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Gastrointestinal stromal tumor – A review of clinical studies

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Abstract

Gastrointestinal stromal tumor (GIST) is the most common mesenchymal tumor of the gastrointestinal tract. With the advent of Imatinib, the treatment of gastrointestinal stromal tumor has been revolutionized as both the progression-free and overall survival rates have increased dramatically. Unfortunately, gastrointestinal stromal tumor patients on Imatinib do eventually fail due to resistance. Even though sunitinib and regorafenib have been shown to be highly effective as second- and third-line treatments, both have limited effects. New treatments are highly warranted for this reason. In this present review, 25 registered pharmacological clinical trials at ClinicalTrials.gov have been reviewed and show promising and encouraging results.

Keywords

Clinical trials, gastrointestinal stromal tumor (GIST), resistance

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Background

Gastrointestinal stromal tumor (GIST) was first named in 1983[1] and arises from the cells of Cajal, the pacemaker cells of the gastrointestinal (GI) tract responsible for the contractions of smooth muscles. Although rare, GIST is the most common mesenchymal tumor of the GI tract.[2,3]

In 1998, Japanese researchers were able to show that mutations in the KIT oncogene contribute to the development of GIST.[4] One year later, a patient with advanced GIST was treated with the tyrosine kinase inhibitor STI571, more commonly known as Gleevec (Imatinib). The results were published in the year 2000 and showed that the patient had a complete metabolic response as well as a significant decrease in tumor volume.[5] Soon thereafter, a randomized multi-center trial showed that patients with advanced GIST exhibit a significant positive response to Imatinib, which also showed better and increased survival in relation to chemotherapy.[6] In February of 2002, Imatinib was approved by the US Food and Drug Administration (FDA) for the treatment of advanced GIST.[7]

In 2003, US researchers showed that close to 35% of GIST patients do not have a mutation in the KIT oncogene, and that the mutation is instead found in the platelet-derived growth factor receptor α (PDGFRA).[8] This finding would later show that there are distinctive features between the KIT and PDGFRA genes, making the latter more difficult to treat with Imatinib.[9,10] Other studies have shown that different exon and codon mutations in both the KIT oncogene and the PDGFRA respond differently to Imatinib treatment. While KIT exon 11 mutations show a better response to Imatinib and contribute to a longer overall-survival, mutations in KIT exon 9 as well as the PDGFRA gene show an inferior response to Imatinib.[11,12]

Some adults (10–15%) and most children (85%) with GIST have no mutations in the KIT or PDGFRA genes. These GISTs are referred to as wild-

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type GISTs with mutations in the succinate dehydrogenase (SDH) gene.[13]

Imatinib resistance

Although Imatinib significantly improves both progression-free survival as well as overall-survival in patients with advanced GIST, most patients ultimately develop a resistance to the medication. Patients showing no response to Imatinib or responding to Imatinib less than six months before acquiring resistance are said to have a primary resistance. Patients developing resistance after six months are said to have acquired a secondary resistance. Among patients with secondary resistance, the median time taken for resistance to develop is close to 24 months,[14] even though long-term survival with Imatinib has been shown.[15]

This unfortunate fact regarding Imatinib resistance has contributed a high-intensive research aiming to either combat Imatinib resistance or to discovering other medications that can be effective after Imatinib resistance. Today, Imatinib is the first-line treatment for advanced GIST. Sutent (sunitinib) and Stivarga (regorafenib) are second- and third-line treatments for advanced GIST, respectively.[16] Unfortunately, both Sunitinib and Regorafenib have a limited effect since resistance to these medications develops promptly; the median time to tumor progression in Sunitinib is 27.3 weeks,[17] while the same figure for Regorafenib is 20.8 weeks.[18] Sunitinib and Regorafenib were approved by the FDA for the treatment of advanced GIST in 2006[19] and 2013,[20] respectively. Figure 1 summarizes the timeline for the most important findings pertaining to a discussion of GIST.

The aim of this review is to summarize current pharmacological trials in advanced GIST treatment.

Method

The website ClinicalTrials.gov, maintained by the United States National Library of Medicine, is a database containing information on various clinical trials regarding a variety of diseases and conditions. The website is the largest world-wide registry and contains information on clinical trials from more than 200 countries.[21,22]

The advanced search option at ClinicalTrials.gov was used until 31 December 2018, to search for active clinical trials registered in the database regarding pharmacological treatment of advanced GIST. Advanced GIST is defined as GIST – regardless of its primary origin – that has metastasized and is unresectable.

Clinical trials on a pediatric population (<18 years) were excluded from the search. No options were chosen in the advanced search subcategories of ''Targeted Search,'' ''Locations'' or ''Additional Criteria''. Figure 2 shows the variables selected and used.

The search results were then read through. Titles, and if needed their descriptions, were read in order to evaluate whether the study was focused on the pharmacological treatment of patients equal to or over 18 years of age with advanced GIST. The included trials were read thoroughly, and their objectives, methods and possible results retrieved.

