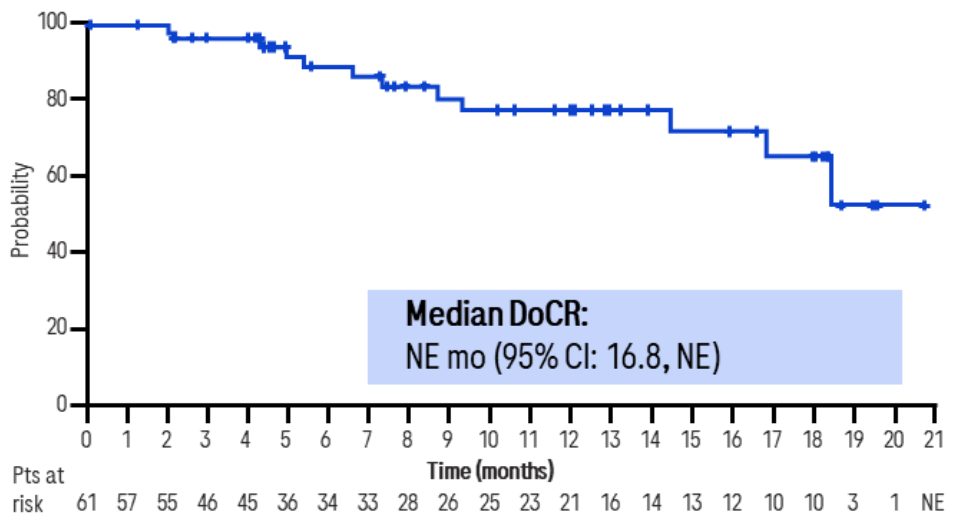
Durable responses maintained after cessation of therapy

Duration of overall response by IRC



	N=80
Median DoR follow-up, mo (range)	10.6 (0–21)
12-months DoR, % (95% CI)	**63.6 (51.1, 76.2)**
ORs ongoing at CCOD, n (%)	53 (66.3)

Duration of complete response by IRC



	N=61
Median DoCR follow-up, mo (range)	10.6 (0–21)
12-months DoCR, % (95% CI)	**77.6 (64.3, 90.8)**
CRs ongoing at CCOD, n (%)	49 (80.3)

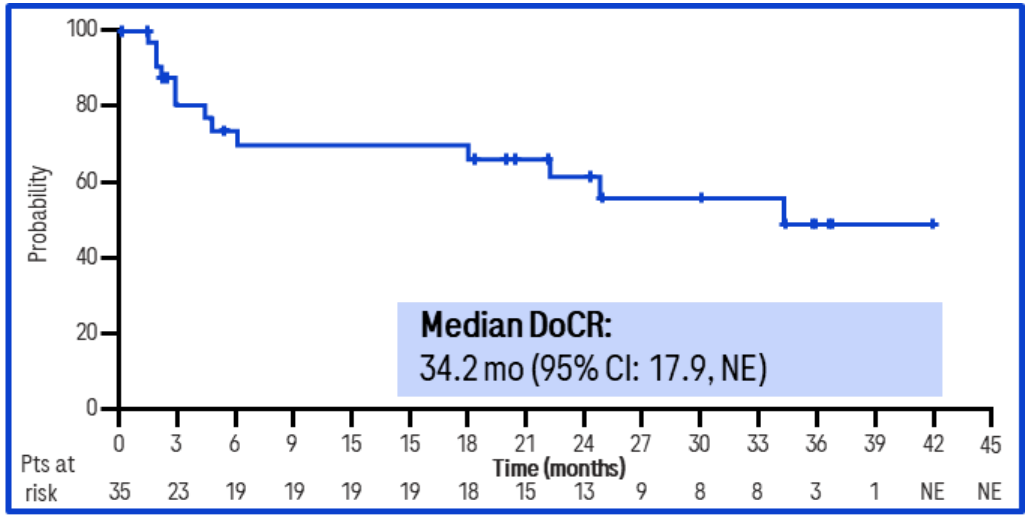
CCOD, clinical cut-off date; mo, months; NE, not estimable.

DoCR in earlier cohorts show durable responses beyond 24 months

Supporting cohort

- Patients in earlier cohorts have extended follow up for duration of response
  - patients with R/R DLBCL, HGBCL, trFL and PMBCL with ≥2 prior lines of therapy (n=101)
  - patients treated with glofitamab doses ≥10mg* (RP2D not included) for a fixed treatment duration of 8–12 cycles (6–9 months)
  - CR rate: 35/101 (35%)†

Duration of complete response by IRC



	N=35
Median DoCR follow-up, mo (range)	**24.8 (0, 42)**
24-months DoCR, % (95% CI)	61.4 (43.1, 79.7)
CRs ongoing at CCOD, n (%)	22 (62.9)

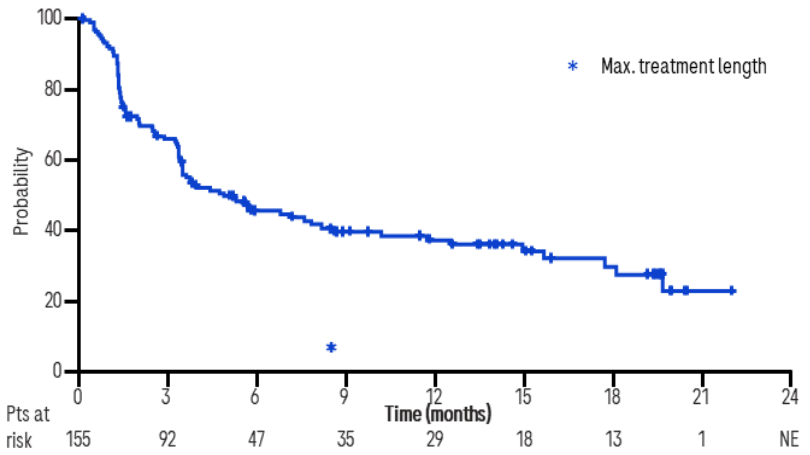
Durable responses beyond 24 months achieved after fixed-duration treatment; median of 34.2 mo

*10mg, 16mg, 25mg, 10/16mg, 2.5/10/16mg; †intent-to-treat population; RP2D, recommended Phase II dose.

Time-to-event endpoints

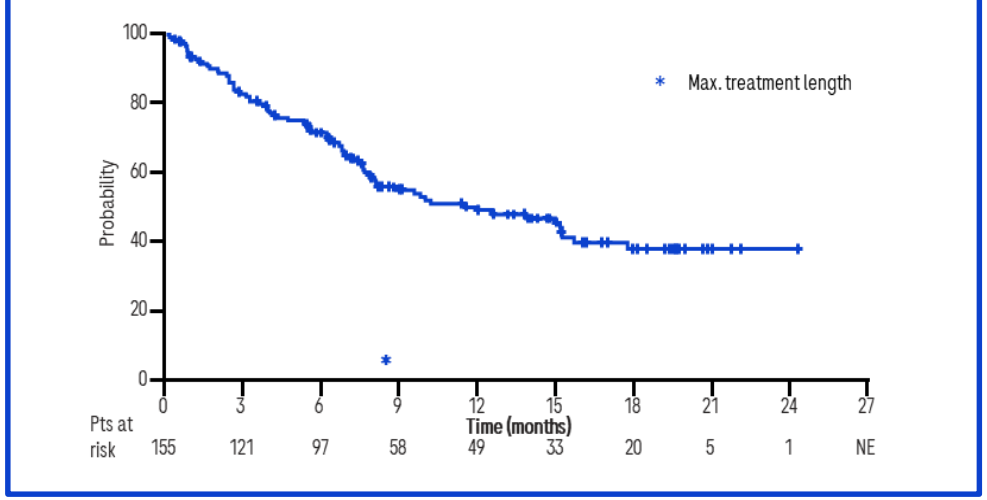
Early trend for plateau observed in PFS and OS curves

Progression-free survival by IRC



	N=155
Median PFS follow-up, mo (range)	12.6 (0–22)
Median PFS, months (95% CI)†	4.9 (3.4, 8.1)
6-month event-free rate, % (95% CI)	45.5 (37.2, 53.8)
12-month event-free rate, % (95% CI)	37.1 (28.5, 45.8)

Overall survival*



	N=155
Median OS, months (95% CI)†	11.5 (7.9, 15.7)
12-month OS rate, % (95% CI)	49.8 (41.1, 58.5)

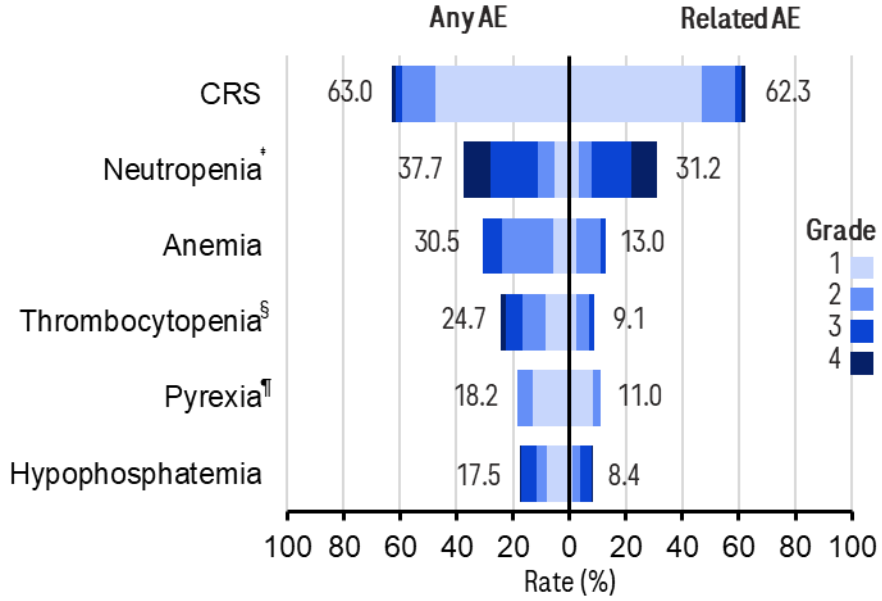
*including four deaths due to COVID-19; †KM estimates

Glofitamab safety profile

Well tolerated, with a favorable safety profile

n (%)*	N=154
Median no. of cycles received (range)	5 (1–13)
Median relative dose intensity, % (range)	100 (94–100)
AE	152 (98.7)
Related AE	140 (90.9)
Grade 3–4 AE	87 (56.5)
Related AE	64 (41.6)
Serious AE	73 (47.4)
Related AE	46 (29.9)
Grade 5 (fatal AE)	8 (5.2)†
Related AE	0
AE leading to treatment discontinuation	14 (9.1)
Related AE	5 (3.2)

AEs (≥15%) by grade and relationship with glofitamab



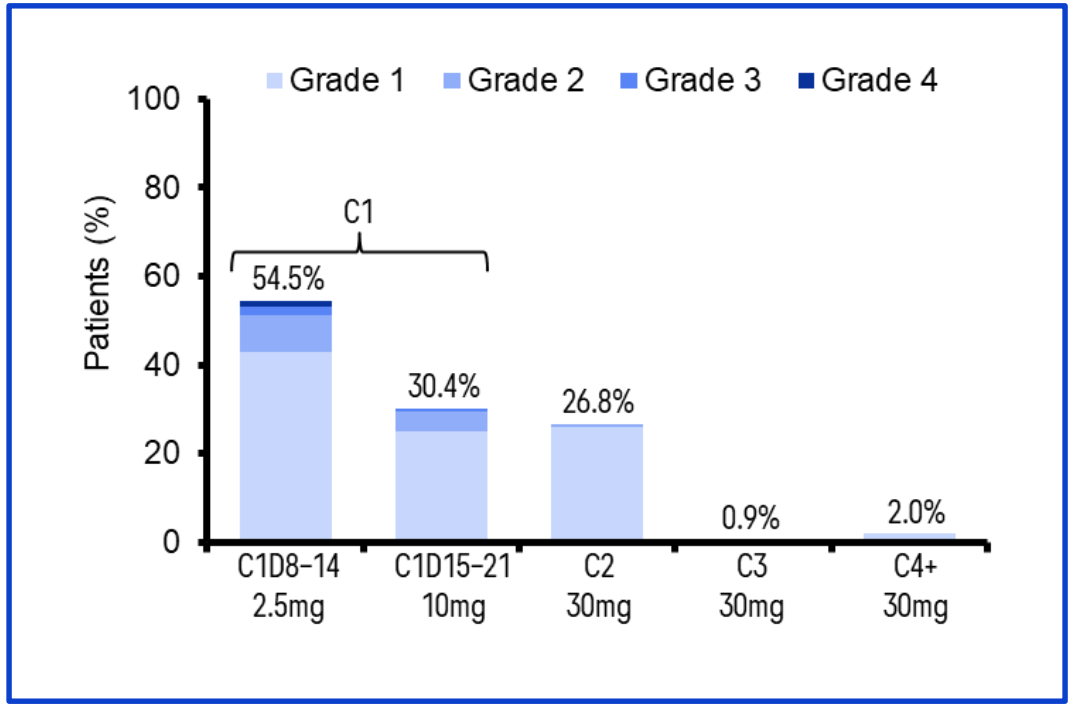
*unless otherwise specified; †COVID-19/COVID-19 pneumonia (n=5); sepsis (n=2); delirium (n=1); ‡includes neutrophil count decreased; §includes platelet count decreased; ¶pyrexia events separate from CRS

Cytokine release syndrome

Mostly low grade, time of onset was predictable, and mostly occurred during cycle 1

n (%)	N=154
CRS (any grade)*	97 (63.0)
Grade 1 (fever)	73 (47.4)
Grade 2	18 (11.7)
Grade 3	4 (2.6)
Grade 4	2 (1.3)
Median time to CRS onset from C1D8 dose, hours (range)	13.6 (6.2–51.8)
Median CRS duration, hours (range)	30.63 (0.5–316.7)
Corticosteroids for CRS management	27/97 (27.8)
Tocilizumab for CRS management	31/97 (32.0)

CRS by cycle and grade†



*CRS was graded by INV according to Lee 2014 criteria (and grade by American Society for Transplantation and Cellular Therapy criteria was derived based on reported data)1,2; †one patient had Grade 1 CRS following obinutuzumab pretreatment due to CART-T re-expansion

1. Lee, at al. Blood 2014; 2. Lee, et al. Biol Blood Marrow Transplant 2019

Other adverse events of interest

Low rate of treatment discontinuations due to AEs and low rate of ICANS events

n (%)	N=154
Infections (all grades)	59 (38.3)
Grade ≥3	23 (14.9)
Neutropenia* (all grades)	58 (37.7)
Grade ≥3	41 (26.6)
Febrile neutropenia (all grades)	4 (2.6)
Grade ≥3	4 (2.6)
Tumor flare events (all grades)	17 (11.0)
Grade ≥3	4 (2.6)
Neurologic AEs† (all grades)	59 (38.3)
Grade ≥3	5 (3.2)
ICANS‡ (all grades)	12 (7.8)
Grade ≥3	4 (2.6)§

n (%)	N=154
AE leading to treatment discontinuation	14 (9.1)
Infections and infestations¶	6 (3.9)
Delirium	2 (1.3)
Neutropenia**	2 (1.3)
Hepatobiliary disorders#	1 (0.6)
Gastrointestinal hemorrhage**	1 (0.6)
CRS**	1 (0.6)
Melanoma recurrent	1 (0.6)

*includes neutrophil count decreased;†neurologic AEs include AEs reported in Nervous System Disorders and Psychiatric Disorders System Organ Class; ‡neurologic AEs potentially consistent with immune effector cell-associated neurotoxicity syndrome (ICANS); §Grade 3 somnolence (n=1), Grade 3 agitation (n=1), Grade 3 delirium (n=1), Grade 5 delirium (n=1);¶COVID-19/COVID-19 pneumonia (n=3), biliary tract infection bacterial (n=1), myelitis (n=1)**, sepsis (n=1); #cholestasis (n=1) and hepatic cytolysis (n=1) in one patient; **related to glofitamab.

