Review

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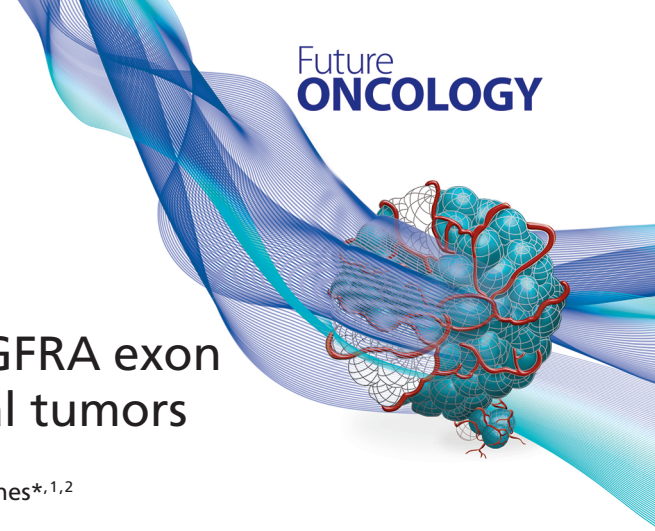

Avapritinib in the treatment of PDGFRA exon 18 mutated gastrointestinal stromal tumors

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Gastrointestinal stromal tumors (GIST) can be molecularly classified based on different subtypes including mutations in *KIT* and *PDGFRA*. Patients with *PDGFRA* mutations are an important subgroup that commonly arise in the stomach and are associated with a more indolent disease course. Importantly, the most common *PDGFRA* molecular subtype, the D842V mutation in exon 18 of the gene which alters the activation loop, is imatinib insensitive in *in vitro* studies. Poor responses to imatinib have been seen clinically compared with *PDGFRA* exon 18 non-D842V-mutated GIST. Avapritinib (BLU-285) is a potent *KIT and PDGFRA*-specific tyrosine kinase inhibitor which has shown >90% response rates in patients with *PDGFRA* exon 18 D842V-mutated GIST. Results from the Phase I trial of avapritinib have indicated that this drug should be the standard of care for patients with *PDGFRA* exon 18 D842V-mutated GIST.

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Gastrointestinal stromal tumors (GIST) can occur anywhere within the digestive tract, though are most commonly found in the stomach and small intestine. GIST are the most common mesenchymal tumor of the gastrointestinal (GI) tract and their cell of origin is thought to be related to the interstitial cells of Cajal [1].

The molecular subtype of GIST is both prognostic and predictive, and molecular testing is considered standard of care for patients undergoing systemic therapy [2]. The majority, around 95% [3], of GIST are positive for c-KIT (CD117) by immunohistochemistry [4]. Around 70–80% of these patients have a *c-KIT* mutation which leads to constitutional kinase activation [3]. The most common mutations affect the juxtamembrane domain of exon 11 (61–71%) causing ligand-independent activation [3,5]. *PDGFRA* mutations represent the oncogenic molecular alteration in 28–35% of non-*KIT*-mutated GIST and are mutually exclusive of *c-KIT* mutations [3,6–8]. Specifically, the frequency of patients with activating *PDGFRA* mutations in Phase III clinical trials is 1.6–2.7% [9], whereas in population studies the incidence is between 7.9 and 14% [9,10]. This may be due to the higher rates of relapse-free survival seen in patients with *PDGFRA* mutations [9]. The most common *PDGFRA* mutation is exon 18 D842V [8] followed by other mutations in exon 18, exon 12, exon 14 and exon 4 [3,11]. Non-*KIT*/*PDGFRA*-mutated GIST subtypes include *NF1*-related, *PI3KCA*, mutations deficiencies in the succinate dehydrogenase complex, *BRAF* mutant and quadruple wild-type (succinate dehydrogenase, *KIT*, *PDGFRA* and *NF1* proficient) [5].

For patients with localized GIST, surgery followed by either surveillance (low-to-intermediate risk) or adjuvant imatinib (high risk) GIST is a standard of care [2,12]. Patients with GIST are risk stratified based on size, location and mitotic rate [13]. For patients who present with metastatic disease, systemic therapy with the tyrosine kinase inhibitor (TKI) imatinib is a standard first-line treatment [2]. However, within the relatively uncommon *PDGFRA* molecular subtype, there is a growing body of literature demonstrating differential responses to imatinib in patients with *PDGFRA* exon 18 D842V mutations and nonexon 18 D842V mutations [10,14,15].

