Oncology R&D Strategy

Maximizing survival through transformational medicines and combinations

Cancer Epigenetics

Immuo-Oncology

Cell & Gene Therapy

GSK pipeline

Long-term survival & cures

Reprogram cancer cells
Stimulate anti-tumour immunity
Cells as medicines

First-in-class medicines

Combination therapy
Main Trends

SOC replacements
Elimination of chemotherapy from SOC regimens

Immune profiling
Patient selection to predict response

New technologies
Expansion of the toolbox

Substantial survival improvements
Across wide populations

Complex combinations
Maximise efficacy

Improved endpoints
Accelerated development

CURE
Oncology – Pipeline Snapshot

**Mechanism**
- OX40 agonist (GSK3174998)
- ICOS agonist (GSK3359609)
- BCMA ADC (GSK 2857916)
- TLR4 agonist (GSK1795091)
- Novel small molecule targets
- ImmTacs
- mAb-dAbs and dual-specific Abs
- BET inhibitor (GSK525762)
- LSD-1 inhibitor (GSK2879552)
- EZH2 inhibitor (GSK2816126)
- PRMT5 inhibitor (GSK3326595)
- PI3K beta inhibitor (GSK2636771)
- Novel small molecule targets
- NY-ESO-1 TCR-T
- CAR-T and TCR-Ts
- Notch2/3 (tarextumab)

**Pre-clinical**
- Solid tumours, Heme Malignancies
- Solid tumours
- Multiple Myeloma
- Cancer
- Solid tumours, Lymphoma
- Prostate cancer

**Phase I**
- Solid tumours, Heme Malignancies
- AML, SCLC
- Solid tumours, Heme Malignancies
- Solid tumours, Lymphoma
- Prostate cancer

**Phase II**
- Sarcoma, Multiple Myeloma, NSCLC, Ovarian cancer, Melanoma
- SCLC

† Collaboration with a third party.
Immuno-Oncology: 3 Generations of Therapies

**Generation 1**
- PROVENGE sipuleucel-T (Cell Therapy)

**Generation 2**
- YERVOY ipilimumab (CTLA-4)
- KEYTRUDA pembrolizumab (PD-1)

**Generation 3**
- OPDIVO nivolumab (PD-1)
- TECENTRIQ atezolizumab (PD-L1)
- BLINCYTO blinatumomab (BITE)
- IMLYGIC T-Vec (Oncolytic Virus)

**Multiple therapies under development**


Approved

Under development

Hoos A, Nat Rev Drug Discov 2016
3rd Generation Opportunities

Spectrum of immuno-oncology modalities

- Adaptive Immunity
- T-Cell Immunity
- B-Cell Immunity
- Innate Immunity

Cytokines

- Cellular Therapies
- Cancer Vaccines
- T-cell Checkpoint Modulators
- "Connector" Bi-specific Abs

- Checkpoint Modulators
- Dual-specific Abs
- Small Molecules
- Oncolytic Viruses
- Adjuvants

- NK Cells

Approved therapies
3rd Generation Opportunities

GSK’s multi-modality pipeline

Adaptive Immunity

T-Cell Immunity

B-Cell Immunity

Innate Immunity

Cytokines

Cellular Therapies

NK Cells*

Cancer Vaccines

T-cell Checkpoint Modulators

Checkpoint Modulators

“Connector” Bi-specific Abs

Dual-specific Abs

Small Molecules

Oncolytic Viruses

Adjuvants

GSK Pipeline * in planning
**GSK2857916: First-in-class anti-BCMA-ADC, proof of concept in multiple myeloma**

- **B Cell maturation antigen (BCMA)**
- **High-expression target in multiple myeloma and some NHL**
- **Antibody drug conjugate (ADC) with MMAF (auristatin derivative)**
- **Immunogenic cell death inducer**
- **Phase I efficacy in refractory population: ~67% RR at > phase II dose**
- **Next steps:**
  - Rapid development for monotherapy
  - Combinations with SOC and novel agents

All doses: ORR = 8/30 (27%; 95% CI: 12.3%, 45.9%)
At >Ph2 dose 3.4 mg/kg: ORR = 6/9 (66.7%; 95% CI: 0.29, 0.92%)

