Discovery of vimseltinib (DCC-3014), a highly selective switch-control inhibitor of CSF1R kinase

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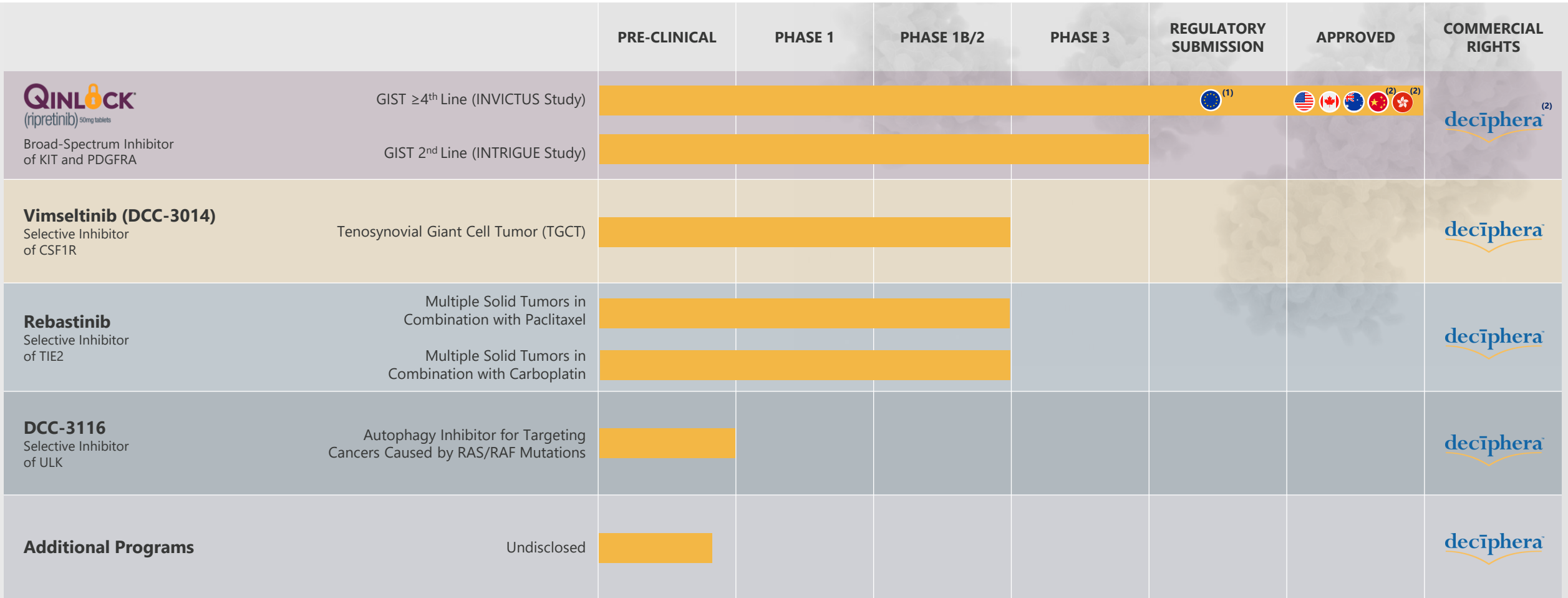
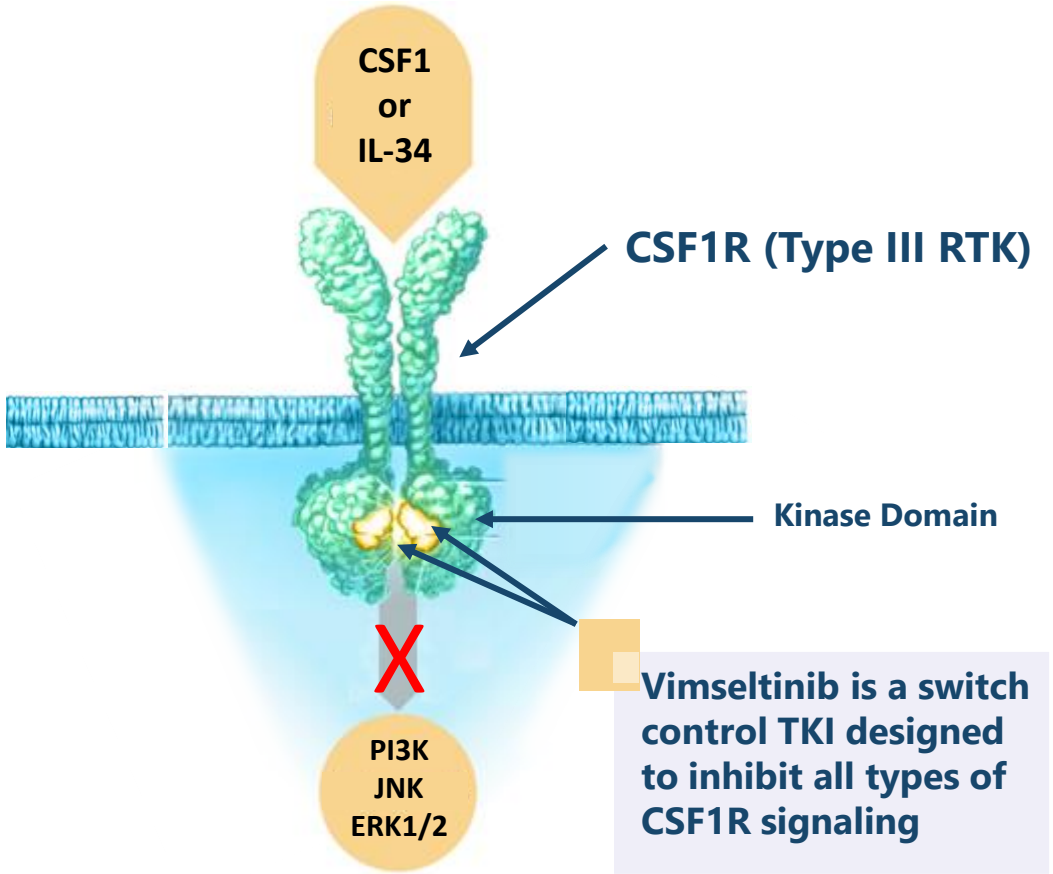
Robust Pipeline of Switch-Control Kinase Inhibitors



Notes: Current as of March 31, 2021; CSF1R=colony-stimulating factor 1 receptor; GIST=gastrointestinal stromal tumor; KIT=KIT proto-oncogene receptor tyrosine kinase; PDGFRA=platelet-derived growth factor receptor α; RAS=rat sarcoma gene; TIE2=TEK tyrosine kinase; TGCT=tenosynovial giant cell tumor; ULK=unc-51-like kinase; (1) Submitted and received validation of a Marketing Authorisation Application for QINLOCK in 4th line GIST by the European Medicines Agency; (2) Exclusive development and commercialization license with Zai Lab in Greater China for QINLOCK.

Vimseltinib: A Highly Potent and Selective CSF1R Inhibitor

Colony Stimulating Factor 1 Receptor (CSF1R, c-FMS)



- Colony-stimulating factor 1 receptor (CSF1R, c-FMS) is a type III receptor tyrosine kinase (RTK). Other members of the type III RTK family include FLT3, KIT, PDGFRα and PDGFRβ.
- Colony-stimulating factor 1 (CSF1) and interleukin-34 (IL-34) have been identified as the endogenous ligands for CSF1R.
- CSF1R is predominantly expressed in cells that come from a myeloid lineage and lymphoid tissue
- CSF1R-mediated signaling is crucial for the survival, function, proliferation, and differentiation of myeloid lineage cells (i.e., monocytes, macrophages, microglia, and osteoclasts). CSF1R signals through the PI3K, JNK and ERK1/2 pathways.
- Aberrant CSF1R signaling has been identified in several different disease states (e.g., cancer, benign tumors, arthritis, inflammatory disorders, Alzheimer's Disease, and Parkinson's Disease)

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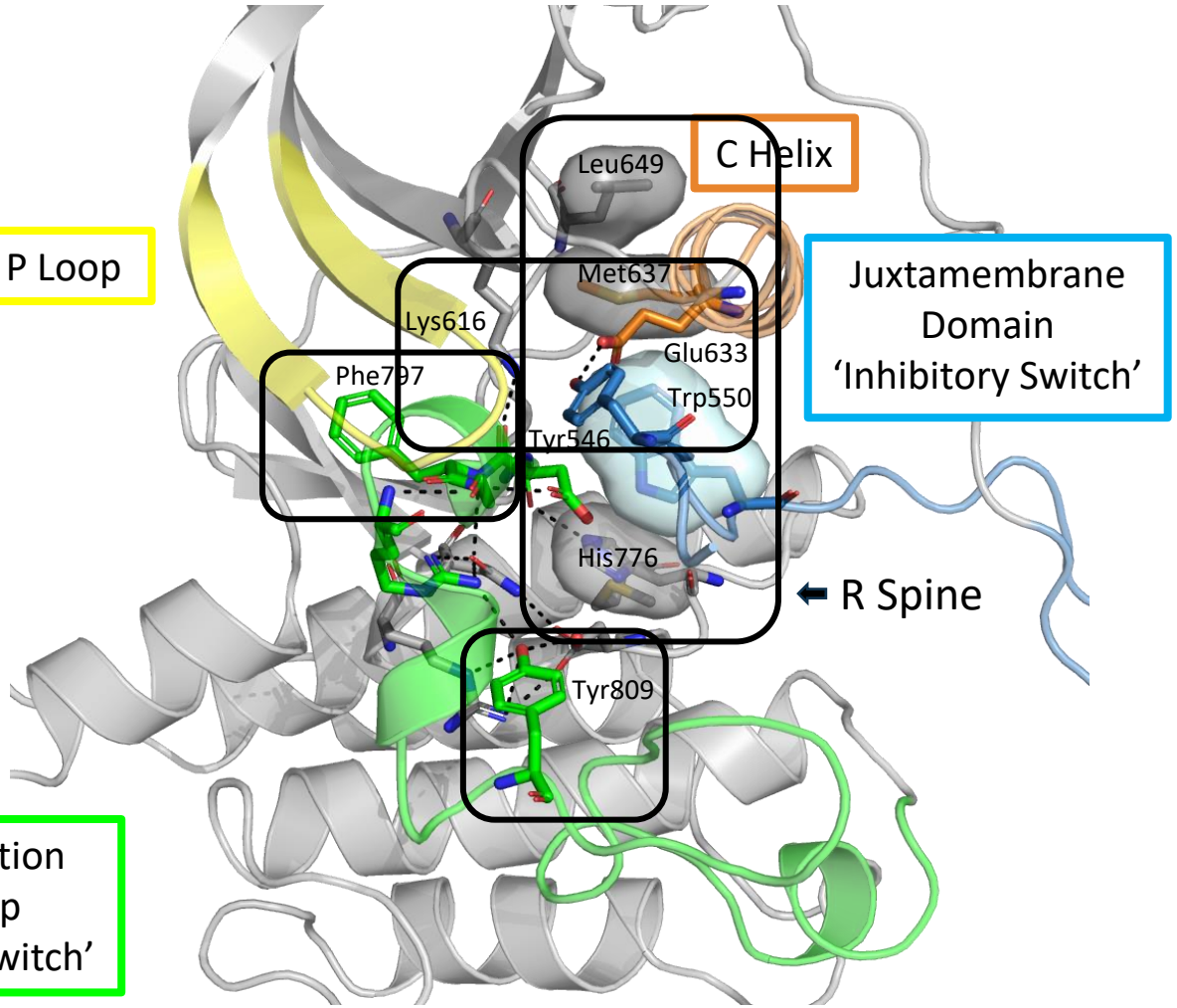
X-Ray Crystal Structure of Autoinhibited CSF1R: PDB 2OGV



- CSF1R shown in the DFG out 'switched off' conformation. Phe797 blocks the approach of ATP to the hinge.
- The R spine is a series of four hydrophobic amino acids that stabilize a kinase either in its activated or autoinhibited conformation. Trp550 occupies the third position of the 'R' spine in the 'off' state and Phe797 occupies this position in the 'on' state.
- The conserved salt bridge between Lys616 and Glu633, necessary for catalytic activity, is broken. Tyr546 has formed a H-bond with Glu633 and Lys616 has formed a H-Bond with carbonyl of Asp796 of the DFG motif.
- Tyr809 acts as a pseudosubstrate blocking the approach of protein substrate. Tyr809 forms the base of a H-Bond network that stabilizes the catalytic machinery of CSF1R in its 'off' state. This H-bond network starts at Lys616 and ends at Tyr809.