This Review will address the treatment of patients with *PDGFRA* exon 18 mutations in the context of the development of the TKI avapritinib.

PDGFRA mechanism of oncogenesis

KIT and *PDGFRA* belong to the same sub-family of Type III receptor tyrosine kinases which transmit downstream signals via JAK/STAT, Ras/ERK, PI3K and AKT pathways [3]. Although the downstream signaling pathways of *KIT* and *PDGFRA* mutant GIST were thought to be similar, gene expression profiling has shown that each class of mutations display differential expression of downstream signaling pathways. In an analysis of 26 GIST, there were higher levels of *AKT*/*PI3K* pathway genes in *KIT*-mutated GIST, while higher levels of genes associated with T-cell receptor signaling were seen in *PDGFRA*-mutated GIST [16]. Whereas, a similar study of 22 GIST suggested variations in expression of 70 genes between *PDGFRA*- and *KIT*-mutated GIST [17]. Though further work is required to fully understand the clinical implications of differential gene expression, it has become clear that an important clinical distinction for some subgroups of patients with *PDGFRA* mutations is a lack of sensitivity to TKI therapy.

The most common mutation is a single nucleotide substitution 2664A→T leading to D842V activating mutation [18]. This mutation results in distortion of the kinase activation loop causing an altered protein conformation which favors the active structure. This leads to imatinib insensitivity in D842V mutants as imatinib can only bind to the inactive form of PDGFRA [5].

The second most common activating substitution is on exon 12, 1821T→A causing the V561D mutation. Other rare mutations including substitutions, deletions, duplications and insertions have been reported that are physically close to exon 18 D842V or exon 12 V561D, however, due to their very low incidence, little is known about the specific behavior of these mutations.

Others are physically close to D842V including D842Y, D842I, D846Y, Y849C and D845Y [18].

PDGFRA clinicopathological characteristics

Patients with *PDGFRA* mutations are predominantly male (58.3–70%), with the majority of patients (91–95%) having a gastric primary [8,9,15,19]. More patients have epithelioid or mixed histological subtypes compared with *KIT* mutants which tend to display a spindle cell morphology [19]. This morphological difference may be due to downstream activation of proteins involved in actin reorganization [20].

Patients with *PDGFRA* mutations have a spectrum of clinical presentations, from benign to malignant [8]. Early studies identified their association with more indolent and low risk disease [8,15,21]. More contemporary retrospective studies have also suggested that *PDGFRA* mutant GIST are significantly more often very low/low risk compared with *KIT* mutants (49 vs 26%), more often had tumors in the stomach (91 vs 45%) and more frequently (70 vs 42%) had <5 mitoses per 50 high power field compared with *KIT* mutant GIST [9]. Within this cohort, low mitotic rate and gastric primary correlated with significant increases in the 5-year recurrence-free survival [9].

In a large European retrospective cohort across 12 institutions, *PDGFRA* mutations were found in 11% (382/3510) patients, with only a small proportion (12.5%, 44/365) of these patients having metastatic disease [11]. In a separate large study of 1056 patients with localized GIST who underwent surgery, included 148 patients with *PDGFRA* mutations (13.6%). Patients with tumors harboring *PDGFRA* mutations had a significantly better disease-free survival compared with those with tumors harboring *KIT* exon 9 and 11 mutations (median disease-free survival, not reached vs 45.5 months, respectively). There was no difference in outcome when *PDGFRA* D842V mutants were compared with all other *PDGFRA* mutants [22].

PDGFRA mutations – therapeutic implications

In vitro data have suggested that imatinib response differs between *PDGFRA* mutants. Nearly all exon 18 D842 mutants (apart from D842Y) have been shown to be imatinib resistant [10,14]. Whereas other *PDGFRA* mutants have been found to be imatinib sensitive [10,14], which should be interpreted with caution given the overall small sample size. However, this *in vitro* finding of differential sensitivity dependent on *PDGFRA* mutation has also been reported in patient cohorts [15].

