ASCO 2022

Virtual IR event

6 June 2022
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Welcome

Bruno Eschli, Ph.D.  
Head of Investor Relations
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

**Compounds**

<table>
<thead>
<tr>
<th>Compound</th>
<th>Indication</th>
<th>Milestone</th>
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<tbody>
<tr>
<td>Vabysmo</td>
<td>nAMD/DME</td>
<td>US/EU approval</td>
</tr>
<tr>
<td>Susvimo</td>
<td>nAMD</td>
<td>EU approval</td>
</tr>
<tr>
<td>mosunetuzumab</td>
<td>3L+ FL</td>
<td>US/EU approval</td>
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<td>Tecentriq</td>
<td>Adjuvant NSCLC</td>
<td>EU approval</td>
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<tr>
<td>Hemlibra</td>
<td>Mild to moderate hemophilia A</td>
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<td>Polivy + R-CHP</td>
<td>1L DLBCL</td>
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<td>glofitamab</td>
<td>3L+ DLBCL</td>
<td>Ph II NF30179</td>
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<td>Tecentriq + tiragolumab + chemo</td>
<td>1L ES-SCLC</td>
<td>Ph III SKYSCRAPER-02</td>
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<tr>
<td>Tecentriq + chemo</td>
<td>Adjuvant SCCHN</td>
<td>Ph III IMv0ke010</td>
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<tr>
<td>Tecentriq + tiragolumab</td>
<td>1L PDL1+ NSCLC</td>
<td>Ph III SKYSCRAPER-01</td>
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<td>Tecentriq</td>
<td>Adjuvant RCC</td>
<td>Ph III IMmotion010</td>
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<tr>
<td>giredestrant</td>
<td>2/3L HR+ mBC</td>
<td>Ph II acelERA</td>
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<tr>
<td>Tecentriq + chemo</td>
<td>Adjuvant HCC</td>
<td>Ph III IMbrave050</td>
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<tr>
<td>Venclexta + dexamethasone</td>
<td>t(11;14) MM</td>
<td>Ph III CANOVA</td>
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<tr>
<td>Tecentriq + chemo</td>
<td>Neoadjuvant NSCLC</td>
<td>Ph III IMpower030</td>
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<td>Tecentriq + tiragolumab + chemo</td>
<td>1L esophageal cancer</td>
<td>Ph III SKYSCRAPER-08</td>
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<td>Alecensa</td>
<td>Adjuvant ALK+ NSCLC</td>
<td>Ph III ALINA</td>
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<tr>
<td>gantenerumab</td>
<td>Alzheimer’s disease</td>
<td>Ph III GRADUATE 1/2</td>
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<tr>
<td>Susvimo</td>
<td>DME</td>
<td>Ph III PAGODA</td>
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<tr>
<td>Susvimo</td>
<td>DR</td>
<td>Ph III PAVILION</td>
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**Phase III / Pivotal Readouts**

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<th>Indication</th>
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</tr>
<tr>
<td>Susvimo</td>
<td>DR</td>
<td>Ph III PAVILION</td>
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**Virtual Events**

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

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1 National Cancer Institute, SEER database, literature review; OS=overall survival
## Upcoming readouts in early disease

Potential to expand existing indications

### Lung / H&N

<table>
<thead>
<tr>
<th>Molecule</th>
<th>Indication</th>
<th>Ph 1</th>
<th>Ph 2</th>
<th>Ph 3</th>
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<tbody>
<tr>
<td>Tecentriq</td>
<td>Adjuvant NSCLC</td>
<td>IMPower010</td>
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<tr>
<td></td>
<td>Neoadjuvant NSCLC</td>
<td>IMPower030</td>
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<td></td>
<td>Adjuvant SCCHN</td>
<td>IMvolve010</td>
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<tr>
<td>tiragolumab</td>
<td>Stage III unres. NSCLC</td>
<td>SKYSCRAPER-03</td>
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<td></td>
<td>Neoadj/Adj NSCLC</td>
<td>SKYSCRAPER-05</td>
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<tr>
<td>Alecensa</td>
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### GI / GU