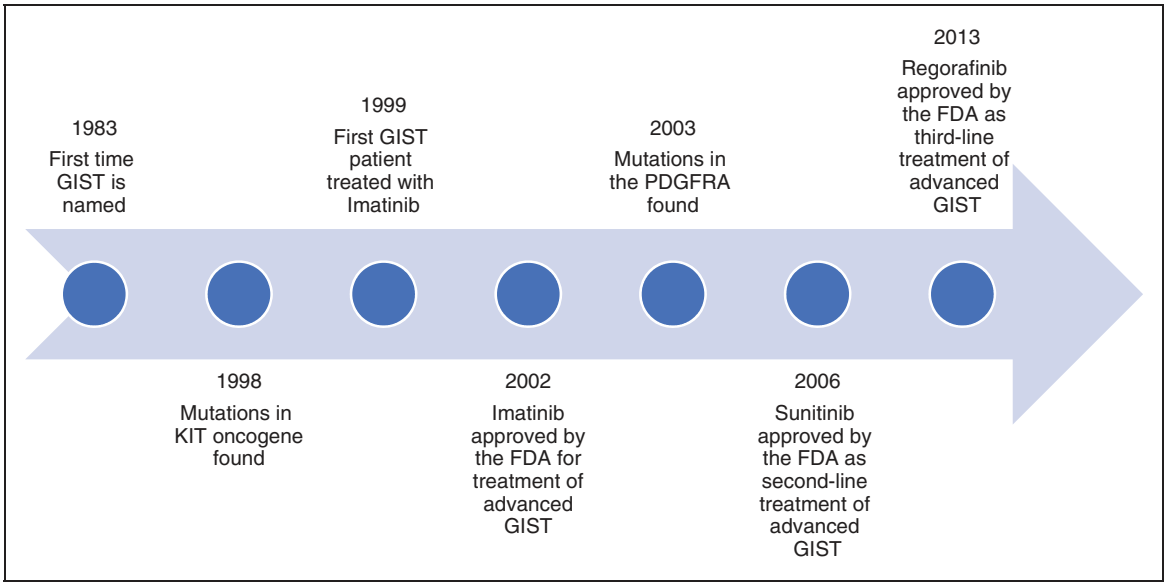

Figure 1. Timeline of the most important events in GIST. GIST: gastrointestinal stromal tumor.

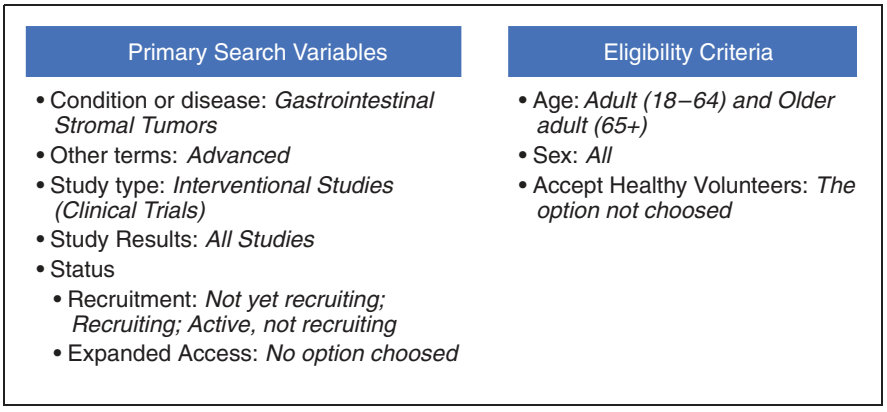

Figure 2. Advanced search variables on ClinicalTrials.gov.

Results

A total of 25 trials was identified, all of which are included in this study (Table 1). The first included trial started in 2010 and the latest in 2018. Most of the included trials started in 2018 ($n = 7$; 28%) and the majority of the trials are "Recruiting" ($n = 14$; 56%) followed by "Active, not recruiting" ($n = 10$; 40%). Most of the trials study tyrosine-kinase inhibitors (TKIs) ($n = 10$; 40%) followed by medications used in immunotherapy ($n = 6$; 24%). The remainder of the trials ($n = 9$; 36%) study medications with other activities.

TKIs

Regorafenib

In 2010, a phase 2 trial was started, evaluating the activity of Regorafenib in advanced GIST patients.[23] According to ClinicalTrial.gov, the trial is "Active, not recruiting," though it has in fact ended, as the results have been published both in 2012[24] and in 2016.[25] The trial was conducted in three locations in the US and was an open-label phase 2 trial with an estimated enrollment of 34 patients. At the end of the study, 33 had been included. The inclusion criteria were patients with advanced GIST who had failed on both Imatinib and Sunitinib. The included patients were prescribed 160 mg of Regorafenib daily for 21 days, with a 7-day medication free period. The primary outcome was clinical benefit defined as either complete response, partial response or stable disease lasting for 16 weeks.