Glofitamab conclusions

- Primary efficacy endpoint met; CR: 39.4% in heavily pre-treated, highly refractory patients with DLBCL
- Consistent CR rate in patients with prior CAR-T; higher CR rate in relapsed vs refractory patients
- CRs achieved early and were durable after the fixed treatment duration
- Glofitamab was well tolerated: low rate of treatment discontinuations; CRS was mostly low grade and during Cycle 1, with predictable time of onset; low rate of ICANS
- Glofitamab is the first T-cell-engaging bispecific monoclonal antibody to demonstrate clinically meaningful outcomes for patients with R/R DLBCL in a pivotal Phase II setting

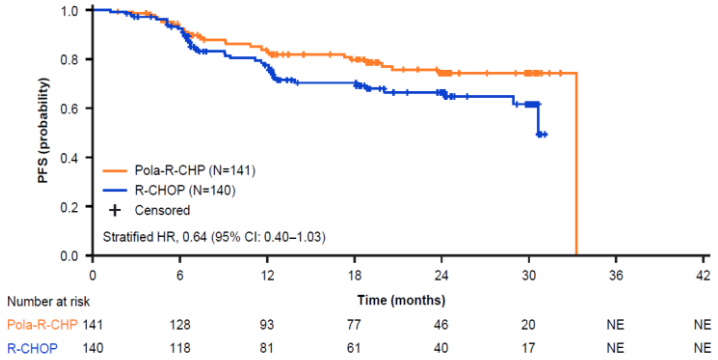
GemOx, gemcitabine plus oxaliplatin; ICANS, neurologic AEs potentially consistent with immune effector cell-associated neurotoxicity syndrome

Asia subpopulation analysis from the Phase III POLARIX trial

Results consistent with the global POLARIX study

The Asia subpopulation (n=281) included patients from mainland China, Japan, South Korea, and Taiwan (enrolled during the global phase), and from the China extension cohort

PFS for Pola-R-CHP vs R-CHOP (ITT)



Secondary endpoints

	Pola-R-CHP (n=141)	R-CHOP (n=140)
EFS, 2-year rate (95% CI)	74.2 (65.7–82.7)	65.6 (56.4–74.8)
HR (95% CI)	0.64 (0.40–1.03)	
CR, n (%)*	116 (82.3)	109 (77.9)
DFS, HR (95%)†	0.67 (0.37–1.23)	

*Measured at end of treatment by blinded independent central review.
†Pola-R-CHP, n=127; R-CHOP, n=114. Patients with an investigator-assessed best response of CR at any time during the study were evaluable for DFS.
CI, confidence interval; CR, complete response; DFS, disease-free survival; EFS, event-free survival; HR, hazard ratio; Pola-R-CHP, polatuzumab vedotin plus rituximab, cyclophosphamide, doxorubicin, and prednisone; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone.

- The 2-year PFS rate was 74.2% (95% CI: 65.7-82.7) with Pola-R-CHP vs 66.5% (95% CI: 57.3-75.6) with R-CHOP
- The overall safety profile was similar between the Pola-R-CHP and R-CHOP arms
- Incidence of peripheral neuropathy (all grades) was 44.3% (Pola-R-CHP) vs 50.4% (R-CHOP)

Song et al ASCO 2022

Early pipeline programs in focus

Johanna Bendell, M.D. |

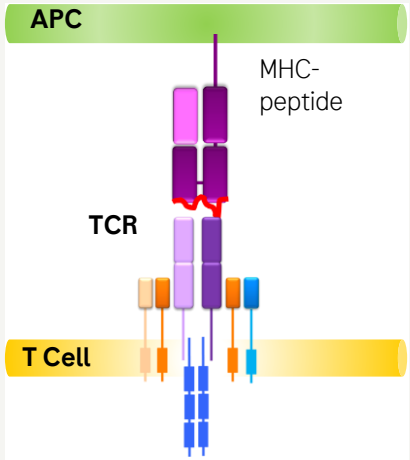
Global Head Oncology, Roche Pharma Research & Early Development (pRED)

pRED oncology strategy

Covering a range of modalities in line with state of the art cancer biology

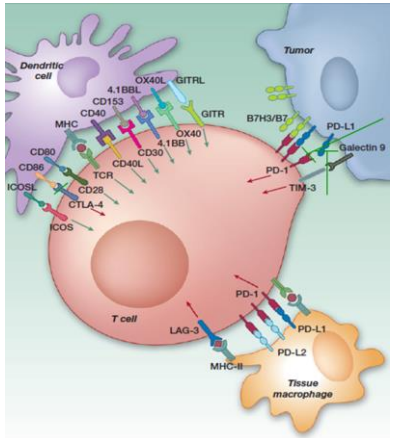
Cancer Immunotherapy (CIT)

T cell redirection



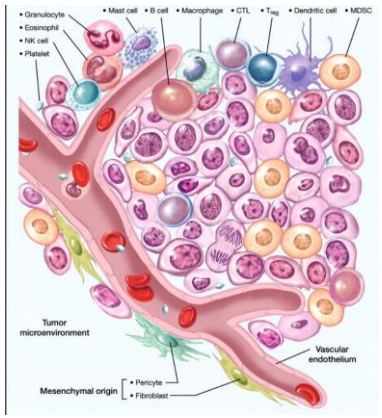
T cell bispecifics (TCBs)
- 2:1 format
- Exploring standard tumor-activated approaches

Immunomodulation



1. Co-stimulators
2. Next generation immunocytokines
3. Counter-inhibitory immunomodulators

T cell generation

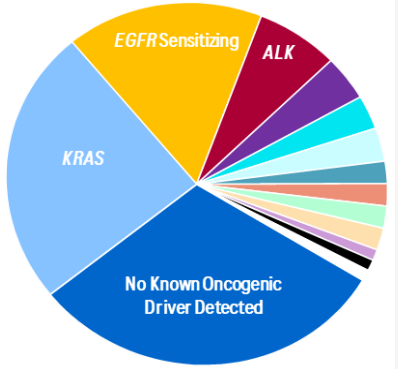


Modified from Cancer Res; 72(13); 3125–30. ©2012 AACR

Targeted myeloid cell agonists

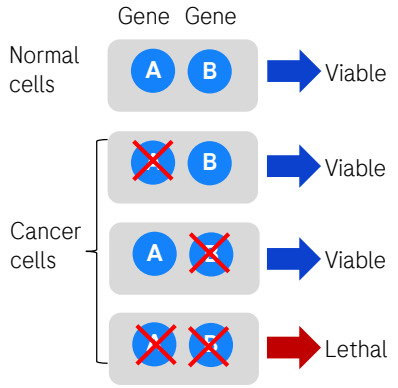
Cancer Cell Targeted Therapy (CTT)

Oncogenic drivers



Inhibitors and modulators for oncogenic drivers

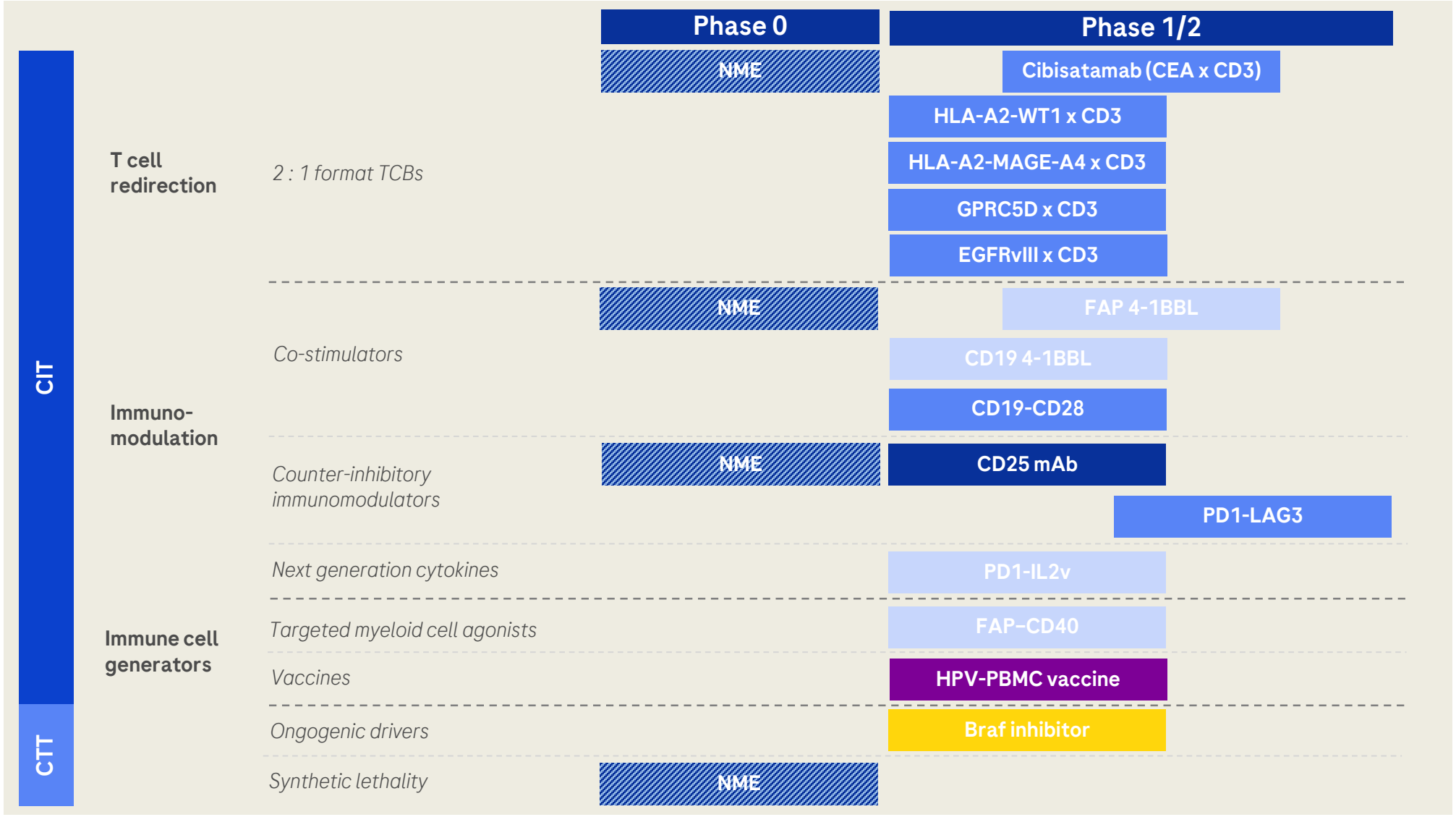
Synthetic lethality



Inhibitors and modulators for paired and non-pairwise relationships

APC=Antigen presenting cells; TCR=T cell receptor

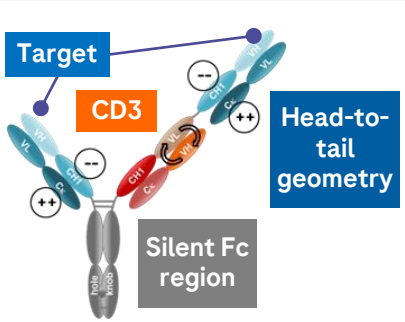
pRED oncology development pipeline



CTT=Cancer cell targeted therapy; CIT=Cancer immunotherapy; NME=New molecular entity; TCBs=T cell bispecifics; mAb=Monoclonal antibody

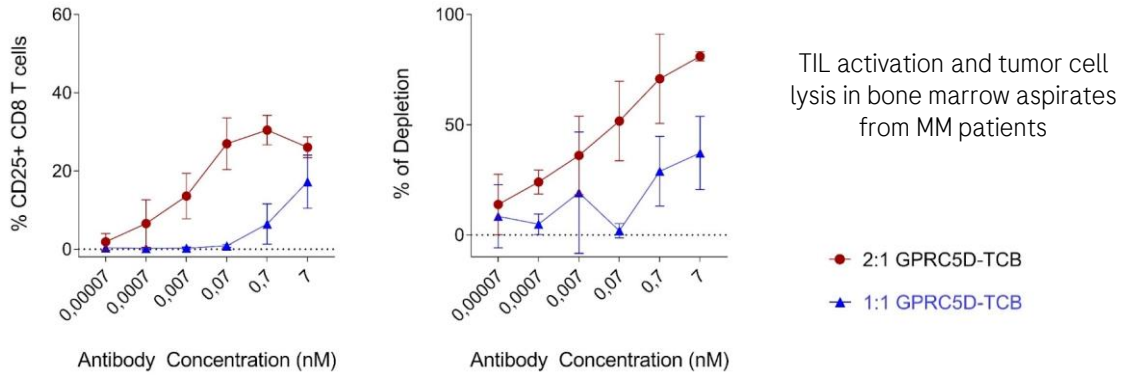
GPRC5D x CD3 TCB (RG6234) in r/r multiple myeloma

Novel 2:1 format T cell bispecific with best-in-class potential

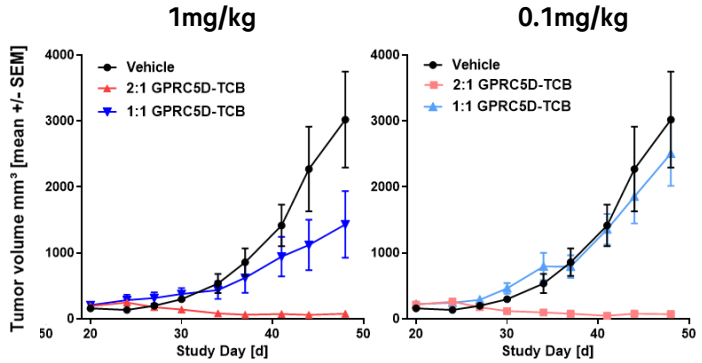


- GPRC5D is the most specific target yet known in MM
- GPRC5D-TCB recruits T cells to the tumor site to elicit an anti-tumor immune response

TIL activation and tumor cell lysis in bone marrow aspirates from MM patients[1]

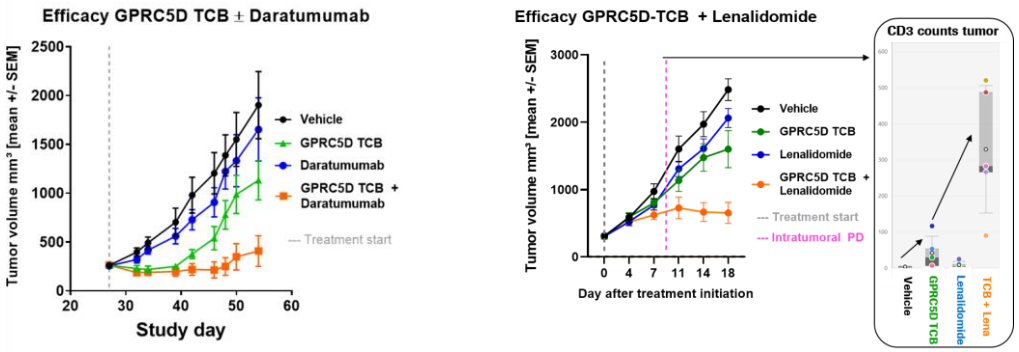


High efficacy at low doses in preclinical models[1]



