Updates in the Management of Unresectable or Metastatic Gastrointestinal Stromal Tumors

Expanding Treatment Options and Improving Outcomes

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Dr Harris is an Associate Professor of Pharmacy Practice at Massachusetts College of Pharmacy & Health Sciences in Boston with a practice site at the Dana-Farber Cancer Institute. Dr Harris is a graduate of the University of Tennessee, where she received her Bachelor of Science and Doctor of Pharmacy degrees. She completed 2 years of residency specializing in oncology, is board certified as a specialist in oncology pharmacy, and is a Fellow of the Hematology Oncology Pharmacists Association. She currently works with patients with soft tissue and bone sarcomas. Other interests in her practice include early-phase clinical trials, the adolescent and young adult population, and integrative therapy in cancer.

Faculty

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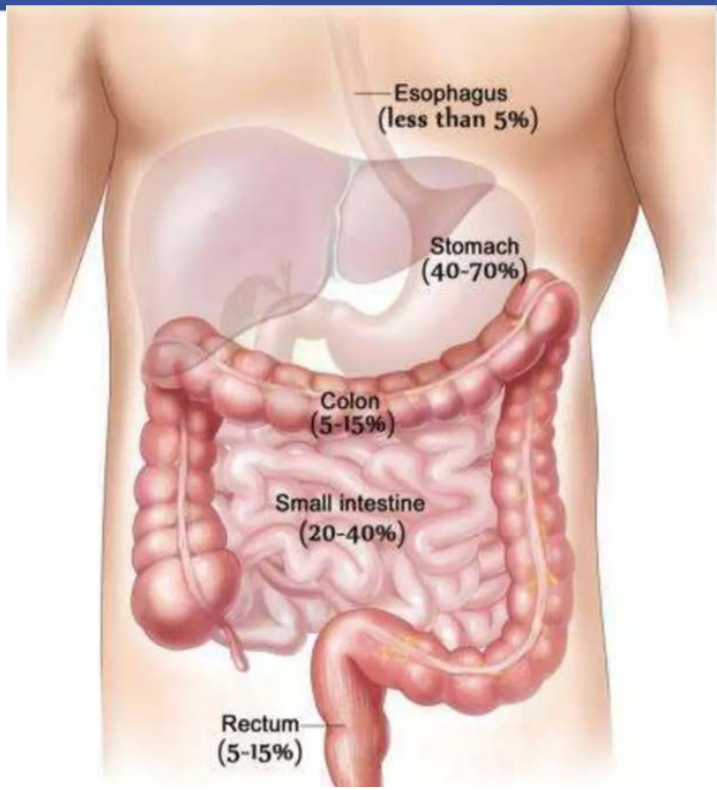
Kathleen Polson received her undergraduate degree in pre-professional biology at Florida Tech and then worked in research in cell biology at Brigham and Women's Hospital. She then completed her BSN and MSN at the Massachusetts General Hospital Institute of Health Professions. She worked in nursing and then as an NP in GYN Oncology at St. Elizabeth's Hospital for 3 years. She then moved to the Center for Sarcoma and Bone Oncology at the Dana Farber Cancer Institute in Boston, where she has worked as an NP with a strong focus in research for the past 17 years.

Learning Objectives

- **Discuss** current and emerging treatment options for unresectable or metastatic gastrointestinal stromal tumors (GIST)
- **Develop** strategies to identify and manage adverse effects of agents used in unresectable or metastatic GIST treatment
- **Formulate** approaches to manage patients receiving GIST therapy, including promoting safe use and optimal treatment adherence

What is GIST?

- Gastrointestinal Stromal Tumors
  - Most common mesenchymal tumors of the GI tract
  - Arise from the interstitial cells of Cajal, the gastric "pacemaker"
  - Rare: 10-14 **per** million people each year; consistent around the world
  - Familial GIST rare



Blay JY. *Cancer Treat Rev.* 2011;37:373-384.

GIST Timeline

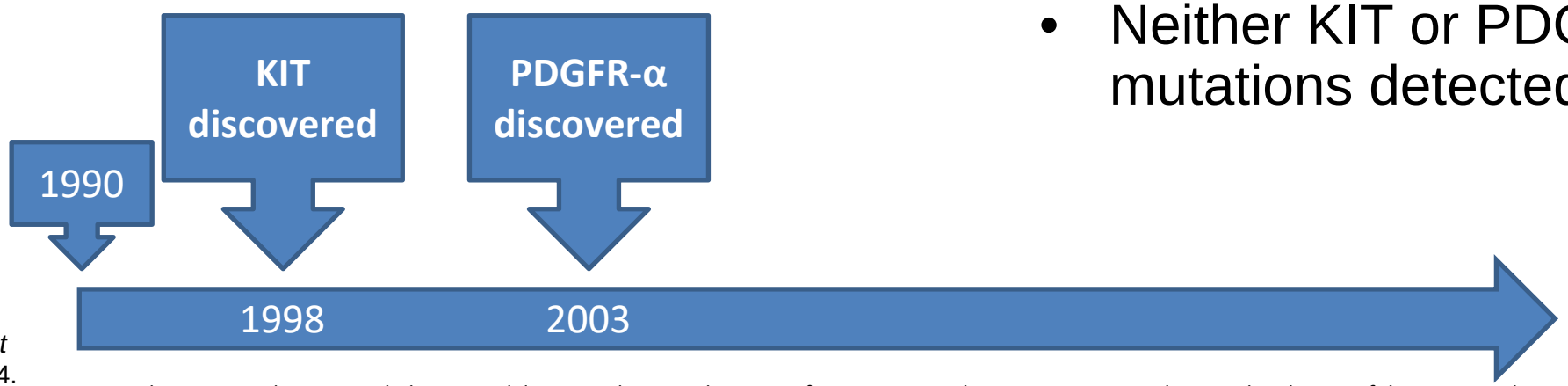
- **1983** GIST first named
- **1998** KIT mutation identified
- **1999** First patient with GIST treated with imatinib
- **2002** Approval of **imatinib** for metastatic GIST
- **2003** Identification of PDGFRα mutations
- **2004** DOG1 identified
- **2006** **Sunitinib** approved; SDH deficiency associated with some GIST
- **2013** **Regorafenib** approved
- **2020** **Ripretinib** and **avapritinib** approved