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<tr>
<td>Tecentriq</td>
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<td>IMmotion010</td>
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<td>Adjuvant HCC</td>
<td>IMbrave050</td>
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<td>HR NMIBC</td>
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<td>SWOG S1605</td>
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<tr>
<td>tiragolumab</td>
<td>Locally adv. ESCC</td>
<td>SKYSCRAPER-07</td>
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### Breast

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<tr>
<td>Tecentriq</td>
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<td>IMPassion031</td>
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<td></td>
<td>Neoadj./Adj. TNBC</td>
<td>NSABPS99/GeparDuOZE</td>
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<tr>
<td></td>
<td>Adjuvant TNBC</td>
<td>IMPassion030</td>
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<tr>
<td>giredestrant</td>
<td>Neoadj. HR+ BC</td>
<td>coopERA*</td>
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<tr>
<td></td>
<td>Adjuvant HR+ BC</td>
<td>lidERA</td>
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### Heme

<table>
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<th>Molecule</th>
<th>Indication</th>
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<td>Polivy</td>
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<td>Venclexta</td>
<td>1L fit AML</td>
<td>VIALE-M</td>
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<tr>
<td>Glofit/Mosun ³</td>
<td>1L DLBCL</td>
<td>Ph 1b</td>
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</tbody>
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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

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Readout expected in 2022

= met primary endpoint
Tecentriq: First-in-class CIT in adjuvant NSCLC

Strong US launch in PD-L1+ 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

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**Tiragolumab (aTIGIT mAb)**

*Comprehensive development program ongoing*

<table>
<thead>
<tr>
<th>Indication</th>
<th>Ph 1</th>
<th>Ph 2</th>
<th>Ph 3</th>
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<td>1L NSCLC: PD-L1 high</td>
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<td>1L ES-SCLC</td>
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<td>Neoadj / Adj NSCLC</td>
<td>SKYSCRAPER-05</td>
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<tr>
<td>1L NSq NSCLC</td>
<td>SKYSCRAPER-06</td>
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<tr>
<td>Locally advanced ESCC</td>
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<tr>
<td>1L ESCC</td>
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<td>2022</td>
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<td>2L+ PD-L1+ Cervical Ca</td>
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<td>2022</td>
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<td>1L SCCHN</td>
<td>SKYSCRAPER-09</td>
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<tr>
<td>HCC (+Tecentriq+Avastin)</td>
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<tr>
<td>Melanoma (+PD1-LAG3)</td>
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**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*

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**Novel mechanisms and technologies**

- **HER2 mAb**
  - Herceptin
  - HER2+ BC

- **HER2 ADC**
  - PERTJETA

- **HER2 TCB mAb**
  - runimotamab (HER2xCD3)

- **CPI mAb**
  - TECENTRIQ

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

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**Breast cancer cases by subtype**

- **HER2+ BC**
- **TNBC**
- **HR+/HER2− BC**
- **HR+/HER2+ BC**
- **HR−/HER2+ BC**
- **Unknown**

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1 Cancer Stats Facts: Female Breast Cancer Subtypes. National Cancer institute. Available at: [https://seer.cancer.gov/statfacts/html/breast-subtypes.html](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

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**Roche**
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

- 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

- 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 neoadjuv. 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

- 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. anastrozole (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*

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### Targeting both early and metastatic disease

<table>
<thead>
<tr>
<th>Endocrine Therapy</th>
<th>eBC</th>
<th>1L mBC</th>
<th>2L/3L mBC</th>
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<tbody>
<tr>
<td>Given until resistance or visceral disease present</td>
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- **ET +/- CDK4/6i**
- **ET + CDK4/6i**
- **ET monotherapy**

### SERD (giredestrant)

- **Giredestrant**
  - lidoERA (adj.)
  - palbo perseVERA
  - acelERA* (adj.)