Efficacy in sc NCI-H929 xenograft in humanized mice

Reduction in tumor volume in combination with SoC in preclinical models[1]



Combination in sc MM xenografts in humanized mice

[1]Roche internal data on file; MM=Multiple myeloma; BIC=Best in class; TCB=T cell bispecific; r/r=Relapsed or refractory; SOC=Standard of care; BM=Bone marrow; SC=Subcutaneous; TIL=Tumor-infiltrating lymphocyte

GPRC5D x CD3 TCB (RG6234) in r/r multiple myeloma

Novel 2:1 format T cell bispecific with best-in-class potential

Compelling emerging clinical activity in heavily pretreated pts with r/r MM[1]

Patient characteristics n=41 patients	
Median age	63 years (range: 27 to 78)
R-ISS stage II or III at study entry	61%
High-risk cytogenetics (t(4;14), t(14;16), del(17p), 1q21 gain)	58%
Median number of prior therapies	5 (range: 2 to 15)
Triple-class refractory	67%
Penta-class refractory	36%
Prior BCMA-directed Tx	15%

Early efficacy data n=34 efficacy-evaluable patients	
ORR	68%
VGPR or better response	50%*
Median time to first response (95% CI)	1.3 month (1.1, 1.6)
Median follow-up	3.5 month (range: 0.03 to 11.7)
Treatment ongoing**	59%
Response ongoing**	78% (of responders)

*including 2/6 BCMA pre-treated patients; **after data cut, January 31, 2022
ORR=Overall response rate; VGPR=Very good partial response; CI=Confidence interval; Tx=Therapy

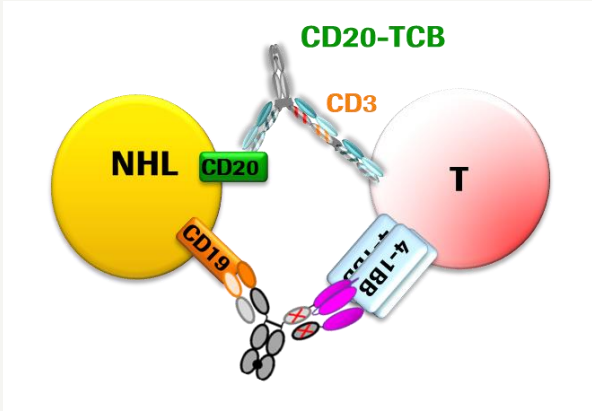
- Emerging Ph1 data demonstrates compelling clinical activity with manageable safety, in a heavily pretreated patient population (EHA 2022, abstract S180[1])
- Ph1 study in r/r MM is ongoing (exploring both IV and SC administration)
- Combination studies are planned with selected standard-of-care agents

[1] Hasselbalch Riley C. et al., EHA 2022; Clinical cut-off date: Jan 31, 2022; MM=Multiple myeloma; r/r=Relapsed or refractory; IV=Intravenous; SC=Subcutaneous

CD19 4-1BBL (RG6076) in r/r NHL

B cell-targeted costimulatory T cell agonist with first-in-class potential

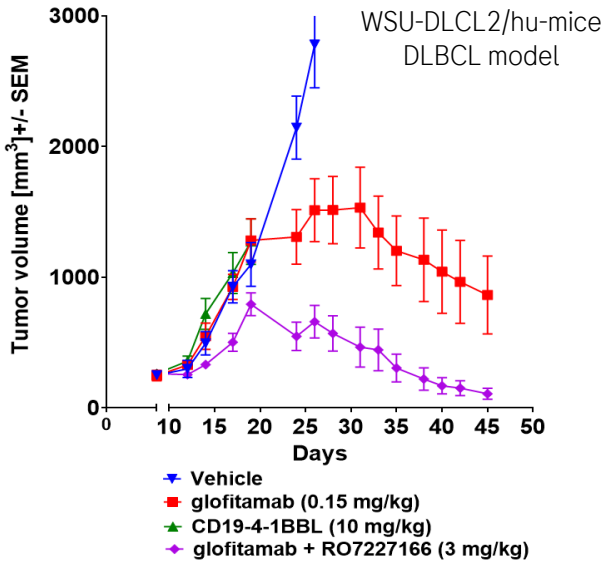
CD19 4-1BBL + CD20xCD3 TCB



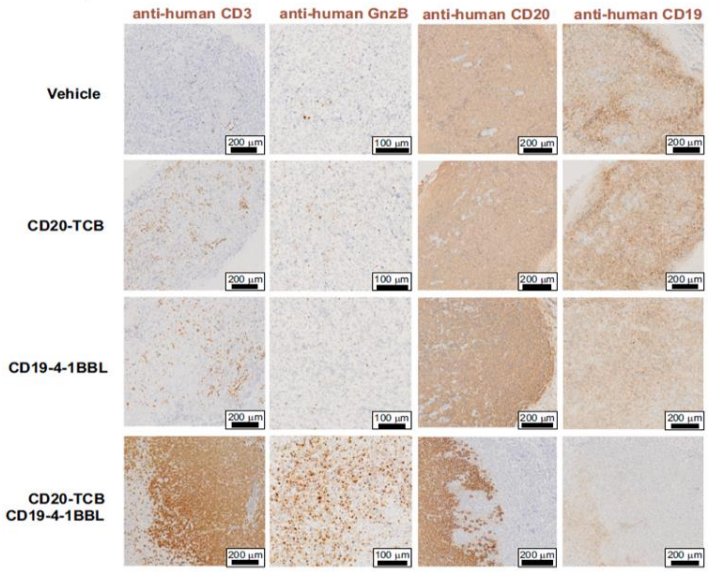
- **Signal 1:** NK or T cell activation delivered by CD20xCD3 TCB
- **Signal 2:** CD19 4-1BBL leads to enhanced NK and T cell activation and promotes a durable immune response
- FIC potential 4-1BB agonist with B cell targeted co-stimulation of T cells

Potential for off-the-shelf alternative to 2nd generation CD19-CAR-T cell

Change in tumor volume over time[1]



Combination of CD20-TCB and CD19 4-1BBL induces intratumoral T cell infiltration (WSU-DLCL2)[1]



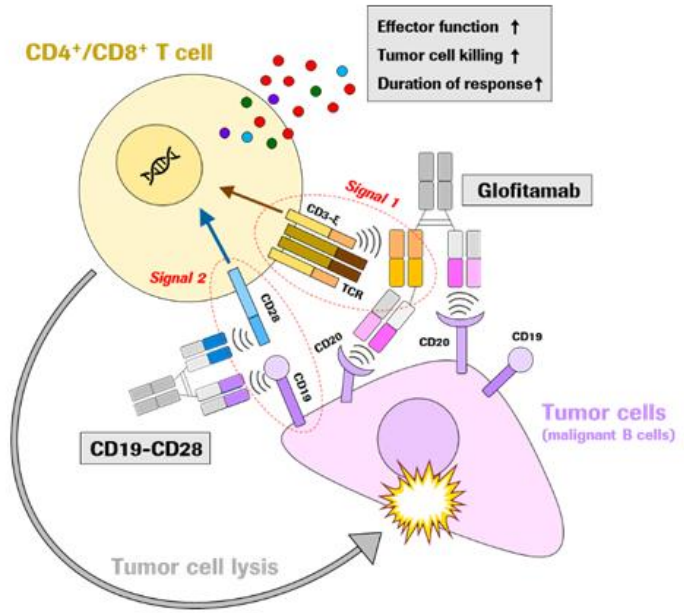
- CD19 4-1BBL enhances in vivo effector function of T cells in the presence of CD19+ tumor cells in combination with glofitamab
- Ph1 in combination with glofitamab in r/r NHL ongoing

[1] Claus et al., 2019 Science Translational Medicine; TCB=T cell bispecific; NK=Natural killer; FIC=First in class; r/r=Relapsed or refractory; NHL=Non-Hodgkin´s lymphoma; DLBCL=Diffuse large B-cell lymphoma

CD19-CD28 (RG6333) in r/r NHL

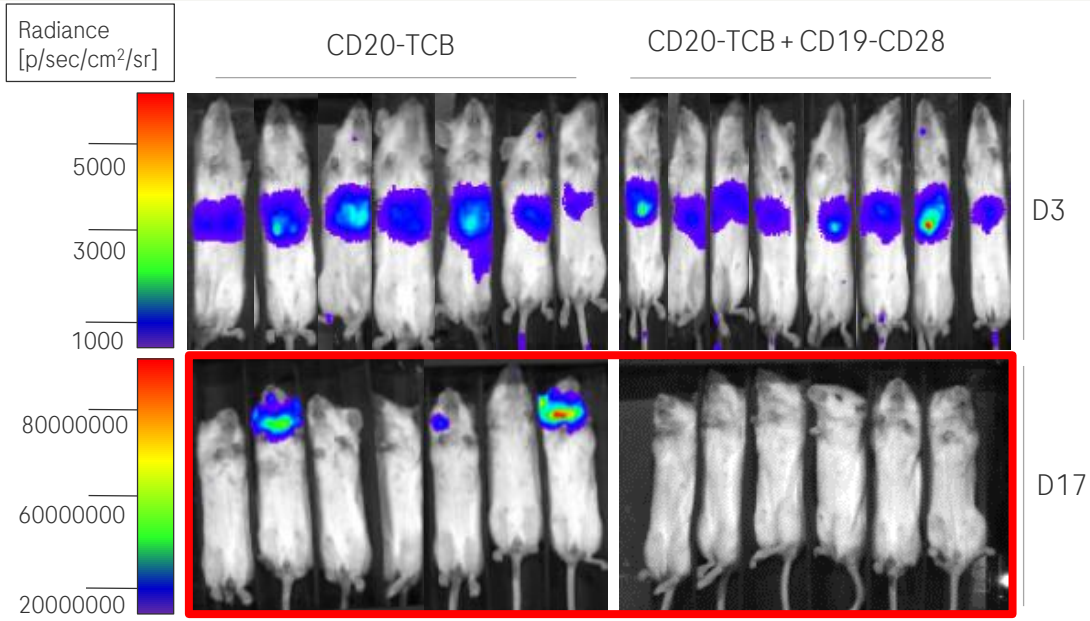
B cell-targeted costimulatory T cell agonist with distinct MoA vs 4-1BB

CD19-CD28 MoA



- 2nd costimulatory T cell agonist
- CD19-CD28 and CD19 4-1BBL have distinct MoAs - CD28 is constitutively expressed vs 4-1BB needs to be activated by signal 1

CD19-CD28 synergizes with CD20-TCB - boosting and prolonging T cell activity



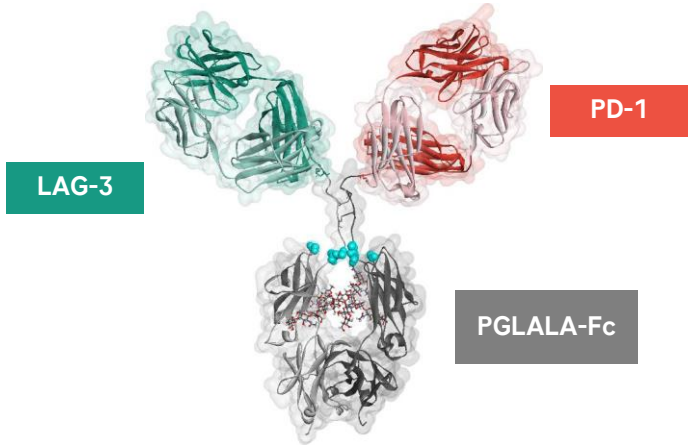
- Strong combination effect of CD19-CD28 with CD20xCD3 TCB in orthotopic DLBCL model, resulting in no detectable tumor signals in 6/8 mice at study day 17 (2 mice progressed and were terminated before study completion)
- Ph1 in combination with glofitamab in r/r NHL started enrollment Q1 2022

Roche internal data on file; MoA=Mode of action; TCB=T cell bispecific; DLBCL=Diffuse large B cell lymphoma; r/r=Relapsed or refractory; NHL=Non-Hodgkin´s lymphoma

PD1-LAG3 (RG6139) in solid tumors

Bispecific checkpoint inhibitor that preferentially targets TILs

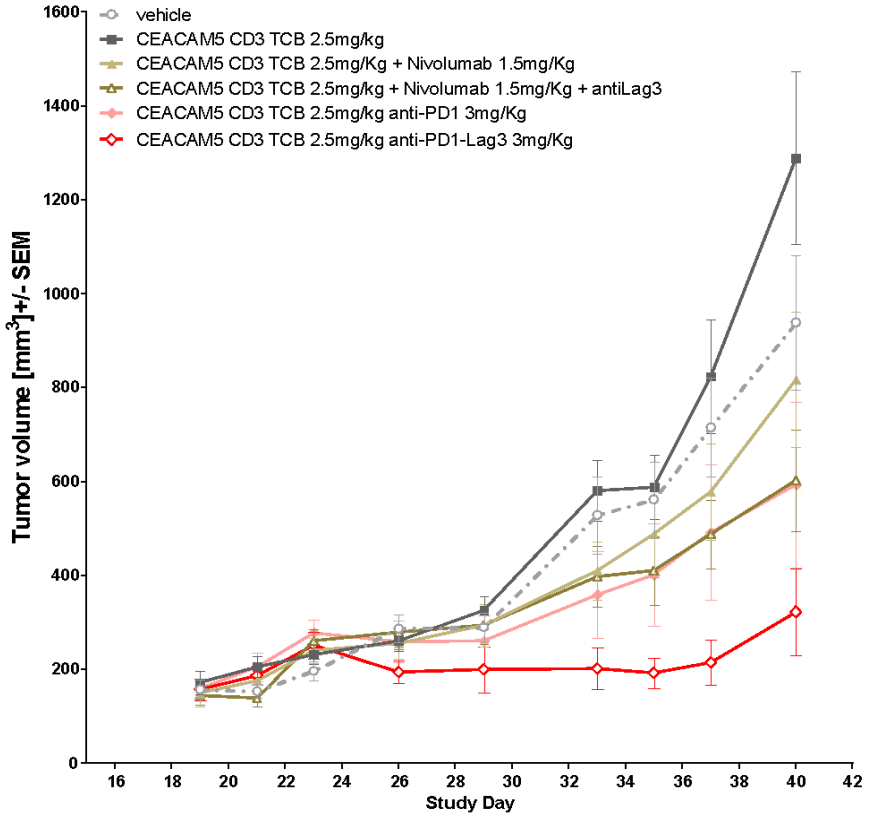
PD1-LAG3 structure and MoA



- Bispecific antibody binding to PD-1 and LAG-3, reinvigorates T cells by blocking two co-inhibitory checkpoint receptors
- Preferential targeting of tumor reactive TILs
- Avoids immunosuppressive effects by preferential binding to T effector cells vs Tregs

PD1-LAG3 has the potential to replace current CPI therapies in inflamed tumor types

