GSK VACCINES: BUILDING A THERAPEUTIC PORTFOLIO

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Immunotherapy in action

Cytolytic T Lymphocyte (CTL)

Tumour cell

Killed (“lysed”) tumour cell

± 20 min (in vitro)
Antigen-Specific Cancer Immunotherapeutics (ASCI): MAGE-A3

- Genuine target: identified via screening with anti-tumour killer T-cells
- Genuinely tumour-specific: not expressed in normal cells

- Easy to detect in patients (RT-PCR on tumour tissue)
- Present in major tumour types
  - Lung: 35-50%
  - Bladder: 30-58%
  - Liver: 24-78%
  - Melanoma: 65%
- Present in early and advanced stages of a given disease

- Potentially associated with poor survival prognosis

Lung cancer and melanoma: need for improved therapies

**Lung cancer: leading cause of cancer death**
- More than 1.3 million new cases a year worldwide
- NSCLC ≈ 85% of lung cancer
- More than 1.1 million deaths a year worldwide
- Expected 5-year survival of only 15%
- Current treatments: surgery, chemotherapy, radiotherapy, targeted therapies
  - No real improvement in 5-year survival over last 35 years

**Melanoma: most deadly skin cancer**
- Approximately 160,000 new cases a year
- Approximately 44,000 deaths a year
- Less than 5% of patients with metastatic disease live beyond 5 years
- Current treatments: surgery, chemotherapy, radiotherapy, immunotherapy
  - No real impact on patient survival so far
MAGE-A3 clinical development programme

Stage IV melanoma

Proof of Activity

PoC in NSCLC

Double-blind, placebo-controlled Phase II study

n=182

MAGE-A3 + AS02B

300 μg selected

New Adjuvant System

AS15

Randomized, open

n=75

MAGE-A3 + AS02B vs. AS15

MAGE-A3 + AS02B vs. AS15

AS selection in melanoma

AS15 selected

MAGRIT Study

Dble-blind, placebo

N=2270

MAGE-A3 + AS15

AS15 selected

DERMA Study

Dble-blind, placebo

Phase III

97 - 00 | 2001 | 2002 | 2003 | 2004 | 2005 | 2006 | 2007 | 2008
MAGE-A3 proof of concept: NSCLC phase II data

NSCLC
Adjuvant setting – stage IB-II
After surgery – no chemo

Double blind, placebo controlled phase II
2:1 MAGE-A3/AS02B:placebo

DFS and Survival
180 patients randomized
Interim end 2005

HR=0.75 (95% CI = 0.46 - 1.23)
one-sided logrank p= 0.122
Median follow-up 44 months

Melanoma
Metastatic setting – stage III-IVa
Progressive

Randomized phase II
1:1 MAGE-A3 AS02B vs AS15

Tumour response / Surv.
68 patients randomized
Results 2006-2009

Median survival (95%CI):
AS15 : 31.1 months
AS02_B : 19.9 months

Median follow-up time: 26.3 months
HR= 0.55 (99.9%CI [0.18 - 1.67])

Æ AS15 selected for Phase III

Kruit et al J Clin Oncol 26: 2008 (May 20 suppl; abstr 9065)
Genetic signature predictive of clinical response

Affymetrix platform: HG-U133.Plus 2.0 gene chips covering 47,000 transcripts

Clinical benefit (Responders)

Progressive disease (Non-Responders)
Predictive signature: benefit in melanoma

Gene signature positive

Louahed et al J Clin Oncol 26: 2008 (May 20 suppl; abstr 9045)
Predictive signature: benefit in NSCLC

Overall study population

HR = 0.75 (95% CI: 0.46-1.23)
One-sided log rank p = 0.122

Gene signature positive

GS+: HR = 0.47 (95% CI: 0.20 - 1.13)

Vansteenkiste et al J Clin Oncol 26: 2008 (May 20 suppl; abstr 7501)
MAGE-A3 phase III: MAGRIT & DERMA

- **NSCLC**
  - Adjuvant setting – stage IB-II-IIla
  - After or without chemo
  - **MAGRIT**
    - (n=2270)
    - 33 countries; 400 sites
    - Elevation of GS as co-primary

- **Melanoma**
  - Adjuvant setting – stage IIIb-c
  - Macroscopic disease
  - **DERMA**
    - (n=1300)
    - 23 countries; 200 sites
    - Elevation of GS as co-primary

- **MAGE-A3 positive**
- **Gene signature positive**

597 randomized
(June 2010)
ASCI: diagnostic strategy

- Pre-treatment tumour sample
- MAGE-A3 expression above threshold
- Presence of an expression pattern
- Q-PCR based
- Multi Q-PCR based
Collaboration with Abbott on MAGE-A3 diagnostic

- Automated molecular diagnostic test
- Based on polymerase chain reaction (PCR) technology
- Using the Abbott m2000™ automated molecular instrument system
- NSCLC deal announced July 2009
- Melanoma deal announced March 2010
Expanding the ASCI portfolio

ASCI

New antigens
WT1
PRAME

Combinations
Chemo-radiotherapy
Immunomodulation
Small molecules

New tumour types
Bladder
Hepatocarcinoma
Gastric
Oesophagus

MAGE-A3

ASCI
Alzheimer’s disease overview

Alzheimer’s disease

- Most common cause of dementia
  - Incidence predicted to double by 2025 as the population ages

- Two candidate vaccines in development
  - Phase I/II

- Targets beta-amyloid
  - Pivotal role in plaque formation

WHO: http://www.searo.who.int/LinkFiles/Health_and_Behaviour_alzheimers.pdf
Licensed from Affiris
Nicotine addiction

- Nicotine conjugate vaccine (NicVAX)
- Over 1 billion smokers worldwide
  - over 5 million tobacco-related deaths each year
- Aid to smoking cessation and long-term abstinence
- Produces antibodies that bind to nicotine in the bloodstream
  - prevents nicotine crossing the blood-brain barrier
- Two Phase III studies ongoing

Licensed from Nabi Biopharmaceuticals
GSK therapeutic vaccines: conclusions

- **ASCI** represent a novel class of compounds based on tumour antigens
  - Novel mechanism of action, tumour-specific, patient-selective

- **Proof of concept for activity** demonstrated in double-blind, randomised, placebo-controlled Phase II in NSCLC

- **Second proof of concept** obtained independently in a Phase II in metastatic melanoma

- **Data** suggest investigational MAGE-A3 ASCI is well tolerated

- **Potential biomarkers** to select the patients who will benefit from the ASCI treatment have been identified in melanoma and in NSCLC

- **Pivotal Phase III trials** ongoing in NSCLC and melanoma, including biomarker validation

- **Recent licensing agreements** in Alzheimer’s disease and nicotine addiction