Neoadjuvant/metastatic disease

Data regarding imatinib use in this relatively uncommon subset of GIST are limited. In a retrospective analysis of the large Phase III trials of first-line imatinib [14], there was no difference found in progression-free survival (PFS), overal survival (OS) or response rate (RR) for patients with exon 11, 9 or *KIT*/*PDGFRA* wild-type GIST at imatinib 400 or 800 mg dosage. It should be noted, however, that 15.9% of patients were *KIT*/ *PDGFRA* wild-type, and in total only 1.1% of patients had tumors with *PDGFRA* mutations. Thus, it is difficult to be certain

if there is a differential benefit to imatinib treatment for patients given the rarity of PDGFRA mutations in patients in these trials [14].

Evidence from retrospective cohorts of *PDGFRA* mutant GIST supports differential imatinib sensitivity between different *PDGFRA* mutations. In a European retrospective study, patients with non-*PDGFRA* D842V mutations had improved response with imatinib compared with those with D842V mutations (D842V progressive disease = 68% vs non-D842V = 12%) [11]. There was a statistically significant difference in PFS between patients with tumors with D842V mutations versus other non-D842V exon 18 mutations (2.8 vs 28.5 months, respectively) on imatinib. The OS was poorer for patients with D842V mutations (14.7 months vs not reached for non-D842V mutations) [11]. Patients with D842V mutations, who had PFS greater than 6 months on imatinib had lower mitotic counts, which may suggest more indolent variants of disease rather than true imatinib effect [11].

In a recent Dutch–American registry study of a cohort of patients with *PDGFRA* D842V-mutated GIST, neoadjuvant or palliative intent imatinib resulted in progressive disease for the majority of patients (10/17, 58.9%), with median time to progression of 8 months. Interestingly, the clinical benefit rate was 29.4%, with 11.8% of patients (2/17) showing partial response to imatinib [15]. Consistent with preclinical data [10,14], 100% (8/8) of patients with non-D842V mutations had clinical benefit from imatinib (75% partial response [PR], 25% stable disease [SD]) [15]. The biological mechanism proposed by the authors is multiple GIST clones existing within a patient, with some harboring imatinib sensitive mutations. These results illustrate that even with *in vitro* data suggesting resistance, clinically there may be some rationale in the use of imatinib at some point for patients with D842V mutations in the absence of a clinical trial [15], novel TKIs or exhausting all other lines of therapy.

Adjuvant imatinib

Given small numbers of patients with *PDGFRA* mutations in the Z9001 trial (4.6–6% of patients had *PDGFRA* D842V mutations), benefit of adjuvant imatinib based on retrospective subgroup analysis was not possible [23]. While type of *KIT* mutation was shown in an exploratory analysis to impact patient outcome for the SSGXVIII/AIO randomized trial, there was no difference for patients with *PDGFRA* mutations [24]. However, analysis was likely limited by the relatively small proportion of patients with *PDGFRA* mutations (12.6%).

A Dutch–American retrospective cohort study, found that all of the 3/11 patients with localized disease treated with adjuvant imatinib remained recurrence-free at 23 months [15]. However, given retrospective data showing improved disease free survival (DFS) and overall low risk features of patients with *PDGFRA*, these results may simply be due to the fact that patients with *PDGFRA* overall have a better prognosis, and/or have a more indolent disease course and/or late metastasis [8,15,21].

Treatment with TKIs beyond imatinib

While patients with non-D842V mutations have been shown to benefit from imatinib treatment, limited data exist regarding the benefit of further TKI use within this population given the limited number of patients with exon 18 mutations enrolled on clinical trials and grouping of *PDGFRA* into *KIT*/ *PDGFRA* wild-type GIST [25]. Long-term disease stability in one patient with a *PDGFRA* exon 18 D842V mutation from a small cohort (n = 20) of patients with metastatic GIST on regorafenib has been reported [26]. Instead, within this specific population, focus has shifted to prioritize these patients for enrollment on clinical trials of novel agents.

Development of avapritinib (BLU-285)

Given the *in vitro* and clinical data indicating imatinib resistance within the D842V mutant patient population, there has been a recognition of the therapeutic need for potent *PDGFRA* exon 18 D842V inhibitors. In addition, the *PDGFRA* D842V structural analog mutation on the *KIT* gene (D816V) is involved in the pathogenesis of systemic mastocytosis, which also represents a condition with limited therapeutic options. This recognition led to the rational identification of BLU-285, now known as avapritinib [27]. *In vitro*, avapritinib was selected due to its specificity for *KIT* activation loop mutations and *PDGFRA* mutants. Specifically, its half maximal inhibitory concentration (IC_{50}) is over 3000-times less than imatinib against *PDGFRA* exon 18 D842V mutants [27]. This activity has been confirmed in GIST xenografts, where avapritinib showed dose-dependent decrease in tumor volume for exon 11, exon 11/17 and exon 9 *KIT* mutant xenografts [28]. Notably, in imatinib resistant cell lines (exon11/17 line), avapritinib inhibited tumor progression significantly better than regorafenib [28].

