FLT3 Ligand (CDX-301) and Stereotactic Radiotherapy for Advanced Non-Small Cell Lung Cancer

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Established 3-week-old Lewis lung tumors

RT: 60 Gy to primary tumor

FLT3L: 500 μg/kg/day × 10 days, initiated one day after RT

Combined treatment
- induced primary and memory tumor-specific immune response
- prevented lung metastasis
- prolonged survival
Fractionated Radiotherapy with 3 x 8 Gy Induces Systemic Anti-Tumour Responses and Abscopal Tumour Inhibition without Modulating the Humoral Anti-Tumour Response

Sub-ablative radiation with FLT3L did not improve survival.

CDX-301 (FLT3 ligand) Background

• Fms-like tyrosine kinase-3 ligand (FLT3L) uniquely binds CD135 (FLT3 receptor) and induces proliferation, differentiation, and mobilization of hematopoietic stem cells, early progenitor cells, and dendritic cells (DCs)
  • Key regulator of DCs inducing marked increases in both myeloid and plasmacytoid DCs

• CDX-301 is the soluble recombinant human protein form of FLT3L.

• Clinical experience (studies by Immunex and Celldex)
  • >500 subjects treated, including >300 cancer patients
    • No significant safety issues
    • 10 to 100+ fold increase in DCs (including CD141+ DCs)
    • Augments humoral and T cell response to NY-ESO-1 vaccine
    • No clear activity as monotherapy in advanced cancer patients
Study Hypothesis

• The combination of stereotactic body radiotherapy (SBRT) to a single pulmonary lesion and CDX-301 will have clinical activity in advanced NSCLC.

Immunogenic cell death: Promotes DC activation and maturation

Expansion of DCs in tissues and tumor

Response in irradiated and non-irradiated lesions

Systemic immune response
Key Eligibility Criteria

• AJCC stage 3 or 4 histologically proven NSCLC not amenable to curative therapy
• Prior treatment with at least one standard chemotherapy regimen or targeted agent prior to enrollment
• Measurable disease that includes:
  • at least one pulmonary lesion ≥ 1 cm in greatest dimension that would be amenable to SBRT
  • at least one measurable lesion that would be outside of the SBRT treatment fields
• ECOG performance status 0-2
• No untreated central nervous system metastases.
• No ongoing or recent use of high dose oral corticosteroids.
• No history of allogeneic organ transplant or autoimmune disease.
Study Design

- One-week treatment course:
  - 5 daily subcutaneous injections of CDX-301 (75 μg/kg)
  - Stereotactic body radiotherapy (SBRT) to a single thoracic lesion
    - Peripheral tumor ≤ 2 cm and > 1 cm from chest wall
    - Peripheral tumor ≤ 5 cm and not eligible for 34 Gy x 1
    - Other thoracic lesions
  - 34 Gy x 1 fraction = 34 Gy
  - 18 Gy x 3 fractions = 54 Gy
  - 10 Gy x 5 fractions = 50 Gy

- Sample size: 29 patients

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Pre-tx</th>
<th>Week 1</th>
<th>Week 2</th>
<th>Week 3</th>
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No additional treatment until disease progression
Endpoints

• Primary endpoint: Progression-free survival 4 months after treatment initiation (PFS4)
  • Scored using Immune-related response criteria (irRC)\textsuperscript{1}
  • H\textsubscript{0}: PFS4 \leq 20\%\textsuperscript{2,3}  H\textsubscript{1}: PFS4 \geq 40.5\%
  • Accept H\textsubscript{1} if PFS4 is achieved in 10/29 subjects

• Secondary endpoints:
  • Adverse events / Dose-limiting toxicities
  • Overall Survival
  • Radiographic responses in lesions not treated with SBRT
    • CT: irRC\textsuperscript{1}
    • PET: PERCIST\textsuperscript{4}
      • Total Glycolytic Activity (TGA): volumetric sum of activity in all hypermetabolic lesions
      • Partial Metabolic Response (PMR): Decrease in TGA of at least 45%

\textsuperscript{1} - Clin Cancer Res 2009;15(23):7412-20  \textsuperscript{2} - J Clin Oncol 2010;28(13):2167
Patient Characteristics (n=9)

- 9 subjects enrolled between October 2016 and September 2017
- 7/9 previously treated with anti-PD-(L)1 therapy
  - 5 with documented progression on anti-PD-(L)1 therapy
  - Median interval from anti-PD-(L)1 therapy termination to study enrollment: 3 months