The trial's results show a significant activity and benefit in advanced GIST patients' resistance to Imatinib and Sunitinib,[24,25] and contributed to the GRID trial which showed a significant effect of Regorafenib on progression-free survival in advanced GIST patients failing on both Imatinib and Sunitinib.[18] The GRID trial led to the approval of Regorafenib as the third-line treatment for advanced GIST.

ALT GIST and SURE

The SURE trial is a non-randomized, single-arm and open-label phase 1b study started in 2014 at a single center in the US.[26] The trials' estimated enrollment is 35 patients. All advanced GIST patients failing on at least Imatinib, Sunitinib and Regorafenib are included. The trial is planned to have two cohorts; one cohort in which dose-escalation and dose-finding are evaluated, and a dose-expansion cohort. The trial studies alternating treatment of Sunitinib and Regorafenib. Included patients are to take Sunitinib for three days and Regorafenib for four days every week. The primary outcome is adverse events.

A phase 2 trial, the ALT GIST,[27] was started in 2015 in 25 different locations all over the world. The study is an open-label randomized trial where advanced GIST patients with no prior TKI for metastatic disease were included and randomized to one of two arms. Arm A entails continuous treatment with 400 mg of Imatinib daily, while Arm B entails treatment with 400 mg of Imatinib daily for 21–25 days, followed by a medication free period of 3–7 days, and then 160 mg of Regorafenib daily for 21 days, followed by a medication free period of 7 days. The estimated enrollment is 240 patients. The primary outcome of the ALT GIST trial is progression-free survival at 24 months as determined in accordance with the RECIST criteria.

Famitinib

Another phase 2 trial evaluates Famitinib.[28] The trial is single-arm, open-label and multicenter. Patients with advanced GIST resistant to Imatinib are eligible for inclusion and a total of 88 patients have been included in the trial, each receiving 25 mg

Table 1. Summary of included trials.

Title	Started	Phase	Primary outcome	Nr.
A study of AUY922 for GIST (gastrointestinal stromal tumor) patients	2011	2	Disease control rate.	NCT01389583
A study of famitinib in patients with gastrointestinal stromal tumor	2012	2	Disease control rate.	NCT02336724
Efficacy and safety of PD-0332991 in patients with advanced gastrointestinal stromal tumors refractory to Imatinib and Sunitinib	2013	2	Efficacy assessment.	NCT01907607
MEK162 in combination with Imatinib mesylate in patients with untreated advanced gastrointestinal stromal tumor (GIST)	2013	1 and 2	Maximum tolerated dose and best response rate.	NCT01991379
Ipilimumab and Imatinib mesylate in treating participants with metastatic or unresectable solid tumors	2013	1	Safety and toxicity profile, maximum toxic dose and dose limiting toxicities.	NCT01738139
Phase Ib study of SUnitinib alternating with REgorafenib in Patients with metastatic and/or unresectable GIST (SURE)	2014	1	Dose-escalation.	NCT02164240
BGJ398 in combination with Imatinib mesylate in patients with untreated advanced gastrointestinal stromal tumor (GIST)	2014	1 and 2	Maximum tolerated dose and response rate.	NCT02257541
Study of the glutaminase inhibitor CB-839 in solid tumors	2014	1	Safety and tolerability.	NCT02071862
(NAVIGATOR) Study of BLU-285 in patients with gastrointestinal stromal tumors (GIST) and other relapsed and refractory solid tumors	2015	1	Maximum tolerated dose, adverse and serious adverse events, as well as overall response rate.	NCT02508532
A randomised trial of Imatinib alternating with Regorafenib compared to Imatinib alone for the first line treatment of advanced gastrointestinal stromal tumour (GIST) (ALT GIST)	2015	2	Progression free survival at 24 months.	NCT02365441
PLX9486 as a single agent and in combination with PLX3397 or PLX9486 with Sunitinib in patients with advanced solid tumors	2015	1 and 2	12 outcomes, among others: adverse events, and clinical benefit rate.	NCT02401815
A safety, tolerability and PK study of DCC-2618 in patients with advanced malignancies	2015	1	Safety and tolerability, Maximum tolerated dose and antitumor activity.	NCT02571036
Randomized trial of crenolanib in subjects with D842V mutated GIST	2016	3	Progression-free survival or death.	NCT02847429
A study to evaluate the safety of intuvax administered intra-tumorally in patients with gastrointestinal stromal tumors	2016	1	Changes in vital signs, changes in lab parameters and adverse events.	NCT02686944
A Study of LY2880070 in Participants with advanced or metastatic cancer	2016	1 and 2	Maximum tolerated dose.	NCT02632448
A Study of BBI503 in adult patients with advanced gastrointestinal stromal tumors	2017	2	Disease control rate.	NCT02232620
A study of MEK162 (Binimetinib) in combination with pexidartinib in patients with advanced gastrointestinal stromal tumor (GIST)	2017	1	Recommended phase II dose.	NCT03158103
Nivolumab and ipilimumab in treating patients with rare tumors	2017	2	Tumor response.	NCT02834013

(continued)

Table 1. Continued.