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Analysis of CSF1R Kinase: Unique Kinase Switch Pocket For Honing Selectivity

Two unique areas of CSF1R were identified that could impart kinase selectivity: Gly 795 and Met 637.

- CSF1R has a small Glycine residue before the DFG ***Switch*** whereas KIT, PDGFRα/β and FLT3 have a larger cysteine residue.

-X-DFG- Motif in KIT, PDGFRa/B, FLT3		
CSF1R	F797	VAKIGDFGLAR
KIT	F805	ITKICDFGLAR
PDGFRα	F831	IVKICDFGLAR
PDGFRβ	F837	LVKICDFGLAR
FLT3	F823	VVKICDFGLAR

- The C-Helix of CSF1R contains a distinctive methionine (Met 637) in the ***Switch Pocket***.
- In the human kinome, only 11 out of 491 kinases contain this combination of AAs.

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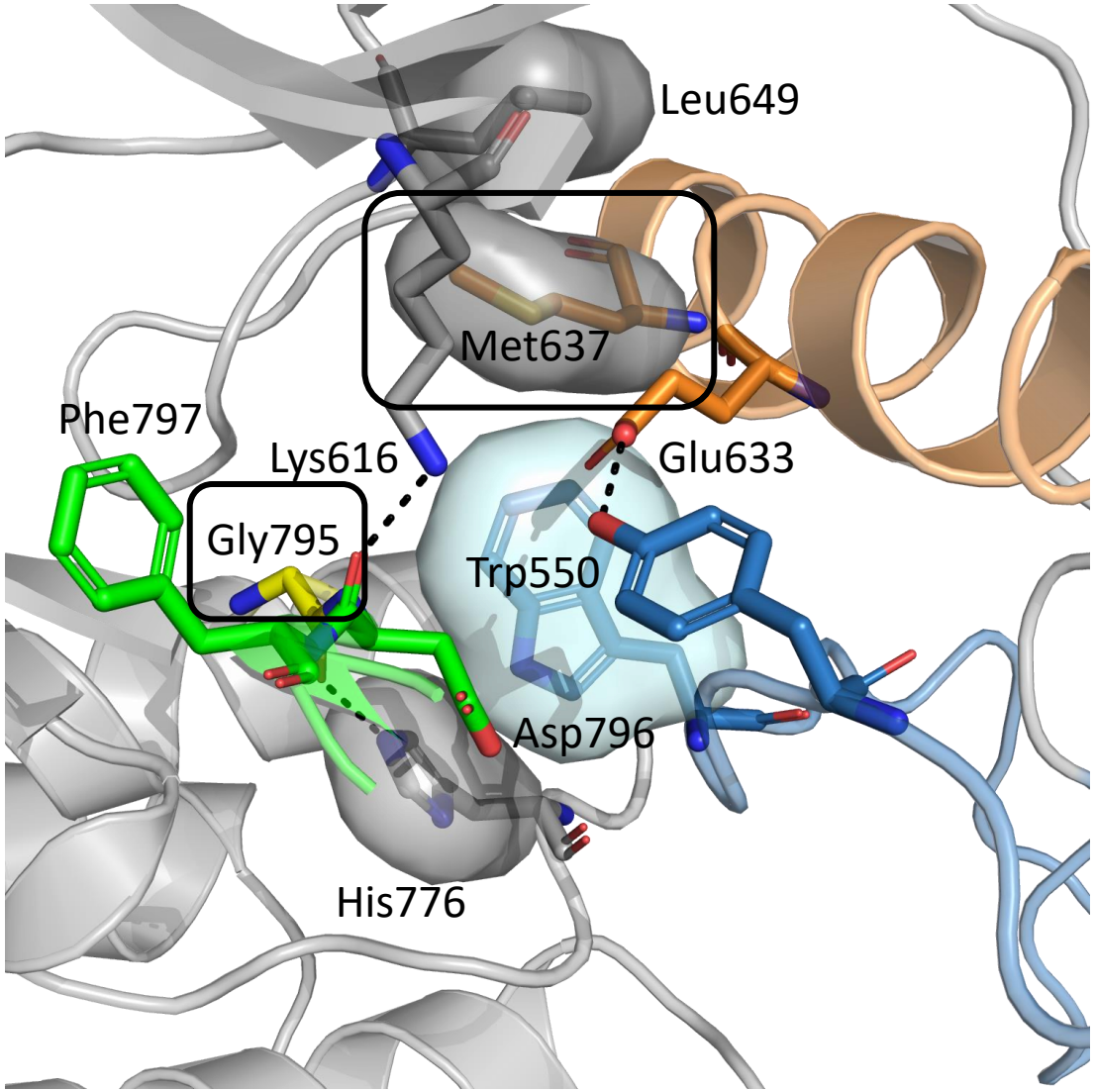
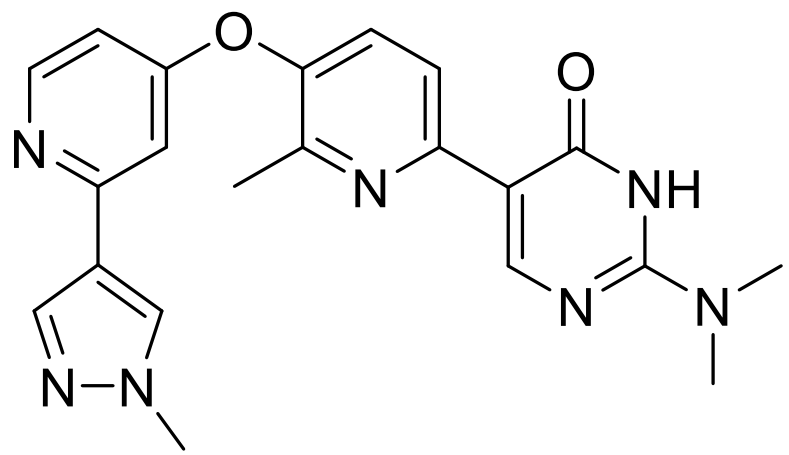
X-Ray Crystal Structure of Autoinhibited CSF1R: 2OGV



Dihydropyrimidones as Selective CSF1R Inhibitors



1

Kinase	IC_{50} (nM)
CSF1R	97
KIT	>3300
FLT3	>3300
PDGFRα/β	1600/>3300
VEGFR2	>3300
MET	>3300

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- Compound **1** showed an interesting profile in terms of kinase selectivity

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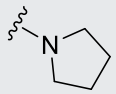
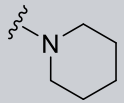
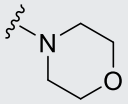
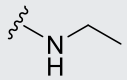
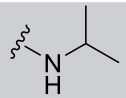
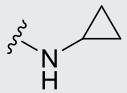
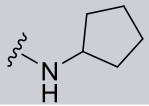
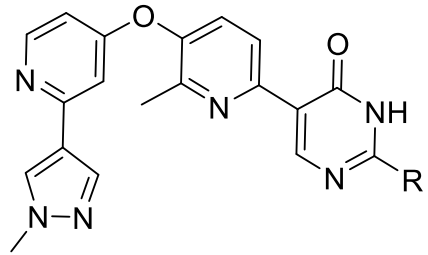
Evaluation of the 2-Amino Substituent on the Pyrimidinone

Compound	R	CSF1R[a]	KIT[a]	PDGFRα/β[a]	FLT3[a]	M-NFS-60 CP[a,b]
1		97	>3300	1600 / >3300	>3300	716
2		14	>3300	>3300 / >3300	2200	56
3		18	>3300	843 / >3300	>3300	30
4		134	>3300	>3300 / >3300	>3300	494
5		107	257	>3300 / >3300	2500	1300
6		13	142	>3300 / >3300	>3300	45
7		1.6	322	1600 / >3300	>3300	3.1
8		3.6	>3300	1300 / >3300	>3300	55
9		10	990	517 / 559	>3300	2.6

[a]All IC50s are reported in nM. [b]M-NFS-60 cellular proliferation is driven by CSF1R.



- Secondary and tertiary 2-amino substituents were tolerated with secondary substituents being more potent.
- Small substituents (e.g., N-Methyl or N,N-Dimethyl) had decreased CSF1R activity
- Larger substituents begin to lose their selectivity

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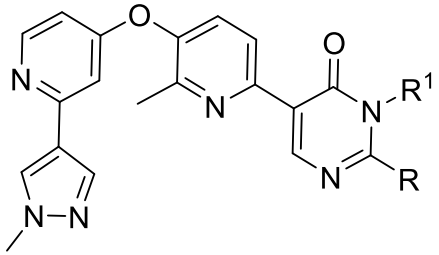
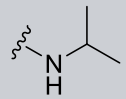
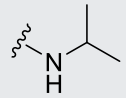
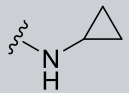
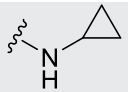
Evaluation of Addition of an N-Methyl Group at the 3-Position on the Pyrimidinone



Compound	R	R^1	CSF1R[a]	KIT[a]	PDGFRα/β[a]	FLT3[a]	M-NFS-60 CP[a,b]	Osteoclast Differentiation[a,c]
7		H	1.6	322	1600 / >3300	>3300	3.1	13
11		Me	3.7	476	436 / 2300	>3300	18	9.3
8		H	3.6	>3300	1300 / >3300	>3300	55	16
13		Me	2.0	1700	>3300 / 100	>3300	18	7.4

[a]All IC50s are reported in nM. [b]M-NFS-60 cellular proliferation is driven by CSF1R. [c]Osteoclast precursor cells are incubated with CSF1 and RANKL in the presence of compound or DMSO control for 7-10 days. Tartrate-resistant alkaline phosphatase activity is measured in the supernatant of cells as a readout of osteoclast differentiation.

- Addition of an N-Methyl Moiety onto the Pyrimidinone was tolerated. Biochemical and cellular activity was very similar to the parent compound.

