Roche Pharma Day 2020

Late Stage Immunology, Ophthalmology & Infectious Disease

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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), PI3Kα (RG6114)
   - HER2+: Tecentriq

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

4. Other oncology
   - CRPC: ipatasertib
   - Thyroid cancer: Gavreto
   - Esophageal cancer: tiragulumab
   - 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
   - Lupus nephritis: Gazyva
   - Crohn’s disease: etrolizumab

8. Ophthalmology
   - nAMD, DME, DR: Port Delivery System
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   - HBV: TLR7 agonist, CpAM, RG6346, RG6084
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Recombinant human Pentraxin-2 in fibrotic diseases

Evaluating new options to treat fibrosis in multiple diseases

**Recombinant human pentraxin-2 (rhPTX-2)**
- First-in-class rhPTX-2
- PTX-2 is an immune regulatory protein that binds DAMPs with specificity for fibrotic tissue
- Received BTD for IPF

**MOA: PTX-2 inhibits fibrosis formation**
- PTX-2 binds monocytes and macrophages via the FcγR and shifts the balance of monocyte differentiation from pro-fibrotic macrophages, fibrocytes to pro-resolutive macrophages
- Serum PTX-2 levels are reduced in patients with IPF, myelofibrosis and other fibrotic diseases; low PTX-2 levels correlate with increased disease severity
- High unmet medical need remains for further slowing lung function decline on top of SOC

**Fibrotic tissue in IPF**

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IPF=interstitial pulmonary fibrosis; PTX-2=pentraxin-2; DAMPs=damages-associated molecular patterns; MOA=mechanism of action; FcγR=Fcy receptor; SOC=standard of care
Recombinant human Pentraxin-2 in IPF
Efficacy as monotherapy or in combination with standard of care

Ph II results in IPF

- rhPTX-2 resulted in a significantly slower decline in lung function over 28 weeks vs placebo (-2.5% vs -4.8%); most patients received parallel treatment with SoC and no unexpected adverse events with combination treatment were noted
- Ph III (STARSCAPE) of rhPTX-2 + SOC (Esbriet or Ofev) in IPF to start in Q4 2020
- Ph II trial in myelofibrosis on-going; first results expected in Q4 2020

Raghu et al; JAMA 2018;319(22):2299-2307; IPF = interstitial pulmonary fibrosis; FVC = forced vital capacity; 6MWD = Six minute walk distance; SoC = standard of care; FPI = first patient in
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Gazyva in B-cell mediated diseases

Potential benefit in B-cell mediated diseases

Gazyva increases B-cell depletion

- Type II anti-CD20 region
  - Increased direct cell death
  - Decreased CDC
  - Reduced CD20 internalization

- Glycoengineered Fc region
  - Higher FcγR affinity
  - Increased ADCC/ADCP

- Greater potency than Rituxan in depleting peripheral and tissue B-cells
- Recent studies suggest that tissue based B-cells play a major role in lupus nephritis and a more complete depletion is needed

Evaluating Gazyva in B-cell mediated diseases with high unmet need

- Autoreactive B cells in LN:
  - Secrete pathogenic autoantibodies & pro-inflammatory cytokines
  - Present self-antigens
  - Activate T cells

- Lupus nephritis (Ph III (REGENCY) to start in Q3 2020)
- Membranous nephropathy (Ph III expected to start H1 2021)
- Potential additional opportunities
  - Non-renal systemic lupus erythematosus
  - Several other diseases

Moessner et al., Blood, 2010; Niederfellner et al., Blood, 2011; Dalle et al., MCT, 2011; Jak et al., Blood, 2011; Alduaij et al., Blood, 2011; Lim et al., Blood, 2011; Honeychurch et al., Blood, 2012; Pievani et al., Blood, 2011; Bologna et al., JI, 2011; Braza et al., Haematologica, 2011; Patz et al., BJH, 2011; CDC=complement-dependent cytotoxicity; ADCC=antibody-dependent cell-mediated cytotoxicity; ADCP=antibody-depandent cellular phagocytosis; MOA=mechanism of action
Gazyva in lupus nephritis (LN)
Ph III (REGENCY) to start in Q3 2020

**Ph II (NOBILITY) results**

- Complete renal response (CRR)
  - Week 52: 35%, 23%
  - Week 76: 40%, 18%

- Overall renal response (CRR or PRR)
  - Week 52: 56%, 36%
  - Week 76: 51%, 29%

**Ph III trial design (REGENCY)**

- Single pivotal Ph III to replicate Ph II (NOBILITY)
- Primary endpoint is complete renal response (CRR); secondary endpoints include partial clinical response (PRR)
- Ph III (REGENCY) to start in Q3 2020

