PLX3397 & CRUK Combinations Alliance
July 2015

Plexxikon Inc.
## Plexxikon’s Oncology Development Pipeline

*Combination Studies with PLX3397*

<table>
<thead>
<tr>
<th>Compound</th>
<th>Relevant Target</th>
<th>Targeted Cancer Indication</th>
<th>Pre-IND</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
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</thead>
<tbody>
<tr>
<td>PLX3397</td>
<td>CSF-1R</td>
<td>Tenosynovial Giant Cell Tumor (TGCT)&lt;sup&gt;1&lt;/sup&gt;</td>
<td></td>
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<tr>
<td>PLX3397 + radiation therapy +</td>
<td>CSF-1R, KIT</td>
<td>Adjuvant Glioblastoma</td>
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<td>temozolomide</td>
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<td>PLX3397 + eribulin</td>
<td>CSF-1R, KIT</td>
<td>Metastatic Breast Cancer</td>
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<td>PLX3397 + paclitaxel</td>
<td>CSF-1R, KIT</td>
<td>Neoadjuvant Breast (I-SPY2)</td>
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<td>PLX3397 + pembrolizumab</td>
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<td>Melanoma, Solid Tumors</td>
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<td>PLX3397 + paclitaxel</td>
<td>CSF-1R, KIT</td>
<td>Advanced Ovarian Cancer</td>
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<td>PLX3397 (China)</td>
<td>KIT</td>
<td>KIT-Mutant Melanoma</td>
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<td>PLX7486</td>
<td>TRK, CSF-1R</td>
<td>Pancreatic, Solid Tumors</td>
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<td>PLX9486</td>
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<td>Gastrointestinal Stromal Tumor, KIT-Mutant Tumors</td>
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<td>PLX8394</td>
<td>BRAF</td>
<td>BRAF-Mutant Tumors</td>
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</table>
PLX3397 is a Selective Inhibitor of FMS and KIT Kinases

Biochemical Assay

PLX3397 Selectivity

Fms, Kit ☑

2 Kinases ≥ 10-fold

227 Kinases > 100-fold

FMS = CSF1R = receptor for ligands M-CSF (CSF-1) and IL-34
• Macrophage target (includes osteoclasts, microglia, MDSCs)

KIT = receptor for ligand SCF
• Mast cell target
PLX3397, First-in-Class Selective FMS/KIT Kinase Inhibitor – Mechanism of Action

- Single-agent activity (e.g. PVNS, KIT-mutant melanoma)
  - Tumors driven by Fms or Kit pathway mutations
- Combination activity: Suppress tumor microenvironment
  - Tumor ⇔ Pro-tumor immunosuppression ⇔ Invasion
  - Targeting tumors with infiltrating macrophages (FMS), myeloid-derived suppressor cells (FMS), microglia (FMS), mast cells (KIT) and bone lysis (FMS)
- Breast, prostate, glioblastoma, many other cancers
PLX3397 - Rationale for Collaboration with CRUK Combinations Alliance

- PLX3397 is the most advanced selective FMS/KIT inhibitor in clinical development
- By targeting FMS (the CSF1 receptor), PLX3397 modulates key cells in the tumor microenvironment
  - CSF1-dependent Macrophages
  - Microglia
  - Myeloid Derived Suppressor Cells (MDSCs)
- Tumors often resist chemo, radiation and immunotherapies by secreting CSF1 and attracting tumor-protective macrophages and MDSCs
- Plexxikon is currently addressing CSF1-mediated resistance in several PLX3397 combination clinical trials:
  - Paclitaxel- and Eribulin-combinations in breast cancer
  - Radiation plus Temozolomide combination in glioblastoma
  - PD-1 combination in melanoma and 10 other tumor types
- Based on strong scientific support, additional Combinations Alliance studies could lead to significant treatment breakthroughs
- Successful proof-of-concept Combinations Alliance trials may lead to Plexxikon-sponsored registration trials
- The first PLX3397 registration trial in PVNS is already in progress
PLX3397 Combination Opportunities

- Immune checkpoint inhibitors
- Anti-angiogenic therapies
- Irradiation
- Chemotherapies
- Targeted therapies
- Adoptive T cell transfer