Based on this initial *in vitro* activity, the Phase I NAVIGATOR study was opened in 2015 for patients with advanced GIST who had been treated with at least two lines of TKI or advanced disease with the D842V mutation [29].

Initial results were presented at the American Society of Clinical Oncology 2017 [30]. The dose escalation component of NAVIGATOR has been completed with the maximum tolerated dose 400 mg po daily. For the 25 patients with exon 18 D842V-mutated GIST, tumor regression was seen across all dose levels (30-400 mg orally daily) [30]. Disease control rate was an impressive 100% using either RECIST 1.1 or Choi criteria (Choi: 25/25 PR vs RECIST 1.1 15/25 PR, 10/25) based on central radiological review. The median PFS was not reached for this cohort. Reported common adverse events were nausea (60%, grade 1–43%), fatigue (53%, grade 1–22%) and vomiting (42%, grade 1–29%). Dose limiting toxicities were hyperbilirubinemia, rash, hypertension and memory impairment [30].

Updated results presented at the Connective Tissue Oncology Society 2018 [31] including 231 patients, out of which 56 (24%) had exon 18 D842V-mutated GIST, continued to demonstrate efficacy within this population [31]. The overall response rate (ORR) was 84% (47/56), with 9% (5/56) complete response (CR), 75% PR (42/56) giving a clinical benefit rate of 96% (54/56) by central review per RECIST 1.1. Final results of the NAVIGATOR study are required to confirm these impressive results. With greater numbers of patients and longer follow-up, memory impairment was documented in 26% (60/231) of patients, with the majority of these patients experiencing grade 1 impairment (19%–45/231). No grade 5 adverse events were reported. The response rate in *KIT* mutant GIST was lower, with ORR 26% (PR: 6/23–26%, CR: 0/23) for patients in 3L/4L regorafenib naive GIST, and a lower response rate for patients treated with ≥4 lines of TKI (ORR: 20%, PR: 21/109–19%, CR: 1/109–1%) [31]. However, it is encouraging that these initial response rates are higher than those for current standard of care options sunitinib (second line, RR = 7% [32]) or regorafenib (third line, RR = 4.5% [33]). Notably, a placebo-controlled Phase III trial, INVICTUS, of the novel TKI ripretinib in the fourth line and beyond setting of metastatic GIST also showed promise in this heavily pretreated group [34]. The response rate for ripretinib versus placebo was 9.4 and 0%, respectively, with the PFS 6.3 versus 1 month, respectively. *In vitro* activity suggests that, while both novel TKIs are more potent than imatinib, avapritinib is more potent than ripretinib for D842V mutations [35]. However, it remains to be seen whether ripretinib will have clinical activity against *PDGFRA* exon D842V mutations.

The NAVIGATOR dose expansion has enrolled two cohorts, *PDGFRA* D842V mutant, and unresectable GIST after imatinib and ≥2 previous TKI [31]. Given the American Society of Clinical Oncology [30] and the Connective Tissue Oncology Society [31] presentations congruent with respect to efficacy, the final results of the Phase I trial [36] have shown an impressive ORR and PFS with avapritinib for patients with *PDGFRA* exon 18 D842V mutations. The cognitive effects represent an important adverse event as they are an unfamiliar side effect compared with other TKIs used in oncology. It is important to explore alternative contributing causes. Early recognition is important, as in the majority of cases memory impairment is manageable with a dose delay and reduction [37]. In addition, the five most common adverse events reported were nausea (61%, 46% was grade 1), fatigue (55%, 21% was grade 1, 28% was grade 2), anemia (46%, 25% was grade 3), periorbital edema (40%, 34% grade 1) and diarrhea (39%, 22% was grade 1) [31]. These adverse events are familiar to clinicians as they do have similarity to other commonly used TKIs. In total, 8.7% of patients discontinued avapritinib due to any adverse event.

Based on priority review of preliminary data from the Phase I trial [30,31], on 9 January 2020, the US FDA approved avapritinib for patients with unresectable or metastatic GIST with *PDGFRA* exon 18 D842V mutation with breakthrough therapy designation [38]. This represents the first approved therapy for patients with *PDGFRA* exon 18 D842V mutations [38].

