A new approach to R&D at GSK

Dr. Hal Barron

25 July 2018
Cautionary statement regarding forward-looking statements

This presentation may contain forward-looking statements. Forward-looking statements give the Group’s current expectations or forecasts of future events. An investor can identify these statements by the fact that they do not relate strictly to historical or current facts. They use words such as ‘anticipate’, ‘estimate’, ‘expect’, ‘intend’, ‘will’, ‘project’, ‘plan’, ‘believe’, ‘target’ and other words and terms of similar meaning in connection with any discussion of future operating or financial performance. In particular, these include statements relating to future actions, prospective products or product approvals, future performance or results of current and anticipated products, sales efforts, expenses, the outcome of contingencies such as legal proceedings, and financial results.

Other than in accordance with its legal or regulatory obligations (including under the Market Abuse Regulations, UK Listing Rules and the Disclosure Guidance and Transparency Rules of the Financial Conduct Authority), the Group undertakes no obligation to update any forward-looking statements, whether as a result of new information, future events or otherwise. Investors should, however, consult any additional disclosures that the Group may make in any documents which it publishes and/or files with the US Securities and Exchange Commission (SEC). All investors, wherever located, should take note of these disclosures. Accordingly, no assurance can be given that any particular expectation will be met and investors are cautioned not to place undue reliance on the forward-looking statements.

Forward-looking statements are subject to assumptions, inherent risks and uncertainties, many of which relate to factors that are beyond the Group’s control or precise estimate. The Group cautions investors that a number of important factors, including those in this presentation, could cause actual results to differ materially from those expressed or implied in any forward-looking statement. Such factors include, but are not limited to, those discussed under Item 3.D ‘Risk factors’ in the Group’s Annual Report on Form 20-F for FY 2017. Any forward-looking statements made by or on behalf of the Group speak only as of the date they are made and are based upon the knowledge and information available to the Directors on the date of this presentation.

A number of adjusted measures are used to report the performance of our business, which are non IFRS measures. These measures are defined and reconciliations to the nearest IFRS measure are available in our second quarter 2018 earnings release on page 39 and Annual Report on Form 20-F for FY 2017.

All expectations and targets regarding future performance should be read together with “Assumptions related to 2018 guidance and 2016-2020 outlook” on page 40 of our second quarter 2018 earnings release.
GSK has a strong presence and history of leadership in four major areas:

### Leadership in Respiratory Medicine

<table>
<thead>
<tr>
<th>Year</th>
<th>Event/Innovation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1990 - 2010</td>
<td><strong>Leadership in Respiratory Medicine</strong></td>
</tr>
<tr>
<td>1992</td>
<td>First rapid-onset efficacy trial in chronic obstructive pulmonary disease (COPD)</td>
</tr>
<tr>
<td>1995</td>
<td>First inhaled nebulizer trial in chronic obstructive pulmonary disease (COPD)</td>
</tr>
<tr>
<td>1997</td>
<td>First inhaled nebulizer trial in chronic obstructive pulmonary disease (COPD)</td>
</tr>
<tr>
<td>2000</td>
<td>First rapid-onset efficacy trial in chronic obstructive pulmonary disease (COPD)</td>
</tr>
</tbody>
</table>

### Leadership in Vaccines

<table>
<thead>
<tr>
<th>Year</th>
<th>Event/Innovation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1894 - 2000</td>
<td><strong>Leadership in Vaccines</strong></td>
</tr>
<tr>
<td>1894</td>
<td>First successful vaccine for smallpox in 1896</td>
</tr>
<tr>
<td>1901</td>
<td>First successful vaccine for smallpox in 1896</td>
</tr>
<tr>
<td>1923</td>
<td>First successful vaccine for smallpox in 1896</td>
</tr>
<tr>
<td>1930</td>
<td>First successful vaccine for smallpox in 1896</td>
</tr>
</tbody>
</table>