- **Giredestrant**
  - Replace ET as SoC in all settings

### PI3Kα (inavolisib)²

- Combine with SOC
  - In PI3Kαm patients

- **Involisib + fulvestrant + palbociclib**
- **INAVO120**

### HR+/HER2- treated population (US/EU5)

- **509K**
- **62K**
- **44K**

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**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

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*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**
  - 1:1 format
  - mosunetuzumab
cevostamab
glofitamab
GPRC5DxCD3
HLA-A2-WT1xCD3
CD19 x CD28

- **Fusion Protein**
  - CD19 x 4-1BBL

- **mAb**
  - tiragolumab

- **Small Molecules**

- **ADC**

- **Glyco-engineered mAb**

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**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

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1 Engert A, et al. Haematologica 2016;101:115-208, 2WHO – 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

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
• Well tolerated safety profile

• Readily available; administered in any oncology facility
• Administered for 6 cycles
• 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

- **Patients**
- **Providers**
- **Payers**

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

- **DLBCL**
  - **1L**: Polivy + R-CHP
  - **R/R**: Polivy + R + benda
  - **3L+**: Glofit + GemOx*, STARGLO
  - **Glofit + R-CHP**
  - **Polivy + mosun**: SUNMO

- **FL**
  - **1L**: G + chemo
  - **2L+**: mosun + len CELESTIMO
  - **3L+**: mosun + len

* = PhIII ✓ = approved or positive read-out

- **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

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*by PET-CT (Lugano criteria);† 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**

<table>
<thead>
<tr>
<th>n (%)*</th>
<th>N=154†</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median age, years (range)</strong></td>
<td>66.0 (21–90)</td>
</tr>
<tr>
<td>Male</td>
<td>100 (64.9)</td>
</tr>
<tr>
<td><strong>ECOG PS‡</strong></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>69 (44.8)</td>
</tr>
<tr>
<td>1</td>
<td>84 (54.5)</td>
</tr>
<tr>
<td><strong>Ann Arbor stage</strong></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>10 (6.5)</td>
</tr>
<tr>
<td>II</td>
<td>25 (16.2)</td>
</tr>
<tr>
<td>III</td>
<td>31 (20.1)</td>
</tr>
<tr>
<td>IV</td>
<td>85 (55.2)</td>
</tr>
<tr>
<td><strong>NHL subtype</strong></td>
<td></td>
</tr>
<tr>
<td>DLBCL</td>
<td>110 (71.4)</td>
</tr>
<tr>
<td>trFL</td>
<td>27 (17.5)</td>
</tr>
<tr>
<td>HGBCL</td>
<td>11 (7.1)</td>
</tr>
<tr>
<td>PMBCL</td>
<td>6 (3.9)</td>
</tr>
<tr>
<td><strong>Bulky disease</strong></td>
<td></td>
</tr>
<tr>
<td>&gt;6cm</td>
<td>64 (41.6)</td>
</tr>
<tr>
<td>&gt;10cm</td>
<td>18 (11.7)</td>
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<tr>
<td><strong>n (%)</strong></td>
<td><strong>N=154</strong></td>
</tr>
<tr>
<td><strong>Median no. of prior lines, n (range)</strong></td>
<td>3 (2–7)</td>
</tr>
<tr>
<td>2 prior lines</td>
<td>62 (40.3)</td>
</tr>
<tr>
<td>≥3 prior lines</td>
<td>92 (59.7)</td>
</tr>
<tr>
<td>Prior anti-CD20 Ab</td>
<td>154 (100.0)</td>
</tr>
<tr>
<td>Prior anthracycline</td>
<td>149 (96.8)</td>
</tr>
<tr>
<td>Prior CAR-T</td>
<td>51 (33.1)</td>
</tr>
<tr>
<td>Prior ASCT</td>
<td>28 (18.2)</td>
</tr>
<tr>
<td>Refractory to any prior therapy</td>
<td>139 (90.3)</td>
</tr>
<tr>
<td>Refractory to last prior therapy</td>
<td>132 (85.7)</td>
</tr>
<tr>
<td>Primary refractory</td>
<td>90 (58.4)</td>
</tr>
<tr>
<td>Refractory to prior CAR-T</td>
<td>46 (29.9)</td>
</tr>
<tr>
<td>Refractory to any prior anti-CD20</td>
<td>128 (83.1)</td>
</tr>
</tbody>
</table>