**Safety observations:**
- Thrombocytopenia, transient
- Corneal toxicity: dry eye, blurry vision, reversible

ASH: American Society of Hematology.
GSK3174998 OX40 agonist mAb

GSK3174998 is one of several OX-40s in clinic

Dual mechanism: enhancing effector T-cell and suppressing T-reg

Collaboration with MD Anderson

Phase I Study under way in eight cancers

Combination with Merck PD1 started 3Q16

Combination with GSK TLR4 expected to start in 2H2017

Source: GSK, data on file.
GSK3359609 First-in-class ICOS agonist mAb

- Uniquely engineered IgG4 mAb with agonist function and no cell depletion
- Evolved from patient selection biomarker
- Enhances T-cells associated with clinical benefit
- Universal mechanism across multiple cancers: Phase I ongoing in 8 cancers
- Possible use after CTLA-4 and PD-1 in unresponsive or refractory patients
- Possible anchor for combinations: Expected start in combo with Merck PD-1 in 2Q17

**ICOS in ipilimumab-treated patients**

**GSK3359609**

**T cell Activation *in-vitro***

- CD69+ CD4 T cells 24hr after stimulation

**T cell Proliferation *in-vitro***

- Ki67+ CD4 T cells 48hr after stimulation

DiGiacomo, Clin Immunol Immunother 2013
GSK1795091: TLR4 agonist

Glycolipid TLR-4 agonist compound

Activates dendritic cells and innate immunity, positively modulates tumour microenvironment

Strong combination potential with several IO agents

Potential mechanistic synergies with OX40 and ICOS agonist mAbs

Phase I in healthy volunteers under way to determine dose and PD effects

Phase I combination with OX-40 in cancer patients expected to start 2H17
NY-ESO-1 TCR-T Cell Therapy

- TCR T-cell therapy
- 50% ORR in synovial sarcoma
- Ongoing studies in myeloma, ovarian cancer and other solid tumours
- Planned studies in combination with checkpoint modulators
- FDA Breakthrough designation
- EMA PRIME designation
- Collaboration with Adaptimmune

Note: GSK3377794 subject to exercise of option by GSK

Sarcoma Phase I/II: Individual patient complete response (CR)

Baseline

Day 2: Inflammation

Day 100: CR

Sarcoma Phase I/II: Best response in treated patients (N=12)*

Subject number

Best response

Stable disease

Confirmed complete or partial response

Source: GSK, data on file.
Partnerships

GSK partnerships in Cell Therapy and Clinical Translational Research

Cell Therapy

And others…

Oncology Clinical & Translational Consortium
Epigenetics clinical programs

DNA methylation
Methyl marks added to certain DNA bases repress gene activity.

Histone modification
A combination of different molecules can attach to the ‘tails’ of proteins called histones. These alter the activity of the DNA wrapped around them.
GSK525762: BET inhibitor

Broad activity across multiple tumor types – preclinical cell line models

‘762 Blocks binding of BET family proteins (BRD2, 3 and 4) to acetylated histones causing targeted changes in gene expression including oncogene silencing

Preclinical data: Activity of GSK525762 in many cancer types (gIC50 < 1 μM)

Nature 2010;468:1119-1123
GSK525762: Potential First-in-class BET Inhibitor

Early clinical efficacy in NMC; Progress in many tumour types

Preliminary evidence of clinical activity in NUT midline carcinoma (NMC) (AACR 2016)
- Across all dose cohort (n=17): 12% RR
- At 80/100 mg doses (n=9): 22% RR

Progress in Ph I since AACR 2016
- Solid Tumor: CRPC and ER positive BC expansion cohorts completed; TNBC, SCLC, NMC cohorts ongoing
- Heme: Dose finding in AML completed; dose finding in NHL and MM ongoing; expansion cohorts commencing April 2017
- Anticipate presenting heme clinical data by YE 2017

Expect start of combination studies in 2017
- Pre-clinical data suggest combination synergy
- Combo in ER positive BC with fulvestrant (active)
- Combo in mCRPC with abiraterone or enzalutamide (start ~2Q)
- Other novel combos in 2017 and 2018

Preliminary evidence of clinical activity in NUT midline carcinoma (NMC) (AACR 2016)

Progress in Ph I since AACR 2016

Expect start of combination studies in 2017

Spider plot of % change from baseline in target lesion diameter

12 / 17 patients with NMC presented (5 non-evaluable).
## Oncology at GSK

**Mission:** Maximise patient survival  
Achieve a long-term leadership position in Oncology

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| • Optimise T-cell Immunity  
• Re-program cancer cells  
• Cells as medicines  
• Synergies and transformational effects through combinations | • Diversified pipeline  
  • Across key modalities  
  • Innovation  
  • 3rd generation targets, modalities & combinations  
• Build world-class discovery and development team  
• Fully-integrated programs from early discovery through licensure  
• Partnerships  
  • Best science  
  • Access to combinations | • Transformational effects for patients  
  • Maximise survival  
• Pipeline sustainability  
• Long-term leadership position in Oncology |