Anti-DLL4 treatment in Combination with anti-PD1: From preclinical to clinical

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January 26, 2017
OncoMed Pharmaceuticals: Targeting Critical Cancer Pathways and TME

### Notch Pathway
- Demcizumab
- Tarextumab
- Brontictuzumab
- Anti-DLL4/VEGF bispecific

### Wnt Pathway
- Vantictumab
- Ipafricept
- Small Molecules

### RSPO/LGR Pathway
- Anti-RSPO3
- Other RSPOs
- Other LGRs

### Immuno-oncology
- Anti-TIGIT
- GITRL-Fc
- IO #3 (undisclosed)

- 7 clinical programs in or achieved to Phase 2
- 14 active clinical trials: evidence of activity
- Data from multiple randomized Phase 2 trials by 2017
OncoMed Tumor Bank: Establishment of Patient Derived Xenografts for Studying Cancer Stem Cells

Established > 210 tumors from 18 different cancer types to date

- Focused on major tumor types
  - Br, Co, Lu, PN, Ov, Mel, Liv etc.
  - Continually expanding

- Extensive genomic characterization
  - Gene expression (mRNA-seq)
  - Oncogene mutational analysis
  - Gene amplifications and deletions

- Models retain tumor cell heterogeneity
  - Better predict clinical outcome
  - Enable CSC characterization and biomarker discovery
Using Preclinical Mouse Models to support drug discovery

**Tumor Models**

**OncoMed**

**Pros:**
- Ability to explore human tumor/immune cell interaction
- Opportunity to utilize valuable PDX tumor models

**Cons:**
- Incomplete immune cell compliment
- Development of GVHD
- New and not fully characterized
- Cost

**Patient derived xenograft (PDX) Models**

**Pros:**
- First-in-class Tumor bank, continually expanding
- Extensive genomic characterization
- Tumor cell heterogeneity
- Enable CSC characterization and biomarker discovery

**Cons:**
- Immunocompromised mice
- Lack of human stroma

**Syngeneic Mouse Models**

**Pros:**
- Full immune cell compliment
- Used to validate current approved Immune checkpoint inhibitors

**Cons:**
- Rapid tumor formation
- Limited tumor models
- Surrogate antibody effects may have limited human translatability

**Genetically Engineered (GEMMs)**

**Pros:**
- Ability to explore human tumor/immune cell interaction
- Opportunity to utilize valuable PDX tumor models

**Cons:**
- Incomplete immune cell compliment
- Development of GVHD
- New and not fully characterized
- Cost

**Humanized Mouse Models**

**Pros:**
- Full immune cell compliment
- Used to validate current approved Immune checkpoint inhibitors

**Cons:**
- Rapid tumor formation
- Limited tumor models
- Surrogate antibody effects may have limited human translatability

**Oncology**

**Immuno-Oncology**
Signal Transduction by the **Notch** Pathway: implicated in many cancer types

- The Notch pathway mediates intercellular signaling in stem cell self-renewal, proliferation, and differentiation and immune cell development.
- OncoMed has developed first-in-class Notch pathway mAbs
  - **Anti-DLL4** (demcizumab)
  - Anti-Notch2/3 (OMP-59R5, tarextumab)
  - Anti-Notch1 (OMP-52M51, brontictuzumab)

[Ref: Nature Reviews Immunology 13, 427-437 (2013)]
Anti-DLL4 Inhibits Tumor Growth And Shows Strong Efficacy With SOC In PDX Models

NSCLC

OMP-LU108 Efficacy

OMP-LU108 Efficacy

OMP-LU121 Efficacy
Anti-tumor MOA of Anti-DLL4

Blocking DLL4 function reduces CSCs and disrupt tumor angiogenesis

**Cancer Stem Cells**

- Anti-DLL4 promotes differentiation and chemosensitization

**Angiogenesis**

- Anti-DLL4 blocks critical DLL4 role in angiogenesis
Therapy against Cancers

Untreated
Standard or Other Targeted Therapy
Immunotherapy (e.g. anti-CTLA4, PD1)
Combination with IO agent
Role of DLL4 in Immune System