Current Opinion in Pharmacology

2015, 23:45–51
Plexxikon’s Latest Combo Trial: PLX3397 + Pembrolizumab

Tumor recruits MDSCs to overcome Host T Cell response

PLX3397 neutralizes tumor resistance mechanism

T Cell intends to lyse Tumor

PLX3397

CSF1

CSF1R

MDSC

Tumor

T Cell

Immunotherapy

Pembrolizumab Anti-PD1 antibody
PLX3397 - Ideas for EOI
Targeting the tumor microenvironment to sensitize to combination partners

Brief synopsis of relevant publications

- **Immunotherapy**
  - PLX3397 sensitizes melanomas to activated T cells
    - Mok et al., Cancer Res 2014
    - Sluijter et al., PLoS One 2014
  - PLX3397 sensitzes pancreatic cancers to anti-PD1 and anti-CTLA4 agents
    - Zhu et al., Cancer Res 2014
  - **Chemotherapy**
    - PLX3397 sensitizes cells to multiple cytotoxic agents
      - Breast cancer, DeNardo et al., Cancer Discovery 2011
      - Pancreatic cancer, Mitchem et al., Cancer Res 2013
  - **Targeted agents**
    - PLX3397 and androgen blockade in prostate cancer
      - Escamilla et al., Cancer Res 2015
    - PLX3397 and rapamycin in MPNSTs
      - Patwardhan et al., Clin Cancer Res 2014
    - PLX3397 and EGFR inhibitors in glioblastoma
  - **Radiation therapy**
    - PLX3397 and radiation in prostate cancer
      - Xu et al., Cancer Res 2013
    - PLX3397 and radiation in breast cancer
      - Shiao et al., Cancer Immunol Res 2015
• KIT inhibition in GIST
  – The role of macrophages
    – Increased KIT inhibition enhances therapeutic efficacy
    • Kim et al., Clin Cancer Res 2014

**Murine germline GIST model**

- GIST
- Normal drinking water or Imatinib & control or PLX3397 chow x 4wk
- Tumor Kit⁺ cell #, size (flow cytometry)

**Human GIST xenograft model**

- T1-NSG⁺
- Normal drinking water or Imatinib & control or PLX3397 chow x 1.5wk
- Tumor volume, weight, KIT⁺ cell # (flow)
PLX3397 - Immunotherapy Combination
Data from selected publications

- Immunotherapy
  - PLX3397 sensitizes melanomas to activated T cells
    - Mok et al., Cancer Res 2014

Combined antitumor activity of ACT immunotherapy and PLX3397 in the OVA and pmel-1 models.
PLX3397 - Immunotherapy Combination (continued)
Data from selected publications

- Immunotherapy
  - PLX3397 sensitizes melanomas to activated T cells
  - Sluijter et al., PLoS One 2014

CSF-1R inhibition enhances CD8-mediated immunotherapy of melanoma.
PLX3397 - Immunotherapy Combination (continued)
Data from selected publications

- Immunotherapy
  - PLX3397 sensitizes pancreatic cancers to anti-PD1 and anti-CTLA4 agents
    - Zhu et al., Cancer Res 2014

CSF1/CSF1R signaling blockade enhances T-cell checkpoint immunotherapy.
PLX3397 – Chemotherapy Combinations
Data from selected publications

- **Chemotherapy**
  - PLX3397 sensitizes cells to multiple cytotoxic agents
- **Breast cancer, DeNardo et al., Cancer Discovery 2011**

Cytotoxic therapy induces macrophage recruitment via CSF1. Dose-dependent expression of CSF1 following chemotherapy.

PTX = paclitaxel
CDDP = cisplatin

Macrophage depletion improves response to chemotherapy.
PTX = paclitaxel
CBDCA = carboplatin

Combined PLX3397 and PTX treatment inhibits metastasis
PLX3397 – Chemotherapy Combinations (continued)
Data from selected publications

- Chemotherapy
  - PLX3397 sensitizes cells to multiple cytotoxic agents
    - Pancreatic cancer, Mitchem et al., Cancer Res 2013

PLX3397 significantly improves gemcitabine effects on pancreatic tumor control in a CD8-T cell dependent fashion

GEM = gemcitabine
CSF1Ri-1 = PLX3397
PLX3397 – Targeted Agent Combinations
Data from selected publications