Current clinical practice: patients with *PDGFRA* exon 18 mutations

Given *PDGFRA* exon 18 mutations are relatively uncommon subtype of GIST patients, it is still important to consider such patients for enrollment on clinical trials.

Neo/adjuvant therapy

For patients with localized GIST with molecular confirmation of a *PDGFRA* exon 18 D842V mutation and upfront resectable disease, resection is recommended. If a patient has locally advanced, unresectable disease, given the impressive response rates, clinicians should strongly consider neoadjuvant avapritinib with the aim of downstaging the tumor to enable complete resection. There is currently no evidence for the use of avapritinib in the adjuvant setting for patients with resected disease. Given the known imatinib insensitivity [10,14], guidelines

recommend against adjuvant therapy with imatinib for patients with tumors harboring D842V mutations [2]. However, in patients with known imatinib sensitive *PDGFRA* mutations, if the patient meets criteria for adjuvant imatinib, this should be offered.

Advanced disease

Based on the preliminary Phase I results from NAVIGATOR [39], in the absence of clinical trials, clinicians should attempt to gain access to avapritinib for their patients with D842V mutations.

For patients with *PDGFRA* exon 18 D842V mutations without access to avapritinib, upfront surveillance could be considered for patients with localized disease given their indolent clinical behavior. For symptomatic patients, local therapy including embolization, ablation [40] and even potentially surgery could be considered based on expert consensus. Metastatic disease can behave aggressively and treatment is very challenging without effective systemic therapy. Informed use of standard of care TKIs can be cautiously considered within this patient population. However, based on the preliminary results of the NAVIGATOR study, avapritinib is the current international standard of care for *PDGFRA* exon 18 D842V mutations. We would advocate for availability of avapritinib for all patients with *PDGFRA* exon 18 D842V-mutated GIST.

For patients with *PDGFRA* exon 18 non-D842V mutations, these have generally been found to be sensitive to imatinib [11,15]. Until there is further comparative data for imatinib and avapritinib, first-line imatinib is recommended in this patient population.

Conclusion

Patients with tumors harboring *PDGFRA* exon 18 mutations are a relatively rare but important molecular subgroup of GIST. Though *PDGFRA* exon 18 mutations are associated with more indolent disease in the localized setting, differential response to imatinib exists between subtypes. Non-D842V mutations are generally imatinib sensitive and this has correlated to a better outcome for these patients. However, though small retrospective cohorts indicate very modest benefit (at best) with imatinib in patients with tumors harboring the D842V mutation, they often have a short PFS and standard of care TKIs provide limited benefit. Avapritinib is a novel TKI identified with specificity for *PDGFRA* and *KIT* mutations. Preclinical data have demonstrated impressive inhibition of both *KIT* and *PDGFRA* including difficult-to-treat *KIT* D816V and its analogous *PDGFRA* exon 18 D842V mutation. Early results of the Phase I NAVIGATOR trial demonstrate notable ORR and clinical benefit rate (CBR) in patients with advanced *PDGFRA* exon 18 D842V-mutated GIST with manageable toxicities. Final results of the Phase I and Phase III VOYAGER study are eagerly awaited to confirm outcomes within the difficult-to-treat D842V cohort and establish avapritinib as the new standard of care for patients with D842V-mutated GIST.

Future perspective

Based on the promising preliminary Phase I results, the Phase III VOYAGER study was opened in March 2018 and has completed enrollment. Patients with advanced GIST who have received imatinib and one or two other TKIs are randomized to regorafenib or avapritinib 300 mg po daily [39]. Crossover is allowed upon progression, which may limit OS analysis. The primary end point is PFS based on RECIST 1.1 and secondary end points include OS, ORR and quality of life. For the population pretreated with 2–3 TKIs, the larger sample size and randomized design will be key to better understand the activity of avapritinib in this cohort and observe adverse events of this novel agent over a larger population [36]. A press release by Blueprint Medicines on 28 April 2020 revealed median PFS of 4.2 and 5.6 months for avapritinib (n = 240) and regorafenib (n = 236), respectively, which was not statistically significant [41]. Interestingly, ORR was higher in the avapritinib-treated patients (17.1% for avapritinib vs 7.2% for regorafenib), with no new safety signals observed [41]. Full results are needed to understand why the difference in response rate did not translate to a PFS benefit, and if specific subgroups may benefit. Clinicians have more experience with regorafenib dose titration compared with avapritinib, and this may have contributed to the regorafenib PFS being slightly higher in VOYAGER (5.6 vs 4.8 months) than observed in the initial Phase III trial of regorafenib for advanced GIST [33].

