Roche Pharma Day 2020

Late Stage Pipeline Oncology & Non-malignant Hematology

Levi Garraway, M.D., Ph.D. | Executive Vice President, Head of Global Product Development and Chief Medical Officer
**Late stage pipeline update**

1. **Hematology franchise**
   - DLBCL: Polivy, glofitamab, mosunetuzumab
   - FL: mosunetuzumab, glofitamab, Polivy
   - AML: Venclexta
   - MM: Venclexta
   - MDS: Venclexta

2. **Breast Cancer franchise**
   - TNBC: Tecentriq, ipatasertib
   - HR+: SERD (RG6171), PI3Kαi (RG6114)
   - HER2+: Tecentriq

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   - NSCLC: Tecentriq, tiragolumab
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   - ROS1+/NTRK+: Rozlytrek
   - RET+: Gavreto
   - KRAS \textit{G12C}+: GDC-6063

4. **Other oncology**
   - CRPC: ipatasertib
   - Thyroid cancer: Gavreto
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   - Melanoma: Tecentriq, Cotellix, Zelboraf

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   - Hemophilia A: Hemlibra
   - Hemophilia A: Factor VIII Gene Therapy
   - PNH: crovalimab

6. **Neuroscience**
   - MS: Ocrevus; fenebrutinib
   - SMA: Evrysdi
   - NMOSD: Enspryng
   - AD: gantenerumab, anti-Tau, brain shuttle
   - Huntington’s disease: tominersen
   - DMD: Micro-dystrophin Gene Therapy
   - Parkinson’s disease: prasinezumab

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   - IPF: rhPentraxin-2, Esbriet
   - Myelofibrosis: rhPentraxin-2
   - Lupus nephritis: Gazyva
   - Crohn’s disease: etrolizumab

8. **Ophthalmology**
   - nAMD, DME, DR: Port Delivery System
   - nAMD, DME, RVO: faricimab

9. **Infectious diseases**
   - HBV: TLR7 agonist, CpAM, RG6346, RG6084
   - Influenza A/B: Xofluza
   - SARS-CoV2: Actemra
   - SARS-CoV2: REGN-COV2

* For further information on target patient populations please consult the appendix; For further details on the late stage pipeline please consult the HY 20 results presentation appendix or visit the IR homepage.
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Hematology: Glofitamab in NHL
Potential for early filing in R/R DLBCL

The ≥10mg cohorts in R/R aNHL showed an ORR of 49.4% and a CR rate of 34.1%; CRs appeared durable with the mDOR not reached after a median follow up of 10.2m

Good safety profile with manageable CRS confined to cycle 1

Combination development with R-CHOP and Polivy in DLBCL on-going

Ph III safety run-in for glofitamab + GemOx in 2L+ DLBCL initiated

CD20 x CD3 program

Ph I (NP30179) dosing in R/R aNHL*

0.6mg 1mg 1.1mg 4mg 10mg 16mg 25mg 50/16mg

Richardson Y, EHA 2020; aNHL=aggressive non-Hodgkin’s lymphoma; DLBCL=diffuse large B cell lymphoma; FL=follicular lymphoma; glofit=glofitamab; GemOx=gemcitabine, oxaliplatin; G=Gazyva; R-CHOP=Rituxan, cyclophosphamide, doxorubicin, vincristine, prednisone; P=Polivy; ORR=overall response rate; CR=complete response; mDOR=median duration of response; CRS=cytokine release syndrome; *Aggressive NHL includes primarily DLBCL, some transformed FL, PMBCL, MCL, transformed MZL and Richter’s transformation
Hematology: Exploring feasible combinations

Initial efficacy and safety data show combination potential

**Ph I results of glofitamab + Tecentriq in R/R NHL**

- **3L R/R DLBCL patient**

  - T-cell activation observed consistent with the hypothesized MOA of the combination
  - Trend towards increased response rate was observed starting at glofitamab doses ≥1.8mg
  - Manageable safety in R/R NHL