- Targeted agents
  - PLX3397 and androgen blockade in prostate cancer
    - Escamilla et al., Cancer Res 2015

CSF1R blockade with PLX3397 lowered TAM-induced tumorigenic factors and delayed the emergence of castrate-resistant prostate cancer.
PLX3397 – Targeted Agent Combinations (continued)
Data from selected publications

- Targeted agents
  - PLX3397 and rapamycin in MPNSTs
    - Patwardhan et al., Clin Cancer Res 2014

Effect of PLX3397 and/or rapamycin treatment in MPNST xenografts.
PLX3397 – Targeted Agent Combinations (continued)
Data from selected publications

- Targeted agents
  - PLX3397 and EGFR inhibitors in glioblastoma

Blockade of CSF-1R with PLX3397 in vivo inhibits microglia/macrophage recruitment to GL261 tumors.

Blockade of CSF-1R with PLX3397 inhibits glioblastoma invasion in vivo
PLX3397 – Radiation Therapy Combination
Data from selected publications

- Radiation therapy
  - PLX3397 and radiation in prostate cancer
    - Xu et al., Cancer Res 2013

CSF1/CSF1R blockade with PLX3397 inhibits tumor growth after irradiation
Ongoing Clinical Trials with PLX3397
PLX Development and Investigator-Sponsored Trials

PLX3397 Phase 3 Study for Pigmented Villonodular Synovitis (PVNS) or Giant Cell Tumor of the Tendon Sheath (GCT-TS)
http://ClinicalTrials.gov/show/NCT02371369

A Phase 1b/2 Study of PLX3397 + Radiation Therapy + Temozolomide in Patients With Newly Diagnosed Glioblastoma
http://ClinicalTrials.gov/show/NCT01790503

A Combination Clinical Study of PLX3397 and Pembrolizumab to Treat Advanced Melanoma and Other Solid Tumors
https://www.clinicaltrials.gov/show/NCT02452424

I-SPY 2 TRIAL: Neoadjuvant and Personalized Adaptive Novel Agents to Treat Breast Cancer
https://clinicaltrials.gov/show/NCT01042379

PLX3397, Radiation Therapy, and Antihormone Therapy in Treating Patients With Intermediate- or High-Risk Prostate Cancer
https://clinicaltrials.gov/show/NCT02472275

PLX3397 in Children and Young Adults With Refractory Leukemias and Refractory Solid Tumors Including Neurofibromatosis Type 1 (NF1) Associated Plexiform Neurofibromas (PN)
https://clinicaltrials.gov/show/NCT02390752

A Study of PLX9486 as a Single Agent and in Combination with PLX3397 in Patients with Advanced Solid Tumors Including GIST
https://clinicaltrials.gov/show/NCT02401815

Safety Study of PLX3397 and Paclitaxel in Patients With Advanced Solid Tumors
http://ClinicalTrials.gov/show/NCT01525602

Phase Ib/II Study of PLX 3397 and Eribulin in Patients With Metastatic Breast Cancer
http://ClinicalTrials.gov/show/NCT01596751

PLX3397 KIT in Acral and Mucosal Melanoma
http://ClinicalTrials.gov/show/NCT02071940
Delayed bone regeneration is linked to chronic inflammation in murine muscular dystrophy.

Pigmented villonodular synovitis: dedicated PET imaging findings.
Amber IB, Clark BJ, Greene GS. *BMJ Case Rep.* 2013 Apr 17;2013.

KIT oncogene inhibition drives intratumoral macrophage M2 polarization.

PSTPIP2 deficiency in mice causes osteopenia and increased differentiation of multipotent myeloid precursors into osteoclasts.

Microglial stimulation of glioblastoma invasion involves epidermal growth factor receptor (EGFR) and colony stimulating factor 1 receptor (CSF-1R) signaling.

CSF1 overexpression has pleiotropic effects on microglia in vivo.

Leukocyte complexity predicts breast cancer survival and functionally regulates response to chemotherapy.

Colony-stimulating factor 1 receptor signaling is necessary for microglia viability, unmasking a microglia progenitor cell in the adult brain.