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Executive summary

- Gastrointestinal stromal tumors (GIST) are most commonly found in the stomach and small intestine are the most common mesenchymal tumor found in the gastrointestinal tract.
- Molecular subtype of GIST has important predictive and prognostic implications.
- *PDGFRA* mutations represented a small but important subgroup of GIST.
- The most common *PDGFRA* mutation is exon 18 D842V.

Therapeutic implications of PDGFRA mutations

- Patients are more often male, with gastric primaries and epithelioid or mixed histological subtypes.
- Retrospectively, patients have been shown to generally have more indolent disease compared with patients with *KIT* mutations.
- *In vitro* and clinical studies have demonstrated *PDGFRA* D842V mutations conferring resistance to imatinib, while other non-D842V mutations are generally imatinib sensitive.

Role of novel tyrosine kinase inhibitor, avapritinib

- Avapritinib is a potent *PDGFRA* exon 18 D842V tyrosine kinase inhibitor and has been approved by the US FDA for patients with *PDGFRA* D842V mutant GIST as of 9 January 2020.
- The final results from the Phase I NAVIGATOR and Phase III VOYAGER (avapritinib vs regorafenib) are awaited to confirm the initial results in the *PDGFRA* exon 18 D842V population.

References

Papers of special note have been highlighted as: • of interest; •• of considerable interest

1. Hulzinga JD, Thuneberg L, Klüppel M, Malysz J, Mikkelsen HB, Bernstein A. *W/kit* gene required for interstitial cells of Cajal and for intestinal pacemaker activity. *Nature* 373(6512), 347–349 (1995).
2. Casali P, Abecassis N, Bauer S *et al.* Gastrointestinal stromal tumors: ESMO–EURACAN clinical practice guidelines for diagnosis, treatment and follow-up. *Ann. Oncol.* 29(Suppl. 4), iv68–iv78 (2018).
3. Corless CL, Barnett CM, Heinrich MC. Gastrointestinal stromal tumors: origin and molecular oncology. *Nat. Rev. Cancer* 11(12), 865–878 (2011).
4. Hirota S, Isozaki K, Moriyama Y *et al.* Gain-of-function mutations of c-kit in human gastrointestinal stromal tumors. *Science* 279(5350), 577–580 (1998).
5. Szucs Z, Thway K, Fisher C *et al.* Molecular subtypes of gastrointestinal stromal tumors and their prognostic and therapeutic implications. *Future Oncol.* 13(1), 93–107 (2017).
6. Heinrich MC, Corless CL, Duensing A *et al. PDGFRA* activating mutations in gastrointestinal stromal tumors. *Science* 299(5607), 708–710 (2003).

•• **Seminal work identifies *PDGFRA* activating mutations as drivers for a subset of gastrointestinal stromal tumors (GIST).**

7. Hirota S, Ohashi A, Nishida T *et al.* Gain-of-function mutations of platelet-derived growth factor receptor α gene in gastrointestinal stromal tumors. *Gastroenterology* 125(3), 660–667 (2003).
8. Lasota J, Dansonka-Mieszkowska A, Sobin LH, Miettinen M. A great majority of GISTs with *PDGFRA* mutations represent gastric tumors of low or no malignant potential. *Lab. Invest.* 84(7), 874–883 (2004).
9. Wozniak A, Rutkowski P, Piskorz A *et al.* Prognostic value of *KIT*/*PDGFRA* mutations in gastrointestinal stromal tumors (GIST): Polish Clinical GIST Registry experience. *Ann. Oncol.* 23(2), 353–360 (2012).

• **Large retrospective cohort of GIST with long-term outcomes based on mutational status, showing better recurrence-free survival for patients with exon 11 or *PDGFRA* mutations.**

10. Corless CL, Schroeder A, Griffith D *et al. PDGFRA* mutations in gastrointestinal stromal tumors: frequency, spectrum and *in vitro* sensitivity to imatinib. *J. Clin. Oncol.* 23(23), 5357–5364 (2005).
11. Cassier PA, Fumagalli E, Rutkowski P *et al.* Outcome of patients with platelet-derived growth factor receptor alpha–mutated gastrointestinal stromal tumors in the tyrosine kinase inhibitor era. *Clin. Cancer Res.* 18(16), 4458–4464 (2012).