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)

<table>
<thead>
<tr>
<th>Efficacy endpoint&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Glofiramab 2.5/10/30mg (n=155)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR rate&lt;sup&gt;*&lt;/sup&gt;</td>
<td>61 (39.4%)</td>
</tr>
<tr>
<td></td>
<td>[95% CI: 31.6%, 47.5%]</td>
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<tr>
<td>ORR&lt;sup&gt;*&lt;/sup&gt;</td>
<td>80 (51.6%)</td>
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<tr>
<td></td>
<td>[95% CI: 43.5%, 59.7%]</td>
</tr>
</tbody>
</table>

- 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)<sup>4</sup>: 35.2% CR rate by IRC significantly greater (p<0.0001) than 20% historical control CR rate<sup>4</sup>

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<sup>*</sup>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%).

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
Durable responses maintained after cessation of therapy

**Duration of overall response by IRC**

- **Median DoR:** 18.4 mo (95% CI: 13.7, NE)
- **Follow-up duration:** 10.6 mo (0–21)
- **12-months DoR:** 63.6% (95% CI: 51.1, 76.2)
- **ORs ongoing at CCOD:** 53 (66.3)

**Duration of complete response by IRC**

- **Median DoCR:** NE mo (95% CI: 16.8, NE)
- **Follow-up duration:** 10.6 mo (0–21)
- **12-months DoCR:** 77.6% (95% CI: 64.3, 90.8)
- **CRs ongoing at CCOD:** 49 (80.3)

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

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

*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

<table>
<thead>
<tr>
<th>Progression-free survival by IRC</th>
<th>Overall survival*</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Graph showing PFS and OS curves" /></td>
<td><img src="image" alt="Graph showing OS curves" /></td>
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</tbody>
</table>

**N=155**

<table>
<thead>
<tr>
<th>Metric</th>
<th>Value</th>
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<tbody>
<tr>
<td>Median PFS follow-up, mo (range)</td>
<td>12.6 (0–22)</td>
</tr>
<tr>
<td>Median PFS, months (95% CI)*</td>
<td>4.9 (3.4, 8.1)</td>
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<tr>
<td>6-month event-free rate, % (95% CI)</td>
<td>45.5 (37.2, 53.8)</td>
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<tr>
<td>12-month event-free rate, % (95% CI)</td>
<td>37.1 (28.5, 45.8)</td>
</tr>
<tr>
<td>Median OS, months (95% CI)*</td>
<td>11.5 (7.9, 15.7)</td>
</tr>
<tr>
<td>12-month OS rate, % (95% CI)</td>
<td>49.8 (41.1, 58.5)</td>
</tr>
</tbody>
</table>

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

*Well tolerated, with a favorable safety profile*

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

*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

[Diagram showing AEs (≥15%) by grade and relationship with glofitamab]
Cytokine release syndrome

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

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

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

Other adverse events of interest

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

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

<table>
<thead>
<tr>
<th>n (%)</th>
<th>N=154</th>
</tr>
</thead>
<tbody>
<tr>
<td>AE leading to treatment discontinuation</td>
<td>14 (9.1)</td>
</tr>
<tr>
<td>Infections and infestations¶</td>
<td>6 (3.9)</td>
</tr>
<tr>
<td>Delirium</td>
<td>2 (1.3)</td>
</tr>
<tr>
<td>Neutropenia**</td>
<td>2 (1.3)</td>
</tr>
<tr>
<td>Hepatobiliary disorders#</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Gastrointestinal hemorrhage**</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>CRS**</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Melanoma recurrent</td>
<td>1 (0.6)</td>
</tr>
</tbody>
</table>