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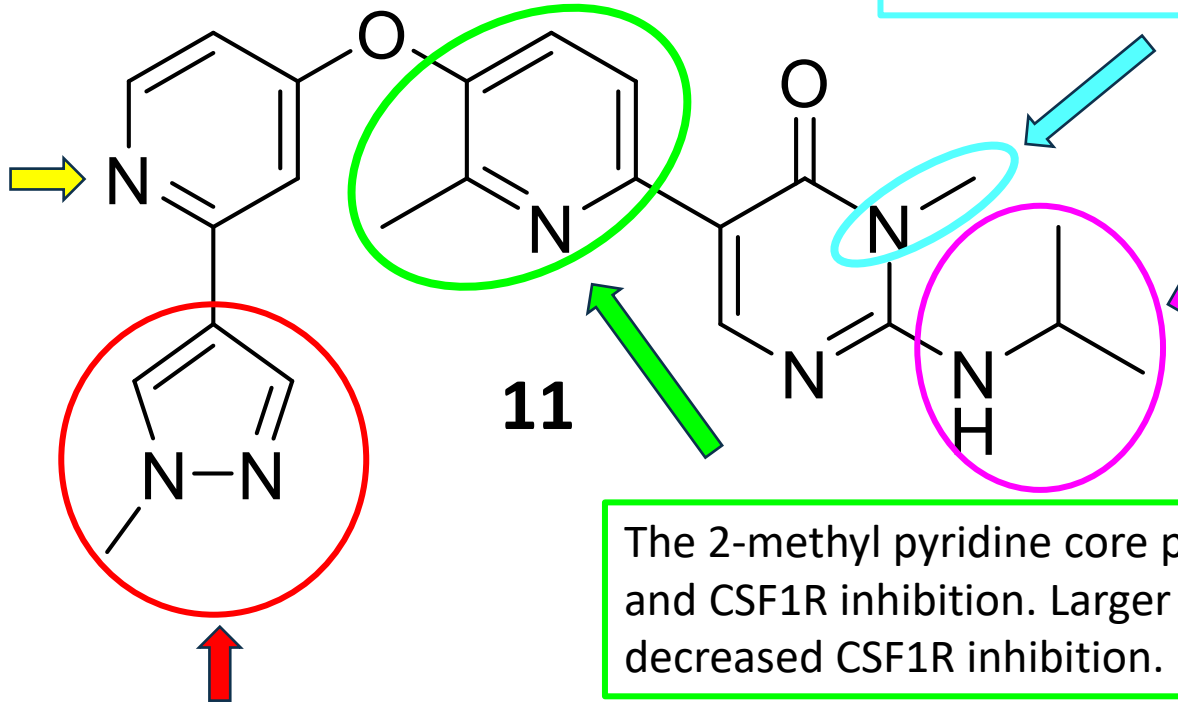
SAR Summary for our Pyrimidinone Series

Addition of an N-Me onto the pyrimidinone did not substantially change biochemical or in vivo activity. Capping the NH group reduces the total NH count to 1.

The Pyridine Nitrogen forms a H-Bond with the NH of Cys666 of the hinge



11

A variety of primary and secondary 2-amino-substituents were tolerated. The i-propylamine group imparted both biochemical and cellular potency. Larger substituents start to lose selectivity.

The 2-methyl pyridine core provides both kinase selectivity and CSF1R inhibition. Larger substituents at the 2-position decreased CSF1R inhibition.

The *N*-Methyl substituent of the pyrazole appears to form a C-H hydrogen bond with the carbonyl of Cys666 at the hinge.

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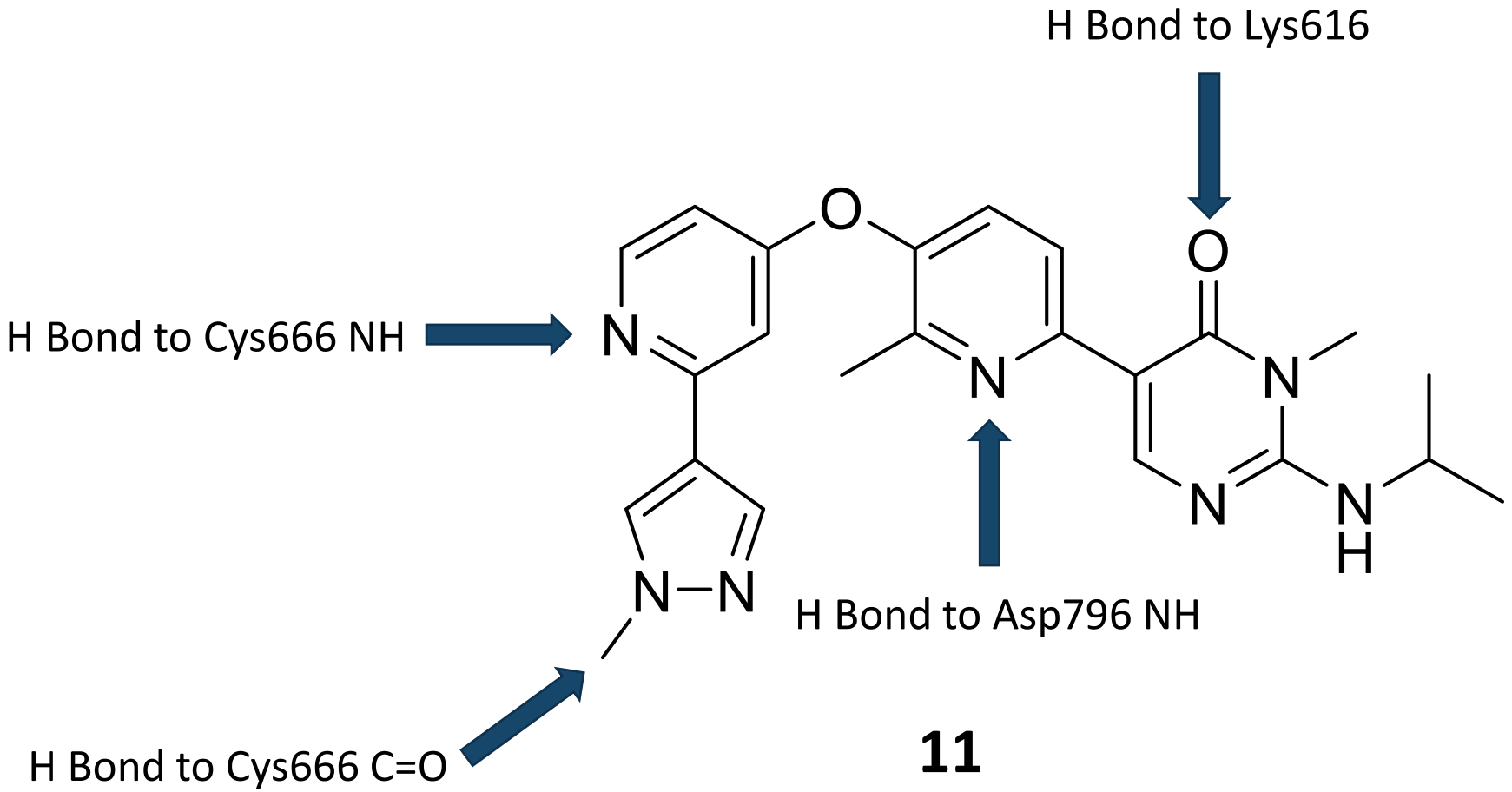
X-Ray Crystallography: Summary of Key Hydrogen Bonds for our Pyrimidinones



11

Four key hydrogen bonds are formed between compound **11** and CSF1R

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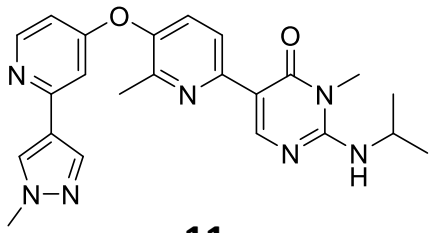
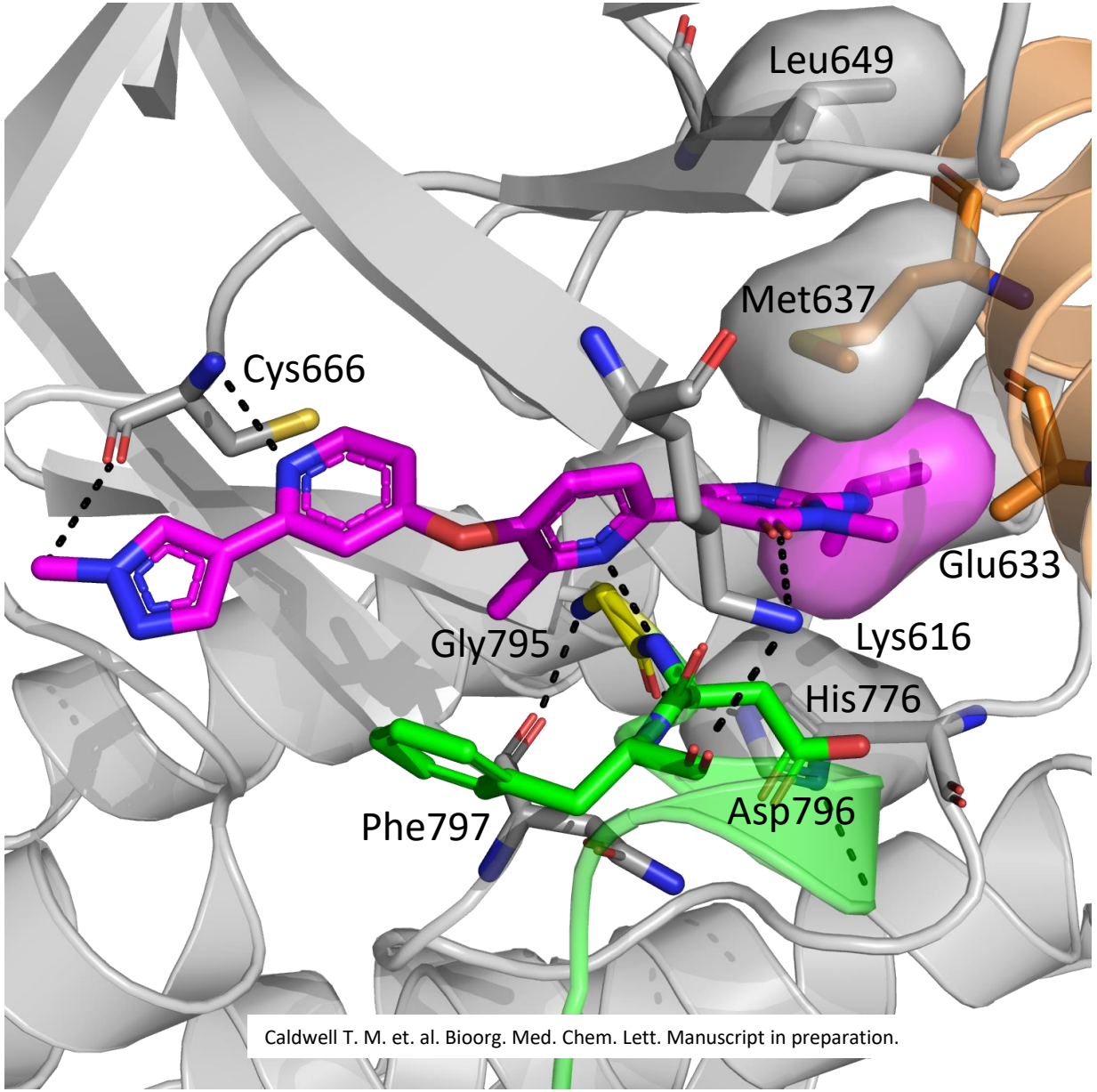
Compound **11** Binds Selectively into the Unique Switch Pocket region of CSF1R



11

- Cys666 forms a bi-dentate H-bond interaction with **11** anchoring the inhibitor to the kinase
- Asp796 NH forms a H-bond with the trisubstituted pyridine nitrogen
- The carbonyl of **11** forms a H-Bond with Lys616 of the conserved salt bridge. The salt bridge necessary for catalytic activity is broken (no density for Glu633).
- Compound **11** binds in a DFG out 'switched off' conformation
- The iPr moiety of Compound **11** displaces Phe797 in the regulatory 'R' spine stabilizing the 'switched off' conformation of CSF1R
- The 2-methyl group of the trisubstituted pyridine occupies the glycine selectivity pocket (Gly795) and Met637 interacts with the pyrimidinone ring.



