

Company

Deciphera Pharmaceuticals

Drug or Device Name

QINLOCK®

Category

Pharmaceutical

Compound/Technical Name

1-(4-Bromo-5-[1-ethyl-7-(methylamino)-2-oxo-1,2-dihydro-1,6-naphthyridin-3-yl]-2-fluorophenyl)-3-phenylurea

Trade Name

QINLOCK®

Date of Approval

05/15/2020

Therapeutic Categories

Antineoplastics (proto-oncogene receptor tyrosine kinase [KIT] and platelet derived growth factor receptor A [PDGFRA] tyrosine kinase inhibitor)

Indications

QINLOCK® is indicated for the treatment of adult patients with advanced gastrointestinal stromal tumor (GIST) who have received prior treatment with 3 or more kinase inhibitors, including imatinib.

Background

GISTs are rare, heterogeneous sarcomas but are also the most common sarcomas of the gastrointestinal tract. An estimated 4000 to 6000 new cases of GIST present clinically in the US each year. The annual worldwide incidence and prevalence of GISTs are estimated to be approximately 10 to 15 per million people and 129 per million people, respectively. KIT and PDGFRA kinase mutations commonly drive GIST disease pathophysiology. About 80% of GIST have primary mutations in KIT, and 5-10% of GIST have a mutation in the homologous PDGFRA. Approximately 10-15% of GIST patients have wild type (WT) mutations (i.e., the disease is not driven by KIT or PDGFRA but by other genetic mutations). Advanced GIST is marked by the development of secondary drug resistance mutations, which play a key role in disease progression. Broad inter-and intra-tumor heterogeneity exists among secondary resistance mutations, whereby a single patient may have multiple mutations within or between tumors. The extensive mutational heterogeneity drives resistance to established therapies. Thus, advanced GIST, a heterogeneous disease with a complex mutational landscape, presents with significant treatment challenges. The standard of care for patients with GIST are tyrosine kinase inhibitors: imatinib (1st-line), sunitinib (2nd-line), and regorafenib (3rd-line). Avapritinib is approved for GIST harboring PDGFRA exon 18 mutations, including the PDGFRA D842V mutation (in about 6% of

patients). There was a need for broad-spectrum inhibition of KIT/PDGFRα primary and secondary kinase mutations that fuel resistance and progression in advanced GIST. Ripretinib was specifically designed to broadly inhibit the function of mutated and WT versions of KIT and PDGFRα kinases, primary drivers of treatment resistance and disease progression in advanced GIST. There was a significant unmet medical need for patients with advanced GIST who progressed on or were intolerant to 3rd-line regorafenib prior to the approval of ripretinib (in 4th-line or later patients) in advanced GIST.

Development

Ripretinib was evaluated in a phase 1 study for safety, pharmacokinetics, and early efficacy. The maximum tolerated dose (MTD) was not reached and recommended phase 2 dose (RP2D) of ripretinib was 150 mg QD. Ripretinib was effective at slowing the progression of unresectable GIST across lines of therapy in phase 1 clinical study. The median progression-free survival (mPFS) was 10.7 months for patients on 2nd-line therapy, 8.3 months (3rd-line), and 5.5 months (4th-line +). The objective response rate (ORR) for 2nd-, 3rd-, and 4th-line+ therapies were 19.4%, 14.3%, and 7.2%, respectively. Based on the proof-of-concept in GIST patients, INVICTUS, an international, multicenter, randomized, double-blind, placebo-controlled phase 3 trial in 129 patients who had received 3 or more prior anticancer therapies for advanced GIST was initiated. Patients had a complex and heterogeneous mutational landscape and were heavily pre-treated. The population was representative of the real-world 4th-line+ patients with advanced GIST. Ripretinib provided clinically meaningful benefit in 4th-line+ advanced GIST in INVICTUS. The mPFS (BICR) was 6.3 months for ripretinib versus 1.0 month for placebo, reducing the risk of progression or death by 85%. Notably, the mPFS of 6.3 months in 4th-line+ GIST exceeds those of both sunitinib in 2nd-line (5.6 months) and regorafenib in 3rd-line (4.8 months). ORR was 9.4% for ripretinib versus 0% for placebo. Patients received a clinically meaningful survival benefit when treated with ripretinib versus placebo (median OS – 15.1 months in the ripretinib group versus 6.6 months in the placebo group). None of the prior phase 3 studies with sunitinib in 2nd-line (median OS: 17.0 months sunitinib versus 14.9 months placebo) or regorafenib in 3rd-line (median OS: 17.4 months for both regorafenib and placebo groups) demonstrated a clinically meaningful OS benefit compared to placebo. Ripretinib was generally well tolerated and patients were able to maintain quality of life in INVICTUS.