### Leadership in HIV/AIDS

<table>
<thead>
<tr>
<th>Year</th>
<th>Event/Innovation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1984</td>
<td>First successful vaccine for smallpox in 1896</td>
</tr>
<tr>
<td>1985</td>
<td>First successful vaccine for smallpox in 1896</td>
</tr>
<tr>
<td>1987</td>
<td>First successful vaccine for smallpox in 1896</td>
</tr>
<tr>
<td>1996</td>
<td>First successful vaccine for smallpox in 1896</td>
</tr>
</tbody>
</table>

### Leadership in Global Health Science and partnership

<table>
<thead>
<tr>
<th>Year</th>
<th>Event/Innovation</th>
</tr>
</thead>
<tbody>
<tr>
<td>2003</td>
<td>First successful vaccine for smallpox in 1896</td>
</tr>
<tr>
<td>2010</td>
<td>First successful vaccine for smallpox in 1896</td>
</tr>
<tr>
<td>2012</td>
<td>First successful vaccine for smallpox in 1896</td>
</tr>
<tr>
<td>2015</td>
<td>First successful vaccine for smallpox in 1896</td>
</tr>
</tbody>
</table>

**Innovation**

**Innovation**
Driving our growth outlook beyond 2020

Continuing growth drivers

Shingrix
Trelegy
Juluca
tafenoquine
Nucala (COPD)
DTG+3TC
CAB+RPV
Trelegy (asthma)
‘916 (BCMA)
fostemsavir

Tivicay and Triumeq
Nucala and Ellipta portfolio
Bexsero and Menveo

Base business portfolio optimisation; limited exposure to patent expiries

Consumer Health power brands

2018-2020

‘091 (TLR4)
‘165 (aGM-CSF)
‘254 (HIV MI)
‘404/’836 (HBV)
‘557 (PI3Kδ)
‘595 (PRMT5 inhibitor)
‘609 (ICOS)
‘656 (leucyl tRNA)
‘672 (IBAT)
‘745 (TRPV4)

2021-2026

‘756 (CXCR2)
‘762 (BET inhibitor)
‘794 (NY ESO-1)
‘847 (IL33R)
‘863 (HIF-PHI)
‘944 (topoisomerase IV inhibitor)
‘998 (OX40)
CAB PrEP (HIV)
Benlysta+ rituximab (SLE)
High performing businesses reinvent themselves

**Reinvent Your Business Before It’s Too Late**
Watch Out for Those S Curves

by Paul Nunes and Tim Breen


SOONER OR LATER, all businesses, even the most successful, run out of room to grow. Faced with this unpleasant reality, they are compelled to reinvent themselves periodically. The ability to pull off this difficult feat—to jump from the maturity stage of one business to the growth stage of the next—is what separates high performers from those whose time at the top is all too brief.

The key is understanding what problem you are trying to solve, and what levers you have to engender the change.
3 Components to our new R&D approach

Science
Technology
Culture
The industry needs more innovative medicines for patients with real unmet needs.

Drugs that modulate the immune system have had profound effects on patients with many different diseases.

Our scientific understanding of the role the immune system plays in the development of human disease is rapidly advancing.

GSK has deep understanding in Immunology, with several promising medicines in the pipeline.
Drugs that modulate the immune system have had profound effects on patients with many different diseases.

- **1950 onwards**: Steroids. Standard of care for respiratory, MS, rheumatic disease, and many more.
- **2011 onwards**: Immuno-oncology.
- **Tomorrow**: Neurodegeneration, Cardiovascular, Metabolic, Ophthalmology, Hepatology, Osteoarthritis, Ageing.