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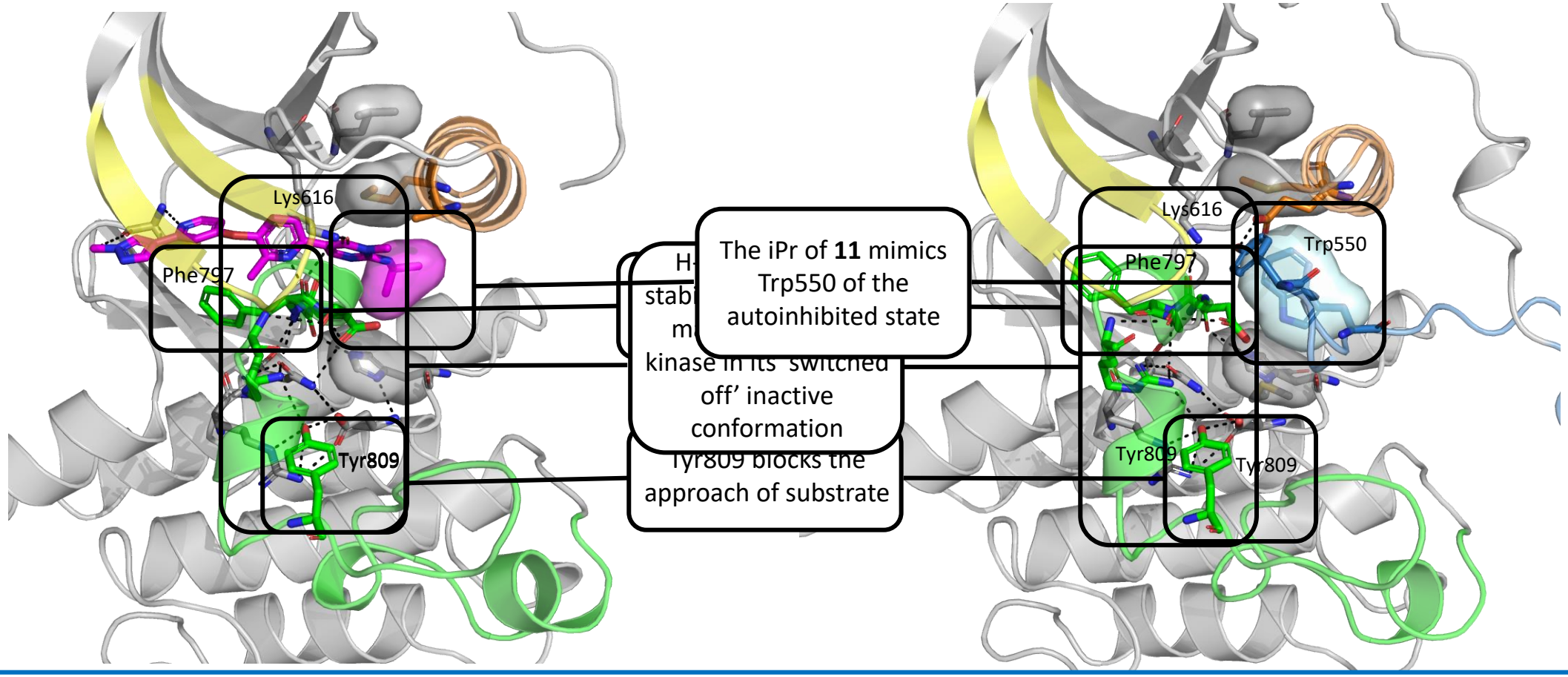
Comparison of **11** and Autoinhibited CSF1R X-Ray Structures

Compound 11 bound to CSF1R

Autoinhibited CSF1R: 2OGV



Compound **11** causes CSF1R to adopt a conformation that mimics the autoinhibited 'switched off' state of CSF1R

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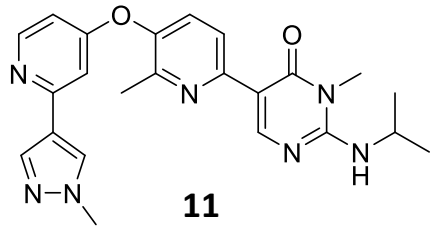
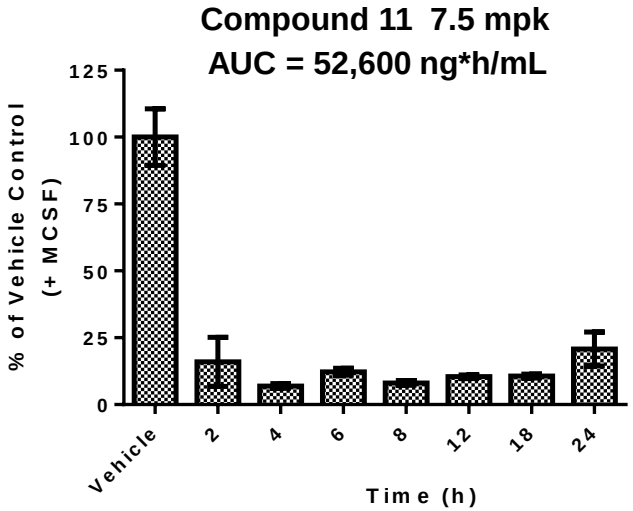
Compound **11** Potently and Durably Inhibits CSF1R in a cFOS PK/PD model



11

	% Inhibition of FOS expression (+ CSF1)						
Compound 11	**2 h**	**4 h**	**6 h**	**8 h**	**12 h**	**18 h**	**24 h**
30 mpk	95%	97%	97%	98%	95%	92%	90%
Conc (ng/mL)	7939	8340	9354	7732	8242	8274	4794
15 mpk	94%	80%	96%	93%	96%	90%	86%
Conc (ng/mL)	8638	8075	9356	7589	4588	2189	1363
7.5 mpk	84%	93%	88%	92%	90%	89%	79%
Conc (ng/mL)	4447	4262	2361	3029	1974	1309	1379
3.75 mpk	69%	68%	87%	77%	75%	82%	77%
Conc (ng/mL)	1689	1612	2783	1795	765	773	1111



Compound **11** was dosed QD PO for 6 days and on day six at specified timepoints CSF1 was administered by injection. CSF1R inhibition was determined by monitoring cFOS mRNA modulation in mouse spleens.

- Over 30 compounds were evaluated in our CSF1R cFOS PK/PD model (various classes of compounds). Almost all compounds evaluated had good oral exposure in mice.
- Compound **11** displayed superior target coverage in our PK/PD model.

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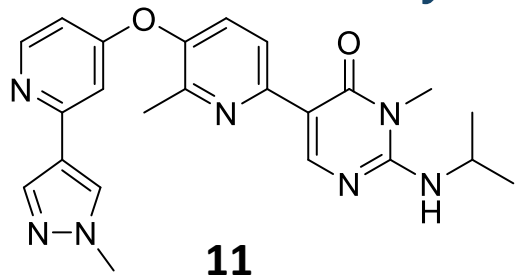
Smith, B.D. *et. al.* Manuscript in Preparation.

Pharmaceutical Profile: Optimization of Physicochemical, ADME and PK Properties



11

MWT = 431
mlogP = 3.2
TPSA = 98

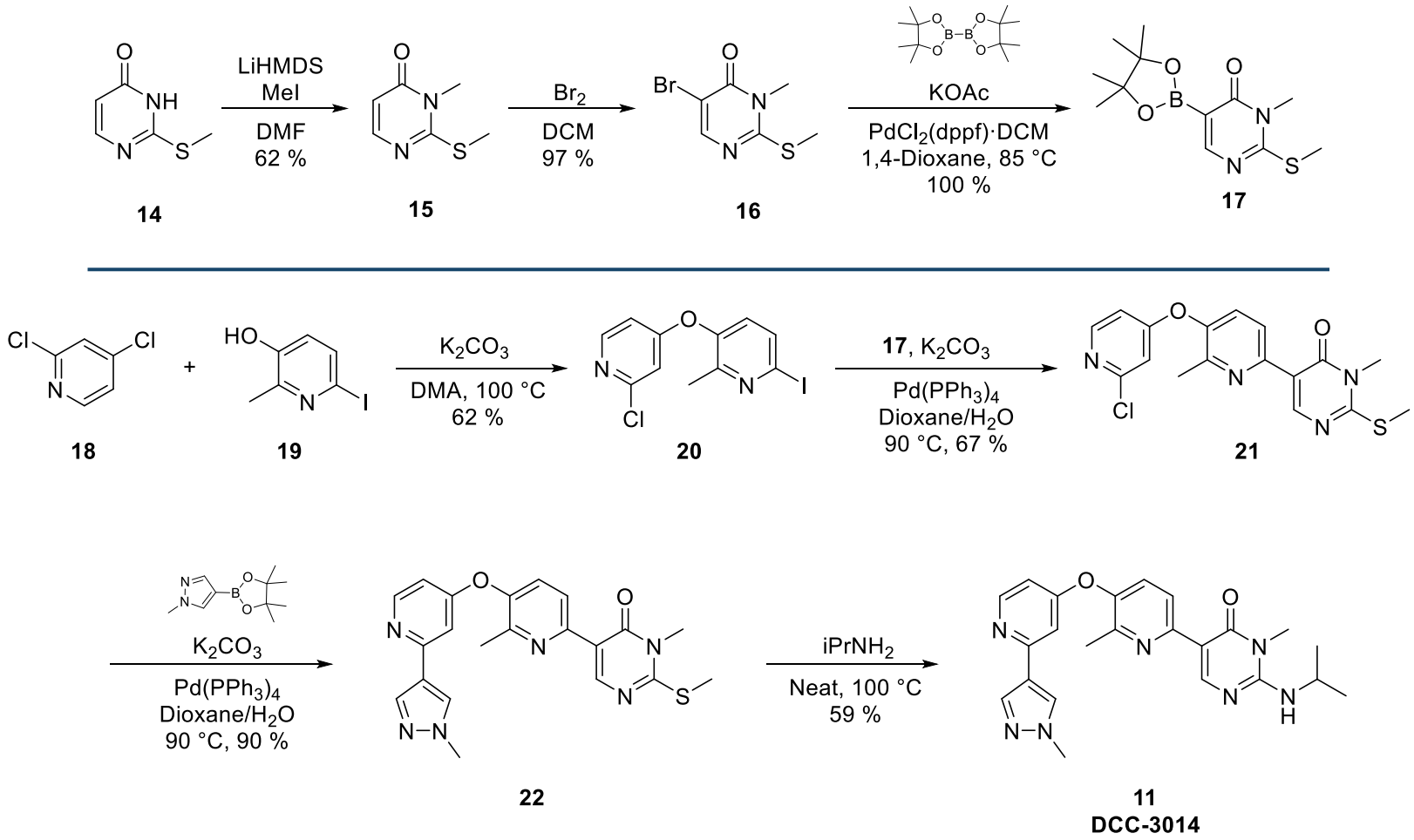
Assay	Result
Solubility at pH 2.0 (μM) Solubility Simulated Int. Fluid (μM)	3325 267
Permeability Caco2 A-B (1 x10^{-6} cm/s), efflux ratio	1.6, 3.3
hERG IC_{20} (μM)	20
Plasma Protein Binding % Bound (mouse, rat, dog, human)	97.4, 99.4, 96.7, 96.1
Microsomal Stability % remaining at 60 min (mouse, rat, dog, human)	97, 95, 95, 98
Human CYP Inhibition 3A4, 2C19, 2D6, 2C9, 1A2 (IC_{50} values, μM)	50, 50, 50, 16, 50

Rat and Dog Pharmacokinetics	
Parameters	C_{max} (nM), $AUC_{(0\text{-}24h)}$ (nM-H), T_{max} (h), Cl (L/h/kg), V_d (L/kg), $t_{1/2}$ (h), %F
Rat Crossover[a]	3735, 38009, 2.67, 0.03, 0.69, 19.8, 76
Dog Crossover[a,b]	1007, 5432, 1.67, 0.15, 1.33, 10.6, 33.3

[a] The oral vehicle was 0.4% HPMC (10 mpk) and the IV vehicle was 20% captisol in normal saline pH 2 (1 mpk). [b]Emesis was observed in these animals and may have contributed to the lower observed bioavailability (%F).