Immune Suppressive Tumor Microenvironment

MDSCs
Tregs
M2 macrophage
Fibroblast
Endothelial cells
Pericytes
Extracellular matrix

Cytotoxic T cell
NK cells
DCs
Neutrophils

Immune suppression by MDSC is a significant impediment to cancer immunotherapy
Role of DLL4 on MDSC:

Immune suppression by MDSC is a significant impediment to cancer immunotherapy

**Regulation of T Cell Activation by Notch Ligand, DLL4, Promotes IL-17 Production and Rorc Activation**

Mukherjee et al., *J Immunol* 2009. 182:7381-88

**IL-17 Promotes Tumor Development through the Induction of Tumor Promoting Microenvironments at Tumor Sites and Myeloid-Derived Suppressor Cells**

He et al., *J Immunol* 2010. 184:2281-88

**Myeloid-Derived Suppressor Cells: Critical Cells Driving Immune Suppression in the Tumor Microenvironment**

Parker KH., Beury, DW., and Ostrand-Rosenberg, S. *Adv Cancer Res* 2015. 128: 95-139
MDSCs Inhibit anti-Tumor Immunity

**G-MDSC**
(ROS, Arginase)
CD11b$^+$ Gr1$^{hi}$
CD11b$^+$Ly6G$^{hi}$Ly6C$^{lo}$

**M-MDSC**
(iNOS, IL10, Arginase)
CD11b$^+$ Gr1$^{lo}$
CD11b$^+$Ly6G$^{-/lo}$Ly6C$^{lo}$
DLL4 Inhibits Murine Tumor Growth in Syngeneic Mice
Anti-DLL4 Significantly Reduces Splenic IL17a as Measured by ELISPOT

CT26.WT

Control Anti-DLL4

4T1

Control Anti-DLL4

IL-17a TOD (x1000)

Control Anti-DLL4

*
Anti-DLL4 Reduces Inflammatory Cytokines

Inflammatory Cytokine Reduction Leads to Decreased Neutrophil Counts in Circulation in 4T1 Tumor bearing mice

**Plasma IL-17**

**Splenocyte IL-6**

**Plasma IL-1B**
Anti-DLL4 Reduced Neutrophils and Increased Lymphocytes in Blood in 4T1 Bearing Mice

Neutrophils ~ MDSCs
Anti-DLL4 Uniquely Decreases Highly Immunosuppressive Monocytic MDSC Cells

**FACS analysis of MDSC**

Gated on CD11b+ in spleen

- **G-MDSC** (ROS, Arginase1)
- **M-MDSC** (iNOS, IL10, Arginase)

**Representative mouse (of 10)**

**Control**

**Anti-DLL4**

**Spleen M-MDSC**

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<thead>
<tr>
<th></th>
<th>Control</th>
<th>Anti-DLL4</th>
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<tr>
<td>% M-MDSC</td>
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<td></td>
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<td>p=0.0008</td>
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**Tumor M-MDSC**

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<th>Control</th>
<th>Anti-DLL4</th>
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<tbody>
<tr>
<td>% M-MDSC</td>
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Gated on CD11b+ in spleen

M-MDSC: CD11b+LY6C+LY6G-

G-MDSC: CD11b+LY6G+LY6Cint

- **T cell Activation**
- **NK cell cytotoxicity**
- **M1 to M2 MΦ**
- **Treg**
Anti-DLL4 Results in Less Suppressive MDSCs

CD4

Control: 17%
Anti-DLL4: 31%

CD8

Control: 15.5%
Anti-DLL4: 29%
Anti-DLL4 inhibits Th17 Response Leading to anti-Tumor Immune Response

CD4 T

CD8 T

DLL4

DC

Th17

Rorγt

IL-17

H2O2·CCL2

NO-IL-2

Arg, Cys, Trp depletion to CD3ζ expression

H2O2

IL-10

ARG1

IDO

TGFβ

IL-6

NK

Tumor
Anti-DLL4 Treatment Significantly Reduces PD-1 Levels in CT26WT Tumors

**Increased Immune Infiltration**

- **CD45**

- *p<0.03

**Decreased PD1 Expression**

- Western Blot

- **PD-1**

- *p<0.03
Anti-DLL4 combined with anti-PD1 significantly inhibits mouse CT26WT tumor growth while enhancing IFN-γ and IL2 but decreasing IL17 cytokines.