CSF1 Receptor Targeting in Prostate Cancer Reverses Macrophage-Mediated Resistance to Androgen Blockade Therapy.

c-Fms signaling mediates neurofibromatosis Type-1 osteoclast gain-in-functions.
Increased KIT inhibition enhances therapeutic efficacy in gastrointestinal stromal tumor.

Targeting tumor-infiltrating macrophages decreases tumor-initiating cells, relieves immunosuppression, and improves chemotherapeutic responses.

Inhibition of CSF-1 receptor improves the antitumor efficacy of adoptive cell transfer immunotherapy.

Sustained inhibition of receptor tyrosine kinases and macrophage depletion by PLX3397 and rapamycin as a potential new approach for the treatment of MPNSTs.

Neurofibroma-associated macrophages play roles in tumor growth and response to pharmacological inhibition.

TH2-polarized CD4+ T cells and macrophages limit efficacy of radiation therapy.

Modulation of macrophage activity during fracture repair has differential effects in young adult and elderly mice.

Inhibition of CSF-1R Supports T-Cell Mediated Melanoma Therapy.

CSF1R signaling blockade stanches tumor-infiltrating myeloid cells and improves the efficacy of radiotherapy in prostate cancer.

CSF1/CSF1R Blockade Reprograms Tumor-Infiltrating Macrophages and Improves Response to T-cell Checkpoint Immunotherapy in Pancreatic Cancer Models.
BACKUP

ASCO POSTER 2011
Pharmacodynamic Activity Demonstrated In Phase 1 for PLX3397, A Selective Inhibitor of Fms and Kit Kinases

S. Anthony, P. Puzanov, E. Kwak, P. Lin, K. Nolop, B. West, D. Von Hoff

1. Evergreen Hematology and Oncology, Spokane WA; 2. Vanderbilt-Ingram Cancer Center, Nashville TN; 3. Massachusetts General Hospital, Boston MA; 4. Plexxikon Inc., Berkeley CA; 5. Virginia G. Piper Cancer Center & TGen, Scottsdale AZ

Introduction

PLX3397 is a selective inhibitor of Fms, Kit, and oncogenic FNR kinase activity. The proliferation and metastasis of a number of tumors are driven in part by FIS, Kit, or Fms activity. These tumors include, but are not limited to, acute myelogenous leukemia (unrelated FIS), gastrointestinal stromal tumor and melanoma (Kit), and glioma, breast cancer, prostate cancer, mantle myeloma, and osteosarcoma (Fms/CSF-1). In preclinical testing, PLX339 has had significant effects on multiple aspects of tumorigenesis, including proliferation, invasiveness, extravasation, and survival of metastases.

The primary objective of this study was to evaluate the safety and pharmacokinetics of orally administered PLX3397 in patients with advanced, incurable, solid tumors in which these target kinases are linked to disease pathophysiology. The secondary objective was to measure the pharmacodynamic activity of PLX3397 in blood, plasma, and urine biomarks of Fms activity.

Study Design

• Oral, single agent, sequential dose escalation
• Standard 3+3 patient cohort design
• 100 and 200 mg 7-day run-in (n=3) for 600 and 500 mg cohorts
• Patients with solid tumors
  a. Refractory to standard therapy, CR standard or curative therapy does not exist or is not considered appropriate by the investigator, and
  b. Tumor progression or metastasis could not be promoted in part by FIS, Kit, or Fms/CSF-1 activity.
  1. ECOG PS 0 or 1
  2. Adequate hematologic, hepatic, and renal function
  3. Continuous dosing in 4-week cycles

Demographics

<table>
<thead>
<tr>
<th>No. Pts</th>
<th>32</th>
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<tbody>
<tr>
<td>Male</td>
<td>19</td>
</tr>
<tr>
<td>Female</td>
<td>13</td>
</tr>
<tr>
<td>Age (yrs) Mean &amp; SD 54.6±14.2</td>
<td></td>
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<tr>
<td>Median</td>
<td>63.5</td>
</tr>
<tr>
<td>Range</td>
<td>23-79</td>
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</table>

| ECOG (n) (%) | 0 (16.4%) |
| Tumor Types | 9 |
| CML          |
| Acute myelogenous leukemia |
| Breast       |
| GIST         |
| Colon        |
| Other        |