Title	Started	Phase	Primary outcome	Nr.
Temozolomide (TMZ) in advanced succinate dehydrogenase (SDH)-mutant/deficient gastrointestinal stromal tumor (GIST)	2018	2	Overall response rate at 6 months.	NCT03556384
A Study of DCC-2618 vs. Sunitinib in advanced GIST patients after treatment with Imatinib	2018	3	Progression-free survival.	NCT03673501
Phase 3 study of DCC-2618 vs. placebo in advanced GIST Patients Who have been treated with prior anticancer therapies	2018	3	Progression-free survival.	NCT03353753
(VOYAGER) Study of Avapritinib vs. Regorafenib in patients with locally advanced unresectable or metastatic GIST	2018	3	Progression-free survival.	NCT03465722
Epacadostat and pembrolizumab in patients with GIST	2018	2	Overall response rate.	NCT03291054
PDR001 plus Imatinib for metastatic or unresectable GIST	2018	1 and 2	Maximum tolerated dose, recommended dose for expansion and disease control rate.	NCT03609424
A study of XmAb® 18087 in subjects with NET and GIST	2018	1	Safety and tolerability, and maximum tolerated dose.	NCT03411915

Famitinib daily. The primary outcome is disease control rate at 12 weeks.

PLX9486

In 2015, a phase 1b/2a trial was started, evaluating PLX9486 as a single agent (phase 1b) and PLX9486 in combination with either PLX3397 or Sunitinib (phase 2b) in patients with advanced GIST.[29] The study is a non-randomized and open-label trial, in which patients with advanced treatment-refractory GIST are included. Fifty-two patients have been included and the primary outcomes are, among others, adverse events and a clinical benefit rate at one year.

Crenolanib

Crenolanib is studied in an international multi-center, randomized, double-blind, placebo-controlled, phase 3 trial which started in 2016. The estimated enrollment is 120 patients, and the inclusion criteria are advanced GIST with a D842V mutation in the PDGFRA gene.[30] Included patients are randomized to either 100 mg of Crenolanib or placebo three times daily. The primary outcome is progression-free survival or death at three years.

NAVIGATOR and VOYAGER

Two ongoing trials are the NAVIGATOR[31] and VOYAGER,[32] which are studying the effects of BLU-285 (also known as Avapritinib) in patients with advanced GIST. The NAVIGATOR is a phase 1, open-label, international multi-center trial hoping to include 250 patients with advanced GIST. The trial started in 2015 and studies dose-escalation (part 1) and expansion (part 2). Patients with GIST failing on Imatinib and at least one more TKI, or who have a GIST with a mutation in the D842V of the PDGFRA gene, are eligible for inclusion and receive Avapritinib on a daily basis. The three primary outcomes for the trial are maximum tolerated dose, rate of adverse events and overall response rate.

The VOYAGER is a phase 3, open-label, randomized, international multi-center trial with an estimated enrollment of 460 patients. The trial started in 2018 and patients with advanced GIST failing on Imatinib and at least one more TKI are eligible, and upon inclusion will be randomized to either Regorafenib (160 mg for three weeks and one-week medication free) or Avapritinib (300 mg daily). The primary outcome is progression-free survival at 24 months.

DCC-2618

There are three trials connected to the evaluation of the drug DCC-2618. The first one started in 2015 as a phase 1, open-label, dose-escalation, international multi-center trial in which 320 patients were estimated to be enrolled.[33] All patients with an advanced GIST failing on one TKI regimen were eligible for inclusion. The three primary outcomes for the trial were safety of DCC-2618, the maximum tolerated dose and the

ani-tumor activity of the drug. Although listed as "Recruiting" on ClinicalTrials.gov, the trial has ended. In this phase 1 trial, DCC-2618 showed positive responses in 141 of the included GIST patients. A recently published abstract states that the safety and tolerability of the DCC-2618 were good and that of the 114 GIST patients followed, 73% remained on active treatment as 56 patients have received the medication for more than six months.[34]

The second study, named INVICTUS, is a randomized, double-blind, placebo-controlled and international multi-center phase 3 trial, which started in 2017. A total of 129 patients with advanced GIST having progressed on Imatinib, Sunitinib and Regorafenib have been included in the trial. The patients were randomized in a 2:1 ratio to either Arm A (DCC-2618, 150 mg on a daily basis) or Arm B (placebo on a daily basis). The primary outcome is progression-free survival at 15 months.[35]

The third and last study, the INTRIGUE, is a randomized, open-label, international multi-center phase 3 trial, which started in 2018.[36] The estimated enrollment is 358 patients who are diagnosed with advanced GIST and have progressed on Imatinib. These patients are randomized to either Arm A (DCC-2618, 150 mg on a daily basis) or Arm B (Sunitinib, 50 mg on a daily basis for 4 weeks, and a medication free period of two weeks). The primary outcome is progression-free survival at 30 months.