- Based upon its performance in our PK/PD model and its optimized ADME and PK properties, compound **11** was nominated as our preclinical candidate and renamed **DCC-3014**.

Synthesis of DCC-3014



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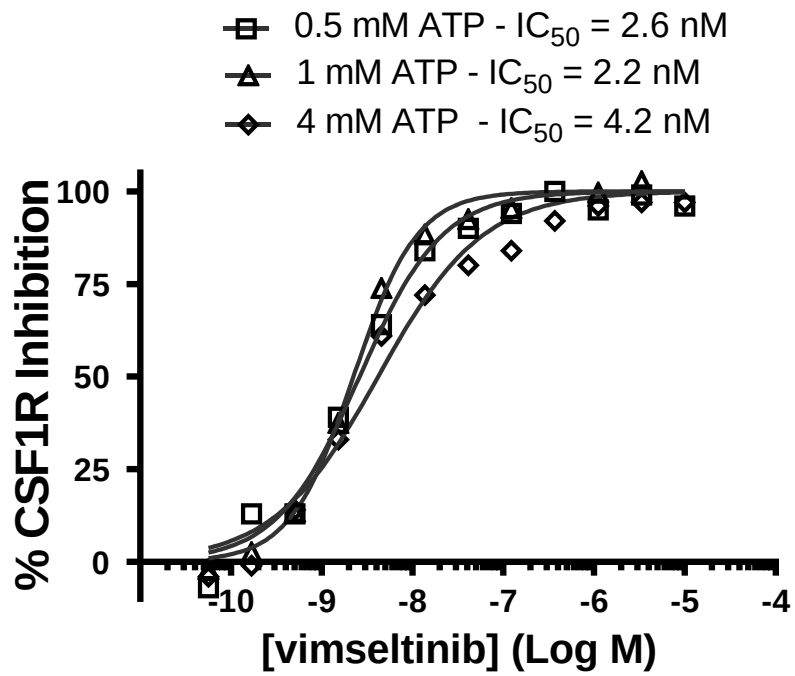
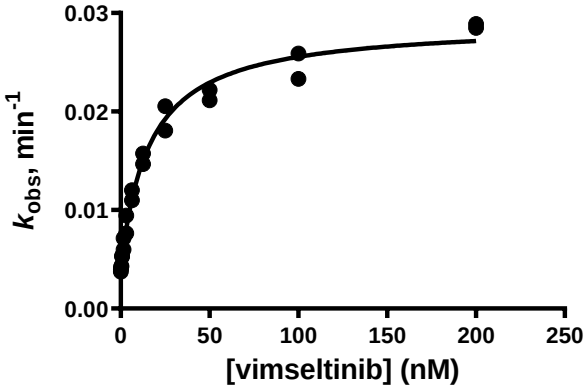
DCC-3014: ATP Resilience and Long off rate

CSF1R kinase inhibition by DCC-3014 at 0.5, 1 and 4 mM ATP



- For DCC-3014, CSF1R inhibition IC_{50} values were unaffected by ATP concentrations. Cellular concentrations of ATP (1-4 mM) can compete with classical ATP-competitive inhibitors for kinase binding.

Rapid dilution determination of CSF1R off-rate



vimseltinib/CSF1R	min^{-1}	$t_{1/2}$, min
k_{off} (off rate)	0.0041	170
k_{on} (on rate)	0.025	28
	nM	
K_d	2.3 nM	

Curve-fit of k_{obs} data for vimseltinib using the equation $k_{obs} = k_4 + k_3 [I/(K_i + I)]$.

- DCC-3014 was found to have an off-rate of 0.0041 min^{-1}, which corresponds to a half-life of 170 min. The calculated dissociation constant (K_d = 2.3 nM) was in agreement with data from CSF1R binding assays.

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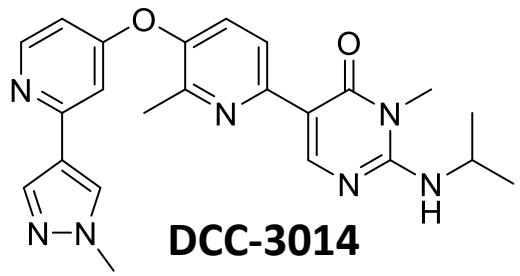
- **DCC-3014 displayed both ATP Resilience and a long off-rate.**

Smith, B.D. *et. al.* Manuscript in Preparation.