Improved tumor growth inhibition in preclinical models[1]



- In preclinical models, PD1-LAG3 is superior to aPD-1, and the combination with aLAG-3, in controlling tumor growth and eradicating the tumor
- Ph1a dose finding in solid tumors completed
- Ph1b/2 studies in esophageal cancer, HCC and neoadjuvant melanoma ongoing

[1]Codarri Deak et al., SITC 2019; TILs=Tumor-infiltrating lymphocytes; MoA=Mode of action; Tregs=Regulatory T cells; CPI=Checkpoint inhibitor; HCC=Hepatocellular carcinoma

PD1-LAG3 (RG6139) in metastatic melanoma

Patient case report

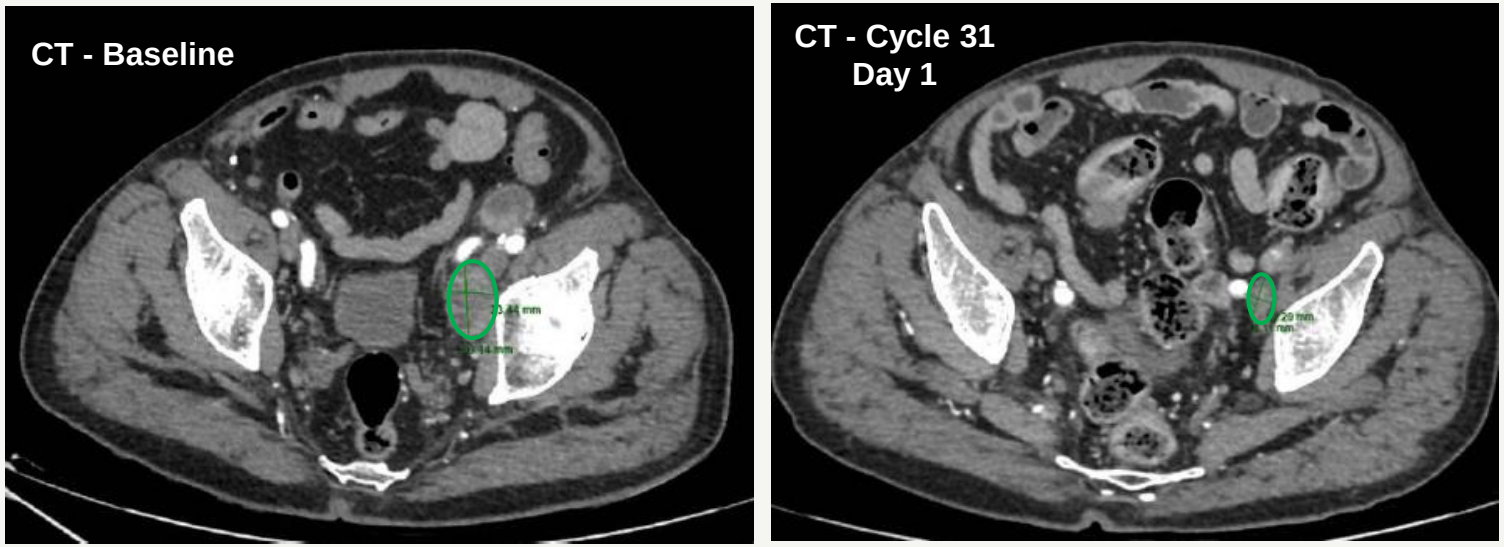
64 year-old Caucasian male with metastatic melanoma:

Prior treatment:
- 1L pembrolizumab
  → best overall response: PD
- 2L pembrolizumab plus FAP-IL2v
  → best overall response: SD

Target lesion(s):
- Skin
- Lymph node (left iliacal)

IHC status:
- PD-L1 10%
- LAG3 20%

Confirmed partial response following 3L treatment with PD1-LAG3



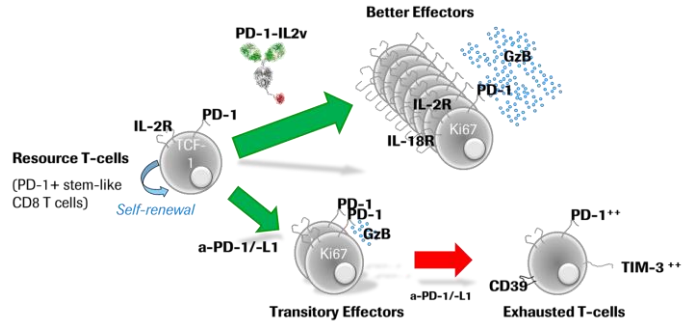
Confirmed PR:
C5D1; **SD** -2.8%; C7unsch; -8.3%, C13D1; **PR** -50%; C17D1; -50%; C21D1; -58.3%; C24unsch; -61.1%; C31D1; -66.7%

Roche internal data on file; PD=Progressive disease; SD=Stable disease; IHC=Immunohistochemistry; CT=Computerized tomography; PR=Partial response; C=Cycle; D=Day; unsch=unscheduled

PD1-IL2v (RG6279) in solid tumors

Targeting IL-2v to PD-1+ T cells to exploit pre-existing endogenous immunity

PD1-IL2v MoA

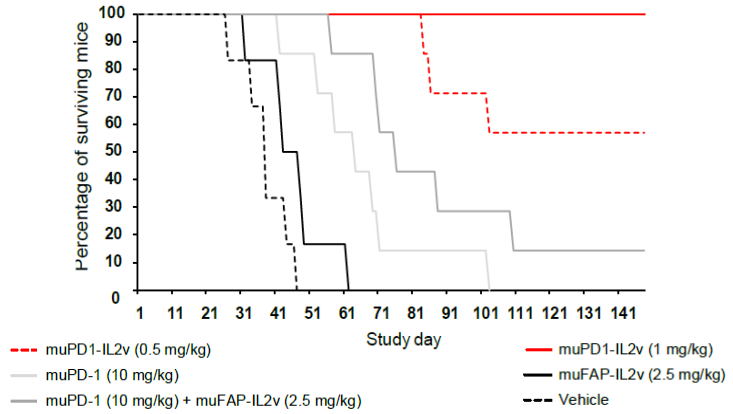


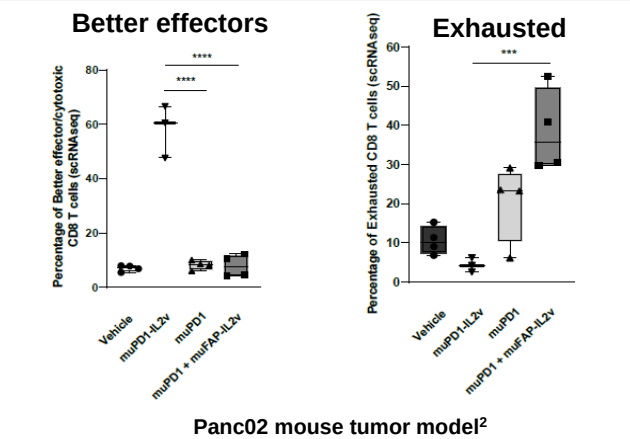
Collaboration with R. Ahmed & M. Hashimoto, Emory University, Atlanta

- 3rd generation IL-2 and first PD-1-targeted immunocytokine to enter clinical trials
- By delivering IL2v to PD-1, PD1-IL2v differentiates the resource T cell subset to the better effector subset
- Ph1a monotherapy study has been completed
- Ph1b in combination with atezolizumab in solid tumors ongoing

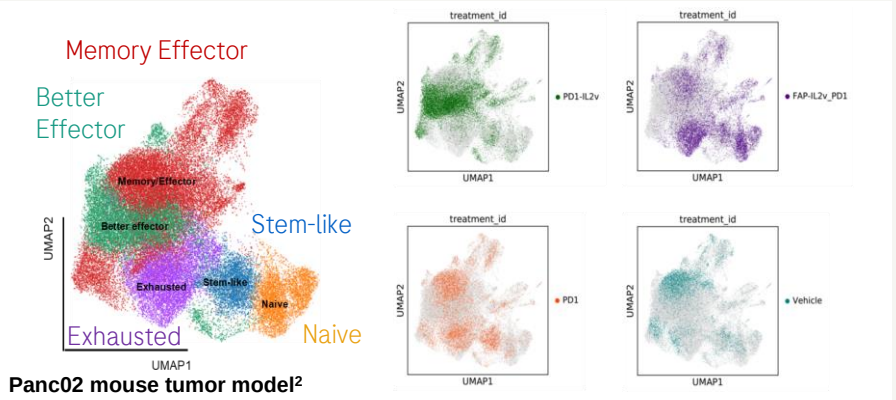
PD1-IL2v: Superior efficacy vs aPD-1 and aPD-1 + FAP-IL2v in preclinical models

Panc02 mouse tumor model[1]





Panc02 mouse tumor model[2]



Panc02 mouse tumor model[2]

Preclinically, PD1-IL2v is superior to aPD-1 as monotherapy and in combination with FAP-IL2v in:

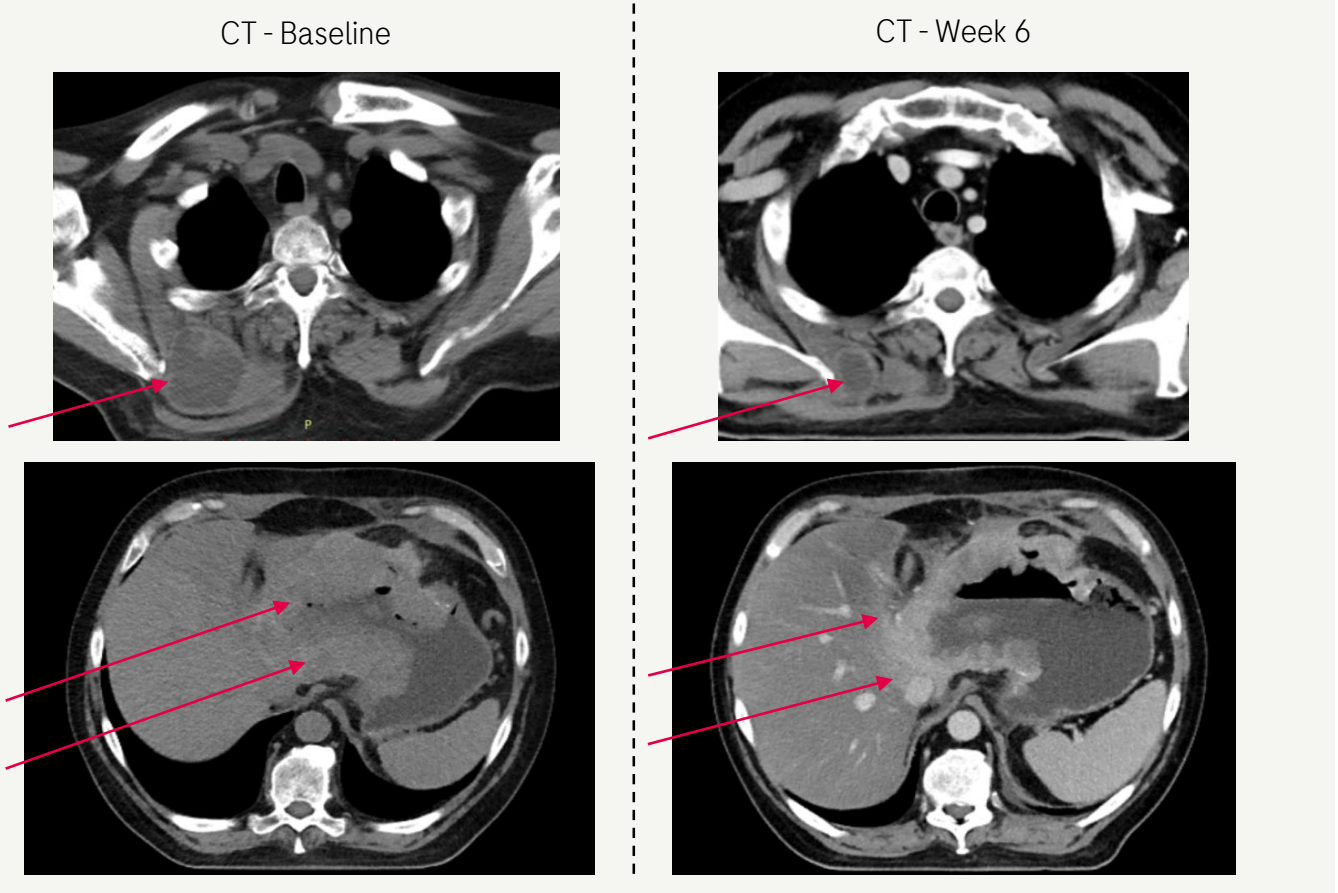
- eradicating Panc02 tumors
- providing long term survival by a unique subset of CD8 TILs endowed with effector functions and no signs of exhaustion

[1]Umaña, P., AACR 2021, [2]Codarri Deak et al. in press; MoA=Mode of action; PD=Progressive disease; SD=Stable disease; CT=Computerized tomography, SC=Subcutaneous, RTx= Radiation therapy

PD1-IL2v (RG6279) in metastatic melanoma

Patient case report

Preliminary signs of clinical activity following 3L treatment with PD1-IL2v



40 year-old male with metastatic melanoma:

Prior treatment
- 1L pembrolizumab
  → best overall response: PD
- 2L ipilimumab
  → best overall response: PD
- Palliative RTx to SC metastasis at neck prior to PD1-IL2v

Target lesions
- Large SC metastases
- Broad infiltration of gastric wall

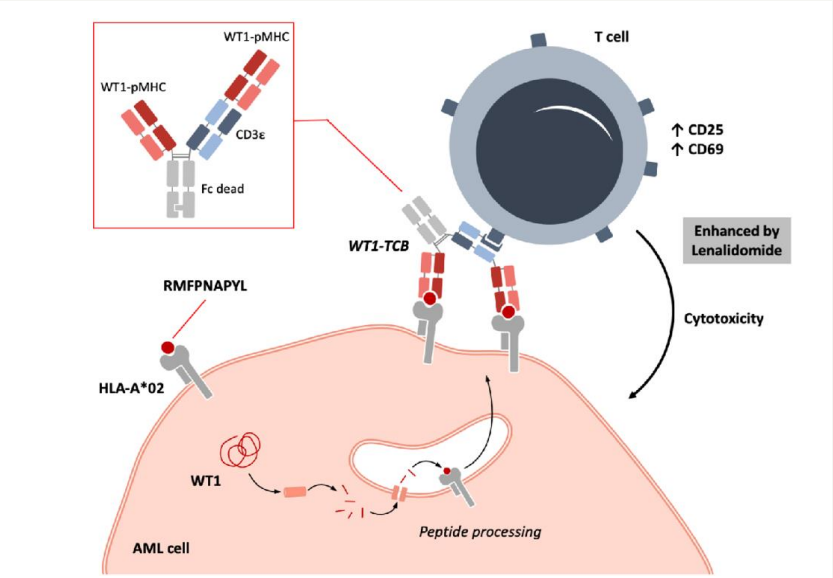
Outcome on PD1-IL2v treatment
- Confirmed PR, with DoR >60 weeks

Roche internal data on file; MoA=Mode of action; PD=Progressive disease; SD=Stable disease; CT=Computerized tomography, SC=Subcutaneous, RTx= Radiation therapy; PR=Partial response; DoR=Duration of response