*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
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

- 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)

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

Secondary endpoints

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

*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.
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*

<table>
<thead>
<tr>
<th>Cancer Immunotherapy (CIT)</th>
<th>Cancer Cell Targeted Therapy (CTT)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>T cell redirection</strong></td>
<td><strong>Oncogenic drivers</strong></td>
</tr>
<tr>
<td><strong>Immunomodulation</strong></td>
<td><strong>Synthetic lethality</strong></td>
</tr>
<tr>
<td><strong>T cell generation</strong></td>
<td></td>
</tr>
</tbody>
</table>

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

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

**Targeted myeloid cell agonists**

**Inhibitors and modulators for oncogenic drivers**

**Inhibitors and modulators for paired and non-pairwise relationships**

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**ACN=Antigen presenting cells; TCR=T cell receptor**
### pRED oncology development pipeline

<table>
<thead>
<tr>
<th>CT=Cell therapy targeted therapy; CIT=Cancer immunotherapy; NME=New molecular entity; TCBs=T cell bispecifics; mAb=Monoclonal antibody</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Phase 0</strong></td>
</tr>
<tr>
<td>NME</td>
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<tr>
<td>2:1 format TCBs</td>
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<tr>
<td>CIT</td>
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<tr>
<td><strong>Immuno-modulation</strong></td>
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<td>NME</td>
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<tr>
<td>Co-stimulators</td>
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<tr>
<td>Counter-inhibitory immunomodulators</td>
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</table>

#### Counter-inhibitory immunomodulators
- PD1-IL2v
- FAP–CD40
- HPV-PBMC vaccine
- Brachytherapy

#### Next generation cytokines
- PD1-LAG3
**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

**High efficacy at low doses in preclinical models**

<table>
<thead>
<tr>
<th>Antibody Concentration (nM)</th>
<th>% CD3+ T Cells</th>
<th>% of Depletion</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0007</td>
<td>0.001</td>
<td>0.01</td>
</tr>
</tbody>
</table>

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

- TIL activation and tumor cell lysis in bone marrow aspirates from MM patients

**Reduction in tumor volume in combination with SoC in preclinical models**

Efficacy in sc NCI-H929 xenograft in humanized mice

<table>
<thead>
<tr>
<th>Efficacy GPRC5D TCB + Daratumumab</th>
<th>Efficacy GPRC5D TCB + Lenalidomide</th>
</tr>
</thead>
</table>

Combination in sc MM xenografts in humanized mice

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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 MM¹

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>Early efficacy data</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=41 patients</td>
<td>n=34 efficacy-evaluable patients</td>
</tr>
<tr>
<td>Median age</td>
<td>ORR</td>
</tr>
<tr>
<td></td>
<td>68%</td>
</tr>
<tr>
<td>R-ISS stage II or III at study entry</td>
<td>VGPR or better response</td>
</tr>
<tr>
<td></td>
<td>50%*</td>
</tr>
<tr>
<td>High-risk cytogenetics (t(4;14), t(14;16), del(17p), 1q21 gain)</td>
<td>Median time to first response (95% CI)</td>
</tr>
<tr>
<td></td>
<td>1.3 month (1.1, 1.6)</td>
</tr>
<tr>
<td>Median number of prior therapies</td>
<td>Median follow-up</td>
</tr>
<tr>
<td></td>
<td>3.5 month (range: 0.03 to 11.7)</td>
</tr>
<tr>
<td>Triple-class refractory</td>
<td>Treatment ongoing**</td>
</tr>
<tr>
<td></td>
<td>59%</td>
</tr>
<tr>
<td>Penta-class refractory</td>
<td>Response ongoing**</td>
</tr>
<tr>
<td></td>
<td>78% (of responders)</td>
</tr>
<tr>
<td>Prior BCMA-directed Tx</td>
<td></td>
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</table>