Steady State PK: Dose Proportionality Observed

PD Markers

- FACS Assay - CD14dim/CD16+ Monocytes
  - CD14+ Day 1 (pretreatment)
  - CD14+ Day 8
- Decreased Bone and Cartilage Tumor Markers
  - uNTx/Cr
  - sCTX
  - Percent Change from Baseline vs. PLX3397 AUC24-72 (nM•h/mL)

Safety

<table>
<thead>
<tr>
<th>Event</th>
<th>Overall AE (%)</th>
<th>Related AE (%)</th>
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<tbody>
<tr>
<td>Patients Reporting at Least One Adverse Event</td>
<td>27 (81.2%)</td>
<td>13 (39.4%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>23 (71.8%)</td>
<td>3 (9.0%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>12 (36.4%)</td>
<td>1 (3.0%)</td>
</tr>
<tr>
<td>Anemia</td>
<td>13 (39.4%)</td>
<td>1 (3.0%)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>7 (21.2%)</td>
<td>2 (6.0%)</td>
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<tr>
<td>Fatigue</td>
<td>12 (36.4%)</td>
<td>1 (3.0%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>8 (24.2%)</td>
<td>1 (3.0%)</td>
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<tr>
<td>Abdominal pain</td>
<td>5 (15.1%)</td>
<td>1 (3.0%)</td>
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<tr>
<td>Constipation</td>
<td>5 (15.1%)</td>
<td>1 (3.0%)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>5 (15.1%)</td>
<td>1 (3.0%)</td>
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<tr>
<td>Headache</td>
<td>2 (6.0%)</td>
<td>1 (3.0%)</td>
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<tr>
<td>Eosinophilia</td>
<td>5 (15.1%)</td>
<td>1 (3.0%)</td>
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<tr>
<td>Neutropenia</td>
<td>4 (12.1%)</td>
<td>2 (6.0%)</td>
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<tr>
<td>Dyspnea</td>
<td>2 (6.0%)</td>
<td>1 (3.0%)</td>
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Dose-Limiting Toxicities

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<tr>
<th>Patient</th>
<th>ID</th>
<th>Dose</th>
<th>Adverse Event</th>
<th>Comment</th>
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<tbody>
<tr>
<td>01-000</td>
<td>300 mg</td>
<td>G3 INR increase and G3 hematuria</td>
<td>On warfarin; possibly related</td>
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<tr>
<td></td>
<td>600 mg</td>
<td>G4 hypotension</td>
<td>Hypotension; unlikely related; possibly disease related (SADDLE)</td>
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<tr>
<td>02-010</td>
<td>600 mg</td>
<td>G4 hematuria</td>
<td>Hematuria; unlikely related; possibly disease related (SADDLE)</td>
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<tr>
<td>02-020</td>
<td>600 mg</td>
<td>G3 lymphoma</td>
<td>Exempted following discussion with FAS; unlikely related</td>
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<tr>
<td>01-001</td>
<td>600 mg</td>
<td>G3 AST</td>
<td>Recovered after drug discontinuation; possibly related</td>
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<tr>
<td>02-030</td>
<td>1200 mg</td>
<td>G4 neutropenia</td>
<td>Recovered after drug discontinuation; possibly related</td>
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Increased Plasma CSF-1 as a Biomarker For Fms Inhibition

<table>
<thead>
<tr>
<th>CSF-1 (ng/mL) from Baseline</th>
<th>PLX3397 Day 15 AUC24-72 (nM•h/mL)</th>
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</thead>
</table>

Decreased Circulating Tumor Cell Counts in 3/5 Patients

| CTC levels per 7.6 | |

Conclusion

- By targeting a key component of the tumor microenvironment, PLX3397 represents a novel therapeutic approach for cancer.
- Dose proportional PK and long half life support a once-daily regimen.
- The selectivity of PLX3397 has translated into a favorable safety profile.
- Biomarker data support a clinically relevant efficacious range for both Fms and Kit inhibition.
- A trial in refractory Hodgkin lymphoma is ongoing. Additional studies are being initiated in recurrent glioblastoma and Ph+ITD > AML.
BACKUP