HLA-A2 WT1 x CD3 TCB (RG6007) in hematologic tumors

TCR receptor-like T cell bispecific targeting intracellular oncoprotein WT1

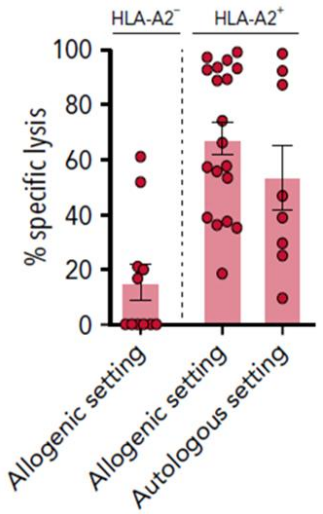
Potential tumor targets beyond cell surface proteins



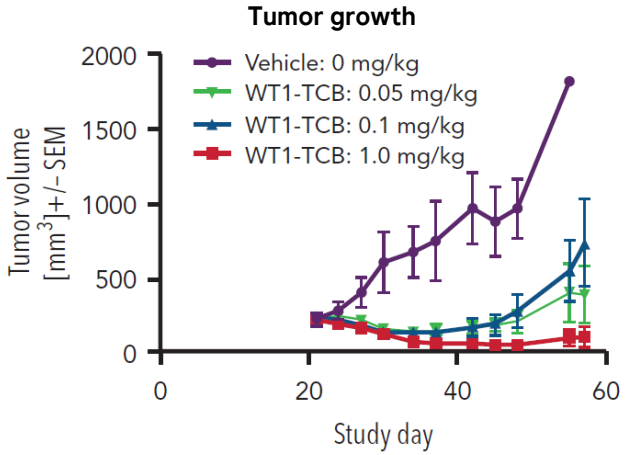
- Targets intracellular proteins via peptide MHC complexes and CD3 T cells
- High specificity for tumor cells, sparing healthy cells
- Potential for development in hematology and solid tumors

WT1-TCB ex vivo activity on primary AML patient samples[1]

AML lysis in panel of AML donor



Dose-dependent reduction of tumor growth in SKM-1 AML xenograft model in humanized mice



- Antibody-mediated T cell cytotoxicity elicited against primary patient-derived AML cells, both using healthy donor PBMCs and PBMCs derived from the AML patients themselves
- Anti-tumor efficacy observed in in vivo xenograft and PDX models
- Ph1 in AML ongoing (IV and SC administration)

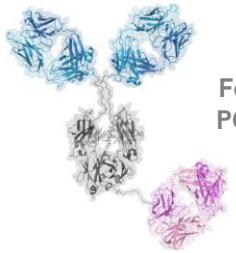
[1] Augsberger et al., Blood, 2021; TCB=T cell bispecific; TCR=T cell receptor; WT1=Wilms tumor protein 1; MHC=Major histocompatibility complex, AML=Acute myeloid leukemia; IV=Intravenous; SC=Subcutaneous

FAP-CD40 (RG6189) in solid tumors

Tumor stroma targeted activator of antigen presenting cells

Targeted myeloid cell activation

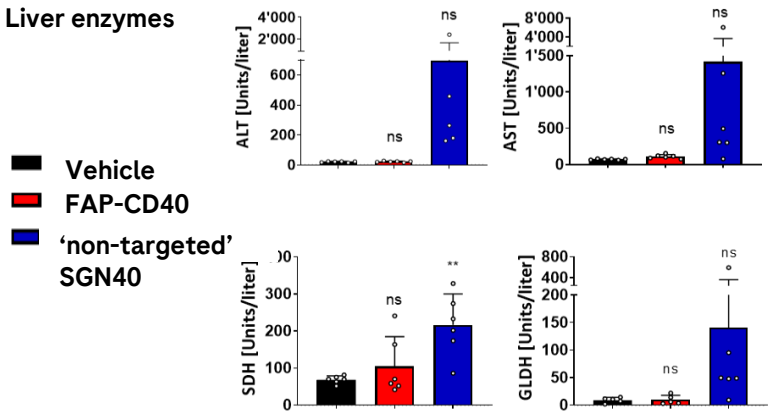
High affinity binding to FAP in tumor stroma



Fc-part: PGLALA

anti-FAP: APC activation by cross-linking CD40 with FAP

Preclinically, a high dose of FAP-CD40 did not result in the typical side effects observed with systemic CD40 agonists[1]

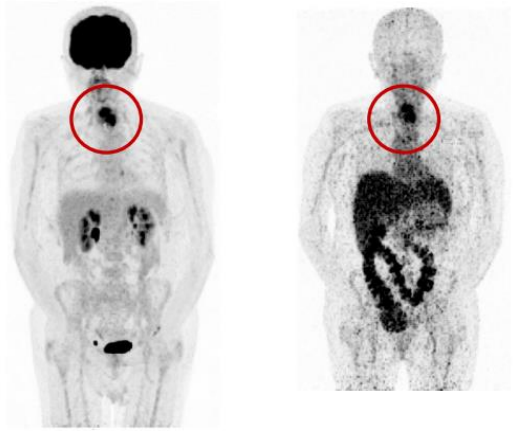


- FAP-CD40 cross-links the CD40 costimulatory receptor expressed on APCs with FAP in tumor stroma in a strictly FAP-dependent manner (i.e. FAP-CD40 is inactive in absence of FAP expression)
  - Enhances antigen presentation in a tumor-specific manner, which may result in anti-tumor immunity and long lasting clinical benefit
  - Strict tumor-specific activity has the potential to reduce systemic toxicity of 1st generation CD40 agonists and enable higher doses to be achieved
- Ph1 single agent in solid tumors ongoing
- pRED's other FAP-targeted program, costimulatory T cell agonist FAP 4-1BBL, is in Ph1b development

Imaging sub-study[2]

Evidence of tumor uptake via 89Zr-radiolabeled compound

2021/12/03 18F-FDG Screening	2021/12/20 ^{89}Zr-PET C1D5



^{89}Zr-RO focal uptake in the tumour lesion in the esophagus

[1]Sum et al., Clinical Cancer Research 2021; [2]Roche internal data on file; APC=Antigen presenting cells; FAP=Fibroblast activation protein

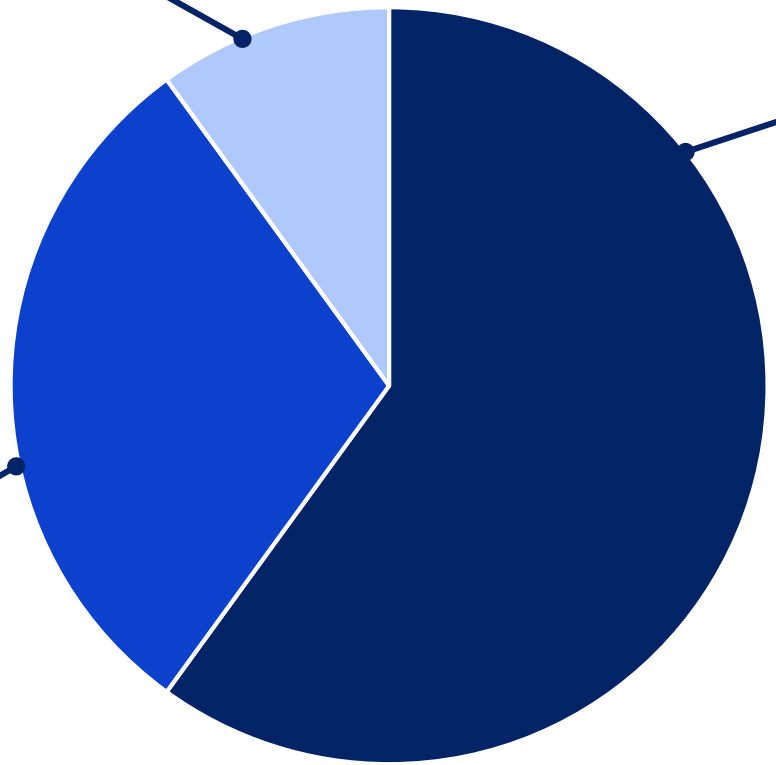
Roche pRED - building for the future in oncology

Managed R&D diversification over time

Opportunistic areas

Committed areas

- T cell redirection
- Immunomodulation
- T cell generation
- Oncogenic drivers
- Synthetic lethality



Exploratory areas

Partnerships to explore innovative new modalities
E.g. license agreement with KaliVir to develop oncolytic viruses
(announced on May 24, 2022)

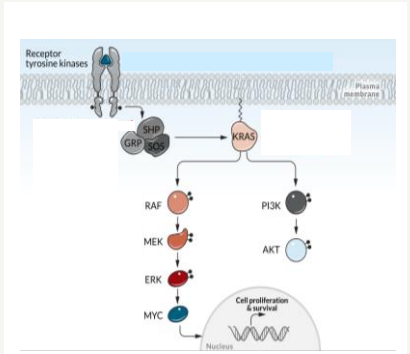
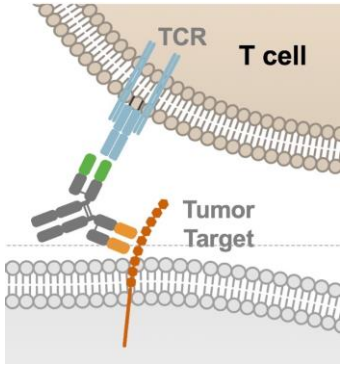
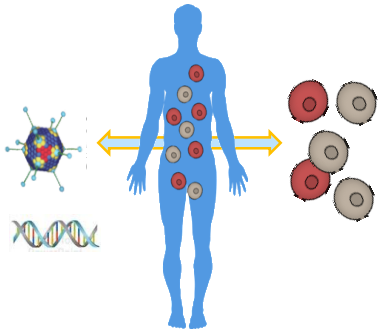
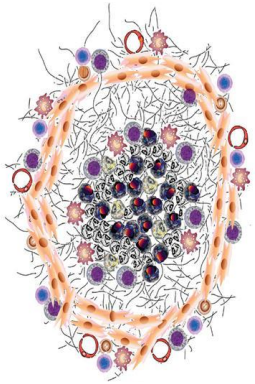
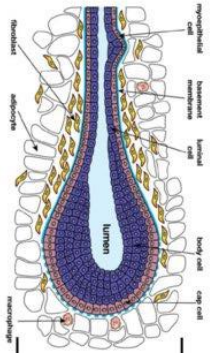
Early pipeline programs in focus

Andrew Chan, M.D., Ph.D. |

Senior Vice President, Research Biology, Genentech Research & Early Development (gRED)

Integrated Oncology Strategy

Diverse approaches to cancer therapeutics to provide the best options for patients

Oncogenic Pathways	Synthetic Immunity	Adaptive & Innate Immunity	Tumor Microenvironment	Lineage Dependencies
				
Target mutant oncoproteins	Immune cell engagers and engineered cells	Augment productive T- and dendritic cell functions Target neo-epitopes	Target immune suppression	Target specific tumor cell identity

Advanced computation & Machine learning (ML)

Analytics

Algorithms

Data platforms

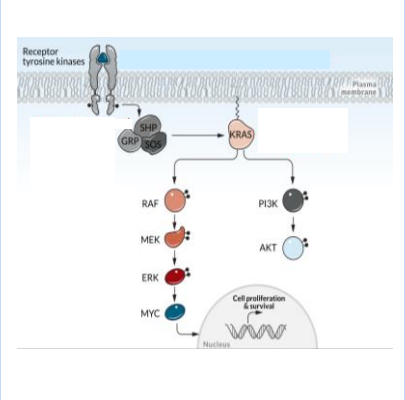
IT/DevOps

- Faster and more efficient data collection
- Better predictions
- Deliver new insights

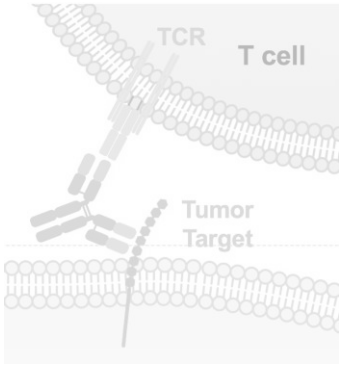
Oncogenic pathways

Roche

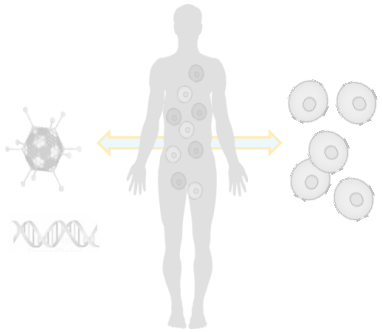
Oncogenic pathways | Synthetic immunity | Adaptive & innate immunity | Tumor microenvironment | Lineage dependencies



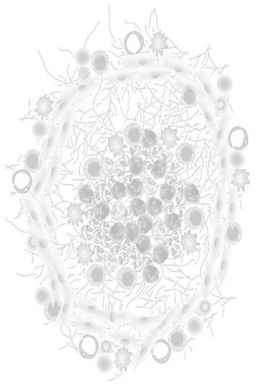
Target mutant oncoproteins



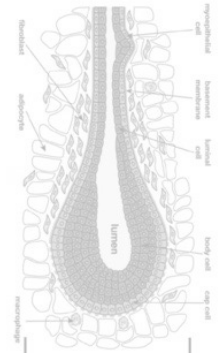
Immune cell engagers and engineered cells



Augment productive T- and dendritic cell functions
Target neo-epitopes



Target immune suppression



Target specific tumor cell identity

Advanced computation & Machine learning (ML)

Analytics

Algorithms

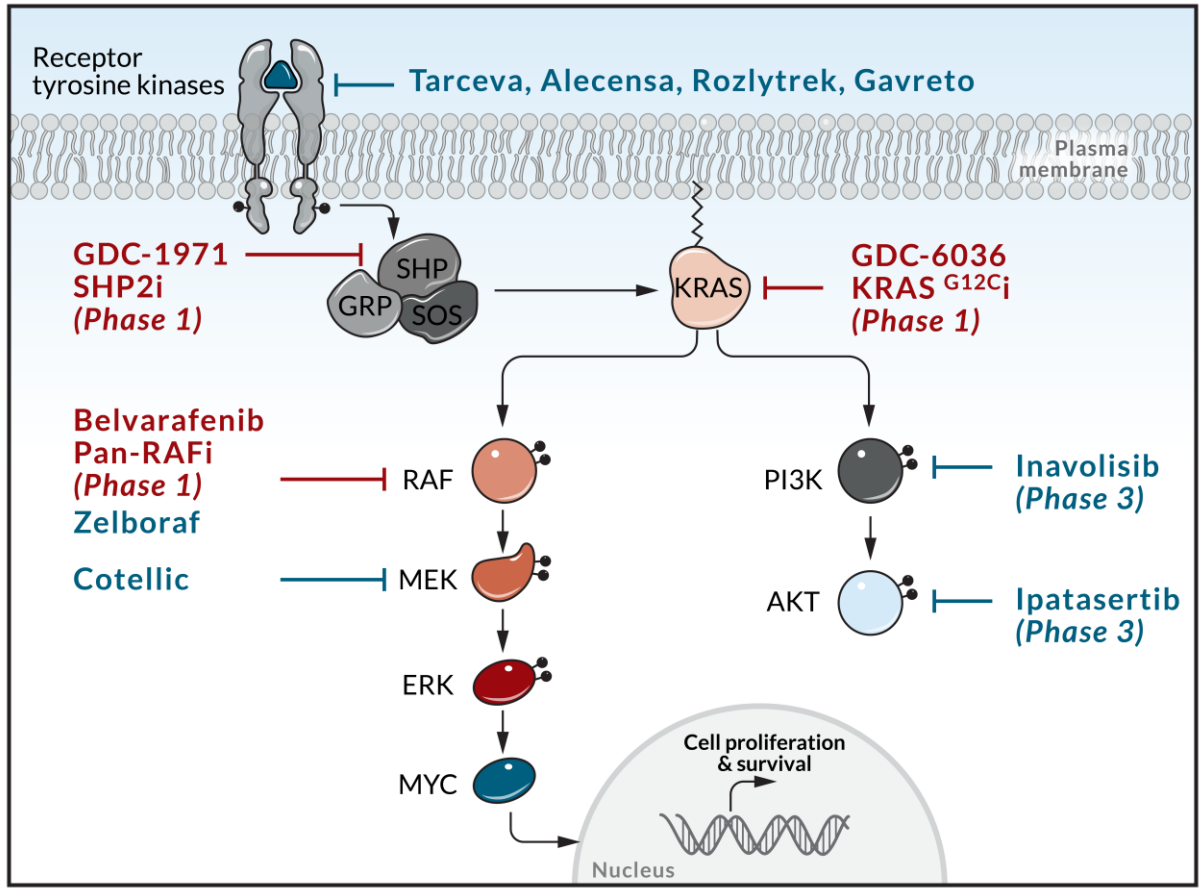
Data platforms

IT/DevOps

- Faster and more efficient data collection
- Better predictions
- Deliver new insights