Immunotherapy

Ipilimumab

A phase 1 trial was started in 2012 in which Ipilimumab, a monoclonal antibody, was used together with Imatinib in patients with advanced solid tumors, including GIST.[37] The study, a single-group, single-center and open-label trial, had an estimated enrollment of 96 patients. Patients with advanced GIST received intravenous Ipilimumab every three weeks in combination with a daily intake of Imatinib. The primary outcomes were adverse events and maximum tolerated dose. Although the status of the trial at ClinicalTrial.gov is given as "Recruiting," the results have been published and show that a total of nine GIST patients were included in the study. All of them had previously received at least two different TKIs. Only one of the GIST patients showed a partial response. The patient had a so-called wild-type GIST.[38] The authors of the study state that the medication has a low tumor activity, which is why the chances of a phase 2 or phase 3 trial seem unlikely.

Another trial on monoclonal antibodies, started in 2016, evaluates the effects of Nivolumab and Ipilimumab in solid tumors, among them GIST.[39] The trial is an open-label, single-arm phase 2 study in which advanced GIST patients failing on at least one TKI regimen are eligible for inclusion. The estimated enrollment is 707 patients who are administered medications in a 42-day cycle. On days 1, 15 and 29, they receive intravenous Nivolumab, and on day 1 intravenous Ipilimumab. The primary outcome is overall tumor response rate (complete or partial tumor response), and the trial has a time frame of up to 10 years.

Intuvax

In 2016, a trial was started, which evaluates the safety and effects of Intuvax, pro-inflammatory allogeneic dendritic cells, in patients with advanced GIST failing on at least two previous TKI regimens.[40] The trial is a single-armed, open-label phase 1 study in which an estimated amount of 12 patients are treated with an Intuvax injection in a tumor on two (patients 1 to 6) or three (patients 7 to 12) occasions. The primary outcomes are changes in vital signs, lab parameters and the incidence of adverse events.

Epacadostat and pembrolizumab

In 2017, a third study with monoclonal antibodies was started.[41] The study, an open-label, multi-center, single-arm, phase 2 trial, has an estimated enrollment of 23 patients. The inclusion criteria are patients with advanced GIST failing on at least two TKI regimens. The trial aims to evaluate overall response rates (complete response, partial response, progressive disease, and stable disease) of the IDO inhibitor Epacadostat, with 100 mg orally administered twice a day, and the anti-PD-1 antibody Pembrolizumab, with 200 mg intravenously administered every three weeks, during the first 24 weeks.

XmAb18087

A fourth study with a monoclonal antibody, XmAb18087, was started in 2018 and focuses both on patients with advanced GIST and patients with neuroendocrine tumors.[42] This open-label, single-arm, multi-center phase 1 trial has an estimated enrollment of 87 patients. Regarding GIST, patients with advanced GIST failing on all available TKIs approved for GIST (Imatinib, Sunitinib and Regorafenib) are eligible for inclusion. Included patients receive XmAb18087 on days 1, 8, 15, and 22 of a 28-day cycle. The primary outcomes of the trial are safety and tolerability of the medication, as well as maximum tolerated dose and recommended dose.

PDR001

A fifth study with a monoclonal antibody, PDR001, in combination with Imatinib was also started in 2018.[43] The study is an open-label, single-arm, single-center phase 1b/2 trial with an estimated enrollment of 41 patients. Patients with advanced GIST failing on Imatinib, Sunitinib and Regorafenib are eligible for inclusion. Included patients receive a combination of both PDR001 and Imatinib; 400 mg of PDR001 is intravenously administrated once a week. Between 200 and 400 mg of Imatinib is orally administrated each day. While the primary outcomes for phase 1b are maximum tolerated dose and recommended dose expansion, the primary outcome for the phase 2 trial is rate of disease control at 12 weeks, defined as objective response and stable disease.

Other medications

AUY922

This is an open-label, single-armed phase 2 trial with an estimated enrollment of 25 patients, which started in 2011. Patients with advanced GIST who failed on Imatinib and Sunitinib received 70 mg of intravenous AUY922, a heat shock protein 90, every week.[44] The primary outcome of the study was rate of disease control defined as complete response, partial response or stable disease equal to or longer than four months.