Trademarks are the property of their respective owners.
Scientific understanding of the role the immune system plays in disease is expanding.
Broad portfolio with strong focus in immunology

**Phase 1**
- 2831761* (LAG3) ulcerative colitis
- 300834 (aVb6 integrin antagonist) IPF
- 3358699* (BET targeted inhibitor) RA
- 3858279* (CCL17 antagonist) OA
- 2636771 (PI3kb inhibitor) cancer
- 2983559 (RIP2k inhibitor) IBD
- 3036656* (leucyl t-RNA inhibitor) TB
- 3640254 (HIV maturation inhibitor) HIV
- 3511294* (IL5 LA antagonist) asthma
- 2292767 (PI3kd inhibitor) COPD/asthma
- 3810109* (broadly neutralizing antibody) HIV

**Phase 2**
- 3196165* (GM-CSF inhibitor) RA
- 3389404*/3228836* (HBV ASO) HBV
- 3772847* (IL33r antagonist) severe asthma
- 2982772 (RIP1k inhibitor) psoriasis/UC
- 3359609* (ICOS receptor agonist) cancer
- 3377949* (NY-ESO-1 TCR) cancer
- 2586881* (rhACE2) acute lung injury/PAH
- 1325756 (danirixin CXCR2 antagonist) COPD
- 2140944 (topoisomerase IV inhibitor) antibacterial
- 2269557 (nemiralisib PI3Kδ inhibitor) COPD
- 230881 (OSM antagonist) systemic sclerosis
- 852**+698* (SAP antagonist) AL/ATTR-CM
- 2881078 (SARM) COPD muscle weakness
- 1795091 (TLR4 agonist) cancer
- 2245035 (TLR7 agonist) asthma
- 2862277 (TNFR1 antagonist) acute lung injury
- 2798745 (TRPV4 antagonist) cough
- 3174998* (OX40 agonist) cancer
- 525762 (BET inhibitor) cancer
- 2330672 (IBAT inhibitor) cholestatic pruritus
- 3326595* (PRMT5 inhibitor) cancer
- GR121619* (oxytocin) postpartum haemorrhage

**Pivotal/Registration**
- Benlysta + Rituxan SLE
- cabotegravir** + rilpivirine* LA HIV
- D3, dolutegravir + lamivudine HIV
- Nucala COPD/HER/nasal polyps
- Trelegy* asthma
- tafenoquine* malaria
- Detova* IV influenza
- 2857916* (BCMA ADC) multiple myeloma

**Vaccines**
- Rotavirus - Phase 3
- MMR - Phase 3 (US)
- Ebola - Phase 2
- Strep pneumoniae next gen - Phase 2
- COPD - Phase 2
- Hepatitis C - Phase 2
- Malaria next gen - Phase 2
- MenABCWY - Phase 2
- Shigella - Phase 2
- Tuberculosis - Phase 2
- RSV - Phase 2
- HIV - Phase 2
- Flu universal - Phase 1

*In-license or other alliance relationship with third party
** Additional indications also under investigation
*** Received FDA approval 20 July 2018
GSK‘165 (aGM-CSF): potential for a disease modifying effect in rheumatoid arthritis (RA) with a unique impact on pain

| The target | – GM-CSF is a pro-inflammatory cytokine that induces differentiation and proliferation of granulocytes and macrophages  
– One of the first cytokines detected in human synovial fluid from inflamed joints  
– Preclinical data suggests a broader range of actions than existing biologics (including a beneficial effect on pain) |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>The agent</td>
<td>– GSK’165 is a fully humanised antibody targeting anti-granulocyte macrophage colony-stimulating factor (aGM-CSF)</td>
</tr>
</tbody>
</table>
| Current status | – Positive Phase 2b results in RA in house; clinical data to be presented at an upcoming conference  
– Discussions with regulators planned to advance development rapidly in RA |

- Unmet need remains in RA despite development of new classes of agent (JAK inhibitors, anti IL6): ~50% of patients do not achieve low disease activity criteria within 12 months of aTNF treatment and ~80% do not achieve Disease Activity Score 28 (DAS28)¹

- Currently 45% of patients report daily pain despite treatment with targeted therapies and pain is the key driver in 25% of switches¹

The target
- Lymphocyte Activation Gene-3
  - Marker of early T-cell activation (predominantly expressed on newly activated CD4+ & CD8+ T-cells)
  - Negative regulator of T-cell response

The agent
- GSK’781 is a humanised monoclonal antibody:
  - Specific to the Lymphocyte Activation Gene-3 (LAG-3) protein
  - Afucosylated to enhance ADCC