12. Judson I, Bulusu R, Seddon B, Dangoor A, Wong N, Mudan S. UK clinical practice guidelines for the management of gastrointestinal stromal tumors (GIST). *Clin. Sarcoma Res.* 7(1), 6 (2017).
13. Miettinen M, Lasota J. Gastrointestinal stromal tumors: pathology and prognosis at different sites. *Semin. Diagn. Pathol.* 23, 70–83 (2006).
14. Heinrich MC, Owzar K, Corless CL *et al.* Correlation of kinase genotype and clinical outcome in the North American Intergroup Phase III trial of imatinib mesylate for treatment of advanced gastrointestinal stromal tumor: CALGB 150105 Study by Cancer and Leukemia Group B and Southwest Oncology Group. *J. Clin. Oncol.* 26(33), 5360 (2008).
15. Farag S, Somaiah N, Choi H *et al.* Clinical characteristics and treatment outcome in a large multicentre observational cohort of *PDGFRA* exon 18 mutated gastrointestinal stromal tumour patients. *Eur. J. Cancer* 76, 76–83 (2017).
16. Subramanian S, West RB, Corless CL *et al.* Gastrointestinal stromal tumors (GISTs) with *KIT* and *PDGFRA* mutations have distinct gene expression profiles. *Oncogene* 23(47), 7780–7790 (2004).
17. Kang HJ, Koh KH, Yang E *et al.* Differentially expressed proteins in gastrointestinal stromal tumors with *KIT* and *PDGFRA* mutations. *Proteomics* 6(4), 1151–1157 (2006).
18. Lasota J, Miettinen M. Clinical significance of oncogenic *KIT* and *PDGFRA* mutations in gastrointestinal stromal tumors. *Histopathology* 53(3), 245–266 (2008).
19. Wardelmann E, Hrychyk A, Merkelbach-Bruse S *et al.* Association of platelet-derived growth factor receptor α mutations with gastric primary site and epithelioid or mixed cell morphology in gastrointestinal stromal tumors. *J. Mol. Diag.* 6(3), 197–204 (2004).
20. Eriksson A, Siegbahn A, Westermark B, Heldin C, Claesson-Welsh L. PDGF alpha-and beta-receptors activate unique and common signal transduction pathways. *EMBO J.* 11(2), 543–550 (1992).
21. Joensuu H, Rutkowski P, Nishida T *et al. KIT* and *PDGFRA* mutations and the risk of GI stromal tumor recurrence. *J. Clin. Oncol.* 33(6), 634–642 (2015).
22. Wozniak A, Rutkowski P, Schöffski P *et al.* Tumor genotype is an independent prognostic factor in primary gastrointestinal stromal tumors of gastric origin: a European multicenter analysis based on ConticaGIST. *Clin. Cancer Res.* 20(23), 6105–6116 (2014).

• **Large retrospective cohort of patients undergo surgical resection for localized GIST which indicates better prognosis for *PDGFRA* exon 18 mutations.**

23. Corless CL, Ballman KV, Antonescu CR *et al.* Pathologic and molecular features correlate with long-term outcome after adjuvant therapy of resected primary GI stromal tumor: the ACOSOG Z9001 trial. *J. Clin. Oncol.* 32(15), 1563 (2014).
24. Joensuu H, Wardelmann E, Sihto H *et al.* Effect of *KIT* and *PDGFRA* mutations on survival in patients with gastrointestinal stromal tumors treated with adjuvant imatinib: an exploratory analysis of a randomized clinical trial. *JAMA Oncol.* 3(5), 602–609 (2017).
25. Reichardt P, Demetri GD, Gelderblom H *et al.* Correlation of *KIT* and *PDGFRA* mutational status with clinical benefit in patients with gastrointestinal stromal tumor treated with sunitinib in a worldwide treatment-use trial. *BMC Cancer* 16(1), 22 (2016).
26. Kollàr A, Maruzzo M, Messiou C *et al.* Regorafenib treatment for advanced, refractory gastrointestinal stromal tumor: a report of the UK managed access program. *Clinic. Sarcoma Res.* 4(1), 17 (2014).
27. Evans EK, Gardino AK, Kim JL *et al.* A precision therapy against cancers driven by *KIT*/*PDGFRA* mutations. *Sci. Transl. Med.* 9(414), eaao1690 (2017).