- Emerging Ph1 data demonstrates compelling clinical activity with manageable safety, in a heavily pretreated patient population (EHA 2022, abstract S180¹)
- Ph1 study in r/r MM is ongoing (exploring both IV and SC administration)
- Combination studies are planned with selected standard-of-care agents

¹Hasselbalch 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**

- [Graph showing change in tumor volume over time with different treatment groups and statistical significance](image)

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

- 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

- 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

- 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%
**PD1-IL2v (RG6279) in solid tumors**

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

- 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 MoA**

[Diagram of PD1-IL2v MoA]

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

- 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

---

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

- 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

- 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

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

Liver enzymes

- Vehicle
- FAP-CD40
- ‘non-targeted’ SGN40

Evidence of tumor uptake via 89Zr-radiolabeled compound

Evidence of tumor uptake via 89Zr-radiolabeled compound

1 Sum et al., Clinical Cancer Research 2021; 2Roche 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

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

Opportunistic areas

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**
- Target mutant oncoproteins

**Synthetic Immunity**
- Immune cell engagers and engineered cells

**Adaptive & Innate Immunity**
- Augment productive T- and dendritic cell functions
- Target neo-epitopes

**Tumor Microenvironment**
- Target immune suppression

**Lineage Dependencies**
- 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

**Oncogenic pathways**

- Synthetic immunity
  - Immune cell engagers and engineered cells
  - Augment productive T- and dendritic cell functions
  - Target neo-epitopes
- Adaptive & innate immunity
- Tumor microenvironment
- Lineage dependencies

**Target mutant oncoproteins**

**Advanced computation & Machine learning (ML)**
- Faster and more efficient data collection
- Better predictions
- Deliver new insights

**Analytics**

**Algorithms**

**Data platforms**

**IT/DevOps**
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**

Proliferation potency/selectivity

- 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**

<table>
<thead>
<tr>
<th>GDC-6036</th>
<th>Monotherapy</th>
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</thead>
<tbody>
<tr>
<td>GDC-6036</td>
<td>+ Tecentriq (anti-PD-L1)</td>
</tr>
<tr>
<td>GDC-6036</td>
<td>+ cetuximab (anti-EGFR)</td>
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<tr>
<td>GDC-6036</td>
<td>+ erlotinib (EGFRi)</td>
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<tr>
<td>GDC-6036</td>
<td>+ GDC-1971 (SHP2i)</td>
</tr>
<tr>
<td>GDC-6036</td>
<td>+ inavolisib (PI3Ki)</td>
</tr>
<tr>
<td>GDC-6036</td>
<td>+ Avastin (anti-VEGF)</td>
</tr>
</tbody>
</table>

- 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*

- 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

---

**Synergy with KRAS G12Ci and SHP2i**

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

- **Vehicle control**
  - GDC-6036 (KRAS G12Ci) 25mg/kg, PO QD
  - GDC-1971 (SHP2i) 60mg/kg, PO BID

- **Combination**

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

---

*Williams et al, AACR 2022*
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 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

- 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)
- 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

<table>
<thead>
<tr>
<th>T-cell bispecific antibody</th>
<th>Ph 1</th>
<th>Ph 2</th>
<th>Ph 3</th>
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</thead>
<tbody>
<tr>
<td>mosunetuzumab (CD20 x CD3)</td>
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<tr>
<td>NHL, CLL</td>
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<td><strong>Approval in 3L+ FL anticipated 2022</strong></td>
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<td>cevostamab (FcRH5 x CD3)</td>
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<tr>
<td>Multiple myeloma</td>
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<td>runimotamab (HER2 x CD3)</td>
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<td>HER2+ breast, gastric cancer</td>
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<td><strong>ImmTAC (MAGEA4 x CD3)</strong></td>
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<td>Multiple solid tumors</td>
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<td>RG6286 (undisclosed target)</td>
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<tr>
<td>Colorectal cancer</td>
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</tbody>
</table>

**Hematology**

**Solid tumor**

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*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