ASCO PRESENTATION 2014
A Pilot Study of PLX3397, a Selective Colony-Stimulating Factor 1 Receptor (CSF1R) Kinase Inhibitor, in Pigmented Villonodular Synovitis (PVNS)

Presenting author: William D. Tap, M.D.  
Memorial Sloan Kettering Cancer Center

Co-authors: Stephen Patrick Anthony¹, Bartosz Chmielowski², Arthur P. Staddon³, Allen Lee Cohn⁴, Geoffrey Shapiro⁵, Igor Puzanov⁶, Eunice L. Kwak⁷, Andrew J. Wagner⁵, Charles Peterfy⁸, Henry H. Hsu⁹, Carolyn Gee⁹, Paul S. Lin⁹, Sandra Tong⁹, Zev A. Wainberg²

¹ Evergreen Hematology and Oncology/US Oncology Research Affiliate; ² University of California, Los Angeles; ³ University of Pennsylvania School of Medicine; ⁴ Rocky Mountain Cancer Center/US Oncology; ⁵ Dana-Farber Cancer Institute; ⁶ Vanderbilt-Ingram Cancer Center; ⁷ Massachusetts General Hospital; ⁸ Spire Sciences, Inc.; ⁹ Plexxikon Inc.
Pigmented Villonodular Synovitis (PVNS)  
Tenosynovial Giant Cell Tumor (TGCT)

- Rare synovial tumor of joints & tendon sheaths
- Incidence ~ 600 new cases per year in US, often young adults

- Clonal neoplastic process resulting in over-expression of CSF1 in synovium
  - Frequently due to genetic translocation: t(1;2) CSF1:COL6A3
  - Propagation of neoplastic clone (autocrine)
  - Reactive inflammatory process with proliferation & recruitment of CSF1R-expressing cells: macrophages, giant cells, osteoclasts
Pigmented Villonodular Synovitis (PVNS)

Gross features:
- Collagen deposition
- Subchondral bone erosions
- Repeat hemorrhage

Clinical features:
- Usually single joint:
  - Swelling
  - Pain
  - ↓ range of motion
  - Stiffness
  - Functional impairment
  - Narcotic use
  - Disability

- No FDA approved treatment (19% ORR with imatinib\(^1\))
- Surgery is standard of care (e.g., joint replacement, amputation)
- Diffuse variant associated with high recurrence rate after surgery

Presented by: William D. Tap, MD

\(^1\) Cassier et al., Cancer. 2012; 118(6)1649-55
PLX3397 is a potent and specific inhibitor of Colony-Stimulating Factor 1 Receptor (CSF1R) kinase activity.

**Kinome Selectivity Comparison**

**Imatinib**

- **IC$_{50}$ = 49 nM**

**PLX3397**

- **IC$_{50}$ = 17 nM**
Can we help patients (PVNS) with a highly targeted therapy (PLX3397) that blocks the CSF1R pathway in this clonal neoplastic process frequently initiated by a single genetic event?
Study Goals

• Evaluate early efficacy signals – clinical and radiographic

• Investigate potential ways to accurately measure efficacy signals

• Understand application of a selective inhibitor in a neoplastic disease that is not necessarily a cancer
Study Design

• Single arm, multi-center, signal finding study

• Expansion cohort (8 sites) of PLX3397 first-in-human solid tumor study
  – Phase 1 dose escalation complete: RP2D 1000 mg daily (600 q am; 400 q pm)

• Histologically confirmed PVNS
  – Demonstrated progression in last 12 months
  – Measurable disease: inoperable, or resectable but requiring mutilating surgery

• Remain on treatment until disease progression or intolerability

Presented by: William D. Tap, MD
Efficacy Assessments

- Imaging at baseline & every ~2 months
  - Local site reading (RECIST 1.1)
  - Independent central reading (Tumor Volume Score)

- Physician assessment of change in pain, stiffness, and daily activities (retrospective) – parallel development of a PVNS-specific PRO
Tumor Volume Score (TVS)

- Novel scoring method developed for PVNS
  - Linear measurements like RECIST suboptimally quantify tumor mass due to highly irregular shape

- Calculates tumor volume as a percentage of the entire synovium, using synovial cavity for standardization
  - Modification of the Whole Organ MRI score\(^1\) commonly used in arthritis