Innovation

Ripretinib is a novel switch control tyrosine kinase inhibitor specifically designed to broadly inhibit KIT and PDGFRα mutated kinases with a unique dual mechanism of action. Ripretinib was developed to block the function of mutated and WT versions of KIT and PDGFRα kinases using Deciphera's proprietary switch-control kinase inhibition drug discovery platform and deep expertise in kinase biology. Ripretinib binds to both the switch pocket region and the activation switch securing the target kinase into an inactive conformation, resulting in the inhibition of downstream signaling and cell proliferation. Portions of ripretinib mimic the inhibitory loop and occupy the switch pocket, thereby preventing the activation switch's entry. Other residues on ripretinib bind to the activation switch, stabilizing it out of the switch pocket and covering the ATP binding site, so phosphorylation cannot occur. Ripretinib has emerged as a new standard of care for patients with 4th-line+ advanced GIST where there was an unmet medical need. Patients progressing on the standard dose of ripretinib could derive further clinical benefit with dose-escalation to 150 mg BID, another area of significant unmet need as options are limited for patients progressing on ripretinib 150 mg QD. The dose-escalation strategy mirrors imatinib dose-escalation in 1st-line patients with GIST. mPFS of 10.7 months in 2nd-line patients with GIST in the phase 1 study provides a rationale for the ongoing INTRIGUE (phase 3) study investigating ripretinib versus sunitinib in 2nd-line GIST. Ripretinib, with its broad-

spectrum activity, has the potential to maximize responses and induce more durable responses in a new generation of combination clinical trials in GIST. Ripretinib is a ground-breaking therapy that has the potential to revolutionize the GIST treatment landscape.