Current status
- Lead indication: ulcerative colitis
- Phase 1b studies ongoing
- PoC data expected 2020

Innovation

GSK‘781: targeting the inflammatory cascade through depletion of recently activated LAG-3+ T cells

ADCC: antibody-dependent cell-mediated cytotoxicity

GSK in house data, after CD28 bead stimulation
Experimental medicine studies support UC as lead indication

Gut transcript levels correlate with endoscopic index of disease activity*  

LAG3+ cell numbers (IHC) reduce in responders but not non-responders to established biologics

Dose dependent depletion of LAG-3 positive cells was demonstrated in FTiH/Phase 1b study

* unpublished Slevin et al. P064, ECCO 2018

FTiH: first time in human
GSK’s expertise in immunology will enable success in immuno-oncology

- Monoclonal Antibodies
- Cellular Therapies
- Synthetic/small Molecules
GSK ‘916: First-in-class anti-BCMA ADC agent for treatment of multiple myeloma

The target
- BCMA plays a key role in plasma cell survival
- It is found on the surfaces of plasma cells and is expressed on malignant plasma cells
- Not expressed in healthy tissues

The agent
- GSK’916 is a humanised IgG1 antibody targeting BCMA (B-cell maturation antigen)
  - Linked to the anti-mitotic agent MMAF
  - Afucosylated to enhance ADCC

Key attributes
- New modality in multiple myeloma: first ADC
- Easy and convenient to administer: 1h infusion q3w
- No pre-medication required for infusion reactions
  - Pre-medication with steroid eye drops
- New MoA enabling diverse combination
- Breakthrough and PRIME designations

Four mechanisms of action:
1. ADC mechanism
2. ADCC mechanism
3. BCMA receptor signaling inhibition
4. Immunogenic cell death

Multiple myeloma, also known as plasma cell myeloma, is a cancer of plasma cells, a type of white blood cell normally responsible for producing antibodies.
- Multiple myeloma is treatable, but generally incurable.
- Globally, multiple myeloma affected 488,000 people and resulted in 101,100 deaths in 2015.
- Without treatment, typical survival is seven months, with current treatments, survival is usually 4–5 years

ADC, antibody-drug conjugate; ADCC, antibody-dependent cell-mediated cytotoxicity; BCMA, B-cell maturation antigen; MMAF, monomethyl auristatin-F
GSK’916 anti-BCMA ADC: robust single agent activity in heavily pre-treated/refractory patients

<table>
<thead>
<tr>
<th>Drug, Sponsor</th>
<th>Line of therapy; Trial</th>
<th>ORR</th>
<th>mPFS</th>
<th>mOS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kyprolis† (IV), monotherapy</td>
<td>3L+, Single arm, N=266</td>
<td>23.7%</td>
<td>3.7m</td>
<td>15.6m</td>
</tr>
<tr>
<td>Darzalex‡ (IV), monotherapy</td>
<td>4L+, Single arm, N=106</td>
<td>29.2%</td>
<td>3.7m</td>
<td>17.5m</td>
</tr>
<tr>
<td>GSK’916 (IV), monotherapy</td>
<td>More than 50% of patients had ≥5 lines (40% Darzalex‡ treated), Single arm, N=35</td>
<td>60%</td>
<td>7.9m</td>
<td>NA</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Most frequent adverse events (AEs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corneal events</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
</tr>
</tbody>
</table>

Corneal events – mostly low grade (9% Gr3)
- Manageable with steroid eye drops
- Dose reductions

Hematologic AEs (including thrombocytopenia)
- Frequent in MM population due to disease

Infusion related reactions 23%
- Occur at first dose without premedication
- Manageable
- Do not recur with subsequent dose

Overall ORR = 60% 95%CI (42.1%,76.1%); n=35

Progression-free survival (months)
- Q1 (95% CI) | 2.3 (0.7, 6.8)
- Median (95% CI) | 7.9 (3.1, -)
- Q3 (95% CI) | N/A