- Partial Response (PR): ≥50% ↓ TVS vs baseline
- Progressive Disease (PD): ≥30% ↑ TVS vs nadir

- Central read: 2 independent musculoskeletal radiologists blinded to time point

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\(^1\) Peterfy et al. Osteoarthritis and Cartilage. 2004; 12(3):177-190

Presented by: William D. Tap, MD
Patient Disposition

Safety Population
Dosed (n = 23)

Efficacy Population
(n = 21)

No post dose efficacy assessment (n = 2)
- Noncompliance (1)
- Patient decision (1)

Scan unevaluable (n = 1)
Time of data censor

MRI unevaluable (n = 7)
- Unevaluable tumor (1)
- No post-dose MRI (1)
- Metallic artifact (4)
- Metastatic dz only (1)

Duration of Treatment
(n = 21)

RECIST 1.1
(local reading)
(n = 20)

Tumor Volume Score
(masked central reading)
(n = 14)

Physician Clinical Assessment
(n = 18)

Presented by: William D. Tap, MD
### Patient Characteristics: Safety Population (n=23)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>N = 23</th>
</tr>
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<tbody>
<tr>
<td>Sex, Female</td>
<td>13 [57%]</td>
</tr>
<tr>
<td>Age, mean (yrs)</td>
<td>46 [range 22-80]</td>
</tr>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>19 [83%]</td>
</tr>
<tr>
<td>African-American</td>
<td>3 [13%]</td>
</tr>
<tr>
<td>Asian</td>
<td>1 [4%]</td>
</tr>
<tr>
<td>Lesion location</td>
<td></td>
</tr>
<tr>
<td>Knee</td>
<td>15 [65%]</td>
</tr>
<tr>
<td>Foot</td>
<td>2 [9%]</td>
</tr>
<tr>
<td>Ankle</td>
<td>2 [9%]</td>
</tr>
<tr>
<td>Hip</td>
<td>2 [9%]</td>
</tr>
<tr>
<td>Elbow</td>
<td>1 [4%]</td>
</tr>
<tr>
<td>Forearm</td>
<td>1 [4%]</td>
</tr>
<tr>
<td>Metastatic</td>
<td>1 [4%]</td>
</tr>
<tr>
<td>BMI, mean (kg/m²)</td>
<td>28 [range 20-45]</td>
</tr>
<tr>
<td>Previous surgery</td>
<td>18</td>
</tr>
<tr>
<td>Previous TKI</td>
<td>4</td>
</tr>
<tr>
<td>Previous radiation</td>
<td>2</td>
</tr>
</tbody>
</table>
Safety: PVNS Expansion Cohort AEs

n = 23 Safety Population

<table>
<thead>
<tr>
<th>Common AEs</th>
<th>Common AEs (&gt;25%)</th>
<th>Treatment-related AEs</th>
<th>≥ Grade 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>18 (78%)</td>
<td>15 (65%)</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Hair colour changes</td>
<td>17 (74%)</td>
<td>17 (74%)</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>15 (65%)</td>
<td>11 (48%)</td>
<td>0</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>9 (39%)</td>
<td>1 (4%)</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>7 (30%)</td>
<td>5 (22%)</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>7 (30%)</td>
<td>5 (22%)</td>
<td>0</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>6 (26%)</td>
<td>5 (22%)</td>
<td>0</td>
</tr>
<tr>
<td>Dizziness</td>
<td>6 (26%)</td>
<td>1 (4%)</td>
<td></td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>6 (26%)</td>
<td>6 (26%)</td>
<td>0</td>
</tr>
<tr>
<td>Periorbital edema</td>
<td>6 (26%)</td>
<td>6 (26%)</td>
<td>0</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>6 (26%)</td>
<td>3 (13%)</td>
<td>0</td>
</tr>
<tr>
<td>Condition</td>
<td>Count</td>
<td>Percentage</td>
<td></td>
</tr>
<tr>
<td>----------------------------</td>
<td>-------</td>
<td>------------</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>1 pt</td>
<td>(4%)</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1 pt</td>
<td>(4%)</td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>1 pt</td>
<td>(4%)</td>
<td></td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>2 pt</td>
<td>(9%)</td>
<td></td>
</tr>
<tr>
<td>Elevated AST/ALT</td>
<td>2 pt</td>
<td>(9%)</td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>1 pt</td>
<td>(4%)</td>
<td></td>
</tr>
</tbody>
</table>
Duration of Treatment (DOT), April 2014 data cutoff: Median 256 days (range 21-585 days)

