Clinical Pipeline Highlights

Geoffrey M. Nichol, M.D., M.B.A.
Senior Vice President, Product Development
Medarex, Inc.

R&D Day December 9, 2005

MDX-070: Anti-PSMA HuMAb for Prostate Cancer

- **Biology**
  - PSMA expressed on human prostate and cancerous tissue
  - Function unknown

- **Rationale**
  - High-density expression per cell
  - ADCC *in vitro*; prolonged dosing of naked antibody at higher doses not previously undertaken
    - Preliminary *in vivo* data suggesting additivity with docetaxel
  - Internalized; candidate for toxin conjugate
MDX-070: Anti-PSMA HuMAb for Prostate Cancer
Phase I Study Design and Status

- Phase I Study in up to 60 patients
  - Open-label, multi-center, dose-escalation study of a single dose
  - Escalating dose levels of 0.1, 0.5, 1.0, 5.0, and 10.0 mg/kg/dose
  - 3-6 patients per level up to MTD

- End points
  - Solid tumors: response by RECIST criteria
  - Non-measurable tumors: PSA increases, decreases and rate of change
  - Safety, immunogenicity and PK end points

- Study is fully enrolled (18 patients)
  - Safe and well tolerated
  - No anti-tumor responses observed

MDX-070 Peak Concentration Dose Proportionality
MDX-070: Anti-PSMA HuMAb for Prostate Cancer Phase I/II Study Design and Status

- Phase I/II Study in up to 28 patients
  - Open-label, multi-center, dose-escalation study of 4 doses given every other week
  - Escalating dose levels of 1.0, 5.0, and 10.0 mg/kg/dose
  - 6 patients per level up to MTD and 10 additional patients at MTD

- End points
  - Solid tumors: response by RECIST criteria
  - Non-measurable tumors: PSA increases, decreases and rate of change and skeletal metabolic parameters
  - Safety, immunogenicity and PK end points

- Study to complete enrollment in January 2006

MDX-070: Phase II Results to Date

- Dosing complete in 1.0 and 5.0 mg/kg cohorts and 4 of 10 patients at 10.0 mg/kg

- Safe and well tolerated at all doses

- No PSA responses observed to date

- Dosing will complete in 10.0 mg/kg cohort in 1Q06
MDX-070: Next Steps

- Review complete naked antibody data 1Q06
- Development options
  - Controlled Phase II trial: taxotere +/- MDX-070
    - Existing naked antibody
    - Defucosylated antibody
  - Toxin conjugate

MDX-070 Taxotere Combination Efficacious in Mouse Model

![Graph showing tumor growth curves for different treatment groups, including MDX-070 Taxotere combination.](image)
**MDX-070 Taxotere Combination Efficacious in Mouse Model**

LNCaP Mean % Body Weight Change

- Vehicle control
- Rituxan 30 mg/kg
- MDX-070 30 mg/kg
- Taxotere 4 mg/kg
- Taxotere 4 Rituxan 30 mg/kg
- Taxotere 4 MDX-070 30 mg/kg

**MDX-214 Binds EGFr and Mediates ADCC**

Signals Immune Killer Cells

Immune Effector Cell

MDX-214 (EGF fused to Anti-CD89 Fab')

Tumor Cell

Signals Apoptosis
MDX-214: An Important Experiment

- Previous experience – expect short intravascular PK but explore potential to label WBC and tumor for longer periods

- Expected side-effects – hypotension
  - Intravenous rEGF induces hypotension in primates\(^1\)
  - Dose-related hypotension observed in toxicology studies
    - Consistent with “EGF equivalents” in MDX-214
    - Predict hypotension at doses of 10-100 mg/m\(^2\) in patient

Source: \(^1\)Keiser (1996) PNAS 93:4957-61

MDX-214: In Vivo Monkey Neutrophil Binding is Dose-Related

“Intermediate” binding zone

![Graph showing dose-response relationship](image-url)
MDX-214: *Ex vivo* Whole Blood ADCC is Maximal at “Intermediate” WBC Saturations

![Graph showing Mean % Specific Lysis for MDX-214 Dose Group]

Female monkeys, n = 3

Male monkeys, n = 3

MDX-214: Early Development Objectives

- “Intermediate” blood levels promote maximal ADCC
  - Too little drug – no significant binding to EGFR or CD89/WBC with minimal cross-linking
  - Too much drug – saturation of all EGFR and CD89/WBC with excess drug – no cross-linking of WBC to tumor
  - Intermediate drug levels – partially labeled WBC can bind to unlabeled EGFR receptors on tumor and vice versa, leading to ADCC with potential for amplification

- In Phase I, can we find a dose that:
  - Does not cause significant hypotension?
  - Partially labels WBC for a useful period of time?
  - Leads to detectable WBC attachment to tumor?
MDX-214: Phase I Study Design & Status
Bi-functional CD89-EGF protein for EGFR expressing tumors

- Phase I study in up to 48 patients with solid tumors
  - Open-label, multi-center, dose-escalation study
  - 0.4, 1, 4, 10, 20, 30, 40, and 100 mg/m² weekly for 4 doses
  - 3-6 patients per level up to MTD

- End points
  - Efficacy: response by RECIST criteria
  - Safety, immunogenicity and PK end points

- MTD reached at 10 mg/m² – hypotension
  - Additional patients to enter at 4 mg/m²
  - Range of 1-10 mg/m² provides acceptable WBC labeling

MDX-214: Rapid Clearance...