DCC-3014: A Highly Selective and Potent CSF1R Inhibitor

DCC-3014 Summary

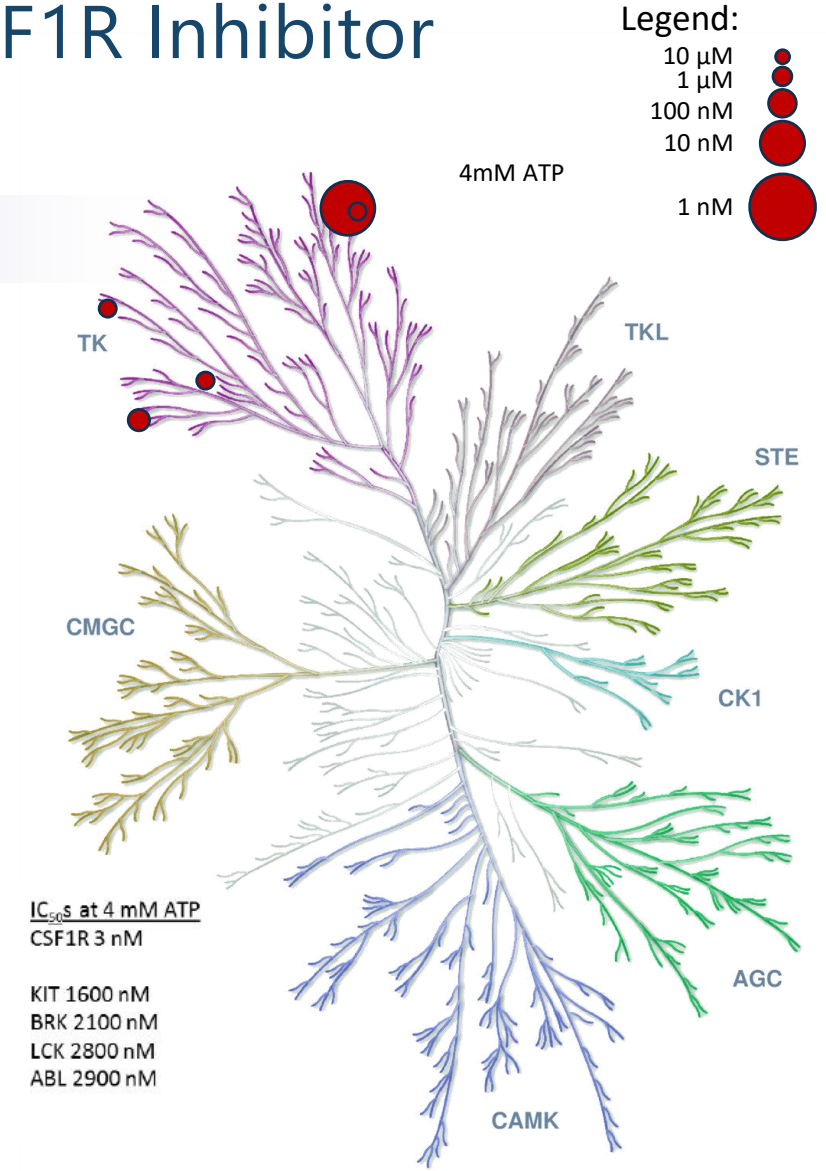


Highly selective, potent, small molecule CSF1R inhibitor

>500-Fold selectivity over closest kinases

IC50's (nM)	CSF1R	KIT	FLT3	PDGFRa	PDGFRb
DCC-3014	3	1600	>3000	>3000	>3000

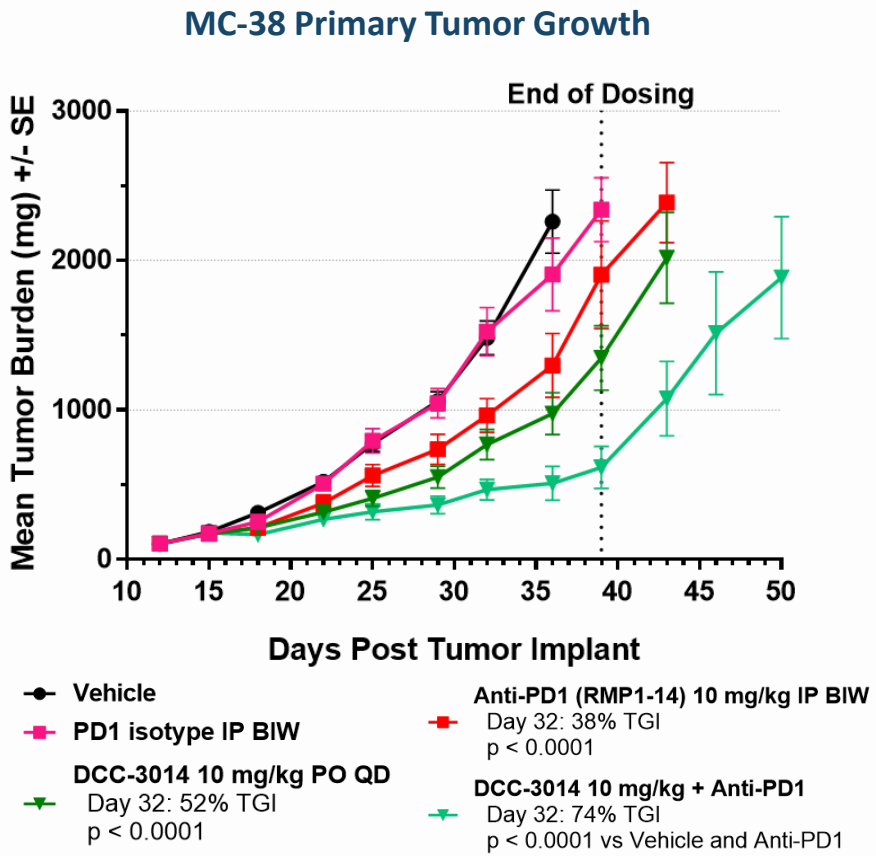
IC_{50}s were determined at 4 mM ATP



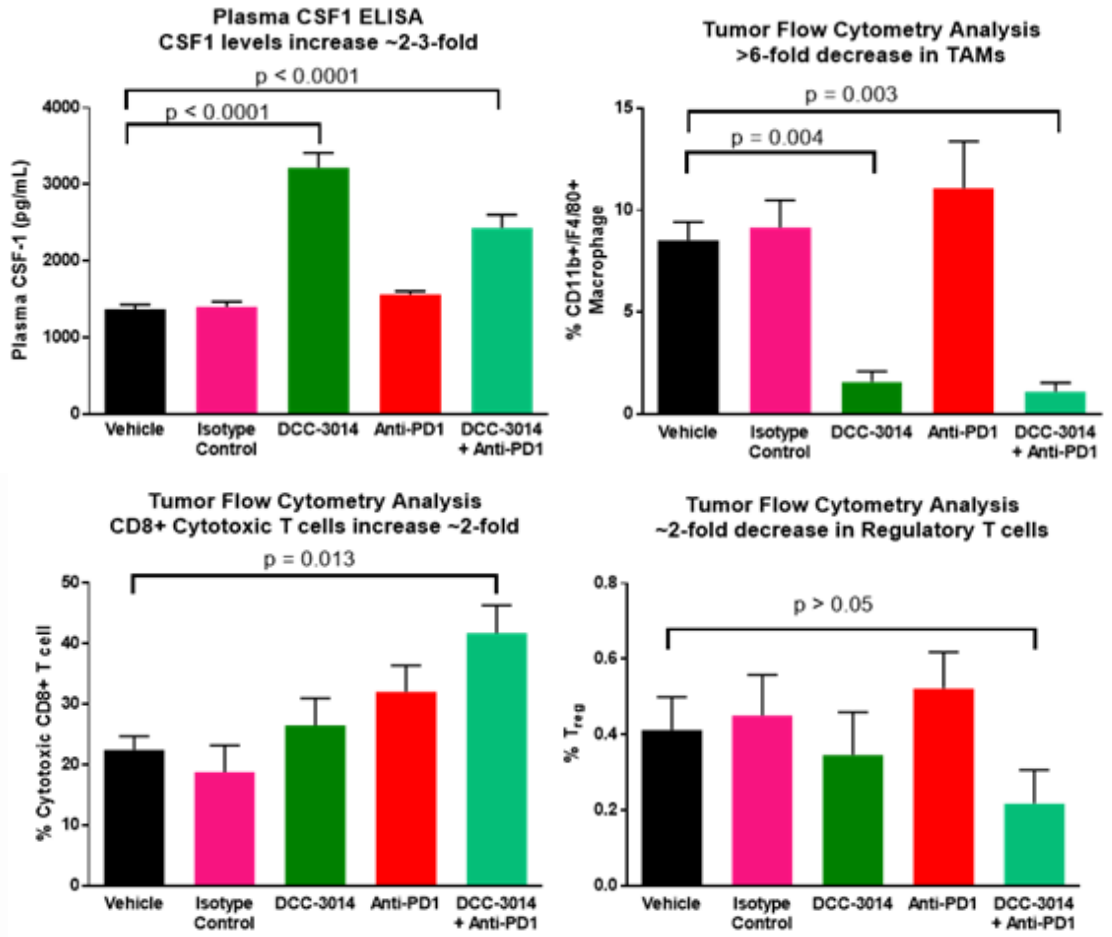
Kinome Profile

DCC-3014 Efficacy in Syngeneic Mouse Colorectal Cancer Model

DCC-3014 Inhibits Growth of Colorectal Tumors in MC-38 Mouse Model Alone and in Combination with anti-PD-1



DCC-3014 Reverses Immunosuppression in MC-38 Mouse Colorectal Tumor Model



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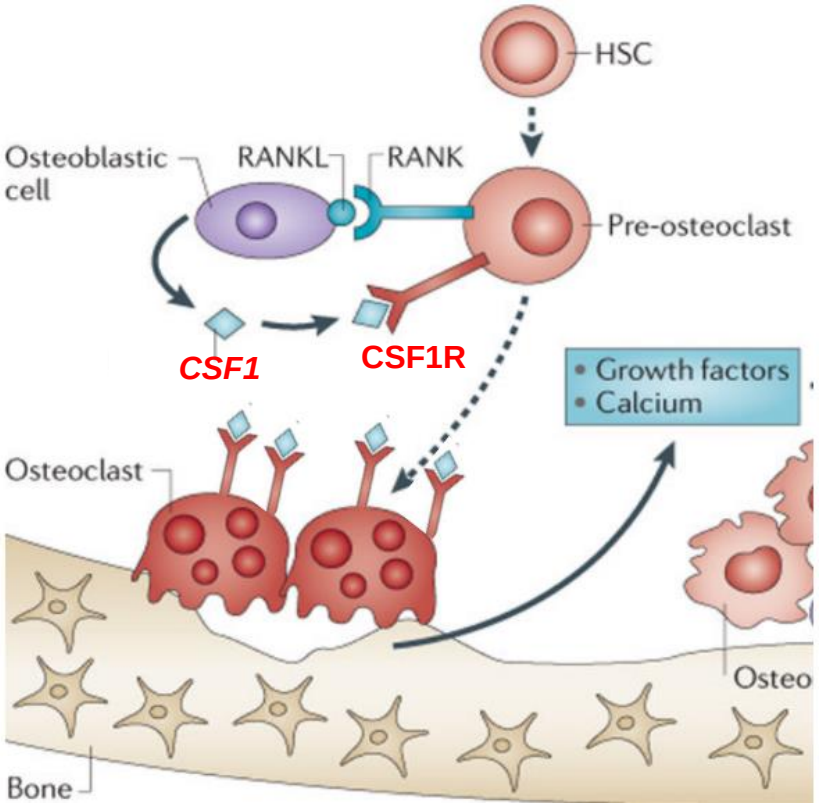
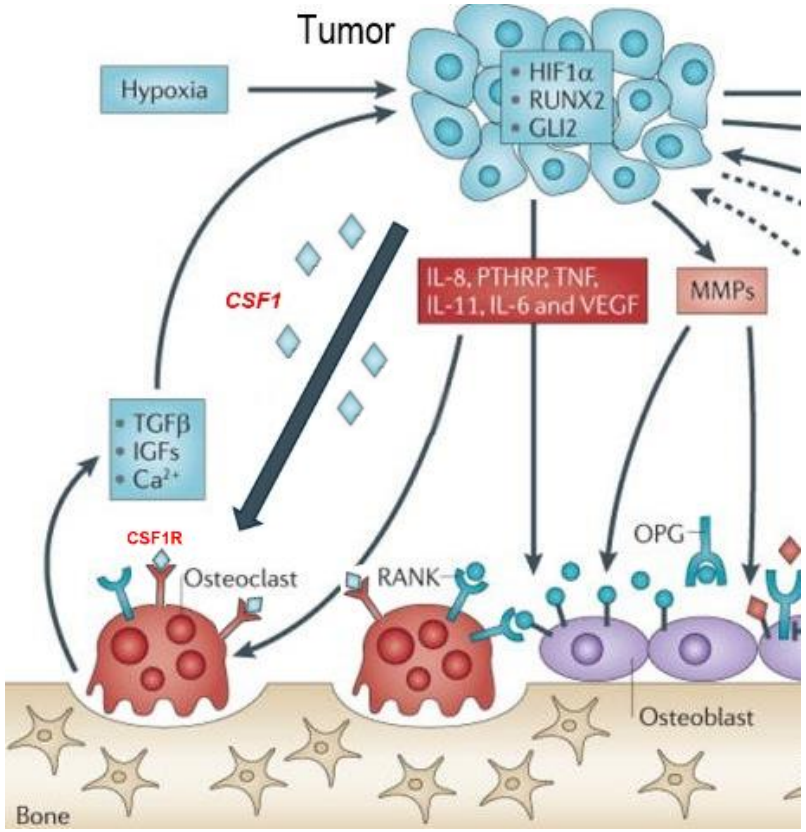
DCC-3014 demonstrated single agent activity in the MC38 colorectal cancer model, with additivity observed in presence of anti-PD1 therapy. DCC-3014 also reverses immunosuppression in this model.

Smith, B.D. *et. al.* Manuscript in Preparation.

CSF1R Activation in the Progression of Cancer Bone Lesions





- CSF1R drives the maturation of pre-osteoclasts to osteoclasts
- These activated osteoclasts cause osteolytic bone lesions

- Osteolysis releases numerous tumor growth factors
- Invading tumor cells can secrete CSF1
- These growth factors contribute to the progression of bone tumor expansion and further bone destruction

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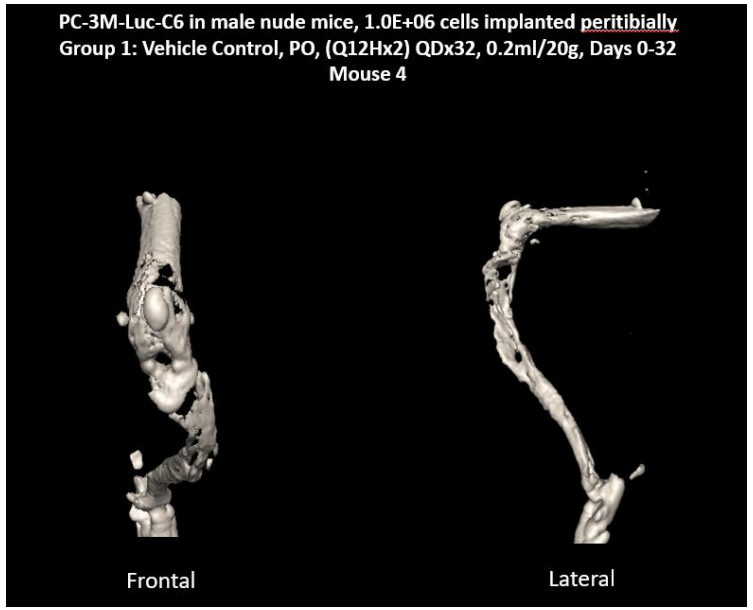
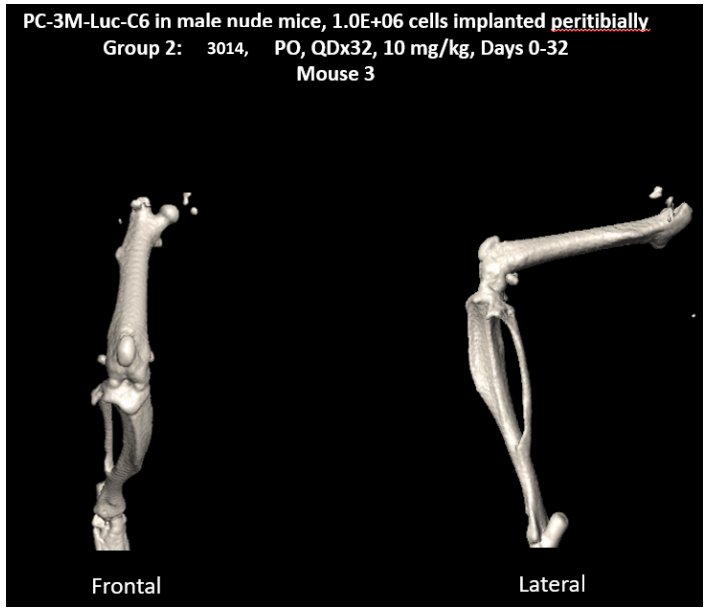
Modified from Weilbaecher et al, Nat Rev Cancer, **2011**, *11*, 411

DCC-3014 Protection from Cancer Bone Invasion

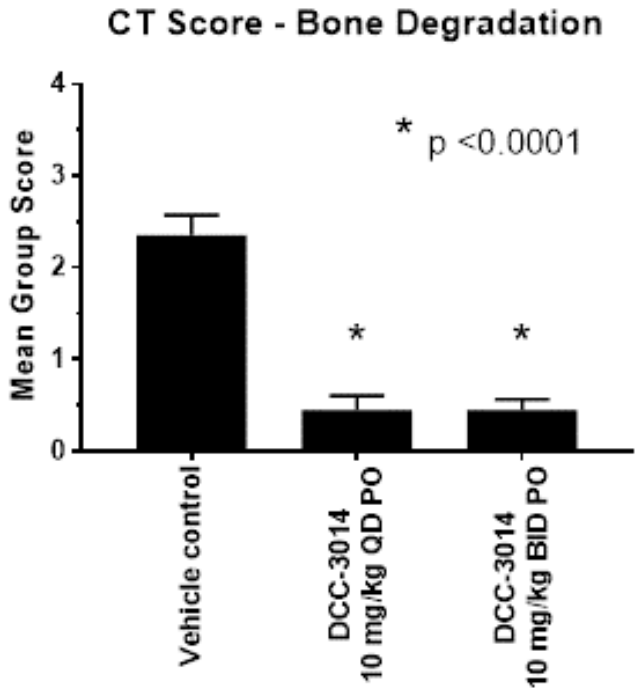
PC-3 prostate cancer peri-tibial invasion model



Vehicle treated for 32 days



DCC-3014 treated for 32 days
(10 mg/kg QD or BID oral gavage)



- PC-3 (human prostate) cells are implanted in the right hind limb of mice
- Limbs then harvested for µCT analysis

- DCC-3014 was able to block osteoclast-mediated tumor invasion of bone

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Smith, B.D. *et. al.* Manuscript in Preparation.