Although the status of the trial at ClinicalTrial.gov is given as ''Recruiting,'' the study has ended, and the results have been published. Of the 25 patients included, 21 were evaluated in regard to tumor response. One patient had an objective response and 15 had a best response of stable disease. The median progression-free survival and median overall survival for all of the included cohort were 3.9 months respective 8.5 months. The authors conclude that the results are the same as that of a placebo in the treatment of GIST, and that heat shock protein 90 may have a limited role in the treatment of GIST.[45]

CYCLIGIST

The CYCLIGIST trial started in 2013 and aims to evaluate the efficacy and safety of PD-0332991, a CDK 4/6 inhibitor, in patients with advanced GIST failing on Imatinib and Sunitinib.[46] A single-arm, multi-center, phase 2 trial, the CYCLIGIST estimates a patient enrollment of 63, who receive 125 mg of the medication orally, on a daily basis for three weeks, with a one week medication free period. The primary outcome is efficacy assessment defined as no disease progression (complete response, partial response and stable disease) at four months.

MEK162

This is a combination study with the MEK inhibitor MEK162 and Imatinib, started in 2013.[47] This phase 1b and phase 2 trial is open-label, single-arm and single-center, estimating to enroll 62 patients. For the phase 1b trial, advanced GIST patients failing on Imatinib are eligible for inclusion. For the phase 2 trial, the patients must either not have been treated with Imatinib or not used adjuvant Imatinib for at least the last three months. Phase 1b is further divided into two different parts: the dose escalation and dose expansion parts. Primary outcome for phase 1b and 2 trials is maximum tolerated dose and best response rate at two years (complete response or partial response), respectively.

In 2017, an open-label, single-arm, single-center phase 1 study was started.[48] The primary outcome is to determine a recommended dose for a coming phase 2 trial, and three patients have been enrolled. The trial evaluates MEK162 (30 mg twice daily) in combination with Pexidartinib (600 mg daily), a CSF1R inhibitor. Patients with advanced GIST are eligible for inclusion in the dose escalation part of the trial, while patients with advanced GIST failing on Imatinib treatment are eligible for the dose expansion part.

Imatinib and BGJ398

Another study evaluating a combination therapy consisting of Imatinib and BGJ398 (a pan-fibroblast growth factor receptor antagonist), was started in 2014.[49] This is an open-label, single-arm, multi-center phase 1b and phase 2 trial. The estimated enrollment is 62 patients. Patients with advanced GIST failing on Imatinib are eligible for inclusion in the phase 1b trial, while patients with advanced GIST still not receiving any TKI treatment are eligible for inclusion in the phase 2 trial. The primary outcome for phase 1b is maximum tolerated dose, and for phase 2 it is tumor response defined as complete or partial response. On ClinicalTrial.gov, the trial is listed as ''Active, not recruiting,'' although the trial has ended. The results from the phase 1b trial were recently published and show that of the 16 patients included only 12 were analyzed in regard to tumor response; 3 of the 12 (25%) showed stable disease for over 32 weeks. Furthermore, the rate of toxicity was high, explaining why the trial was stopped and not continued into a phase 2 study as planned.[50]

CB-839

A phase 1 trial on solid tumors, among them SDH deficient GIST, started in 2014.[51] This is an open-label, single-arm, multi-center trial evaluating the safety and tolerability of CB-839, a glutaminase

inhibitor. The estimated enrollment is 205 patients, and patients with various solid tumors failing on all available medications are eligible for inclusion. The trial is further divided into two parts: part 1 is a dose escalation study and part 2 will evaluate the medication in regard to eight different types of solid tumors, one of them being SDH deficient GIST.

BBI503

An open label, multi-center, phase 2 study which started in 2014, this trial includes patients with advanced GIST failing on currently approved medications.[52] The trial evaluates the effect of BBI503, a cancer cell stemness kinase inhibitor, on tumor response defined as complete response, partial response or stable disease at right weeks. The actual enrollment is, according to the information available on ClinicalTrials.gov, two patients.

LY2880070

An open-label, parallel-assignment, multi-center phase 1b and phase 2a trial was started in 2015, in which the CHK1 inhibitor LY2880070 was evaluated in patients with advanced cancer, including GIST.[53] The trial plans to enroll 151 patients with advanced cancer failing at least on one systematic therapy, and consists of two parts: monotherapy with LY288070 and combination therapy with LY288070 and Gemcitabine. The primary outcome of the trial is maximum tolerated dose. Secondary outcomes are, among others, progression-free and overall survival at four and one year, respectively.

Temozolomide

In 2018, a study evaluating the overall response rate of Temozolomide, an oral chemotherapy, on SDH deficient GIST was started.[54] The study is an open-label, single-arm, single-center phase 2 trial with an estimated enrollment of 23 patients. Included patients will receive Temozolomide (85 mg) orally each day for three weeks, followed by one week without the administration of Temozolomide. The primary outcome of the trial is overall response rate at six months.

Discussion

The above review summarizes 25 current pharmacological trials in advanced GIST as registered on ClinicalTrials.gov. Some of the trials are shown to have ended, while most of the included studies are still ongoing. For many of them it will, however, be years before any preliminary or final results can be presented. Nonetheless, this review is believed to be of value as it can function as a knowledge support for both researchers and clinicians in the field of GIST, indicating which studies are currently ongoing.