**Ph I results of glofitamab + Gazyva in R/R NHL**

- Highly promising activity in heavily pre-treated patients
- ORR and CR rates by investigator assessment were 54% (15/28 pts) and 46% (13/28); CR appear durable
- Safety profile consistent with known safety profiles of the individual drugs

Further development work needed to identify most promising paths forward for chemo-free combinations

Hematology: Mosunetuzumab in NHL 
Potential for early filing in R/R FL; SC data to be presented at ASH

- Pooled data from 2.8mg to 13.5mg cohorts showed an ORR of 62.7% and CR of 43.3%; 82.8% patients remain in complete remission for up to 26m off initial treatment
- Overall CRS rate of 28.9% (predominantly fever Gr1) with only 1.1% CRS events of Gr≥3

Mosunetuzumab in 3L+ FL

Tumor responses

- Indolent NHL: FL (Grade 1–3A), marginal zone lymphoma and small lymphocytic lymphoma
- Data submitted to ASH 2020

CD20 x CD3 program

<table>
<thead>
<tr>
<th>Combination</th>
<th>Indication</th>
<th>Ph1</th>
<th>Ph2</th>
<th>Ph3</th>
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<tr>
<td>mosun+ten</td>
<td>R/R FL</td>
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<tr>
<td>mosun+CHOP</td>
<td>1L DLBCL</td>
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<tr>
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<tr>
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<tr>
<td>mosun SC</td>
<td>R/R DLBCL/FL</td>
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- Ph III safety run-in for mosunetuzumab + lenalidomide in R/R FL initiated
- First Ph I data on mosunetuzumab SC to be presented at ASH 2020

Shuster, S.J., et al., ASH 2019; NHL=non-Hodgkin's lymphoma; DLBCL=diffuse large B cell lymphoma; FL=follicular lymphoma; CHOP=cyclophosphamide, doxorubicin, vincristine, prednisone; P=Polivy; T=Tecentriq; mosun=mosunetuzumab; ORR=overall response rate; CR=complete response; CRS=cytokine release syndrome; R/R=relapsed/refractory; mDOR=median duration of response; SC=subcutaneous
Hematology: Venclexta in CLL, AML, MM, MDS
Ph III studies to be initiated in various indications

Venclexta program

Bcl-2 inhibitor

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<tr>
<td>V/P+R</td>
<td>R/R DLBL-FL</td>
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<tr>
<td>V/G</td>
<td>1L unfit CLL</td>
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<td>R/R CLL</td>
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<td>V</td>
<td>R/R CLL 17p</td>
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<td>V/R</td>
<td>R/R CLL after bendamustine</td>
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<tr>
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<td>1L fit CLL</td>
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<td>R/R AML</td>
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Ph III (VIALE-A) results in 1L unfit AML

Overall survival

- Ph III (Viale-A) results in 1L unfit AML filed in US (RTOS) and EU
- Ph III (Viale-M) in 1L fit AML initiated
- Ph III (CristaLLo) in 1L fit CLL with MRD as primary endpoint started in Q2 2020
- Additional Ph III studies in AML and MDS planned
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TNBC franchise: Tecentriq + nab-pac new SOC in 1L

Positive Ph III results in neoadjuvant

Ph III (IMpassion130) results in 1L

Clinically meaningful OS improvement (2nd interim)
PDL1+ population

Stratified HR = 0.71* (95% CI: 0.54, 0.94)

\[ \Delta \text{7 mo} \]

18.0 mo (13.6, 20.1) 25.0 mo (19.6, 30.7)

Time (months)

Overall survival (%)

TNBC program covering all lines of treatment*

- Positive Ph III (IMpassion031) results for Tecentriq+nab-pac in neoadjuvant TNBC announced; data to be presented