VIMSELTINIB

(DCC-3014)

Clinical Trials

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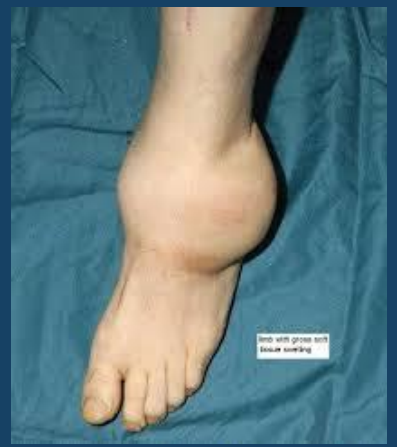
Tenosynovial Giant Cell Tumor (TGCT) is a Locally Aggressive Tumor Associated with Substantial Morbidity

Localized TGCT

Coroneos CJ, et al. J Hand Surg Am. 2012

Diffuse TGCT



The Foot 16 (2006) 214–215

	Localized TGCT	Diffuse TGCT
U.S. Incidence	~13,000[1]	~1,300[1]
Disease characteristics	▪ TGCT is caused by genetic translocations involving the *CSF1* gene causing overexpression of *CSF1*. This overexpression triggers migration of inflammatory cells including CSF1R-expressing tumor-associated macrophages (TAMs) to tumor sites[1] ▪ Typically occurs in people 30-50 years old[2]	
	▪ Tumors are typically confined to a portion of smaller joints and are more well-defined	▪ Tumors typically occur in and around larger joints and are less well-defined
Common locations	▪ Wrists and Fingers ▪ Knees, Ankles and Toes	▪ Knees, Ankles and Hips ▪ Shoulder and Elbows

Significant unmet need exists for an effective agent with a favorable safety profile

- Pexidartinib is only approved agent for TGCT patients no longer amenable to surgery (FDA approval in August 2019)
  - FDA label includes boxed warning, Risk Evaluation and Mitigation Strategy (REMS), and intensive liver monitoring due to possible off-target hepatotoxicity risks
  - The EMA adopted the decision of refusal of the pexidartinib MAA in November 2020

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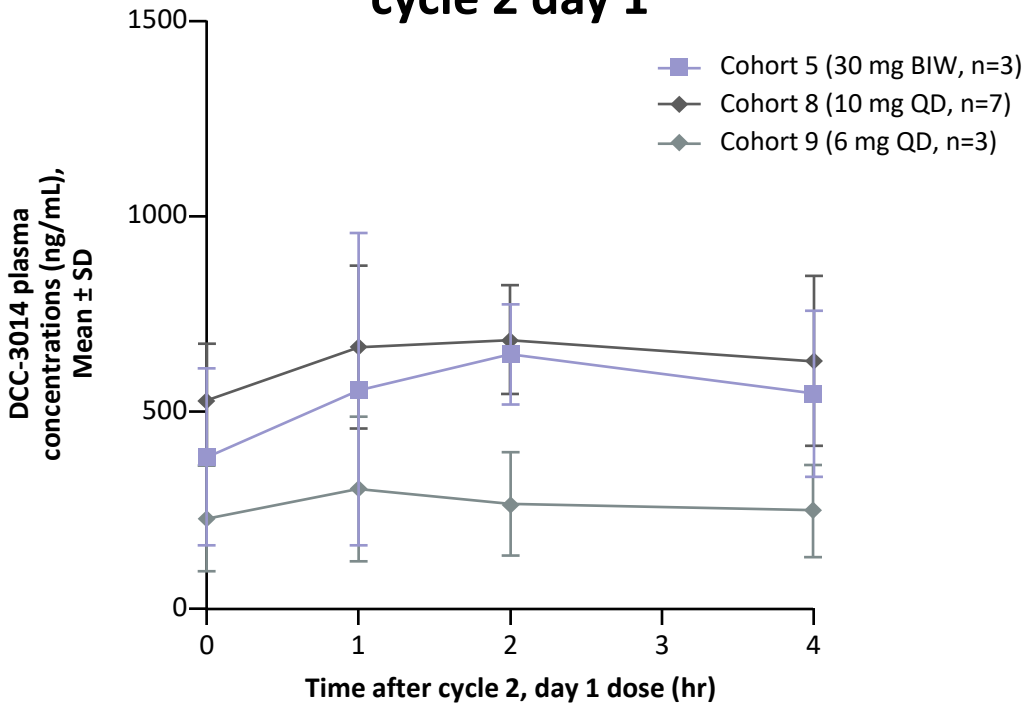
Notes: CSF1=colony-stimulating factor 1; CSF1R=colony-stimulating factor 1 receptor; QOL=quality of life; TAMs= tumor-associated macrophages; TGCT=tenosynovial giant cell tumor; (1) West et al. Proc Natl Sci USA. 2006; 103:690-695; (2) Mastboom et al. Acta Orthopaedica. 2017;88:688-694.

DCC-3014 Pharmacokinetic in TGCT Patients

Steady state DCC-3014 exposure in TGCT patients at cohorts 5, 8, and 9 was characterized

Cohorts 5 and 8 had similar PK at cycle 2, day 1

Repeat dose DCC-3014 concentration-time profile, cycle 2 day 1



CD, cluster of differentiation; CSF1, colony-stimulating factor 1; IL, interleukin; PK, pharmacokinetics; QD, daily; SD, standard deviation; TGCT, tenosynovial giant cell tumor.

CTOS Annual Meeting, Nov 18–21, 2020

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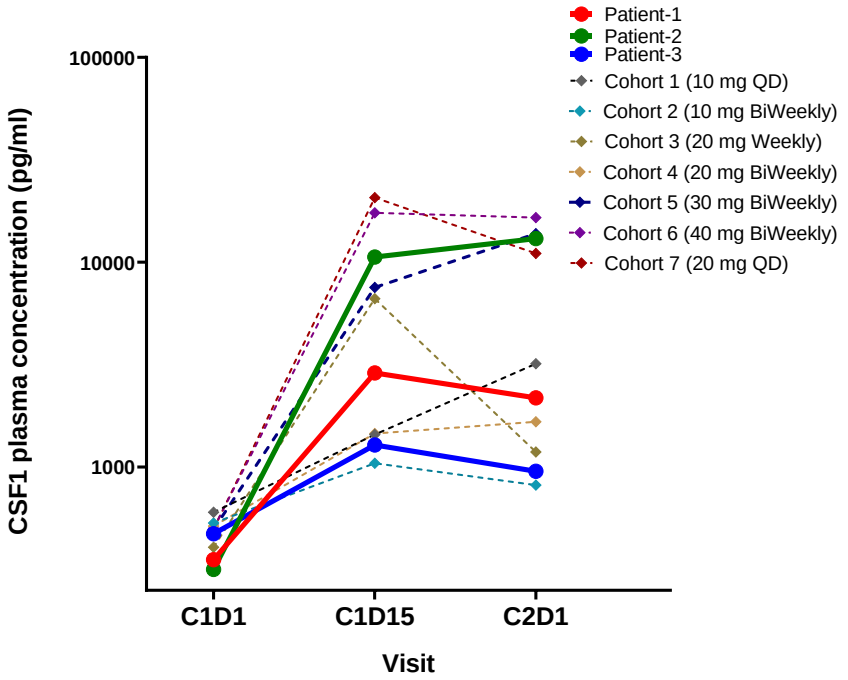
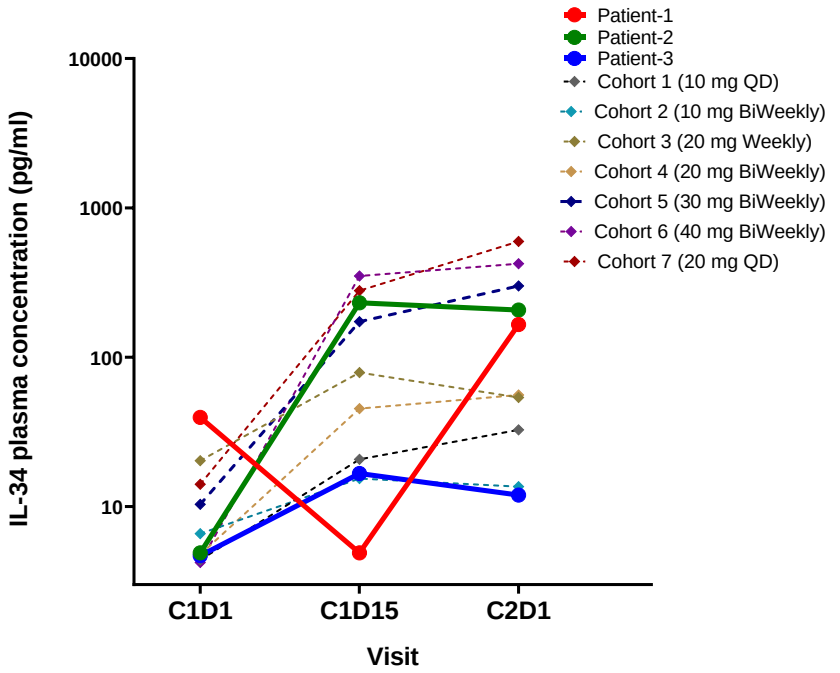
DCC-3014 PK/PD Assessment (Circulating CSF1, IL34 and Nonclassical Monocytes)

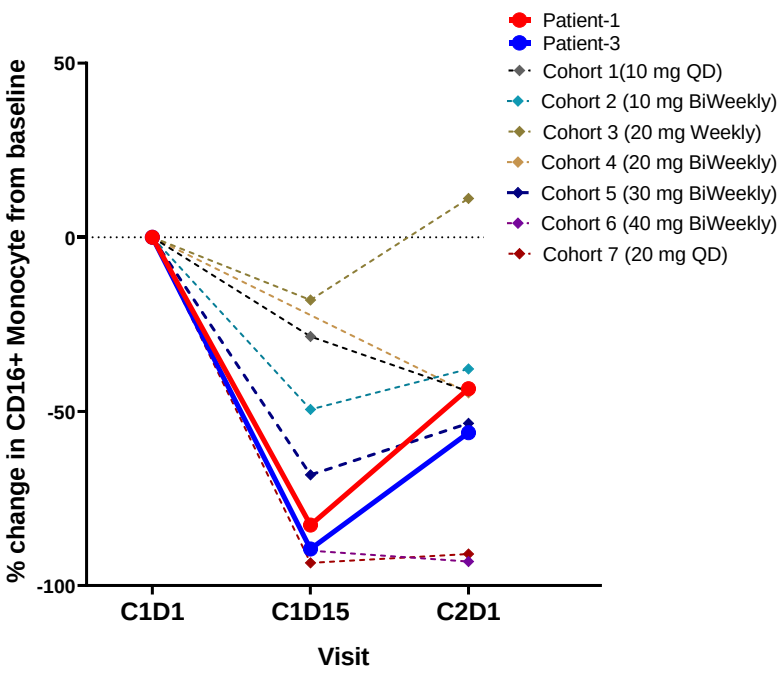
Circulating CSF1 Levels



Circulating IL34 Levels



Nonclassical Monocytes



Across all cohorts, DCC-3014 treatment led to:

- Increased CSF1 (2.8–41-fold) and IL-34 levels (1.4–13-fold) in plasma
- Decreased non-classical subtype of monocytes $CD14^{dim}/CD16^{hi}$ (59–87%) in the peripheral blood

