The highly specific CSF1R inhibitor DCC-3014 exhibits Immunomodulatory and anti-invasive activities in cancer models

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ABSTRACT

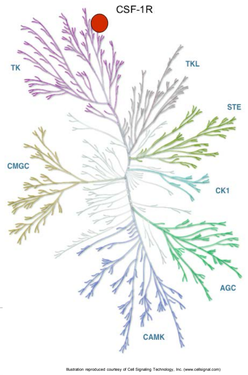
The role of tumor-associated macrophages (TAMs) in promoting an invasive and immunosuppressive tumor microenvironment is well established. TAMs mediate tumor growth, angiogenesis, invasiveness, and immunosuppression through the secretion and response to a variety of factors.[1-5] TAMs are dependent on CSF1R kinase activity for proliferation and differentiation, thus several inhibitors targeting CSF1R have been advanced into the clinic as potential immunotherapies. Many of these drugs, however, also inhibit the closely related CSF1R family members KIT, PDGFRα/β and FLT3, which may limit their utility due to off-target toxicity. Antibodies targeting CSF1R are much more specific, yet result in >10,000-fold increases in plasma levels of the ligand for CSF1R,[5] due to blockage of the pathway for clearance of CSF1, among other drawbacks. Specific small-molecule CSF1R inhibitors would be ideal for use in combination with immune checkpoint inhibitors and/or chemotherapeutic agents. DCC-3014, a highly specific CSF1R inhibitor, was developed based on Deciphera's switch control inhibitor platform.

DCC-3014 exhibited nanomolar (IC_{50} 5 nM) potency for inhibition of CSF1R, sparing highly related kinases KIT, PDGFRα/β, and FLT3 by >100-fold, and sparing other kinases by >1,000 fold. Cellular inhibition of CSF1R was resilient to high levels of the CSF1R ligand MCSF. DCC-3014 inhibited CSF1R in THP-1 monocytes (IC_{50} 11 nM), M-NFS-60 cells (IC_{50} 4 nM), human osteoclast precursors (IC_{50} 9 nM), and in monocytes in a human whole blood assay (IC_{50} 260 nM). *In vivo*, DCC-3014 exhibited sustained inhibition of CSF1R in a murine PK/PD model, affording >90% inhibition through 24 h post dose. In the MC38 syngeneic colorectal cancer model, DCC-3014 depleted infiltrating TAMs, repolarized the adaptive immune cell population to an anti-tumoral profile, and decreased circulating CD16+ monocyte populations. DCC-3014 demonstrated additive effects in combination with a murine anti-PD1 antibody in this model. Additionally, DCC-3014 blocked tumor growth, invasion, and bone degradation in the PC3 prostate cancer model. DCC-3014 exhibits optimized biopharmaceutical properties, including a favorable ADME and PK profile in preclinical studies.

DCC-3014 is a highly specific CSF1R inhibitor, and finds potential utility as a macrophage immunomodulatory agent for clinical evaluation in combination with immune checkpoint inhibitors and/or chemotherapeutic agents. DCC-3014 is concluding IND-enabling activities, with a FIH study targeted in 2016.

BACKGROUND

Scientific Rationale & Preclinical Data	Switch Control inhibitor targeting CSF1R • *Potent and ultra-selective inhibitor:* >100-1000x selectivity for CSF1R in 300-kinase panel. Cellular assays used to measure inhibition of CSF1R and its closely-related kinase family (KIT, PDGFRα/β, and FLT3) showed >50x selectivity for CSF1R • *Prevents in vivo invasion*: Blocks invasion *in vivo* and protects bone in a PC-3 peritibial implant mode • *In vivo immunomodulation*: Single-agent depletion of TAMs, repolarization of adaptive immune system, and modulation of circulating CSF1R biomarkers • *In vivo activity in combination with anti-PD1 therapy*: The combination of TAM depletion with PD1 checkpoint inhibition leads to synergy in inhibition of tumor growth and repolarization of the adaptive immune system • Highly soluble, low clearance • Dose proportional exposure in preclinical models • Clean CYP profile, no time-dependent inhibition of any CYP isoform • No hERG liability (IC_{50} >25 μM) • Clean CEREP profile
Development Status	• Four-week GLP toxicology studies completed • Safety pharmacology studies completed • Manufacturing in progress
Upcoming Milestones	2H 2016 IND filing and FIH study



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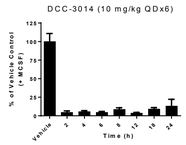
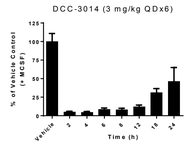
RESULTS - *in vivo*

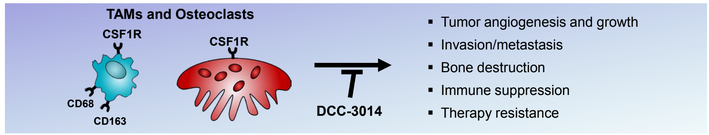
Pharmacodynamic/pharmacokinetic analysis of DCC-3014 inhibition of CSF1R at steady-state *in vivo* was determined by following cFOS mRNA modulation in DBA1 mouse spleens. DBA1 mice were given doses (QDx6; PO) of compound in 0.4% HPMC vehicle. On day 6 at specified time points post dose, mice were injected i.v. with the ligand CSF1 15 minutes prior to harvest of spleens. cFOS levels were measured by qPCR of total spleen RNA. DCC-3014 exhibits dose-dependent, potent and durable inhibition of CSF1R for >24 hours after an oral dose as low as 3 mg/kg.