Schmid P, et al. ASCO 2019 (Data cutoff: January 2, 2019); Schmid P, et al. ESMO 2018; TNBC=triple negative breast cancer; nab-pac=nab-paclitaxel (Abraxane); HR=hazard ratio; OS=overall survival;

*Not formally tested due to pre-specified hierarchical analysis plan (data included in the EMA label); *Outcome studies are event-driven: timelines may change
HR+/HER2- franchise: Potentially best in class 3rd gen SERD
Strong efficacy as a single agent and in combination

**Selective ER degrader (SERD)**
**RG6171 (GDC-9545)**

- 3rd generation oral SERD
- Highly potent in vitro and improved efficacy in vivo versus previous SERDs
- High potency + minimal safety findings lead to wide nonclinical safety margins
- First SERD with positive combination data with a CDK4/6 inhibitor

**Ph I b results: Tumor responses RG6171 +/- palbociclib**

- Strong potentially best-in-class efficacy as single agent or in combination with a CDK4/6 inhibitor in pre-treated ER+ patients, regardless of ESR1 resistance mutations
- Well-tolerated up to doses of 100 mg daily
- Expansion cohort at 30 mg daily on-going given the promising efficacy with a clinical benefit rate of 50%*

LM E. et al., ASCO 2020; Metcalfe C. et al., SABCS 2018; HR=hormone receptor; mBC=metastatic breast cancer; ER=estrogen receptor; LHRH=luteinizing hormone/releasing hormone; * At 30 mg no bradycardia events reported to date
HR+/HER2- franchise: Potentially best in class 3rd gen SERD
Ph III program in 1L+ and eBC initiated

3rd gen SERD: Overcoming fulvestrant limitations
Improved MOA for a well established target

Ph III trial design in 1L mBC

- 3rd generation SERD RG6171 (GDC-9545)
- RG6171 is a 3rd generation SERD with improved bioavailability and a novel MOA: Increased efficacy is due to “ER immobilization” which suppresses transcriptional activity prior to ER degradation

- Ph III RG6171 + palbociclib in 1L mBC to start in 2H 2020
- Ph II RG6171 + palbociclib in neoadjuvant started in Q3 2020; Ph III adjuvant study planned
- Pivotal Ph II RG6171 in 2/3L to start in Q4 2020; results expected in 2022
HR+/HER2- franchise: PI3Kαi in PIK3CA-mutant tumors

*Ph III for potentially best in class PI3Kα inhibitor started*

**PI3Kα selective inhibitor + mutant PI3Kα degrader**

- Dual MOA: More potent and selective for PI3Kα + degrades mutant PI3Kα
- Greater safety margins
- Better in vivo efficacy
- Greater, more durable target inhibition
- Combinations with other therapies

**Ph I (dose escalation and expansion cohort)**

- Strong efficacy in on-going Ph I/II as single agent or as combo with ET (letrozole or fulvestrant) +/- palbociclib in patients with locally advanced or metastatic PIK3CA-mutant solid tumors
- Good safety as single agent or combined
- Ph III (INAVO120) RG6114* + palbociclib + fulvestrant in 1L PIK3CA-mutant HR+/HER2- mBC started in Q1 2020

Jhaveri, K., et al, SABCS 2019; Kalinsky K. et al., AACR 2020; ET=endocrine therapy; HR=hormone receptor; BC=breast cancer; ORR=overall response; * GDC-0077
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Lung franchise

*Integrated value proposition for patient classification & care*

Evolution of lung cancer classification

- Roche uniquely positioned to establish integrated PHC solutions
- Develop rare mutation agents faster and cheaper leveraging B-FAST, FMI, Flatiron, PHC
- Multiple lung pilots focused on integrated offerings underway (Taiwan, Croatia, Australia)

Lung franchise: Overview adjuvant program
NSCLC, HER2+ BC, SCCHN reading out in 2021