...but WBC Saturation Lasts Longer...
1.0 mg/m² Cohort

4.0 mg/m² Cohort
MDX-214: Next Steps

- Evaluate more patients at 4mg/m²
- Explore optimum scanning technique to evaluate tumor labeling
- Issues
  - Short duration of WBC labeling – may mandate infusion or multiple daily doses/cycle
  - Sensitivity of WBC scanning techniques
- Expected data and Go/NoGo 1H06
MDX-060: Anti-CD30 HuMAb

- Binds to CD30 with nanomolar affinity
- Kills Hodgkin’s disease and anaplastic large cell lymphoma (ALCL) cell lines in vitro by ADCC
- Markedly inhibits tumor growth in xenograft tumor models
- Cross-reacts with activated T cells from cynomolgus monkeys
  - Doses of 30mg/kg x3 and 50mg/kg x13 were well-tolerated
  - No drug-related clinical or pathological findings
- May be additive with chemotherapy
CD30 Ligation Can Lead to Apoptosis


ADCC Mediated by CD30-specific HuMAbs
Localized Xenograft Mouse Tumor Model

SCID mice implanted subcutaneously with 10 million CD30+ L540 cells.
Tumor volume measured, treatment initiated on day 6 post implantation (tumor size ~160 mm³).

Effect of MDX-060 on Disseminated Tumors

Tumor was given intravenously on day 0
Animals were dosed on days 1, 5, 9, and 13
MDX-060: Phase I/II Trial

- MDX-060 given 0.3 – 15.0mg/kg weekly x4 in Hodgkin’s disease and ALCL (n=72)
- Safe and well-tolerated
- No infusion reactions
- No detectable HAHA to date
- Responses seen in Hodgkin’s and ALCL with and without concomitant steroids

Percent Change In Tumor Burden At Week 8

![Percent Change In Tumor Burden At Week 8](chart.png)
Association of Low Baseline Plasma Soluble CD30 Levels With Response

Monte Carlo two-sided exact test
Responders vs. non-responders, p=0.0093
Responders vs. SD, p=0.0828
Responders vs. PD, p=0.0051

MDX-060 Exhibits Dose Proportional Pharmacokinetics

PK Findings
• PK is dose proportional
• Blood levels accumulate with repeated dosing
• No evidence of immunogenicity (HAHA response) in any tested sample
MDX-060: Response in ALCL

Pretreatment

6 weeks post treatment

Ways to Improve Response Rate

- Increase duration of treatment
- Add concomitant chemotherapy\(^1\)
- Screen based on baseline sCD30

Source: \(^1\)Hueck et al 2004, J immunother 27:347-353
MDX-060: Phase II Program

- Evaluate 3 months of dosing in monotherapy in refractory Hodgkin’s disease
- Evaluate combination with gemcitabine in Hodgkin's disease
- Evaluate ALCL patients at Hodgkin’s sites

MDX060-03 Study Design

**Anti-CD30 HuMAb for Hodgkin's Disease**

- Phase II study in up to 84 patients
  - Open-label, multi-center, EU based
  - 10 mg/kg administered weekly for 12 doses
  - Non-responders may be treated with MDX-060 plus gemcitabine

- End points
  - Efficacy: Best objective response rate at day 106
  - Safety, immunogenicity and PK end points
MDX060-05 Study Design
Anti-CD30 HuMAb for Hodgkin’s Disease

- Phase II study in up to 90 patients
  - Open-label, randomized, multi-center, US based
  - Three arms
    - 4 weekly doses of MDX-060 10 mg/kg plus 3 weekly doses of gemcitabine 1000 mg/m²
    - 4 weekly doses of MDX-060 10 mg/kg plus dexamethasone 40 mg po
    - 3 weekly doses of gemcitabine 1000 mg/m²
  - Continuation study allows additional dosing for responders and MDX-060 for patients on gemcitabine alone arm

- End points
  - Efficacy: Best objective response rate at day 50
  - Safety, immunogenicity and PK end points

MDX060-04 Study Design
Anti-CD30 HuMAb for Anaplastic Large Cell Lymphoma

- Phase II study in up to 45 patients
  - Open-label, multi-center, global
  - Patients with either cutaneous or visceral disease (alk-1 + & -) may enroll
  - 3 mg/kg weekly times 4 weeks

- End points
  - Efficacy: Best objective response rate at day 106
  - Safety, immunogenicity and PK end points
MDX-060: Next Steps

- Phase II data expected 2H06
- If ORR adequate in MDX060-03 (3 months monotherapy), continue Hodgkin’s program to Phase III with MDX-060
  - Trial defucosylated anti-CD30 antibody (MDX-1401) as follow up
- If not, fully roll program over to back-up MDX-1401 program

MDX-1100: Anti-IP-10 HuMAb

- Strong pre-clinical data supporting activity in multiple indications
  - Inflammatory bowel disease
  - Multiple sclerosis
  - Rheumatoid arthritis
- IND open – Phase I trial underway
  - Single-dose, dose-escalating trial in patients with active ulcerative colitis
  - Evaluate safety and PK; potential to see clinical activity signal in single-dose setting
  - Study enrolling
  - Data targeted 2H06
- SQ formulation in development