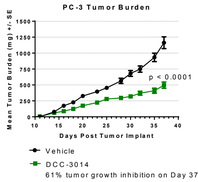


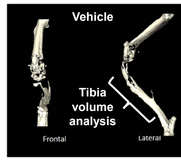


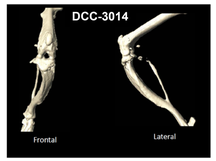
Pharmacokinetic Parameter	10 mg/kg	3 mg/kg
C_{max} (ng/mL)	10738	3226
t_{max} (hr)	6	6
$AUC_{(0\text{-}24)}$ (ng•hr/mL)	170035	49314
$t_{1/2}$ (hr)	11.11	8.96
Vz_obs (L/kg)	0.731	0.661
Cl_obs (L/hr/kg)	0.046	0.051

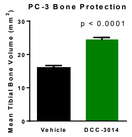
In order to test the effects of DCC-3014 on the myriad roles of TAMs and osteoclasts in cancer, two *in vivo* animal models were used. The PC-3 peritibial implant prostate cancer model was used to test the effects of CSF1R inhibition on invasion to the bone, as well as tumor growth.



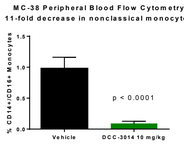


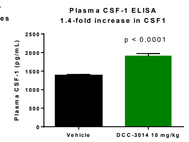


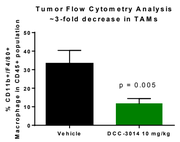


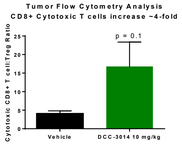


To determine the effects of DCC-3014 on primary tumor growth, macrophages, and the adaptive immune system, the syngeneic, immunocompetent MC38 colorectal cancer model was used. As a single agent dosed for seven days in the MC38 model, DCC-3014 (10 mg/kg PO, QD) significantly reduced CD16+ nonclassical monocytes in the circulation by 11-fold, as well as macrophages by 3-fold within CD45+ population of cells in the primary tumor. Plasma CSF1 levels modestly increased by ~1.4-fold, in stark contrast to the >10,000-fold increases in CSF1 observed in studies with CSF1R antibodies. Small-molecule inhibitors do not block clearance of the ligand CSF1, reducing the risk of rebound or other effects. DCC-3014 also led to a 4-fold increase in the ratio of cytotoxic CD8+ T cells to regulatory T_{reg} cells, indicating repolarization of the adaptive immune system away from an immunosuppressive state.



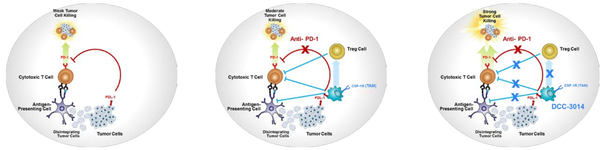




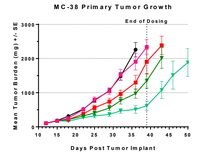


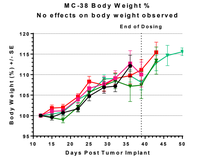
DCC-3014 / ANTI-PD1 COMBINATION

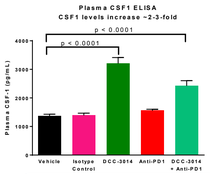
The combination a CSF1R inhibitor with an anti-PD1 antibody could result in greater tumor cell killing by the adaptive immune system.

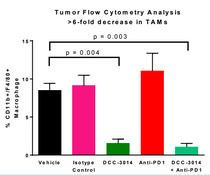


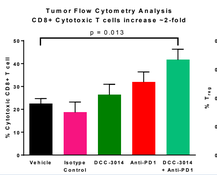
In the MC-38 immunocompetent colorectal cancer model, DCC-3014 exhibited additive effects with an anti-PD1 antibody in blocking tumor growth and affording immunomodulatory activity. Dosing for all agents started on day 12 and ended on day 39. Single agent DCC-3014 had a tumor growth inhibition (%TGI) = 52%, anti-PD1 treatment had a %TGI = 38%, and the combination had a %TGI = 74%. Body weight was not affected by any treatment. Plasma CSF1 levels were elevated by only ~2-3 fold in DCC-3014 treated cohorts. TAMs were significantly reduced by >6-fold in the primary tumor, whereas cytotoxic CD8+ T cells increased, by ~2-fold in the combination group. Although only low numbers of T_{regs} were detected in this study, they trended towards a decrease, especially in the combination group by ~2-fold.

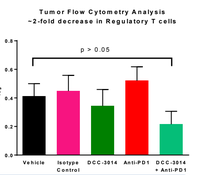












CONCLUSIONS

DCC-3014 is a highly selective CSF1R inhibitor, which exhibits single-agent effects on primary tumor growth, tumor invasion and destruction of adjacent bone, and immunomodulation. DCC-3014 exhibits synergy in combination with an anti-PD1 therapy. DCC-3014 only moderately increases CSF1 levels, lessening likelihood of rebound effects. As a small molecule, DCC-3014 is likely to exhibit better tumor distribution than antibody therapies, especially to hypoxic areas of the tumor abundant in pro-tumoral TAMs. DCC-3014 is dosed orally, which allows for more flexibility in combination therapies and dosing regimens. DCC-3014 is concluding IND-enabling activities, with a FIH study in patients with solid tumors targeted in 2016.

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