TKIs

This review showed that most of the trials included, focus on the study of TKIs ($n = 10$; 40%). Looking at the ongoing TKI-trials, the common theme is to either overcome resistance to current TKIs or find new medications for the treatment of GIST. In discussing the former, both the ALT GIST[27] and SURE[26] trials are studies trying to overcome, or at least delay, resistance to TKI. Both trials hypothesize that alternating pharmacological treatment (Imatinib versus Regorafenib and Sunitinib versus Regorafenib respectively) will allow tumor stem cells to again enter the cell cycle and thus be susceptible to a TKI once again. Alternating regimens in cancer treatment has previously been shown to be effective.[55–59] However, since GIST cells have shown a disturbing persistence regarding TKI-resistance irrespective of the TKI and its function, it remains highly dubious as to how effective an alternating regimen is in the treatment of GIST.

In regard to developing a new medication or studying a current medication that can be used in the treatment of GIST, this review shows that there are three interesting trials (Famitinib, PLX9486 and Crenolanib) and four highly promising trials (NAVIGATOR, VOYAGER, INVICTUS and INTRIGUE).

Famitinib, a Sunitinib analogue, is a multi-targeting TKI. It was evaluated in a phase 1 trial and showed good tolerability. A total of 55 patients were included in the trial, of which two were diagnosed with GIST. One of the GIST patients who had not previously treated with any TKIs showed a significant response, having a progression-free survival of 31.5 months. The other GIST patient showed a tumor regression of less than 30%.[60] The long-term effect of Famitinib in regard to progression-free survival in one of the patients is probably due to the fact that the patient was treatment-naïve. It has previously been shown that other TKIs may be as good or even better than Imatinib in patients with treatment-naïve GIST.[61,62] However, the anti-tumor activity of Famitinib in GIST, shown in the phase 1 trial despite the few patients included, is worth studying further and may have some limited effect on patients failing on the three approved TKIs for the treatment of GIST.

In regard to PLX9486, a recent abstract states that 36 patients with advanced GIST were included in the study and showed good tolerability for both PLX9486 as a monotherapy and also in combination with PLX3397 and Sunitinib. PLX9486 showed some

anti-tumor activity as two out of 31 patients had a partial response, and a progression-free survival of more than 24 weeks was observed. PLX9486, in combination with PLX3397, showed a partial response in 1 out of 11 patients. The median progression-free survival in this study was not reached at the time the abstract was published.[63] The full results of this trial, not least its phase 2, are yet to be published. These results are, nonetheless, somewhat disappointing in comparison to in vitro and in vivo studies showing encouraging anti-tumor activity of PLX9486.[64]

In contrast to most of the drugs discussed in this review, Crenolanib is a TKI with the unique quality of having a promising activity in GISTs with D842V mutation in the PDGFRA gene. In a previous study on PDGFRA-mutant kinases resistance to Imatinib, Crenolanib showed a significant effect on the cell lines studied.[65] For this reason, it is recommended that Crenolanib should already be considered as the treatment of such GIST patients.[66] Whatever the final results of the Crenolanib trial[30] may be, Crenolanib has already shown that a treatment for D842V mutation in the PDGFRA gene is highly possible and that more research is required.

The NAVIGATOR and the VOYAGER are two highly promising and important ongoing trials studying the effects of Avapritinib in patients with GIST. The background of the trials is a previous study on three patient-derived xenograft GIST models with mutations in the KIT gene, in which Avapritinib was compared to a vehicle, Imatinib and Regorafenib at different doses. In all models, Avapritinib showed a significant anti-tumor activity, as well as indications of being superior to both Imatinib and Regorafenib.[67] Avapritinib has thus yielded highly promising results, and these two present trials offer a large amount of hope. We may, in fact, be looking at a possible fourth-line treatment for patients with advanced GIST.

The INVICTUS and the INTRIGUE studies are two other promising trials studying DCC-2618 and its effects on patients with advanced GIST. A highly potent and selective inhibitor of mutant KIT and PDGFRA, similar to Avapritinib, DCC-2618 is a good and capable candidate for, at least, the fifth-line treatment of advanced GIST. In fact, the INTRIGUE trial may very well remove Sutent as the third-line treatment, in favor of DCC-2618.

Immunotherapy

Almost a quarter ($n = 6$; 24%) of the included trials studied different immunotherapy drugs in patients with advanced GIST. Immunotherapy has shown significant and revolutionary effects in different cancer forms, and it is thus really no surprise that such research has also been conducted in regard to GIST. Of the six immunotherapy trials, five concern monoclonal antibodies, of which four are ongoing (Nivolumab and Ipilimumab, Epacadostat and Pembrolizumab, XmAb18087, and PDR001).