- **TNBC**
  - Neoadjuvant: IMpassion 031
    - Tecentriq + nab-paclitaxel
  - Neoadjuvant + Adjuvant:
    - NCT02620280 (sponsor Fondazione Michelangelo)
      - Tecentriq + nab-paclitaxel + carboplatin
    - NCT03281954 (sponsor NSABP/GBG)
      - Tecentriq + carboplatin + paclitaxel
  - Adjuvant: IMpassion 030
    - Tecentriq + paclitaxel followed by AC followed by Tecentriq

- **HER2+ BC**
  - Neoadjuvant: IMpassion 050
    - H+P + chemo + Tecentriq / surgery / Tecentriq + chemo
  - Adjuvant: IMpower 030
    - Tecentriq + platinum based chemo
  - Adjuvant: IMpower 010
    - Tecentriq following adjuvant cisplatin based chemo

- **NSCLC**
  - Neoadjuvant: ALINA
    - Alzaferrax

- **RCC**
  - Adjuvant: IMmotion 010
    - Tecentriq

- **SCCHN**
  - Adjuvant: IMvocate 010
    - Tecentriq

- **HCC**
  - Adjuvant: IMbrave 050
    - Tecentriq + Avastin

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= interim  = positive results

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Lung franchise: Tiragolumab + Tecentriq in NSCLC & SCLC
Pivotal Ph III study in stage III NSCLC initiated

Anti-TIGIT mAb

- Fully human IgG1/kappa Ab with intact Fc region that blocks the binding of TIGIT to its receptor PVR
- Could restore anti-tumor response and could complement the activity of anti-PD-L1/PD-1 antibodies

Randomized Ph II (CITYSCAPE) in 1L NSCLC

- Tiragolumab + Tecentriq showed clinically meaningful improvement in ORR and PFS in the ITT population with a greater magnitude of improvement in the PD-L1 TPS ≥ 50% subgroup
- Tiragolumab + Tecentriq was well-tolerated with a safety profile similar to the control arm
- Ph III in 1L PDL1+ NSCLC (SKYSCRAPER-01), 1L ES-SCLC (SKYSCRAPER-02) and stage III NSCLC (SKYSCRAPER-03) on-going
- Ph II (CITYSCAPE) update including OS in 2021

Johnson et al. Cancer Cell 2014; Rodriguez-Abreu D. et al., ASCO 2020; Follow-up data cut-off: 02 December, 2019; Ab=antibodies; ORR=overall response rate; PFS=progression free survival; HR=hazard ratio; NE=non evaluable; ITT=intention-to-treat; TPS=tumor proportion score; ES-SCLC=extensive stage SCLC; OS=overall survival; * unstratified HR
Lung franchise: Gavreto new SOC in RET+ mNSCLC

Strong and durable responses including CNS disease control

- Oral small molecule kinase inhibitor
- Highly selective for RET fusions and mutations, including predicted resistance mutations
- Brain penetrant and CNS active
- ~1-2% of NSCLC patients with RET fusions, thereof ~40% with brain metastases

Ph I/II (ARROW) results in RET fusion+ mNSCLC

- 70% ORR in naive including 11% CR and 57% ORR in post-platinum patients including 6% CR*
- CNS ORR at 56% (n=9) including 33% CR; rapid and durable responses; mDOR not reached
- Well-tolerated across tumor types with most AEs of grade 1–2
- Ph III (AcceleRET Lung) in 1L advanced or metastatic RET+ NSCLC on-going
- US accelerated approval in RET+ mNSCLC achieved in Q3 2020; filed in the EU

Gainor J. F. et al, ASCO 2020; *Data in the label; SOC=standard of care; CNS=central nervous system; BTD=break through designation; mNSCLC=metastatic non small cell lung cancer; MTC=medullary thyroid cancer; ORR=overall response rate; CR=complete response; mDOR=median duration of response; AE=adverse events; Gavreto (pralsetinib) in collaboration with Blueprint Medicines; Gavreto, Blueprint Medicines and associated logos are trademarks of Blueprint Medicines Corporation; Gavreto was discovered by Blueprint Medicines
Lung franchise: GDC-6036 (KRAS G12C inhibitor) in solid tumors