Subject ID
n = 21

n= 20
ORR evaluable by RECIST local read:
60% PR (12/20)
35% SD (7/20)
5% PD (1/20)

Median PFS: not reached
14 patients evaluable with TVS

**Safety Population**
Dosed (N = 23)

- Physician Clinical Assessment (n = 18)
- Tumor Volume Score (masked central reading) (n = 14)
- RECIST 1.1 (local reading) (n = 20)

- MRI unevaluable (n = 7)
  - Unevaluable tumor (1)
  - No post-dose MRI (1)
  - Metallic artifact (4)
  - Metastatic dz only (1)

- No post dose efficacy assessment (n = 2)
  - Noncompliance (1)
  - Patient decision (1)

**Efficacy Population**
Post-dose MRI or clinical assessment (n = 21)

- Scan unevaluable (n = 1)
  - Time of data censor

- Tumor Volume Score (masked central reading) (n = 14)

- Duration of Treatment (n = 21)

- RECIST 1.1 (local reading) (n = 20)

- Physician Clinical Assessment (n = 18)

Presented by: William D. Tap, MD
Efficacy Evaluation by Tumor Volume Score (TVS)
Rapid & Sustained Tumor Size Reductions in Most Cases
Efficacy Evaluation by Tumor Volume Score (TVS)
79% overall response rate

- 11/14 evaluable patients with PR (≥ 50% reduction in TVS)
- 3/14 with SD

61% mean tumor size reduction
Example of Objective Response: Patient #205

85% response by Tumor Volume Score

Baseline 2 months 4 months

Presented by: William D. Tap, MD
Example of PET Response: Patient #205

2 weeks on PLX3397

SUV 21.7

SUV 6.4
# PVNS Patients on PLX3397: Marked Clinical Improvement

## Physician Assessment of Clinical Change (baseline to most recent visit)

<table>
<thead>
<tr>
<th>N =18</th>
<th>Marked worsening</th>
<th>Moderate worsening</th>
<th>Minimal to mild worsening</th>
<th>Stable, no noticeable change</th>
<th>Minimal to mild improvement</th>
<th>Moderate improvement</th>
<th>Marked improvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAIN</td>
<td>0</td>
<td>1 (6%)</td>
<td>1 (6%)</td>
<td>0</td>
<td>3 (17%)</td>
<td>6 (33%)</td>
<td>7 (39%)</td>
</tr>
<tr>
<td>STIFFNESS</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>4 (22%)</td>
<td>3 (17%)</td>
<td>3 (17%)</td>
<td>8 (44%)</td>
</tr>
<tr>
<td>DAILY ACTIVITIES</td>
<td>0</td>
<td>0</td>
<td>1 (6%)</td>
<td>2 (11%)</td>
<td>3 (17%)</td>
<td>4 (22%)</td>
<td>8 (44%)</td>
</tr>
</tbody>
</table>

*retrospective

Example: Patient #209

---

2 months on PLX3397

Presented by: William D. Tap, MD
Example of Clinical Benefit: Patient #205

Walking with cane
Unable to straighten knee
Narcotics for pain
Unable to work
Amputation considered

4 months on PLX3397

Walking unassisted
Improved range of motion
Off narcotics
Back to work

Presented by: William D. Tap, MD
Conclusions

• PLX3397 demonstrated encouraging activity in patients with advanced/diffuse PVNS in this Phase 1 expansion study
  – 79% overall response rate by Tumor Volume Score (60% by RECIST)
  – Early, dramatic, and sustained reduction in tumor mass
  – Associated with substantial clinical benefit (physician assessment)

• In this clonal neoplastic disease frequently initiated by a single genetic event, patients can benefit significantly when the CSF1R signaling pathway is blocked by PLX3397

• PLX3397 is well tolerated with long term dosing (>580 days), with manageable side effects

• PLX3397 is a very promising novel treatment for patients with advanced PVNS

• A Phase 3 study is planned
THANK YOU!