- Ph II (NOBILITY) met both primary and key secondary endpoints with no new safety signals
- BTD for Gazyva in LN awarded by the FDA
- Ph II update (104 weeks) to be presented

Furie R. et al; ACR 2019; MMF=mycophenolate mofetil
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Inflammatory bowel disease (IBD) program on-going

Ph III program of etrolizumab in Crohn’s Disease reading out in 2021

Etrolizumab
- Gut-selective, dual α4β7/αEβ7 anti-integrin antibody
- Development of novel patient-reported outcome measures for UC and Crohn’s disease continues

IL-22-Fc fusion protein
- Novel non-immunosuppressive MOA
- Restores and protects gut epithelium
- Ph IIb in UC ongoing; N~270

RG6287
- Preserves epithelial cell survival
- Ph I on-going

IgG-IL-2 fusion protein
- Promotes regulatory T-cell proliferation
- Ph Ib on-going

Etrolizumab in CD: Ph III (BERGAMOT) interim results

- >70% of patients in cohort 1 were TNF IR, representing a population with high unmet need; symptomatic remission was seen at week 6 and observed through week 14; clinically meaningful endoscopic improvement was demonstrated
- Well tolerated; frequency of adverse events comparable to placebo
- Ph III enrolling with final data expected in 2021

Sandborn et al; UEGW; October 2017; Barcelona, Spain; CD=crohn’s disease; UC=ulcerative colitis; MOA=mechanism of action, TNF IR is defined as patients who are refractory to or intolerant of TNF inhibitors
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Late stage ophthalmology progressing rapidly
PDS and faricimab with the potential to address key unmet needs

Opportunity to differentiate on durability and improved efficacy

- Faricimab: potential to improve on efficacy
- Anti-VEGF monotherapies
- Faricimab: Potential to improve on durability of response
- Port Delivery System with ranibizumab: reduces real world Tx burden

Current Real World Outcomes

Efficacy (BCVA change, letters)

Durability of response

For illustrative purposes only
Port Delivery System (PDS) Platform
New indications and next generation bispecifics (DutaFabs)

Ph III trial design (PAGODA) in DME

- In the US and EU diabetic eye disease (DME, DR) is the leading cause of vision loss in working age adults
- Ph III (PAGODA) results in DME expected in H1 2022
- Ph III (PAVILION) in DR started in Q3 2020

DutaFabs: A new PDS compatible bispecific format

- DutaFabs are a novel bispecific Fab format significantly smaller than traditional full sized bispecific antibodies
- DutaFabs are compatible with the PDS technology, potentially enabling increased durability beyond Q6M
- 3 DutaFabs with novel dual MOAs in development

CI-DME= center-involved diabetic macular edema, DR=diabetic retinopathy; BCVA=best corrected visual acuity; mAb=monoclonal antibody; MOA=mechanism of action
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Faricimab in nAMD
Potential to stabilize retinal vasculature and improve treatment durability

- First bispecific Ab in ophthalmology binding simultaneously to VEGF and Angiopoietin2 (Ang2)
- Ang2 inhibition may improve vascular stability and reduce retinal inflammation

**Anti-VEGF/Ang2 bispecific mAb**

**Ph II (STAIRWAY) results in nAMD**

- BCVA gains with faricimab Q16W flexible dose and Q12W comparable with ranibizumab Q4W
- 12 weeks after last loading dose 65% of patients had no disease activity and could potentially benefit from Q16W dosing
- Ph III (TENAYA and LUCERNE) enrollment completed; results expected Q1 2021

Khanani et al, AAO Subspecialty Day 2018; nAMD=neovascular age-related macular degeneration; VEGF= vascular endothelial growth factor; BCVA= best-corrected visual acuity; *Linear model adjusted for baseline BCVA, previous macular laser treatment status, BCVA category (≥ 64 letters vs ≤ 63 letters)
Faricimab in DME
Potential for improved efficacy and durability

Ph II (BOULEVARD) results in DME

- Robust BCVA efficacy gains with a mean of +13.9 letters from baseline
- Statistically significant gain of +3.6 letters over Lucentis
- Durability shown with median time to disease reactivation of 15.1 weeks for faricimab vs 8.6 weeks for Lucentis

Ph III trial design (YOSEMITE, RHINE)

- Primary endpoint: Mean BCVA \( \Delta \) from baseline at 1yr; arm B to evaluate personalized treatment interval of Q12W or Q16W
- Ph III data expected in Q4 2020
- Ph III in RVO to start in 2021

Sahni et al, Ophthalmology 2019;126:1155-1170; DME=diabetic macular edema; BCVA= best-corrected visual acuity; *Linear model adjusted for baseline BCVA, previous macular laser treatment status, BCVA category (≥ 64 letters vs ≤ 63 letters); RVO= retinal vein occlusion
Doing now what patients need next