G12C driver mutations found in 12% of all NSCLC patients

**KRAS G12C inhibitor**

- Highly potent irreversible covalent inhibitor of the KRAS G12C mutant protein, which becomes locked in an inactive state
- Minimal safety findings leading to wide nonclinical safety margins

**In vitro and in vivo tumor growth inhibition**

- **In vitro cell line potency**
  - GDC-6036 causes tumor growth inhibition in multiple patient derived KRAS G12C+ cell lines and in xenograft mouse models
  - GDC-6036 synergizes with multiple targeted therapies; strong scientific rationale for combining with medicines that act on other parts of RAS pathway to deepen responses, extend duration of disease control, and limit treatment resistance.
  - Ph I dose escalation and expansion in KRAS G12C+ solid tumors started in Q2 2020

- **Tumor regression in G12C mutant xenograft mouse models**
Lung franchise: Blood-based NGS ctDNA assays
30% of lung cancer patients with insufficient biopsy material

Ph III trial design (B-FAST) for 1L treatment naive NSCLC

- Allows for serial liquid biopsy testing to follow tumor evolution and resistance
- RWD cohort paired with NGS testing provides additional natural history & epidemiological data
- Primary endpoint in the ALK+ cohort met; filed in Q1 2020

Blood based biomarkers

- Liquid biopsy test that detects the 4 main classes of genomic alterations (324 genes), bTMB, MSI
- Comprehensive genomic profiling including resistance mutations or fusions in NSCLC
- Guides therapy selection and clinical trials

Mok T. et al., WCLC 2017; NGS=next generation sequencing; ctDNA=circulating tumor DNA; RWD=real world data; bTMB=blood tumor mutational burden; MSI=microsatellite instability
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   - Myelofibrosis: rhPentraxin-2
   - Lupus nephritis: Gazyva
   - Crohn’s disease: etrolizumab

8. **Ophthalmology**
   - nAMD, DME, DR: Port Delivery System
   - nAMD, DME, RVO: faricimab

9. **Infectious diseases**
   - HBV: TLR7 agonist, CpAM, RG6346, RG6084
   - Influenza A/B: Xofluza
   - SARS-CoV2: Actemra
   - SARS-CoV2: REGN-COV2

* For further information on target patient populations please consult the appendix; For further details on the late stage pipeline please consult the HY 20 results presentation appendix or visit the IR homepage.
Gu franchise: Ipatasertib in 1L mCRPC
Positive Ph III results for patients with PTEN loss

**Highly selective AKT inhibitor**

- Oral, highly specific inhibitor of all three activated isoforms of AKT and potentially preventing cancer cell growth and survival
- Clinical development in tumors with high frequency of PI3K/AKT pathway activation (CRPC, TNBC, HR+ mBC)

**Ph II (A.MARTIN) results**

<table>
<thead>
<tr>
<th>Biomarker assay</th>
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<td>Roche VENTANA PTEN (SP218)</td>
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<tr>
<td>• IHC detection of PTEN protein loss in formalin-fixed, paraffin-embedded tissue</td>
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<tr>
<td>• Strong concordance to DNA technologies (NGS and FISH)</td>
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</table>

**Ph II (400mg dose) in PTEN loss patients**

- rPFS was prolonged in the ipatasertib 400 mg arm (8.2m vs 6.4m; HR=0.75); Dose-dependent improvement was observed in OS
- PTEN loss was associated with an improved rPFS outcome (HR of 0.39 at 400mg dose) as measured by NGS, FISH and IHC
- Ph III (IPATential150) met co-primary endpoint of rPFS in patients with PTEN loss