**Tumor Growth**

- Control
- Anti-DLL4
- Anti-PD1
- Anti-DLL4 + Anti-PD1

**ELISPOT**

- IL17α
- IFN-γ
- IL2

Control  anti-DLL4  Anti-PD1  Combo
Anti-DLL4 reduces IL17 and M-MDSCs in Tumor
Mice Previously Treated with Anti-DLL4 and Anti-PD1 are Resistant to Tumor Re-challenge

**Second Re-challenge** | **% Protection**
--- | ---
Naive | 0 (0/10)
Anti-PD1 | 40% (2/5)
Anti-PD1/DLL4 | 100% (11/11)
Anti-DLL4 inhibits Th17 Response Leading to anti-Tumor Immune Response

Checkpoint Inhibitors

Immune Memory

H₂O₂-CCL2
NO-IL-2
Arg, Cys, Trp depletion to CD3ζ expression

CD8 T

Tumor

Treg

IL-10 TGFβ

IL-17

Th17 Rorγt

CD4 T

Dll4

Notch

CD8 T

H₂O₂ TGFβ

IL-6 TGFβ

NK
Anti-DLL4 Use in Humanized SGM3 Models
Establishing Humanized Mice (JAX)

- Three week old NSG/SGM3 mice are engrafted through the tail vein with purified human CD34+ HSCs.
- Twelve weeks later the circulating human CD45+ cell population is quantitated and confirmed to be at least 25% of the cell population.
- Selected human PDX tumors are then engrafted subcutaneously into the mice.
- Major human immune cell types: T cells, B cells, and myeloid cell lineages (limited NK and DCs).
- Tumors have been shown to grow regardless of HLA match/mismatch.
- Great opportunity to test PDX tumor models with human-specific humanized antibody biologics.
Effects of Human Anti-DLL4 + Anti-PD1 on OMP-M9 Melanoma PDX in hSGM3 mice
Effects of Human Anti-DLL4 + Anti-PD1 on OMP-LU121 (AdC) in hSGM3 mice
Anti-DLL4 and Anti-PD1 (Keytruda) Combination Increases T Cells and Decreases MDSCs in the Tumor
Anti-DLL4 and Anti-PD1 (Keytruda) Combination Decreases PD1 Expression in Splenic CD4+ and CD8+ T Cells
Dual Blockade of DLL4 and PD1 Increases T Cell to MDSC Ratio
A phase 1b study with Anti-DLL4 in combination with anti-PD1 is on going.
Multiple Mechanisms of Anti-DLL4

Blocking DLL4 reduces CSCs, disrupt tumor angiogenesis, and inhibits MDSCs

**Cancer Stem Cells**
- Anti-DLL4 promotes differentiation and chemo sensitization

**Angiogenesis**
- Anti-DLL4 blocks critical DLL4 role in angiogenesis

**MDSCs**
- Anti-DLL4 reduces and inhibits MDSCs
Acknowledgements

**Tumor Immunology**
- Minu Srivastava
- Hyun-Bae Jie
- Rui Yu
- Erin Mayes

**ARF**
- Kellie Pickell
- Xiaomei Song
- Roger Lopez

**Molecular Biology**
- Austin Gurney
- Fumiko Axelrod
- Jorge Monteon
- Cecile Chartier
- May Ji
- Andrew Lam

**Caner Biology**
- Tim Hoey
- Chris Murriel
- Jean Yen
- Marcus Fischer

**Trans Med**
- Ann Kapoun
- Belinda Cancilla
- Fiore Cattaruzza
- Erwan LeScolan
- Jennifer Cain
- Pete Yeung
- Min Wang
- Chun Zhang
- Alayne Brunner
- Akbar Currimbhoy

**Process Dev**
- Peter Stathis
- John Burky
- Joy Chen
- Esohe Idusogie
- Jim Burrell
- Ruby Casareno

**Janes Keck and The Jackson Labs**

**John Lewicki (CSO)**
**Paul Hastings (Chairman, CEO)**