RAS-MAPK pathway

Drugging "undruggable" targets and opening new combinations



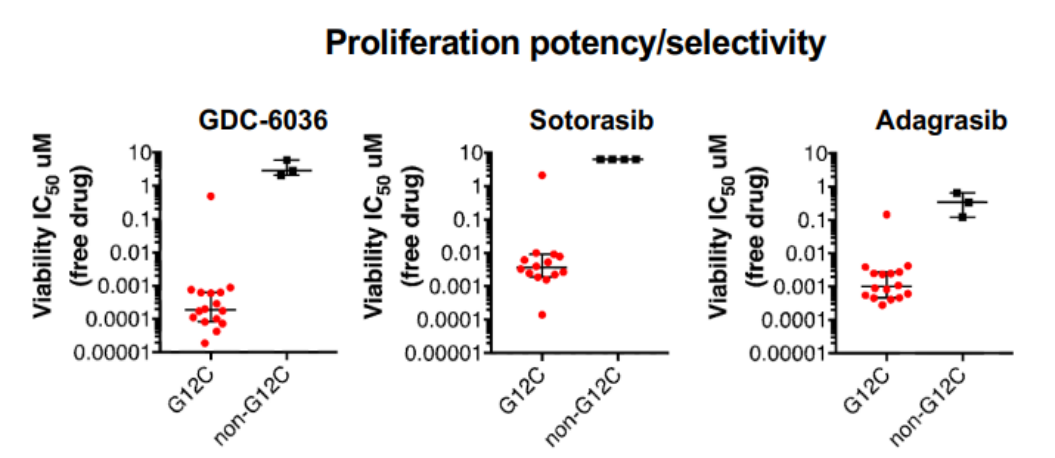
Optimal clinical effectiveness requires combination strategies to target cross-talk, feedback and resistance mechanisms.

- *gRED portfolio*
- *Late stage portfolio / marketed*

GDC-6036 (KRAS G12C inhibitor)

KRAS is the most frequently mutated oncogene, occurring in more than 25% of all cancers

KRAS G12C inhibitor



- Irreversible covalent inhibitor of the KRAS G12C mutant protein resulting in locked inactive conformation
- Best-in-class potential: more potent and selective *in vitro* than sotorasib and adagrasib
- Minimal safety findings leading to wider non-clinical safety margins
- Ph I data to be presented this year at an upcoming medical congress

Ph 1b clinical development program

GDC-6036		Monotherapy
GDC-6036	+	Tecentriq (anti-PD-L1)
GDC-6036	+	cetuximab (anti-EGFR)
GDC-6036	+	erlotinib (EGFRi)
GDC-6036	+	GDC-1971 (SHP2i)
GDC-6036	+	inavolisib (PI3Ki)
GDC-6036	+	Avastin (anti-VEGF)

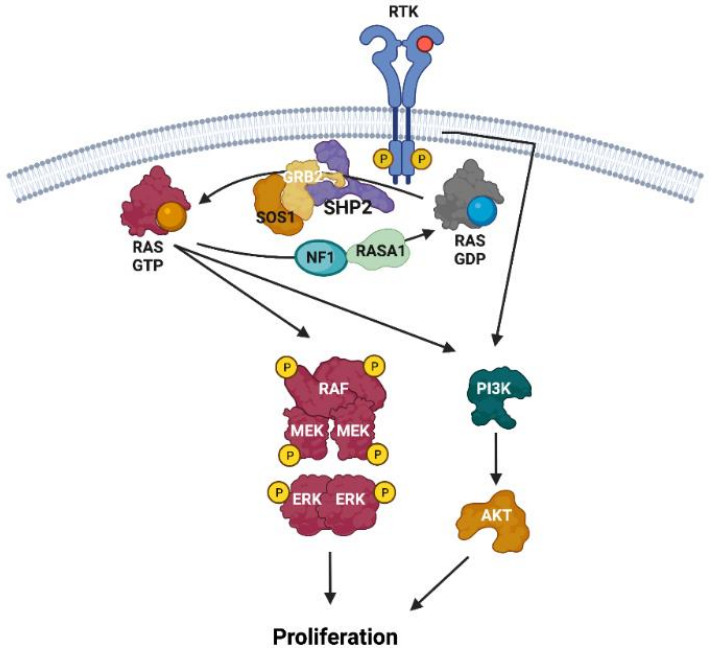
- Advancing with monotherapy and in multiple combinations, including CPI, oncogenic drivers and anti-angiogenics
- Pivotal Ph 3 trial in 2L+ NSCLC trial to be initiated in 2022

Purkey, AACR 2022, CPI= checkpoint inhibitors; NSCLC= non-small cell lung cancer

GDC-1971 (SHP2 inhibitor)

Highly potent; potential for differentiation from other SHP2i

GDC-1971 SHP2 inhibitor

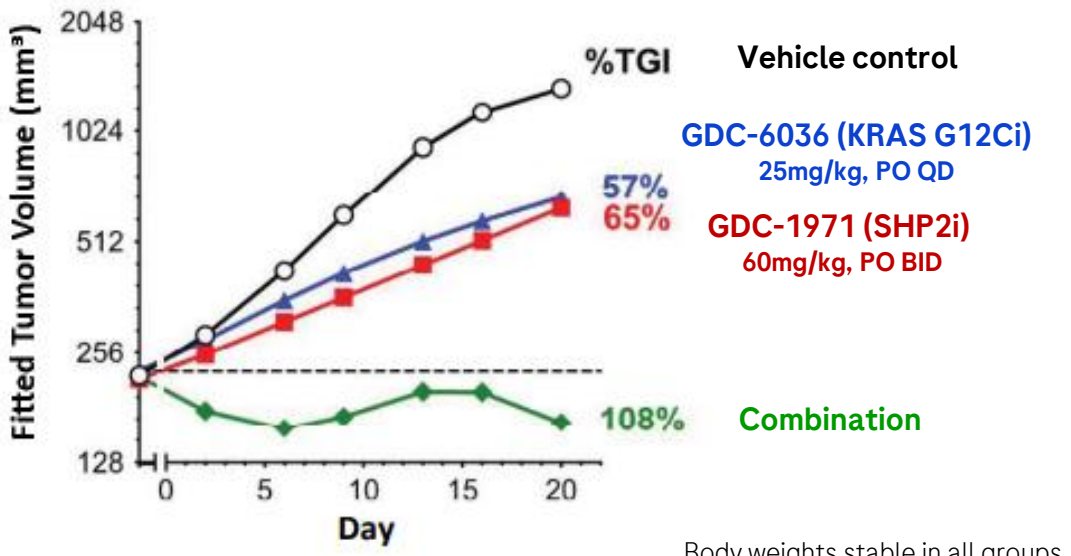


- Orally bioavailable allosteric small molecule inhibitor of SHP2 (PTPN11)
- SHP2i maintains KRAS in the "off" state longer and can enhance KRAS G12C target occupancy by GDC-6036
- Inhibition of SHP2 attenuates MAPK signaling and cellular proliferation

Williams et al, AACR 2022

Synergy with KRAS G12Ci and SHP2i

Combination of GDC-1971 and GDC-6036 results in tumor regressions *in vivo*

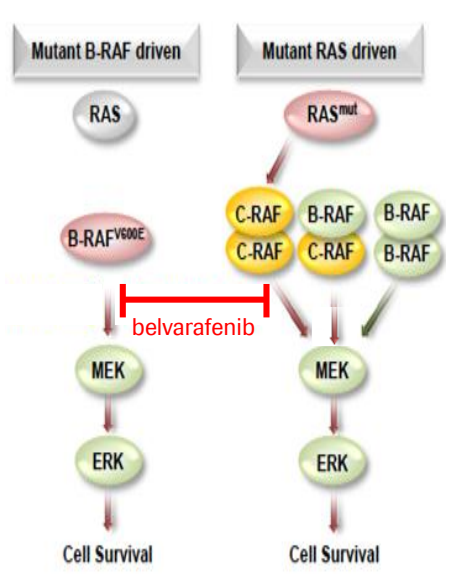


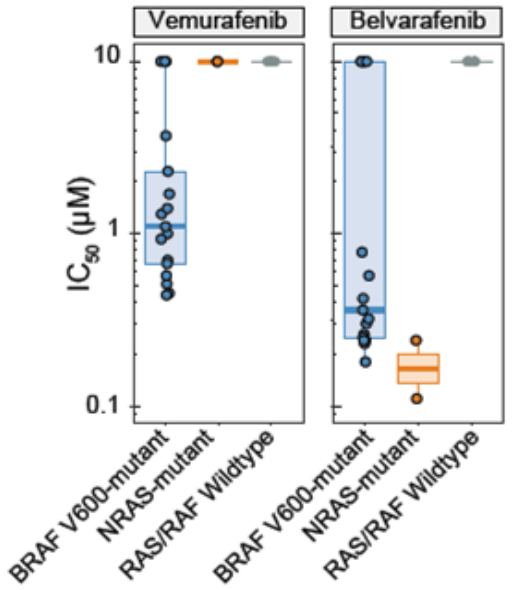
Body weights stable in all groups

- Phase I combination trial of GDC-1971 and GDC-6036 initiated in 2021 with established continuous daily dosing schedule

Belvarafenib is a potent and selective RAF dimer inhibitor

Selective inhibition of mutant RAF dimers

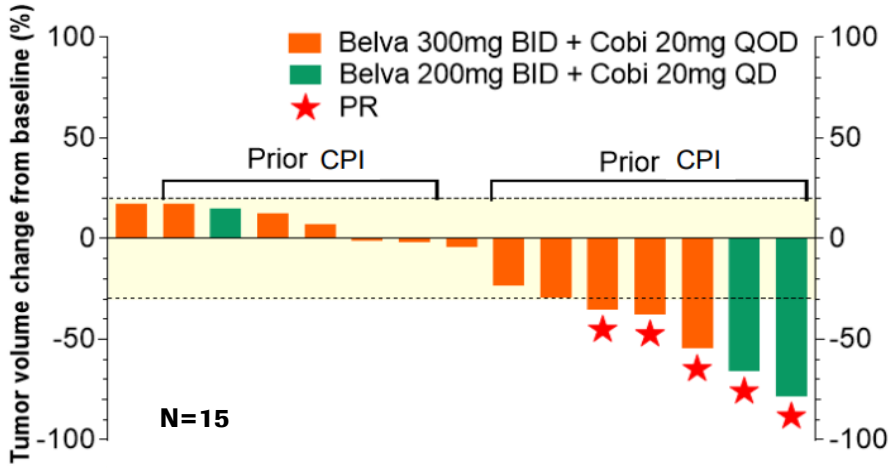




- Inhibition of RAF dimers and monomers with equal potency
- Inhibits mutant RAF and NRAS driven tumors
- Mitigates paradoxical activation of MEK/ERK signaling
- High drug distribution in brain (based on preclinical data) provides additional clinical opportunities

Efficacy in CPI-experienced NRASmt melanoma

Belvarafenib + Cobimetinib: Ph 1b expansion in NRAS melanoma

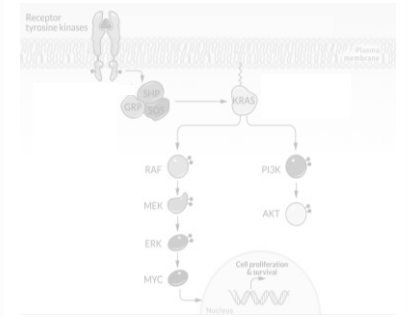


- Belvarafenib in combination with cobimetinib exhibits encouraging anti-tumor activity in patients with NRASmt melanoma who previously received CPI
- Belvarafenib + cobimetinib combination showed acceptable tolerability
- Ongoing trial in NRASmt melanoma (~25% of melanoma pts, +/- atezolizumab)
- Ongoing TAPISTRY trial is signal seeking in patients with BRAF non-canonical mutations (tumor agnostic)

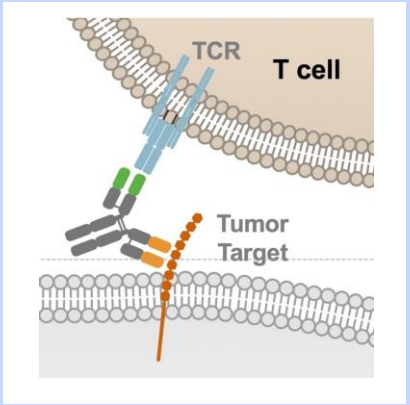
Kim et al, ESMO poster 2021; CNS=central nervous system; CPI=checkpoint inhibitor; TAPISTRY=Tumor-Agnostic Precision Immuno-oncology and Somatic Targeting Rational for You

Synthetic immunity

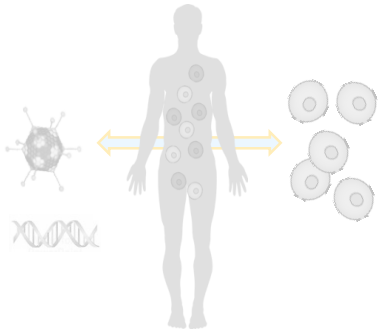
Oncogenic pathways | **Synthetic immunity** | Adaptive & innate immunity | Tumor microenvironment | Lineage dependencies



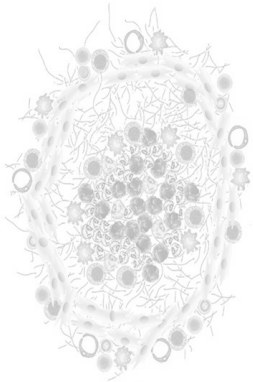
Target mutant oncoproteins



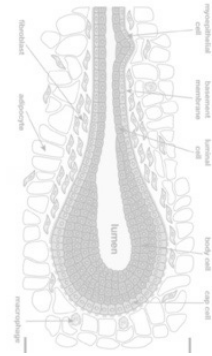
Immune cell engagers and engineered cells