In discussing the combination therapy of Nivolumab and Ipilimumab,[39] an interim analysis of 14 included patients showed that three out of seven patients treated with Nivolumab alone had stable disease and a progression-free survival of eight weeks. In the group treated with the combination of Nivolumab and Ipilimumab, two out of five patients showed partial response and stable disease respectively.[68] The results are thus interesting, and the full results may well show the positive effects of immunotherapy on GIST which many hope for.

In regard to the combination therapy with Epacadostat and Pembrolizumab, a previous study of 62 patients with solid tumors, none having GIST, who received the above regimen, achieved inspiring results when the objective response of the tumors was measured.[69] Whether the same effects can be achieved in advanced GIST patients remains to be seen.

The two other monoclonal antibody treatments, XmAb18087 and PDR001, have both showed notable anti-tumor activities. While XmAb18087 has shown potent anti-tumor activity in both in vitro and in vivo studies,[70] the PDR001 has, in a previous phase 1 study on patients with advanced solid tumors, shown that the medication is well tolerated and has a sound safety profile.[71]

The Intuvax trial is the only non-monoclonal antibody trial. Intuvax activates the immune system when administered intratumorally and has previously been used in the treatment of renal and hepatic malignancies with promising results. This allows for the speculation that a positive effect may also be observed in patients with GIST.[72]

Other medications

Nine trials (36%) study medications not deemed to be TKIs or immunotherapy. Seven of the studies are ongoing (CYCLIGIST, two trials on MEK162, CB-839, BBI503, LY2880070 and Temozolomide).

The CYCLGIST trial studies PD-0332991.[46] The drug has previously shown some promising results in the treatment of breast cancer,[73] in various types of human tumor xenografts[74] and in the treatment of liposarcoma,[75] which is why it may also have a positive effect in the treatment of GIST.

Two trials on MEK162 were identified: a combination therapy with MEK162 and Imatinib,[47] as well as a combination therapy with MEK162 and Pexidartinib.[48] In discussing the former, a recently

published abstract on the phase 1b study of the trial shows that the included patients ($n = 18$) displayed a good tolerability for the drug, and that of the 15 patients evaluated by radiology, five had partial response in accordance with the Choi criteria. Further, nine had stable disease at eight weeks as measured in accordance with the RECIST criteria.[76] In discussing the latter trial (MEK162 and Pexidartinib), a previous study has shown that Pexidartinib has an efficacy superior to Imatinib when administrated to preclinical GIST models.[77] Together with MEK162, which has shown interesting results in the treatment of melanoma[78] and cancer of the biliary tract,[79] it is believed that GIST cancer cells can be more effectively inhibited.

CB-839 is another drug which is evaluated for the treatment of advanced GIST, and is probably one of only a few drugs in this review for which we have very limited information regarding its effect on GIST. In combination with Everolimus and Cabozantinib, CB-839 has yielded highly encouraging results in the treatment of renal cell cancer[80] and was recently granted the FDA fast track designation for metastatic renal cell carcinoma.[81] The role of CB-839 in GIST is unclear, which indicates the current trial's importance.

Another drug that is quite unknown in regard to GIST treatment is BBI503. It remains to be seen how effective this treatment is in advanced GIST patients, but the notion of using it is quite interesting. In 2010, researchers published results indicating that resistance to TKIs is caused when cancer cells show a lack of dependence to KIT, and that medications targeting cancer stem cells may be effective.[82]

LY2880070 is a CHK1 inhibitor and has previously shown a disturbing toxicity profile,[83] which is why the phase 1b trial presented above is important for evaluating the toxicity of the drug. The drug has an interesting record; in a recently published phase 2 trial on high-grade serous ovarian cancer, LY2880070 contributed to partial response in 8 out of 28 women included.[84] LY2880070 thus shows a promising antitumor activity.

The Temozolomide trial is perhaps one of the more interesting trials since Temozolomide is a chemotherapy, and it is well-known that GISTs are highly resistance to chemotherapy. Furthermore, a previous phase 2 trial on patients with advanced GIST and other soft tissue sarcomas has shown Temozolomide to have a limited effect. The trial included 60 patients of which 19 had GIST. The GIST patients received 85 mg of Temozolomide orally for 21 days, followed by a 7-day medication free period. No objective response was seen in 17 of the 19 GIST patients, and the median time to disease progression was 2.3 months. The authors concluded that Temozolomide has little activity on patients with GIST.[85]

This current Temozolomide trial registered on ClinicalTrials.gov is though focused on SDH deficient GIST, which has a different pathology than regular KIT GIST.[54] However, a previous study has shown a limited effect of chemotherapy in SDH deficient GIST as well.[86]

Conclusion

There are numerous ongoing clinical trials on the treatment of advanced GIST. Although the focus of this current review is on pharmacological treatments, there are also ongoing surgical trials. This current review has summarized the ongoing pharmacological clinical trials on GIST as registered on ClinicalTrials.gov and shows that there are several trials that are highly promising and encouraging.

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