•• **Initial development, *in vitro* and *in vivo* testing of avapritinib (BLU-285) in *PDGFRA* D842V-mutated GIST and systemic mastocytosis.**

28. Gebreyohannes YK, Wozniak A, Zhai M-E *et al.* Robust activity of avapritinib, potent and highly selective inhibitor of mutated *KIT*, in patient-derived xenograft models of gastrointestinal stromal tumors. *Clin. Cancer Res.* 25(2), 609–618 (2019).
29. NCT02508532: (NAVIGATOR) Study of BLU-285 in patients with gastrointestinal stromal tumors (GIST) and other relapsed and refractory solid tumors. (2020). https://clinicaltrials.gov/ct2/show/NCT02508532
30. Heinrich MC, Jones RL, von Mehren M *et al.* Clinical activity of BLU-285 in advanced gastrointestinal stromal tumor (GIST). *JCO.* 15, 11081 (2017).
31. Heinrich M, von Mehren M, Jones RL *et al.* Avapritinib is highly active and well-tolerated in patients with advanced GIST driven by a diverse variety of oncogenic mutations in *KIT* and *PDGFRA*. Presented at: *CTOS Annual Meeting.* Rome, Italy (2018).
32. Demetri GD, van Oosterom AT, Garrett CR *et al.* Efficacy and safety of sunitinib in patients with advanced gastrointestinal stromal tumour after failure of imatinib: a randomised controlled trial. *Lancet* 368(9544), 1329–1338 (2006).
33. Demetri GD, Reichardt P, Kang Y-K *et al.* Efficacy and safety of regorafenib for advanced gastrointestinal stromal tumors after failure of imatinib and sunitinib (GRID): an international, multicentre, randomised, placebo-controlled, Phase III trial. *Lancet* 381(9863), 295–302 (2013).
34. von Mehren M, Serrano C, Bauer S *et al.* INVICTUS: a Phase III, interventional, double-blind, placebo-controlled study to assess the safety and efficacy of ripretinib as ≥4th-line therapy in patients with advanced gastrointestinal stromal tumors (GIST) who have received treatment with prior anticancer therapies (NCT03353753). *Ann. Oncol.* 30, v925–v926 (2019).

35. Smith BD, Kaufman MD, Lu W-P *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* 35(5), 738–751.e739 (2019).

36. Heinrich M, Jones RI, Von Mehren M *et al.* Avapritinib in advanced *PDGFRA* D842V-mutant gastrointestinalstromal tumor (NAVIGATOR): a multicentre, open label, Phase I trial. *Lancet Oncol.* (2020) (In Press).

•• **Final results of the Phase I NAVIGATOR study of avapritinib in *PDGFRA* D842V mutant and unresectable GIST after imatinib and ≥3 previous tyrosine kinase inhibitor, full result publication is expected later this year.**

37. Joseph CP, Abaricia SN, Angelis MA *et al.* Avapritinib for the treatment of GIST: analysis of efficacy, safety, and patient management strategies at the recommended Phase II dose. *Connective Tissue Oncology Society.* Tokyo, Japan (2019).

38. US FDA. FDA approves avapritinib for gastrointestinal stromal tumor with a rare mutation. (2020). https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-avapritinib-gastrointestinal-stromal-tumor-rare-mutation

39. NCT03465722: (VOYAGER) study of avapritinib vs regorafenib in patients with locally advanced unresectable or metastatic GIST. (2020). https://clinicaltrials.gov/ct2/show/NCT03465722?term=avapritinib&cond=GIST&draw=2&rank=1

• **Ongoing study of avapritinib in the third- or fourth-line setting for patients with nonwild-type GIST. Final results are expected this year.**

40. Jones R, McCall J, Adam A *et al.* Radiofrequency ablation is a feasible therapeutic option in the multi modality management of sarcoma. *Eur. J. Surg. Oncol.* 36(5), 477–482 (2010).

41. Blueprint Medicines. Announces top-line results from Phase III VOYAGER trial of avapritinib versus regorafenib in patients with advanced gastrointestinal stromal tumour. (2020). http://ir.blueprintmedicines.com/news-releases/news-release-details/blueprint-medicines-announces-top-line-results-phase-3-voyager