Augment productive T- and dendritic cell functions
Target neo-epitopes



Target immune suppression



Target specific tumor cell identity

Advanced computation & Machine learning (ML)

Analytics

Algorithms

Data platforms

IT/DevOps

- Faster and more efficient data collection
- Better predictions
- Deliver new insights

T-cell bispecifics

Strong clinical POC for platform in hematologic indications, advancing in solid tumors

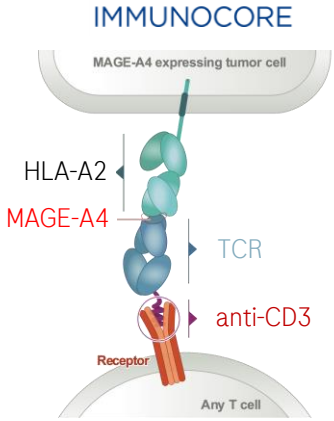
T-cell bispecific pipeline

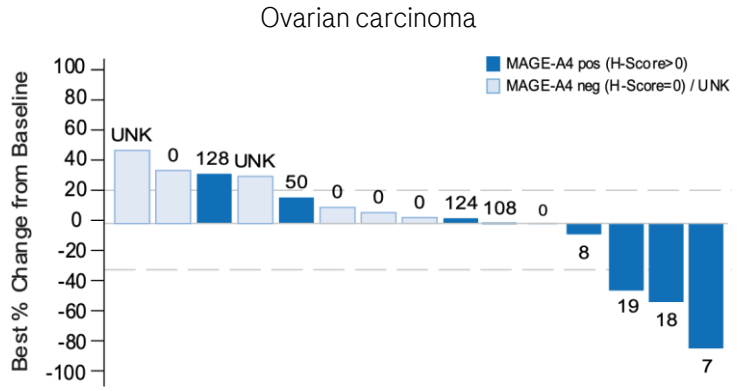
	Ph 1	Ph 2	Ph 3
mosunetuzumab (CD20 x CD3) NHL, CLL	*Approval in 3L+ FL anticipated 2022		
cevostamab (FcRH5 x CD3) Multiple myeloma			
runimotamab (HER2 x CD3) HER2+ breast, gastric cancer			
****ImmTAC (MAGEA4 x CD3)** Multiple solid tumors			
RG6286 (undisclosed target) Colorectal cancer			

Hematology

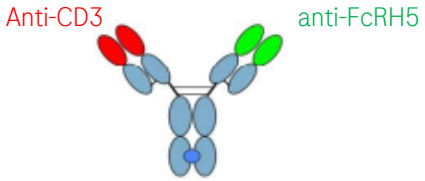
Solid tumor

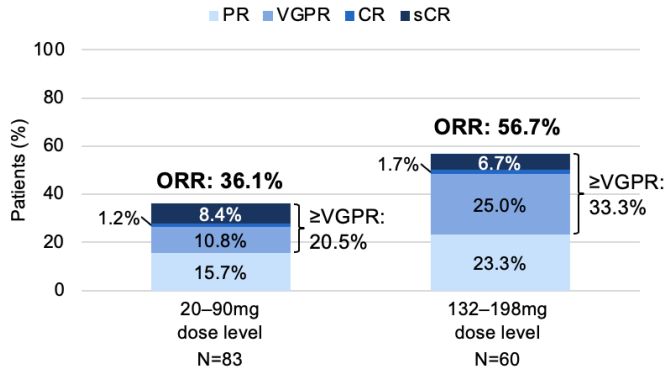
MAGE-A4 x CD3 (ovarian, NSCLC, gastric, head & neck)





Cevostamab (FcRH5 x CD3) in R/R MM



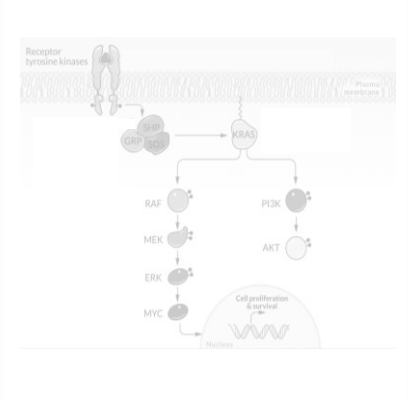


*CHMP recommends EU conditional approval of Roche's potential first-in-class bispecific antibody mosunetuzumab for people with relapsed or refractory follicular lymphoma; **In partnership with Immunocore
Trudel et al, ASH 2021; NSCLC=non-small cell lung cancer; R/R=relapse refractory; MM=multiple myeloma; NHL=non-Hodgkin's lymphoma; CLL=chronic lymphocytic leukemia; ORR=objective response rate; PR=partial response; sCR=stringent complete response; VGPR=very good partial response

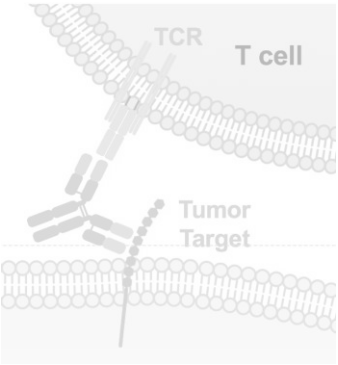
Adaptive immunity

Roche

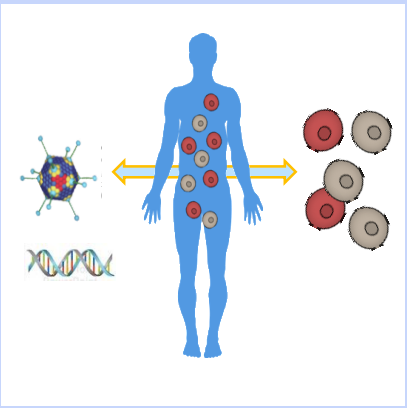
Oncogenic pathways | Synthetic immunity | **Adaptive & innate immunity** | Tumor microenvironment | Lineage dependencies



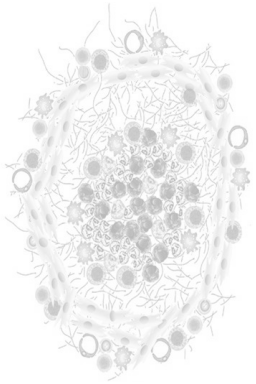
Target mutant oncoproteins



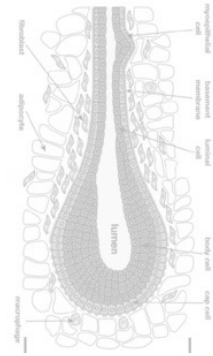
Immune cell engagers and engineered cells



Augment productive T- and dendritic cell functions
Target neo-epitopes



Target immune suppression



Target specific tumor cell identity

Advanced computation & Machine learning (ML)

Analytics

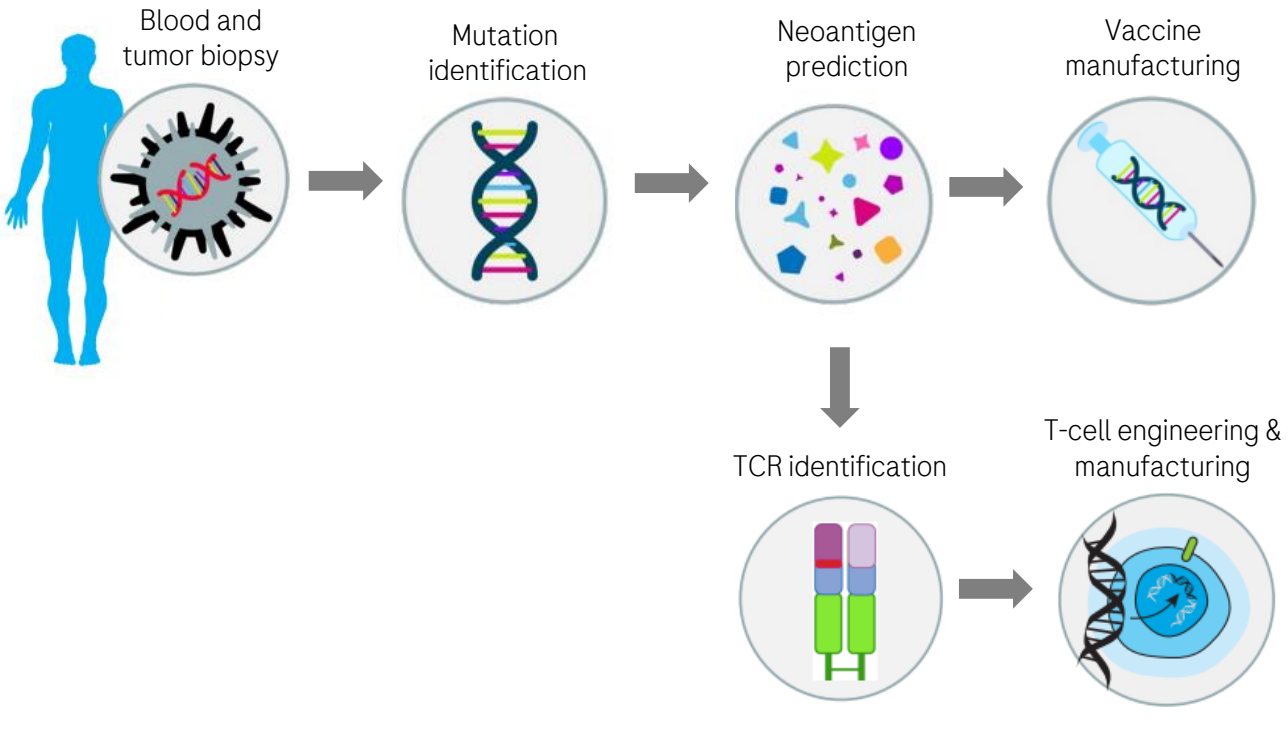
Algorithms

Data platforms

IT/DevOps

- Faster and more efficient data collection
- Better predictions
- Deliver new insights

Neoantigen specific therapies require individualized approaches



- **Autogene cevumeran:** Individualized mRNA vaccine directed against patients' unique tumor neoantigens
- **VB10.NEO:** Individualized DNA vaccine targeting neoantigen delivery to APCs (cross presentation)

- **Neoantigen directed T-cell therapy:** T-cell therapies containing T-cell receptors targeting patient's unique tumor neoantigens
- **Off-the-shelf cell therapy:** Allogeneic personalized iPSC derived T-cells

TCR=T-cell receptor; APC=antigen presenting cell; iPSC=induced pluripotent stem cell

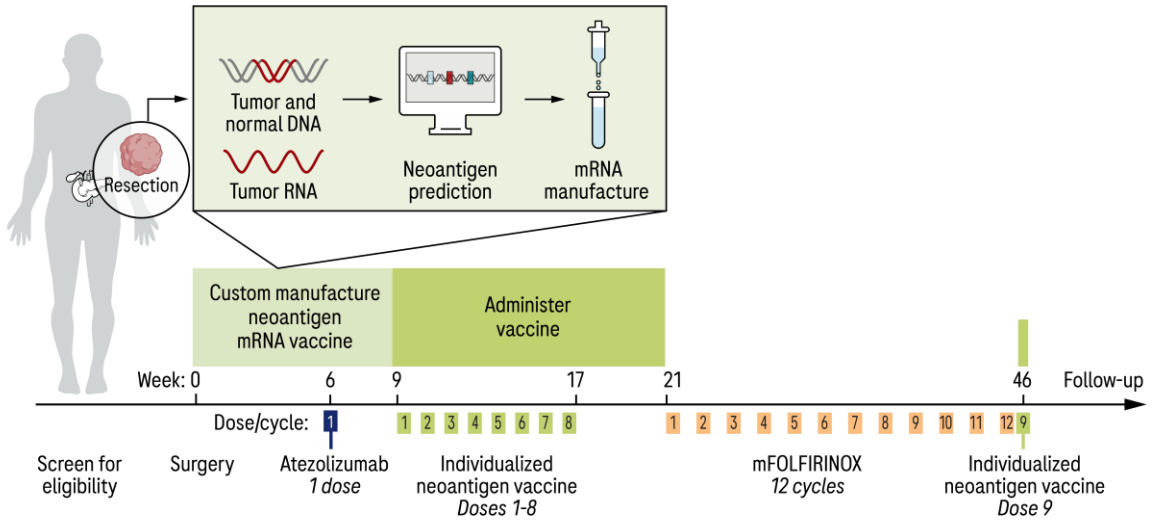
Autogene cevumeran, individualized neoantigen mRNA vaccine

Substantially and durably expand T-cells, correlating with delayed recurrence

ASCO 2022

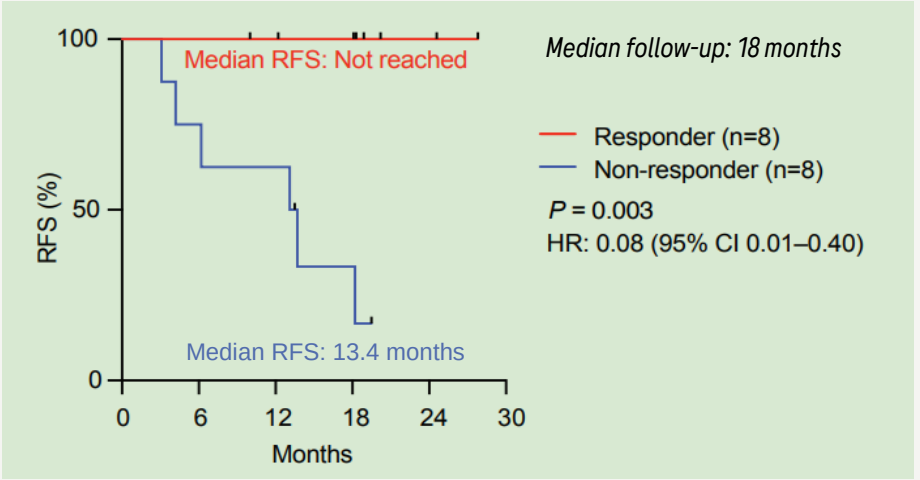
Phase I study in surgically resectable PDAC (target n=20)

Investigator-initiated single-center trial



In collaboration with Memorial Sloan Kettering Cancer Center BIONTECH

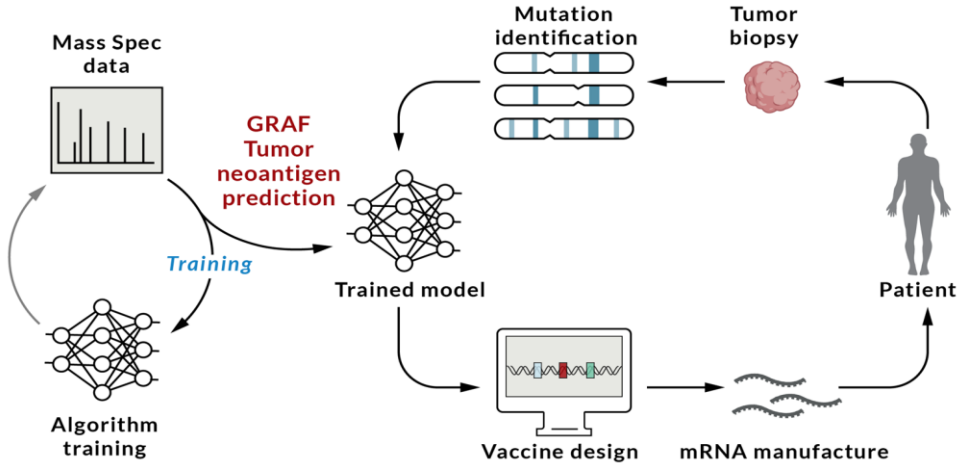
Vaccine induced T-cell response is associated with longer RFS