1: Siegel et al. Blood (2012); 2: Lonial et al., Lancet (2016). GSK’916 data presented at ASH 2017; †Trademarks are the property of their respective owners
## GSK‘916: broad development plan initiated

First launch in 4L in 2020; 2L launch planned for 2023

### Development strategy for use in:

<table>
<thead>
<tr>
<th>Study start</th>
<th>Est launch</th>
</tr>
</thead>
</table>

#### 4L/3L

**Monotherapy and combinations**

<table>
<thead>
<tr>
<th>Study start</th>
<th>Est launch</th>
</tr>
</thead>
</table>

#### 2L

**Combination with SOC**

<table>
<thead>
<tr>
<th>Study start</th>
<th>Est launch</th>
</tr>
</thead>
</table>

#### 1L

**Combination with novel and SOC agents**

<table>
<thead>
<tr>
<th>Study start</th>
<th>Est launch</th>
</tr>
</thead>
</table>

* Treatable patients in G7 (US, EU5, Japan). Kantar Health 2031 projected; 3L pts 26k, 4L 10k;~65-70% 1L MM pts undergo transplant (source IPSOS, March 2018)

SOC: standard of care
Early stage oncology portfolio with near term data read outs

**GSK’609 ICOS agonist**
- Humanised IgG4 anti-ICOS agonist monoclonal antibody, engineered to provide non-depleting ‘best in class’ agonist activity
- First-in-human trial ongoing across several cancers
- Clinical activity observed with both monotherapy and PD-1 combination (pembrolizumab)
- Several combinations to be tested in platform study starting year end 2018

Confirmed PR in 64yr old male head & neck cancer patient
PoC anticipated 2H 2018

**GSK’998 OX40 agonist**
- Humanised, engineered IgG1 OX40 agonist mAb
- Mono and PD-1 combo dose escalation completed
- Clinical activity observed in monotherapy and PD-1 combination (pembrolizumab)
- TLR4/OX40 combo dose escalation is ongoing

Confirmed PR in 66yr old female liposarcoma patient
PoC anticipated 2H 2020

**GSK’595 PRMT5 inhibitor**
- First-in-class agent with potential broad activity across multiple haematologic and solid cancers
- Dose escalation ongoing
- PRMT5 highly expressed in cancers; high expression associates with poor survival
- Clinical responses seen in cervical cancer and adenoid cystic carcinoma (ACC)

Confirmed PR in 38yr old female cervical cancer patient
PoC anticipated 2H 2019

**GSK’762 BET inhibitor**
- Oral epigenetic-targeted drug, being developed as a novel treatment for a broad range of solid and blood cancers
- Evidence of activity as monotherapy in NUT midline carcinoma
- Ongoing combination studies in breast and prostate cancer with read outs in 2019

Confirmed PR in 18yr old male NUT midline carcinoma patient
PoC anticipated 2H 2019

PoC: proof of concept
Drug discovery and development is very risky with <10% of drugs that undergo clinical testing ultimately becoming medicines\(^1\).

Medicines with genetic validation succeed nearly 2x more often than those without\(^2\).

“Genetically validated” targets have a higher probability of success

GWAS focuses on diseases of interest and looks for genetic associations

Drugs with human genetic evidence nearly 2x more likely to be successful

GWAS: genome-wide association study; SNP: single nucleotide polymorphism

1. Adapted from Nelson et al, Nature Genetics, 47,856-860 (2015)
Heterozygous carriers of PCSK9 loss-of-function alleles have lower LDL and fewer CV events

Evolocumab and clinical outcomes in patients with cardiovascular disease


PheWAS can enable discovery of novel genetic associations

Large-scale phenome-wide association study of PCSK9 loss-of-function variants demonstrates protection against ischemic stroke

Abhiram S. Rao¹, Daniel Lindholm²,³, Manuel A. Rivas⁴, Joshua W. Knowles⁵, Stephen B. Montgomery⁶,⁷, Erik Ingelsson⁸*