De Bono J.S. et al., ESMO 2016; mCRPC=metastatic castration resistant prostate cancer; rPFS=radiographic progression free survival; HR=hazard ratio; abi=abiraterone; OS=overall survival; NGS=next generation sequencing; FISH=fluorescence in situ hybridization; IHC=immunohistochemistry; * unstratified HR; 90% CI
GI franchise: Tiragolumab in esophageal cancer (EC)

Pivotal Ph III studies initiated

Ph III trial design (SKYSCRAPER-07) in locally advanced EC

- Locally Advanced Esophageal
  - All-cancer
  - Definitive platinum-based chemotherapy and radiation therapy and no progression
  - ECOG PS 0-1
  - Squamous

1. n=750
   - Tecentriq (1200) + tiragolumab (600) q3w up to 12m (n=250)
   - Tecentriq (1200) + placebo q3w up to 12m (n=250)
   - placebo + placebo q3w up to 12m (n=250)

- Until disease progression or unacceptable toxicity

Randomized 1:1:1 within 1-42 days (TBD)

- 1EP: PFS A vs C; OS (hierarchical) A vs C; OS (hierarchical) B vs C
- 2EP: ORR; DOR; safety; QoL

Ph III trial design (SKYSCRAPER-08) in 1L esophageal squamous cancers (ESCC)

- 1L Esophageal Squamous
  - Measurable metastatic disease
  - ECOG PS 0-1
  - No prior systemic treatment

1. n=450
   - 1EP: OS; PFS
   - 2EP: DOR; ORR; safety; QoL

- Tucinertib (1200) + tiragolumab (600) + cisplatin + paclitaxel (n=225)
- placebo + placebo + cisplatin + paclitaxel (n=225)
- placebo + placebo

- Until disease progression or unacceptable toxicity

- No crossover

- Preliminary Ph Ib safety and efficacy data in EC to be presented at upcoming conference
- Global development program with focus on Asia, especially China
- Ph III starts expected in 2020

Ab=antibodies; ORR=overall response rate; TPS=tumor proportion score; PFS=progression free survival; NE=non evaluable; ITT=intention-to-treat; * unstratified HR
Thyroid cancer franchise: Gavreto in RET+ TC
Excellent efficacy and durability across thyroid cancer types

**RET inhibitor**

- Oral small molecule kinase inhibitor
- Highly selective for RET fusions and mutations, including predicted resistance mutations
- Brain penetrant and CNS active
- 90% of advanced MTC patients with RET activating mutations and ~10-20% of PTC patients with RET fusions

**Ph I/II (ARROW) results**

**Tumor responses**

RET mutation+ medullary TC (MTC)*

- All RET mutant MTC patients (400 mg QD) per central radiology

**Tumor responses**

other RET fusion+ TC

- RET+ MTC: ORR 74% in naive patients and 60% ORR in pretreated patients; mDOR not reached *
- RET+ TC: 91% ORR and 6-month DOR stands at 100%
- Registrational data on Ph I/II (ARROW) MTC results to be presented at ESMO
- Ph III (AcceleRET MTC) in MTC to start in H2 2020
- US priority review and RTOR for advanced or metastatic RET+ thyroid cancer on-going

* MTC data released by Blueprint Medicines on April 1, 2020; Subbiah V. et al, ASCO 2020; SOC=standard of care; TC=thyroid cancer; MTC=medullary thyroid cancer PTC=papillary thyroid cancer; CNS=central nervous system; BTD=breakthrough therapy designation; RTOR=real time oncology review; ORR=overall response rate; mDOR=median duration of response; Gavreto (pralsetinib) in collaboration with Blueprint Medicines; Gavreto, Blueprint Medicines and associated logos are trademarks of Blueprint Medicines Corporation; Gavreto was discovered by Blueprint Medicines
Melanoma franchise: Tecentriq + Cotellic + Zelboraf
First CIT+targeted therapy in BRAF V600+ melanoma