- Autogene cevumeran expanded polyclonal IFNγ-producing neoantigen-specific CD8 + T-cells in 50% (n = 8/16) of patients from undetectable levels to large fractions (median 2.9%) of all blood T-cells
- Planning ongoing for a randomized Ph 2 trial in PDAC

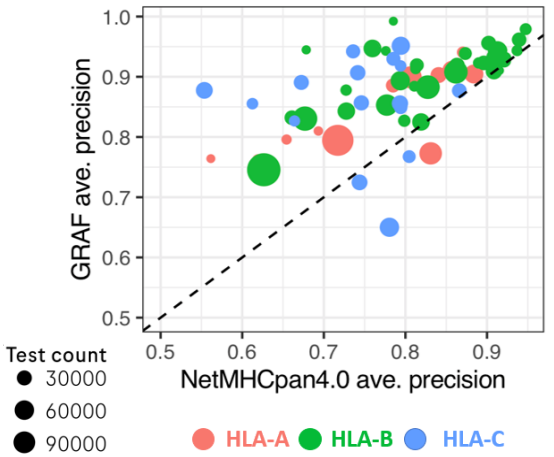
In collaboration with IMcore; Balachandran ASCO 2022; PDAC=pancreatic ductal adenocarcinoma; RFS=relapse free survival

Machine learning improves neoantigen prediction

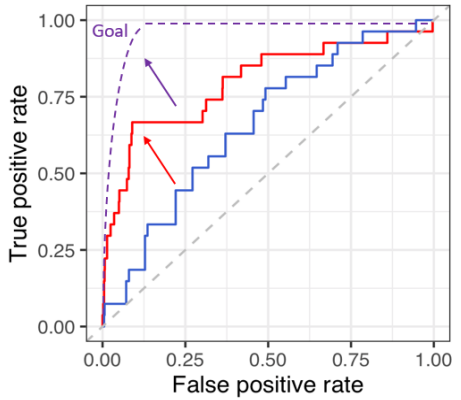


- Success of individualized immunotherapy requires accurate prediction of immunogenic neoantigens for each cancer patient
- A key determinant of immunogenicity is peptide presentation by the major histocompatability complex (MHC)
- **Genentech Recurrent Attention Framework (GRAF)** is a deep learning model trained on large immunopeptidomics data set

Peptide-MHC prediction derived from ML of mass spectroscopy data from cell lines



Testing of GRAF algorithm on Phase 1 clinical data set (N=44)



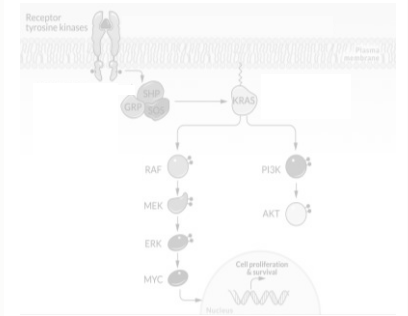
GRAF elution score (AUC = 0.80)
IEDBv2.13 (AUC 0.66)

		GRAF	NetMHC pan-4.0	IEDBv2.13BA
Peptide Presentation Performance	AP	0.88	0.73	0.55
	F1	0.82	0.69	0.56
Immunogenicity performance*	AUC	0.80	0.79	0.66

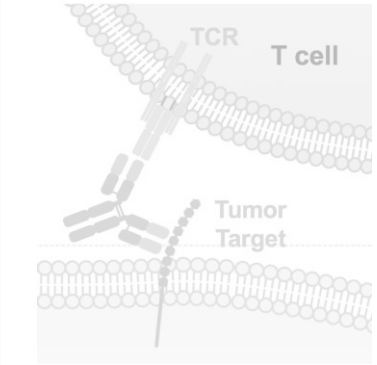
*T cell response, ELIspot, Tetramner assay; AP=average precision; F1=harmonic mean of precision and recall.; AUC=area under curve

Tumor microenvironment

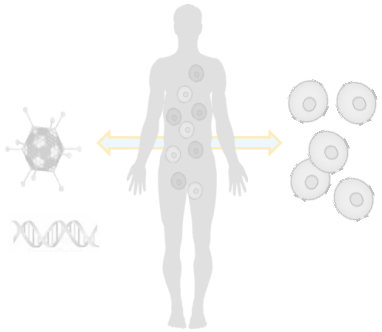
Oncogenic pathways | Synthetic immunity | Adaptive & innate immunity | **Tumor microenvironment** | Lineage dependencies



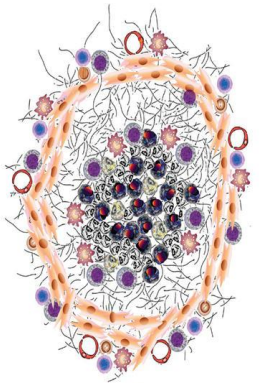
Target mutant oncoproteins



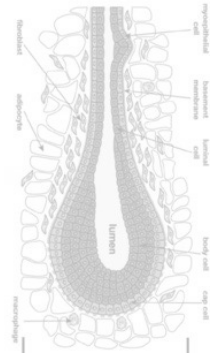
Immune cell engagers and engineered cells



Augment productive T- and dendritic cell functions
Target neo-epitopes



Target immune suppression



Target specific tumor cell identity

Advanced computation & Machine learning (ML)

Analytics

Algorithms

Data platforms

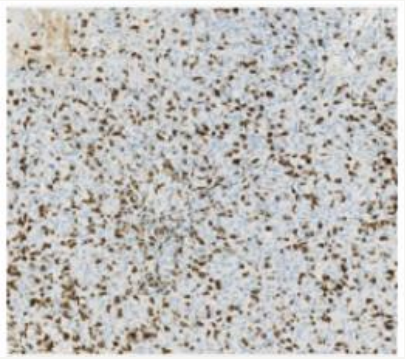
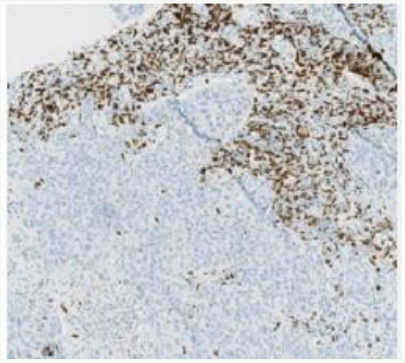
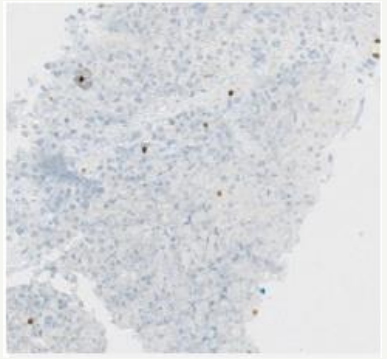
IT/DevOps

- Faster and more efficient data collection
- Better predictions
- Deliver new insights

Tumors exhibit one of three basic immune phenotypes

Prioritizes immune profiles that represent the greatest unmet need and opportunity

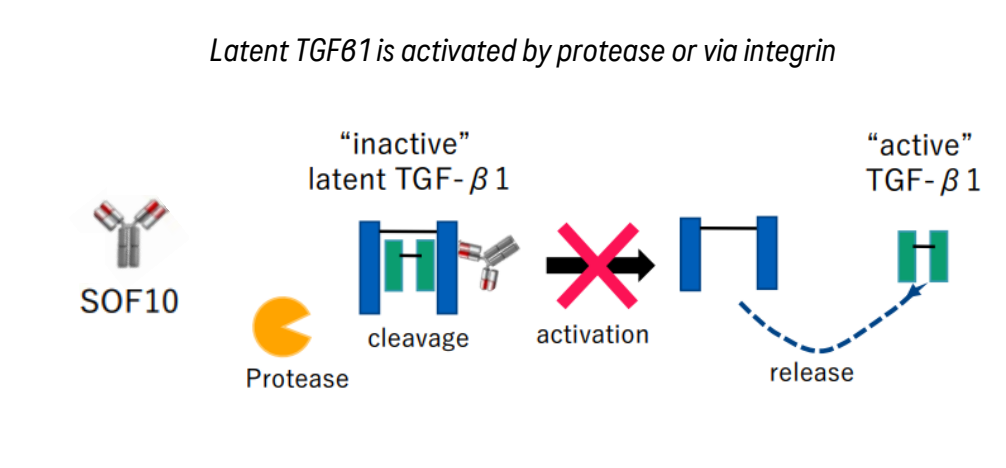
Targets for immunomodulation

	T cell signature	TGFβ Signature	neuroendocrine signature
			
	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 periphery
Incidence			
CRC	12%	70%	25%
NSCLC	31%	44%	25%
mUC	26%	47%	27%
TNBC	36%	47%	17%

TGF=tumor growth factor; CRC=colorectal cancer; NSCLC=non-small cell lung cancer; mUC=metastatic urothelial carcinoma; TNBC=triple negative breast cancer

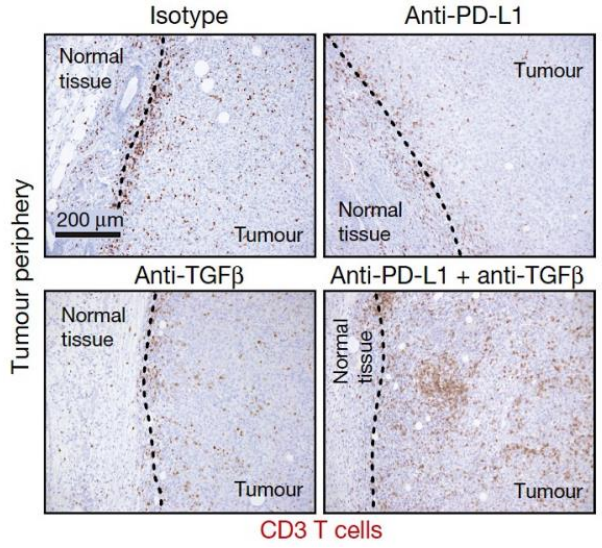
SOF10 / RG6440 (anti-latent TGFβ1)

SOF10 selectively binds to TGFβ1



- TGFβ1 is known as a key regulator of tumor microenvironment which forms a "physical barrier" for T-cell infiltration.
- Due to risk of toxicity caused by pan-TGFβ inhibition*, SOF10 targets protease mediated activation of latent TGFβ1.
- SOF10 provides opportunity to covert immune excluded to inflamed tumors.

Anti-TGFβ and PD-L1 increases T-cell infiltration into tumors



In the mouse EMT6 immune excluded tumor model, blocking latent TGFβ1 in combination with aPD-L1[1]:

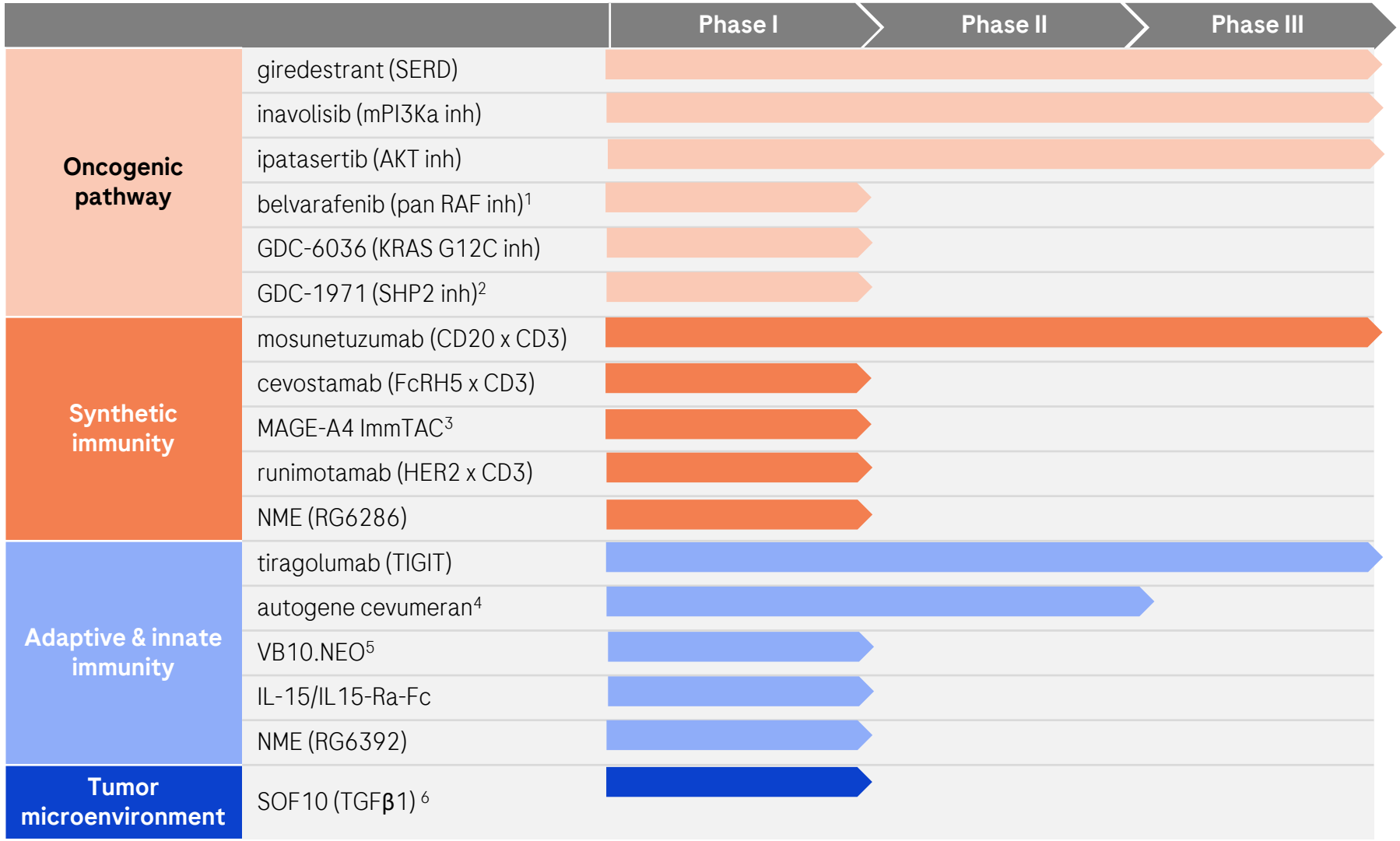
- Reduces TGFβ signaling in stromal cells
- Facilitates T-cell penetration into the center of tumors
- Enhances anti-tumor immunity and induces tumor regression

*Pan-TGF-β inhibitors have been shown to have cardiac toxicity by inhibiting TGF-β in nonclinical studies

[1] Mariathasan S. et.al., Nature 554,544-548 (2018)

gRED oncology portfolio

12 molecules in early development (Ph 1 / 2)



[1] In partnership with Hanmi ; [2] In partnership with Relay ; [3] In partnership with Immunocore ; [4] In partnership with BioNtech ; [5] In partnership with Nykode ; [6] In partnership with Chugai

Doing now what patients need next