PheWAS focuses on SNP/gene of interest and looks for phenotype associations
A new approach to drug discovery is needed to make this a reality
A new approach to drug discovery is needed to make this a reality
A new approach to drug discovery is needed to make this a reality
23andMe database metrics: massive engaged database

- **5m+ customers**
- **>80% consent to research and recontact**
- **1.5b+ survey questions answered**

- Genotype data
- Phenotype data
- Biobanked samples
- Longitudinal data
- Ability to re-contact

No individual will be identifiable to GSK. Continued protection of data and privacy is the highest priority for both GSK and 23andMe.
Leucine rich-repeat kinase 2 (LRRK2): a genetically validated target for Parkinson’s Disease

- 2nd most prevalent neurodegenerative disease
- Genetically validated targets provide an opportunity to treat earlier in the disease
- If LRRK2 inhibition benefits the rare genetically driven patients it may work in others (as in PCSK9)

---

**The target**
- Leucine rich-repeat kinase 2 (LRRK2) is a genetically validated target for Parkinson’s disease

**The agents**
- GSK’984 and GSK’813 are LRRK2 kinase inhibitors
- Opportunity to modify disease, while current therapies symptomatic only
- Early treatment to prevent disease is possible if LRRK2 inhibition is shown to modify disease

**Current status**
- 2 diverse GSK molecules poised to enter the clinic in 2019
- Opportunity to accelerate

---

**LRRK2 kinase in Parkinson’s disease**

6 APRIL 2018 • VOL 360 ISSUE 6384 sciencemag.org SCIENCE

Highly potent, selective, and brain penetrant LRRK2 inhibitors have been reported. Such drugs could benefit not only individuals bearing LRRK2 mutations but also other patients in whom LRRK2 activity is driving the disease. Much research is taking place to develop tests to interrogate LRRK2 activity and function in patients.
Identifying eligible participants is a time intensive and costly process

In the US:
- ~1M individuals with Parkinson’s Disease
- ~135,000 LRRK2 G2019S carriers
- ~10,000-15,000 Parkinson’s Disease patients who are LRRK2 G2019S carriers

Clinical trial sites would need to genotype 100 Parkinson’s Disease patients to find one LRRK2 G2019S carrier

23andMe database currently includes:
- >10,000 re-contactable individuals with Parkinson’s Disease
- >3,000 re-contactable LRRK2 G2019S carriers
- >250 re-contactable LRRK2 G2019S carriers with Parkinson’s Disease
- Ongoing efforts to increase and engage the LRRK2 G2919S cohort to identify newly diagnosed individuals

23andMe provides expedited and focused clinical trial recruitment
- Strategic trial site selection to maximize enrollment at each site
- Flexible and streamlined recruitment: pace recruitment appropriate to sites’ ability to screen, randomize and treat participants; ability to screen on comorbidities and select inclusion criteria
- Opportunity to significantly reduce total clinical trial recruitment duration
23andMe and GSK exclusive collaboration

Collaboration offers scale, diversity, sustainability for advancing therapeutic programs

Questionnaire yields unique phenotype information vs other biobanks

Can deploy custom surveys to dive deeper into specific diseases

Allows rapid recruitment of clinical trials based on genotype, phenotype and proximity to study centres

Improved target selection (higher PoS, and safer, more effective medicines)

Allows more efficient/effective identification and recruitment of patients for clinical studies

Empowers patients!

PoS: probability of success
Technology has been a driver of innovation in many industries, especially science and medicine.
Reverse genetics (think PheWAS) is the process of going from genotype to phenotype.

Functional genomics: the power of gene editing to unravel biology at scale

Genetic interactions reveal functional relationships

Genetic interaction maps systematically measure how the presence of one gene modulates the phenotype of another gene.
Functional genomics (the power of gene editing) combined with machine learning will be very powerful.

Gene x Gene

~200 million combinations

Cell types x genome x (gene x gene) => a lot of data points!
Science and technology together to drive better R&D success

“Artificial Intelligence is the new electricity and is changing industry after industry.”
Stanford School of Business lecture by Andrew Ng

Machine Learning will enable the fields of science and medicine to evolve from an era of “Big Data” to an era of “Understanding Data”
Cell and Gene Therapy is a potentially disruptive technology that has the potential to transform medicine.