Ph III (IMspire150/TRILOGY) results in BRAF+ melanoma

- Statistically significant and clinically meaningful improvement in investigator-assessed PFS (HR=0.78; 15.1m vs 10.6m) and clinically meaningful improvement in mDOR (21.0m vs 12.6m); no new safety signals were identified
- OS data not mature but favored triplet; next interim expected H1 2021
- FDA approval granted in Q2 2020 under priority review and being part of FDA’s project Orbis

McArthur G.A. et al., AACR 2020; CIT=cancer immuno therapy; Atezo=atezolizumab (Tecentriq); CI=confidence interval; Cobi=cobimetinib (Cotellic); Pbo=placebo; Vem=vemurafenib (Zelboraf); PFS=progression free survival; Cotellic in collaboration with Exelixis; Zelboraf in collaboration with Plexxikon
Late stage pipeline update

1. Hematology franchise
   - DLBCL: Polivy, glofitamab, mosunetuzumab
   - FL: mosunetuzumab, glofitamab, Polivy
   - AML: Venclexta
   - MM: Venclexta
   - MDS: Venclexta

2. Breast Cancer franchise
   - TNBC: Tecentriq, ipatasertib
   - HR+: SERD (RG6171), PI3Kαi (RG6114)
   - HER2+: Tecentriq

3. Lung Cancer franchise
   - NSCLC: Tecentriq, tiragolumab
   - SCLC: Tecentriq, tiragolumab
   - ALK+: Alecensa
   - ROS1+/NTRK+: Rozlytrek
   - RET+: Gavreto
   - KRAS G12C+: GDC-6063

4. Other oncology
   - CRPC: ipatasertib
   - Thyroid cancer: Gavreto
   - Esophageal cancer: tiragolumab
   - Melanoma: Tecentriq, Cotelic, Zelboraf

5. Non-malignant hematology
   - Hemophilia A: Hemlibra
   - Hemophilia A: Factor VIII Gene Therapy
   - PNH: crovalimab

6. Neuroscience
   - MS: Ocrevus; fenebrutinib
   - SMA: Evrysdi
   - NMOSD: Enspryng
   - AD: gantenerumab, anti-Tau, brain shuttle
   - Huntington’s disease: tominersen
   - DMD: Micro-dystrophin Gene Therapy
   - Parkinson’s disease: prasinezumab

7. Immunology
   - IPF: rhPentaxin-2, Esbriet
   - Myelofibrosis: rhPentaxin-2
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* For further information on target patient populations please consult the appendix; For further details on the late stage pipeline please consult the HY 20 results presentation appendix or visit the IR homepage.
Non-malignant hematology: RG6357 (SPK-8011) in hem A
Early efficacy and safety data after 2 to 3.3 years of follow-up

Hemophilia A gene therapy

• Bio-engineered adeno-associated viral (AAV) vector utilizing the AAV-LK03 capsid (Spark200)
• Contains a codon-optimized human factor VIII gene under the control of a liver-specific promoter

Ph I/II (SPK-8011) results

• Data from 5 participants in the 5x10^{11} and 1x10^{12} vg/kg dose cohorts and 7 participants in the 2x10^{12} vg/kg dose cohort showed a 91% ABR reduction and a 96% reduction in FVIII infusions
• The 5 participants in the 5x10^{11} and 1x10^{12} vg/kg cohorts demonstrated durable and stable FVIII expression, had a clinically significant reduction in bleeding and factor use and showed an acceptable safety profile for 2 to 3.3 years of follow up
• Further dose optimization and selection of immunomodulatory regimen on-going
• Ph III to be initiated in 2021

Annualized bleed rate (ABR) of participants with sustained expression (n=12)*

- Spontaneous Bleed
- Traumatic Bleed

91% Reduction in Bleeding Rate

* Excludes 2 participants who lost expression
Non-malignant hematology: Crovalimab in PNH
Recycling Ab for maximal inhibition of C5