Pubmed

A Pubmed literature search and Deciphera Publications from 2019-2021 are listed below: Pubmed Search 1: Dhillon S. Ripretinib: First Approval. *Drugs*. 2020 Jul;80(11):1133-1138. doi: 10.1007/s40265-020-01348-2. Erratum in: *Drugs*. 2020 Dec;80(18):1999. PMID: 32578014; PMCID: PMC7595980. 2: Drugs and Lactation Database (LactMed) [Internet]. Bethesda (MD): National Library of Medicine (US); 2006-. Ripretinib. 2021 Jan 18. PMID: 33226755. 3: Lostes-Bardaji MJ, García-Illescas D, Valverde C, Serrano C. Ripretinib in gastrointestinal stromal tumor: the long-awaited step forward. *Ther Adv Med Oncol*. 2021 Jan 7;13:1758835920986498. doi: 10.1177/1758835920986498. PMID: 33473249; PMCID: PMC7797597. 4: Florou V, Trent JC, Wilky BA. Precision medicine in gastrointestinal stromal tumors. *Discov Med*. 2019 Nov-Dec;28(155):267-276. PMID: 32053767. 5: Reiter A, George TI, Gotlib J. New developments in diagnosis, prognostication, and treatment of advanced systemic mastocytosis. *Blood*. 2020 Apr 16;135(16):1365-1376. doi: 10.1182/blood.2019000932. PMID: 32106312. 6: Falkenhorst J, Hamacher R, Bauer S. New therapeutic agents in gastrointestinal stromal tumours. *Curr Opin Oncol*. 2019 Jul;31(4):322-328. doi:10.1097/CCO.0000000000000549. PMID: 31033566. 7: Serrano C, George S. Gastrointestinal Stromal Tumor: Challenges and Opportunities for a New Decade. *Clin Cancer Res*. 2020 Oct 1;26(19):5078-5085. doi: 10.1158/1078-0432.CCR-20-1706. Epub 2020 Jun 29. PMID: 32601076. 8: Farag S, Smith MJ, Fotiadis N, Constantinidou A, Jones RL. Revolutions in treatment options in gastrointestinal stromal tumours (GISTs): the latest updates. *Curr Treat Options Oncol*. 2020 May 27;21(7):55. doi: 10.1007/s11864-020-00754-8. PMID: 32462367; PMCID: PMC7253383. 9: Mazzocca A, Napolitano A, Silletta M, Spalato Ceruso M, Santini D, Tonini G, Vincenzi B. New frontiers in the medical management of gastrointestinal stromal tumours. *Ther Adv Med Oncol*. 2019 May 17;11:1758835919841946. doi: 10.1177/1758835919841946. PMID: 31205499; PMCID: PMC6535752. 10: Martin-Broto J, Moura DS. New drugs in gastrointestinal stromal tumors. *Curr Opin Oncol*. 2020 Jul;32(4):314-320. doi: 10.1097/CCO.0000000000000642. PMID: 32541319. 11: Kelly CM, Gutierrez Sainz L, Chi P. The management of metastatic GIST: current standard and investigational therapeutics. *J Hematol Oncol*. 2021 Jan 5;14(1):2. doi: 10.1186/s13045-020-01026-6. PMID: 33402214; PMCID: PMC7786896. 12: Vallilas C, Sarantis P, Kyriazoglou A, Koustas E, Theocharis S, Papavassiliou AG, Karamouzis MV. Gastrointestinal Stromal Tumors (GISTs): Novel Therapeutic Strategies with Immunotherapy and Small Molecules. *Int J Mol Sci*. 2021 Jan 6;22(2):493. doi: 10.3390/ijms22020493. PMID: 33419029; PMCID: PMC7825300. 13: Mohammadi M, Gelderblom H. Systemic therapy of advanced/metastatic gastrointestinal stromal tumors: an update on progress beyond imatinib, sunitinib, and regorafenib. *Expert Opin Investig Drugs*. 2021 Feb;30(2):143-152. doi: 10.1080/13543784.2021.1857363. Epub 2020 Dec 3. PMID: 33252274. 14: Italiano A. New insights into the clinical management of advanced gastrointestinal stromal tumors. *Expert Opin Pharmacother*. 2021 Mar;22(4):439-447. doi: 10.1080/14656566.2020.1828346. Epub 2020 Dec 14. PMID: 33307872. 15: Blay JY, Kang YK, Nishida T, von Mehren M. Gastrointestinal stromal tumours. *Nat Rev Dis Primers*. 2021 Mar 18;7(1):22. doi: 10.1038/s41572-021-00254-5. PMID: 33737510. 16: Roskoski R Jr. Properties of FDA-approved small molecule protein kinase inhibitors: A 2021 update. *Pharmacol Res*. 2021 Mar;165:105463. doi: 10.1016/j.phrs.2021.105463. Epub 2021 Jan 26. PMID: 33513356. 17: Yonkus JA, Alva-Ruiz R, Grotz TE. Surgical Management of Metastatic Gastrointestinal Stromal Tumors. *Curr Treat Options Oncol*. 2021 Mar 20;22(5):37. doi: 10.1007/s11864-021-00837-0. PMID: 33743084. 18: Al-Share B, Alloghbi A, Al Hallak MN, Uddin H, Azmi A, Mohammad RM, Kim SH, Shields AF, Philip PA. Gastrointestinal stromal tumor: a review of current and emerging therapies. *Cancer Metastasis Rev*. 2021 Apr 19. doi:

10.1007/s10555-021-09961-7. Epub ahead of print. PMID: 33876372. 19. Shomali W, Gotlib J. Response Criteria in Advanced Systemic Mastocytosis: Evolution in the Era of KIT Inhibitors. *Int J Mol Sci*. 2021 Mar 15;22(6):2983. doi: 10.3390/ijms22062983. PMID: 33804174; PMCID: PMC8001403. Deciphera Publications (2019-2021) 1. George S, Janku F, Chi P. et al. Population pharmacokinetics of ripretinib in patients with advanced malignancies. Poster presented at the AACR Virtual Annual Meeting 2021, April 10–15. 2. Li X, Shelton MJ, Meade J, et al. Effect of gastric acid reduction and strong CYP3A induction/inhibition on the pharmacokinetics of ripretinib, a switch control tyrosine kinase inhibitor. Poster presented at the AACR Virtual Annual Meeting 2021, April 10–15. 3. George S, Heinrich MC, Zalcborg J, et al. Safety profile of ripretinib, including impact of alopecia and palmar plantar erythrodysesthesia syndrome (PPES) on patient reported outcomes (PROs), in 74th line advanced gastrointestinal stromal tumors (GIST): Analyses from INVICTUS. Poster presented at the ASCO Annual Virtual Meeting, May 29-31, 2020. 4. Heinrich MC, George S, Zalcborg J, et al. Quality of life (QoL) and self reported function with ripretinib in 74th line therapy for patients with gastrointestinal stromal tumors (GIST): Analyses from INVICTUS. Poster presented at the ASCO Annual Virtual Meeting, May 29-31, 2020. 5. Blay J-Y, Serrano C, Heinrich MC, et al. Ripretinib in patients with advanced gastrointestinal stromal tumours (INVICTUS): a double-blind, randomised, placebo-controlled, phase 3 trial. *Lancet Oncol*. 2020;21(7):923-934. 6. Serrano C, Heinrich MC, George S, et al. Efficacy and safety of ripretinib as 74th-line therapy for patients with gastrointestinal stromal tumor (GIST) following crossover from placebo: Analyses from INVICTUS. Oral presentation at ESMO World Congress on Gastrointestinal Cancer virtual meeting, 2020. 7. Zalcborg J, Heinrich MC, George S, et al. Clinical Benefit with Ripretinib as 74th Line Treatment in Patients with Advanced Gastrointestinal Stromal Tumors (GIST): Update from the Phase 3 INVICTUS Study. Oral presentation at ESMO Virtual Congress, September 19-21, 2020. 8. Janku F, Chi P, Heinrich MC, et al. Ripretinib intra-patient dose escalation (IPDE) following disease progression provides clinically meaningful progression-free survival (PFS) in gastrointestinal stromal tumor (GIST) in phase 1 study. Oral presentation at Virtual ESMO congress. September 19-21, 2020. 9. Janku F, Abdul Razak AR, Chi P, et al. Switch control inhibition of KIT and PDGFRA in patients with advanced gastrointestinal stromal tumor: A phase I study of ripretinib. *J Clin Oncol*. 2020;32(28):3294-3303. 10. Schöffski P, Bauer S, Heinrich M, et al. Ripretinib demonstrated activity across all KIT/PDGFRA mutations in patients with fourth-line advanced gastrointestinal stromal tumor: Analysis from the phase 3 INVICTUS study. Poster presented at CTOS Virtual Meeting; November 18-21, 2020. 11. Bauer S, Schöffski P, Heinrich M, et al. Characterization of the extensive heterogeneity of KIT/PDGFRA mutations in patients with fourth-line advanced gastrointestinal stromal tumor: Genomic analysis of the phase 3 INVICTUS study. Oral presentation at CTOS Virtual Meeting; November 18-21, 2020. 12. Janku F, Heinrich M, Chi P, et al. Ripretinib (DCC-2618) pharmacokinetics (PK) in a phase 1 study in patients with gastrointestinal stromal tumors (GIST) and other advanced malignancies: a retrospective evaluation of the PK effects of proton pump inhibitors (PPIs). Poster presented at the American Association for Cancer Research (AACR) annual meeting, March 29-April 3, 2019; Atlanta, Georgia. 13. von Mehren V, Bauer S, George S, et al. INVICTUS: A phase 3, interventional, double-blind, placebo-controlled study to assess the safety and efficacy of ripretinib as 74th line therapy in patients with advanced gastrointestinal stromal tumors (GIST) who have received treatment with prior anticancer therapies (NCT03353753). Oral presentation at ESMO Congress, September 27-October 1 2019; Barcelona, Spain. 14. Chi P, Janku F, Heinrich M, et al. Updated results of phase 1 study of ripretinib (DCC-2618), a broad-spectrum KIT and PDGFRA inhibitor, in patients with gastrointestinal stromal tumor (GIST) by line of therapy (NCT02571036). Poster presented at AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics. October 26-30, 2019; Boston, MA. 15. Smith BD, Kaufman MD, Lu WP, et al. Ripretinib (DCC-2618) is a switch control kinase inhibitor of a broad spectrum of oncogenic and drug-resistant KIT and PDGFRA variants. *Cancer Cell*. 2019;35(5):738-751. 16. Nemunaitis J, Bauer S, Blay J-Y, et al. Intrigue:

Phase III study of ripretinib versus sunitinib in advanced gastrointestinal stromal tumor after imatinib. Future Oncol. 2019;16(1):4251-4264. 17. Zalcborg JR. Ripretinib for the treatment of advanced gastrointestinal stromal tumor. Ther Adv Gastroenterol. 2021;14:1-12 (ahead of print). DOI: 10.1177/17562848211008177

Attachments

- 1621614603QINLOCK_Prescribing_Information.pdf
- 1621265519Product_Prix_Galien.docx
- 1621265697Background_Prix_Galien.docx
- 1621265775Development_Prix_Galien.docx
- 1621265843Innovation_Prix_Galien.docx
- 1621265937Pubmed_Prix_Galien.docx

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