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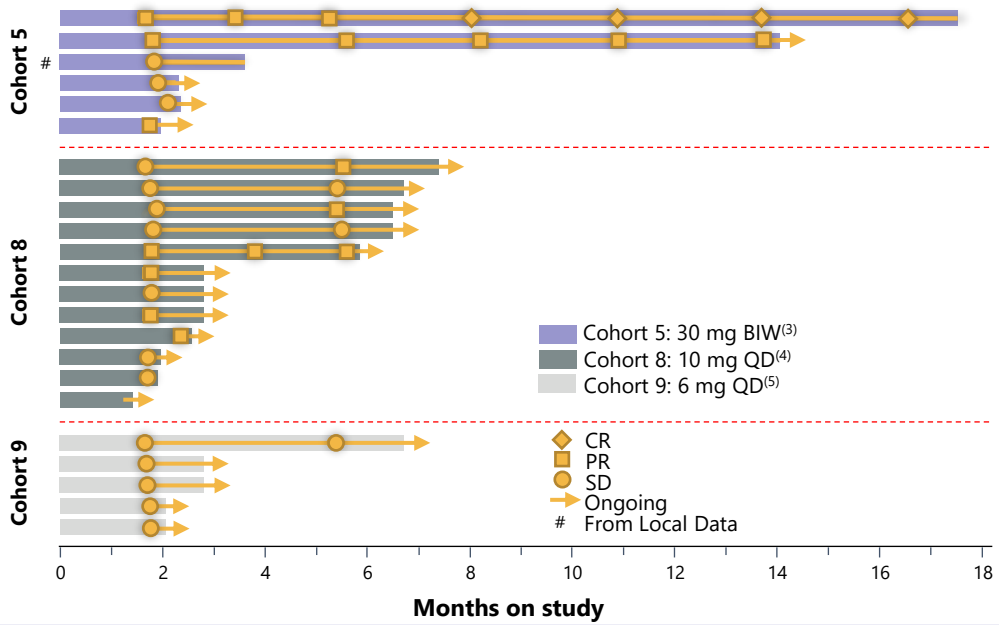
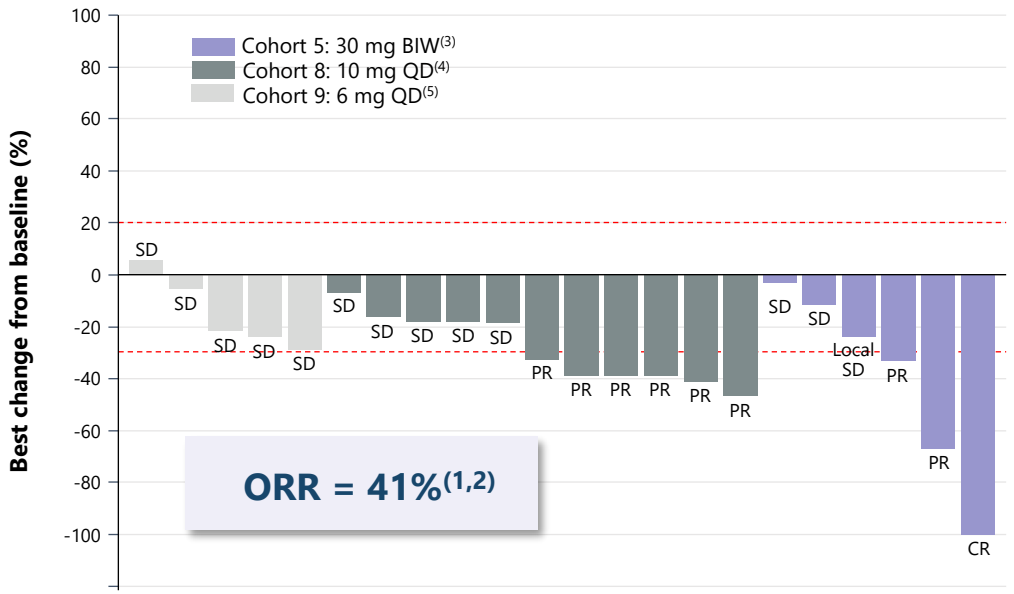
Vimseltinib (DCC-3014): Dose Escalation in Phase 1 Shows Encouraging Tolerability and Anti-Tumor Activity in TGCT Patients

Time on Treatment



Best Percent Change from Baseline in Tumor Size(1,2)



Encouraging Preliminary Anti-Tumor Activity(6,7)

- 9/22 patients (41%) across all TGCT cohorts achieved an objective response (1 complete, 8 partial)
- 7 of the 9 responders (78%) had a partial response at their first restaging scan evaluation (week 9)

Preliminary Safety Data Shows DCC-3014 is Well Tolerated in TGCT Patients

- TEAEs occurring in ≥25% of patients regardless of relatedness were blood CPK increased (52%), AST increased (44%), periorbital edema (44%), fatigue (40%), lipase increased (32%), and ALT increased (28%). No SAEs related to DCC-3014 were reported.
- Observed transaminase and pancreatic enzyme elevations are consistent with the mechanism of action of CSF1R inhibitors. All bilirubin levels were within the normal limit and observed transaminase and pancreatic enzyme elevations were asymptomatic and not clinically significant
- One patient (4%) discontinued treatment due to an adverse event (Grade 3 AST elevation from Grade 1 at baseline)

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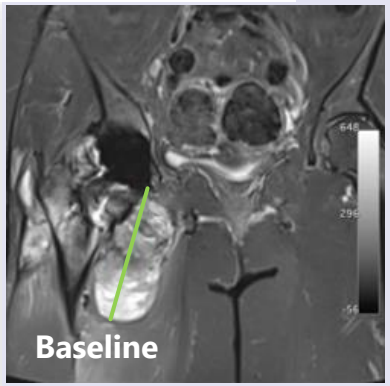
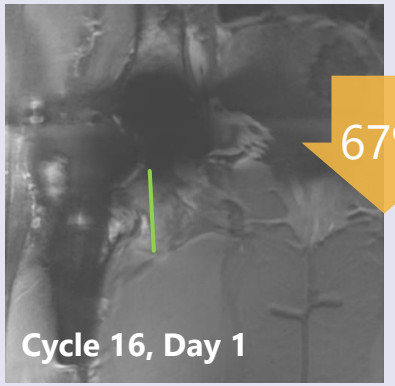
Notes: Data presented at the Connective Tissue Oncology Society (CTOS) Annual Meeting 2020; results are reported for patients with TGCT with data cutoff for safety as of September 23, 2020 and efficacy as of October 5, 2020; safety population n=25, modified intent-to-treat population n=22; AST=aspartate aminotransferase; ALT=alanine aminotransferase; BIW=twice weekly; CR=complete response; CPK=creatine phosphokinase; ORR=objective response rate; PR=partial response; QD=daily; SAE=serious adverse event; SD=stable disease; TEAE=treatment-emergent adverse events; TGCT=tenosynovial giant cell tumor; (1) Waterfall plot excludes 3 patients yet to reach the study's first efficacy assessment timepoint; (2) Dotted lines denote 30% decrease and 20% increase in tumor size cutoffs for partial response and progressive disease, respectively; (3) After 5-day 30 mg QD loading dose; (4) After 3-day 30 mg QD loading dose; (5) After 3-day 20 mg QD loading dose; (6) Assessed by independent central review unless otherwise noted (RECIST v1.1); (7) Includes 1 complete response (confirmed) and 8 partial responses (2 confirmed and 6 to be confirmed at future follow up).

Vimseltinib (DCC-3014): TGCT Case Studies from Phase 1

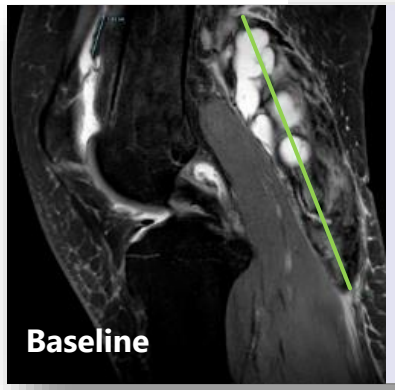
Case Study 1

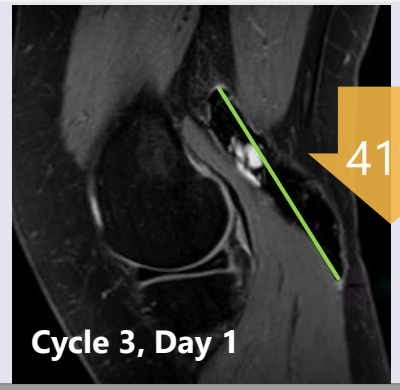




- 57-year-old female diagnosed with TGCT (hip) in 2014
- Prior surgeries: 2 resections, 2 synovectomies, 1 total hip replacement, and 1 cryoablation (2014-2019)
- No prior systemic therapy
- Enrolled in July 2019 (cohort 5 – vimseltinib dose: 30 mg twice weekly[1])
  - Dose reduced to 20 mg twice weekly in cycle 6 due to grade 3 urticaria, re-escalated in cycle 10
- Partial response after 2 cycles (33% decrease from baseline)
- Treatment ongoing in cycle 16 (67% decrease at cycle 16, day 1)

Case Study 2





- 39-year-old female diagnosed with TGCT (knee) in 2020
- No prior systemic therapy or surgery
- Enrolled in June 2020 (cohort 8 – vimseltinib dose: 10 mg daily[2])
- Partial response after 2 cycles (41% decrease from baseline)
- Treatment ongoing in cycle 4

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Patients provided informed consent for use of these images. **Notes**: Data presented at the Connective Tissue Oncology Society (CTOS) Annual Meeting 2020; TGCT=tenosynovial giant cell tumor; (1) After 5-day 30 mg QD loading dose; (2) After 3-day 30 mg QD loading dose.

Expected 2021 Milestones for Vimseltinib (DCC-3014)

Ongoing Phase 1/2 study enrolling up to 60 patients into two expansion cohorts:

- TGCT patients with no prior exposure to anti-CSF1/CSF1R agents (n=40)
- TGCT patients with prior exposure to anti-CSF1/CSF1R agents (n=20)

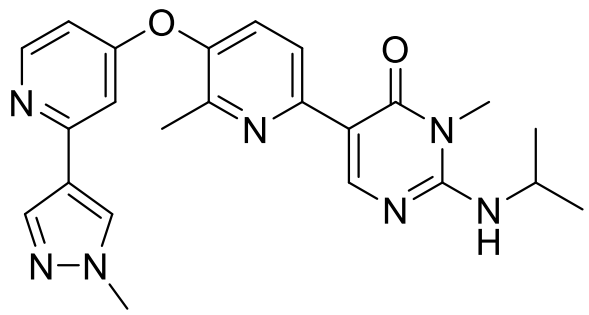
Enrollment of an additional six patients in cohort 9 of the dose escalation portion of the study is ongoing (NCT03069469)

Update Phase 1/2 Data in TGCT Patients
(expected in 2H 2021)

Finalize Pivotal Development Plan
(expected in 2H 2021)

Notes: CSF1=colony-stimulating factor 1; CSF1R=colony-stimulating factor 1 receptor; TGCT=tenosynovial giant cell tumor.

Vimseltinib Summary : A Potent and Selective Inhibitor of CSF1R



Vimseltinib / DCC-3014

- Profound inhibition of CSF1R observed in a preclinical c-fos PK/PD model
- Single agent activity demonstrated in the MC38 colorectal cancer model, with additivity observed in presence of anti-PD1 therapy
- Single agent activity demonstrated in a peri-tibial osteolytic cancer model (anti-osteoclast mechanism)
- Optimized pharmaceutical properties provide high exposures upon oral administration and for combinability with other treatment modalities
- Preliminary results from the Phase 1/2 study showed highly encouraging signs of antitumor activity in TGCT patients (n=22)[(1)]
  - 41% ORR (9 of 22 evaluable patients)
  - 78% of responders had a PR at first restaging scan
- Vimseltinib was generally well-tolerated with treatment emergent adverse events mostly grade 1/2

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[1]Data presented at the Connective Tissue Oncology Society (CTOS) Annual Meeting 2020

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