GSK is positioned to lead the field through:

**Pioneer in autologous cell therapy**
- Early clinical and manufacturing expertise gained with Strimvelis*, and other rare disease candidates
- Key: ability to scale autologous cell therapy for immuno-oncology
- Requires automation and “close-system” manufacturing
- Miltenyi Biotec collaboration

**Patented enabling technology**
- Autologous cell therapy: manual approaches to transfection (viral vector generation) and transduction have high COGS, limiting potential applicability
- Industry-wide shortage of viral vector
- GSK’s patented proprietary SCLT** technology industrializes lentivirus vector production; expected to reduce COGS 5-10-fold
- Opportunity to licence technology and leverage royalty opportunities

**Strong pipeline of candidate antigens, including:**
- Leading TCR-T capability, accessing solid tumours
- Access to further target antigens through partners (Adaptimmune, Miltenyi Biotec, others)
- Novel technologies to enhance activity of engineered cell products in solid cancer

---

*GSK retains 19% stake in Orchard Therapeutics, focused on providing ex vivo cell therapies for rare diseases
**SCLT: Stable cell line technology
The target

- NY-ESO-1 has significant expression in several tumour types, including NSCLC, sarcoma and myeloma

The agent

- GSK’794 is a TCR-T cell therapy targeting the NY-ESO peptide
- In-licensed from Adaptimmune
- NY-ESO-1 provides PoC for the TCR technology and access for a portfolio of new targets
- Next generation engineering will allow us to assess technologies to enhance activity and/or synergistic combinations that can be utilized across the whole portfolio

Current status

- Ongoing studies in synovial sarcoma, MRCLS, MM and NSCLC
- Completed transition to GSK in July 2018

NY-ESO-1 c259 TCR-T: affinity-enhanced TCR enabling identification and killing of target tumor cells

Natural NY-ESO-1 TCR $K_D = 9.3 \mu M$
NY-ESO-1 c259 TCR $K_D = 0.73 \mu M$
Affinity-enhancement: enables recognising tumour antigens expressed at low levels
GSK’794 NY-ESO-1c259 TCR-T is transformational in improving ORR and mOS in synovial sarcoma

- Confirmed antitumour activity in 10/12 subjects treated
- Tumour shrinkage over several months.
- Circulating NY-ESO-1c259T cells detectable in all patients and persisting >6 months in all responders
  - Central memory and stem cell memory cells that remained polyfunctional with no evidence for T cell exhaustion

**Confirmed antitumour activity**

Expanding the power of our strategy through Business Development

<table>
<thead>
<tr>
<th>Therapeutic opportunities</th>
<th>New programs that enhance our strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Targets aimed at modulating the immune system</td>
<td>- Identify partners who can accelerate the delivery of medicines from our portfolio to patients</td>
</tr>
<tr>
<td>- Genetically validated targets</td>
<td></td>
</tr>
<tr>
<td>- Targets that complement our current pipeline</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Platforms and technologies opportunities</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Human Genetics &amp; Functional Genomics</td>
</tr>
<tr>
<td>- Immune Biology</td>
</tr>
<tr>
<td>- Machine Learning &amp; Data Analytics</td>
</tr>
<tr>
<td>- Genetic &amp; Health Databases</td>
</tr>
<tr>
<td>- Cell &amp; Gene Therapy</td>
</tr>
<tr>
<td>- New/complementary therapeutic modalities</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Out-licensing opportunities</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Collaborations that amplify or leverage our capabilities</td>
</tr>
</tbody>
</table>

Collaborations that enable us to focus on what we do best
Culture matters. A lot!
**Culture change will drive solutions to problems that need to be fixed**