Oncogenic pathways

Target mutant oncoproteins

Synthetic immunity

Immune cell engagers and engineered cells

Adaptive & innate immunity

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

Tumor microenvironment

Target immune suppression

Lineage dependencies

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

Great Ape Adenovirus

Cloning capacity >9 Kb

Maximum antigen length tested:

2,200 amino acids
(>80 neo-antigens of 25 aa)
Neoantigen specific therapies require individualized approaches

- **Mutation identification**
- **Neoantigen prediction**
- **Vaccine manufacturing**
- **TCR identification**
- **T-cell engineering & manufacturing**

**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

**AutoGene Cevumeran**: Individualized mRNA vaccine directed against patients’ unique tumor neoantigens

**VB10.NEO**: Individualized DNA vaccine targeting neoantigen delivery to APCs (cross presentation)

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

Phase I study in surgically resectable PDAC (target n=20)
Investigator-initiated single-center trial

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 histocompatibility complex (MHC)
- Genentech Recurrent Attention Framework (GRAF) is a deep learning model trained on large immunopeptidomics data set

<table>
<thead>
<tr>
<th></th>
<th>GRAF</th>
<th>NetMHC pan-4.0</th>
<th>IEDBv2.13BA</th>
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<td>Peptide Presentation Performance</td>
<td>AP</td>
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<td>0.73</td>
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<tr>
<td></td>
<td>F1</td>
<td>0.82</td>
<td>0.69</td>
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<tr>
<td>Immunogenicity performance*</td>
<td>AUC</td>
<td>0.80</td>
<td>0.79</td>
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</tbody>
</table>

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

Oncogenic pathways
- Target mutant oncoproteins

Synthetic immunity
- Immune cell engagers and engineered cells

Adaptive & innate immunity
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Tumor microenvironment

Target immune suppression

Lineage dependencies
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Advanced computation & Machine learning (ML)
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Analysis
Algorithms
Data platforms
IT/DevOps
Tumors exhibit one of three basic immune phenotypes
Prioritizes immune profiles that represent the greatest unmet need and opportunity

<table>
<thead>
<tr>
<th>Targets for immunomodulation</th>
<th>T cell signature</th>
<th>TGFβ Signature</th>
<th>neuroendocrine signature</th>
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<tbody>
<tr>
<td>Immune Inflamed</td>
<td>CD8+ T cells infiltrated, but insufficient</td>
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<tr>
<td>Immune Excluded</td>
<td>CD8+ T cells do not efficiently infiltrate out from stroma</td>
<td></td>
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<tr>
<td>Immune Desert</td>
<td>CD8+ T cells absent from tumor periphery</td>
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</table>

<table>
<thead>
<tr>
<th>Incidence</th>
<th>Incidence</th>
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<tbody>
<tr>
<td>CRC</td>
<td>12%</td>
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<tr>
<td>NSCLC</td>
<td>31%</td>
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<tr>
<td>mUC</td>
<td>26%</td>
</tr>
<tr>
<td>TNBC</td>
<td>36%</td>
</tr>
</tbody>
</table>

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.

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

**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-L1¹:
- Reduces TGFβ signaling in stromal cells
- Facilitates T-cell penetration into the center of tumors
- Enhances anti-tumor immunity and induces tumor regression

¹Mariathasan S. et.al., Nature 554,544-548 (2018)
## gRED oncology portfolio

12 molecules in early development (Ph 1 / 2)

<table>
<thead>
<tr>
<th>Pathway</th>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
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<tr>
<td><strong>Oncogenic pathway</strong></td>
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<tr>
<td>giredestrant (SERD)</td>
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<td>inavolisib (mP13Ka inh)</td>
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<td>belvarafenib (pan RAF inh)</td>
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<td><strong>Synthetic immunity</strong></td>
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<td>autogene cevumeran⁴</td>
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<td>NME (RG6392)</td>
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<td>SOF10 (TGFβ1)⁶</td>
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</tbody>
</table>

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