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<td>1 fraction</td>
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</tr>
<tr>
<td>3 fractions</td>
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</tr>
<tr>
<td>5 fractions</td>
<td>7</td>
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Adverse Events
Possibly/probably related to study therapy, scored using CTCAE v 4.0

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<th>Grade 3+</th>
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<tr>
<td>Dyspnea</td>
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<tr>
<td>Esophagitis</td>
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<tr>
<td>Fatigue</td>
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<td>1</td>
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</table>

• No dose-limiting toxicities observed
• One case of delayed pneumonitis attributed to prior immune checkpoint inhibitor therapy
CDX-301 Increases DCs and Monocytes
Clinical Outcomes (n=9)

- PFS4 achieved in 5 subjects (based on CT/irRC)
- 6 subjects currently alive with disease
- 10 month median follow-up duration for surviving patients
### Best Responses (excluding SBRT target): CT/irRC v. PET/PERCIST

<table>
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<tr>
<th>Response Type</th>
<th>CT/irRC</th>
<th>PET/PERCIST</th>
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<tr>
<td>Stable Disease</td>
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<tr>
<td>Progressive Disease</td>
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Kappa = 0.481  
Weighted Kappa = 0.667  
(moderate to good agreement)
Responses on PET (excluding SBRT Targets)

• 9 subjects
  • 5 demonstrated Partial Metabolic Response on Week 8 PET
Responses on PET (excluding SBRT Targets)

- 9 subjects
  - 5 demonstrated Partial Metabolic Response on Week 8 PET
    - All 5 previously received immunotherapy

- No Prior Immunotherapy
  - 9 subjects
  - 5 demonstrated Partial Metabolic Response on Week 8 PET
    - All 5 previously received immunotherapy

- Prior Immunotherapy
  - 4 subjects
  - 3 demonstrated PD
    - (3 fx)
  - 1 demonstrated PMR
    - (1 fx)
Patient 2

- 55 year-old female with right lung adenocarcinoma, left lung nodules
  - 1\textsuperscript{st} line: carboplatin, pemetrexed (PD)
  - 2\textsuperscript{nd} line: nivolumab (arthralgias), discontinued June 2016
- Nov 2016: SBRT + CDX-301
Patient 2

- 55 year-old female with right lung adenocarcinoma, left lung nodules
  - 1st line: carboplatin, pemetrexed (PD)
  - 2nd line: nivolumab (arthralgias), discontinued June 2016
  - Nov 2016: SBRT + CDX-301
  - May 2017: PD in left lung
  - April 2018: clinically well without additional treatment
Patient 3

- 80 year-old female with right lung squamous cell carcinoma, bone metastases
  - 1\textsuperscript{st} line: carboplatin, gemcitabine (SD, then PD)
  - 2\textsuperscript{nd} line: nivolumab (PR, then PD), discontinued Dec 2016
- Feb 2017: SBRT + CDX-301
Patient 3

- 80 year-old female with right lung squamous cell carcinoma, bone metastases
  - 1\textsuperscript{st} line: carboplatin, gemcitabine (SD, then PD)
  - 2\textsuperscript{nd} line: nivolumab (PR, then PD), discontinued Dec 2016
  - Feb 2017: SBRT + CDX-301
  - Feb 2018: PD in right lung
  - April 2018: On pembrolizumab
Response on Week 8 PET and Overall Survival

![Graph showing overall survival over time from study treatment].

- Partial Metabolic Response, n=5
- No Partial Metabolic Response, n=4
Study Conclusions

• This “bench to bedside” trial explores the combination of ablative radiotherapy and FLT3L as an *in situ* vaccine.

• The combination of SBRT and CDX-301 is well tolerated in patients with advanced NSCLC.

• SBRT + CDX-301 has clinical activity ("abscopal effects") in advanced NSCLC
  - rapid and durable responses
Study Conclusions (cont.)

- SBRT + CDX-301 may be particularly effective in patients who have previously received anti-PD(L)1 therapy.
  - Including patients who have progressed
- Early PET findings after treatment may predict long-term clinical outcomes.
- Enrollment to further characterize the safety and efficacy of this regimen is ongoing.
Future Directions

• Optimize treatment regimen
  • Add “Booster” doses of SBRT + CDX-301
  • Add activating anti-CD40 antibody
    • CDX-1140, currently in phase I trials

• Explore combinations with immune checkpoint inhibitors
  • anti-PD(L)1 → SBRT+CDX-301 → anti-PD(L)1

http://dendritic-cells-research.com
Guha Laboratory