<table>
<thead>
<tr>
<th>Following the science</th>
<th>Smart risk-taking</th>
<th>Single accountable decision making</th>
<th>Focus</th>
<th>Outstanding people</th>
</tr>
</thead>
<tbody>
<tr>
<td>Therapeutic area and modality agnostic approach in research</td>
<td>Incentivise people to make courageous and “smart” decisions</td>
<td>Consensus can kill innovation and dramatically slow down decision making</td>
<td>Aggressively resource your big ideas and stop other projects</td>
<td>Demand, develop and retain the best - outstanding talent attracts outstanding talent</td>
</tr>
</tbody>
</table>
Smart risk-taking

Good outcome

Good decision

Success
Celebrate the good decision and successful outcome

Bad decision

Lucky!
Do not celebrate - luck is not a strategy

Bad outcome

Smart risk-taking
Needs to be celebrated to foster innovation

A learning opportunity

Innovation
Focus: prioritisation is critical

“More organizations die of indigestion than starvation.”
David Packard

“I’m as proud of many of the things we haven’t done as the things we have done. Innovation is saying no to a thousand things.”
Steve Jobs

Refocusing to reinvest

65 Decisions made to terminate, partner or divest programmes since April 2017*

42 programmes were in clinical phase, and the remainder were preclinical

>400 FTEs re-allocated to priority programmes

*Includes transfer of Rare Disease assets to Orchard Therapeutics (announced April 2018) and divestment of dermatology asset tapinarof to Dermavant Sciences (announced July 2018)

FTE: full time employee
Upcoming milestones that will inform our progress

<table>
<thead>
<tr>
<th>Year</th>
<th>Submission</th>
<th>Pivotal data</th>
<th>PoC data</th>
</tr>
</thead>
<tbody>
<tr>
<td>2H 2018</td>
<td>dolutegravir+lamivudine (D3) HIV</td>
<td>dolutegravir+lamivudine (D3) HIV</td>
<td>GSK’609 (ICOS) cancer therapy</td>
</tr>
<tr>
<td>1H 2019</td>
<td>fostemsavir (attachment inhibitor) HIV</td>
<td>Trelegy asthma</td>
<td>GSK’294 (IL5 LA antagonist) asthma</td>
</tr>
<tr>
<td>2H 2019</td>
<td>cabotegravir+rilpivirine HIV treatment</td>
<td>Trelegy asthma</td>
<td>GSK’254 (maturation inhibitor) HIV</td>
</tr>
<tr>
<td>1H 2020</td>
<td>GSK’916 (BCMA) 4L MM monotherapy</td>
<td>mepolizumab HES</td>
<td>GSK’811 (oncostatin M) SSc</td>
</tr>
<tr>
<td>2H 2020</td>
<td>mepolizumab NP</td>
<td>belimumab+rituximab SLE</td>
<td>GSK’109 (bNAb N6LS) HIV</td>
</tr>
</tbody>
</table>

43HES: hypereosinophilic syndrome; IPF: idiopathic pulmonary fibrosis; MM: multiple myeloma; NP: Nasal polyposis; PAH: pulmonary arterial hypertension; RA: rheumatoid arthritis; SLE: systemic lupus erythematosus; SSc: systemic sclerosis; UC: ulcerative colitis;
New R&D approach will support the development of current clinical portfolio

From

- Spend spread thinly across too many programmes ("shots on goal" strategy)
- Consensus-driven decision making
- R&D/Commercial silos
- Limited Business Development activity

To

- Backing the best assets, and removing those that don’t look promising
- Culture of accountability where smart risk-taking and courageous decisions are made by individuals and rewarded
- Robust governance model with scientific peer review, commercial input and data-driven decisions
- Leveraging Business Development to optimise our portfolio
We will seek to understand how the immune system causes disease in a therapeutic area agnostic manner and use human genetics to generate new targets and direct our focus.

We will invest in advanced technologies (such as functional genomics, machine learning and cell therapy) to leverage this science.

We will create a culture that incentivises courageous and smart risk-taking, ensures clarity of decision-making and hires and retains outstanding people.

- High quality targets with higher success rates
- Faster development more life-cycle options
- Transformative therapies
Science
Technology
Culture
= 
Next generation of medicines for patients
Thank you