Anti-C5 mAb

1. High affinity binding
2. Preferential Ab uptake of antigen-bound Ab (PI engineering)
3. Acid-sensitive antigen release
4. C5 degradation in the endosome
5. Ab recycling by FcRn engineering, protecting Abs from degradation

Ph I/II (COMPOSER) results

Sustained low free C5 levels

- Ph I/II (COMPOSER) results show complete complement inhibition and a well-tolerated safety profile in C5i-naive patients and eculizumab pre-treated patients
- Efficacy was maintained over long-term treatment (44 patients treated for a median of 71 weeks) and breakthrough hemolysis events were infrequent
- Ph III switch and naive studies (COMMODORE 1/2) in PNH to start in 2020
- Development in additional complement-mediated diseases is being explored

Normalized LDH levels due to sustained hemolysis control

Clinico-Genomic Database

Combining RWD and genomics drives R&D

Database R&D applications:
- Understanding genomics of rapidly progressive disease
- Natural history cohorts for defined populations (ALK, NTRK, EGFR, ROS-1, RET, KRAS, etc.), including patterns of metastatic spread
- Mechanisms of resistance
- Improved prognostic classifiers

Recent R&D examples:
- Analysis found cumulative incidence of brain metastases in patients with a certain mutation is significantly higher than in patients with wild-type allele or other mutations; decision to develop brain-penetrant molecule as part of the broader development strategy
- Analysis of CGDB used to decipher a molecular mechanism for checkpoint inhibitor resistance and ultimately helped address a fundamental question that can potentially benefit many cancer immunotherapy projects

Linking advanced tumor genetics with clinical outcomes drives scientific hypothesis generation

RWD=real world data; CGDB=Clinico-Genomic Database
## Our technology platforms keep expanding*

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<thead>
<tr>
<th>Small molecules</th>
<th>Bi-specifics</th>
<th>Fusion protein</th>
<th>mAb</th>
<th>Antibody drug conjugate</th>
<th>Personalized mRNA vaccine</th>
<th>Personalized T cells</th>
<th>RNA technologies</th>
<th>Gene therapy</th>
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### Target oncogenes, induce apoptosis, suppress tumor growth
- Gavreto
- Alecensa
- ipatasertib
- RG6614
- RG6171
- KRAS G12C

- mosunetuzumab
- golfituzumab
- cibatuzumab
- Her2 x CD3
- glycancan-3 x CD3
- FcRHI5 x CD3
- PD1 x TIM3
- PD1 x LAG3
- BMCA x CD16a

- FAP x IL2v
- PD1-IL2v
- CD19-4-1BBL
- FAP-4-1BBL
- MAGE-A4
- LmtmAC
- IL15/IL15Ra-Fc

- tiragolumab
- CD25 mAb
- CD47 mAb
- selicremumab
- codrituzumab

- Polivy
- Kadcyla

- iNeST platform: mRNA-LPX Liposome

- Activated T cell with neoantigen specificity

- programmed T cells

- tominersen
- UBE3A-LNA
- Factor B ASO
- HBV siRNA
- Luxatumma
- SPK-8011
- SPK-8016
- SPK-7001
- SRP-9001
- 4D-R110

### Recombinant proteins
- Evryladi
- fenebrutinib
- raltnatorm
- TLR7 agonist
- GABA Aaa5 PAM
- PTH1R agonist

- Hemlibra
- faricimab
- FXa x FX
- FGFR1 x KLB

- brain shuttle gantenerumab
- IL22-Fc
- IgG-IL2

- Enspryn
- crrovilumab
- gantenerumab
- prasinezumab
- semoreinmab
- TLR4 mAb
- ST2 mAb
- REGN-Cov2

- Anti-S-SAureus TAC

- Activase
- Pulmozyme
- rH Pentraxin-2

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* List of pipeline and launched molecules shown is not complete; iNeST=Individualized Neoantigen-Specific Therapy

![checkmark] = Oncology

[checkmark] = Products approved
Doing now what patients need next