Abbreviations: DOG-1, discovered on GIST-1; PDGFR-α: platelet-derived growth factor receptor α; SDH, succinate dehydrogenase.

What Causes GIST?

- KIT (CD117 antigen) and PDGFR-α mutations
  - Gain-of-function mutations
  - Mutually exclusive

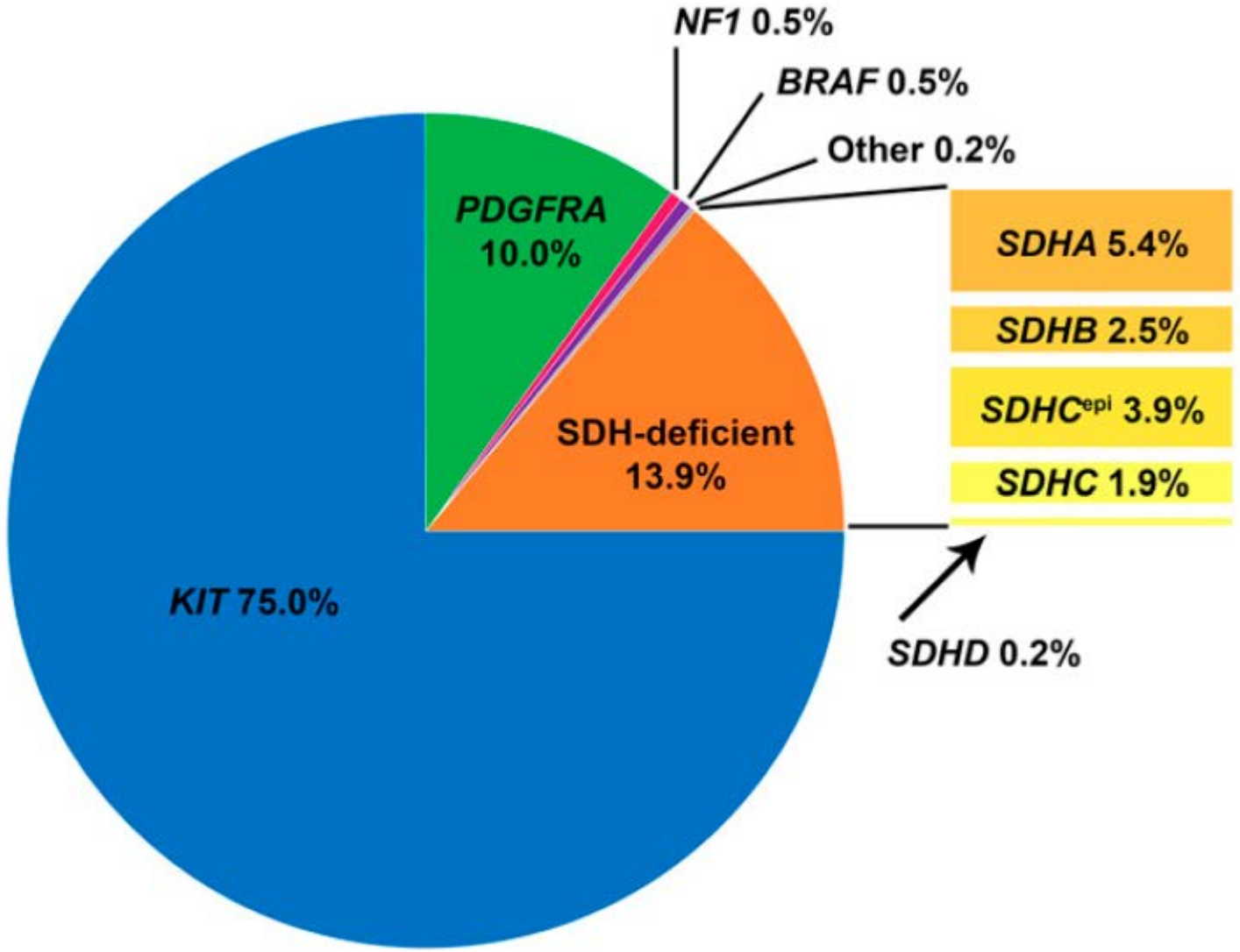
- KIT: ~80%; stem cell factor receptor
  - Exon 9, 11, 13, 14
- PDGFR-α; ~5%
  - Exon 17, 18
- Wild-type GIST; 12-15%
  - Neither KIT or PDGFR-α mutations detected



Blay JY. *Cancer Treat Rev.* 2011;37:373-384.

GIST Mutations

- KIT gain of function mutation
  - Exon 11 – most common, higher risk of recurrence
  - Exon 9 – almost exclusively found in small bowel, more resistant
  - Exons 13-14, 17-18
- PDGFR gain of function mutation
  - Often found in gastric wall
  - Exons 12,18
- Wild-type GIST
  - 10-15% adults, 85% children



Inga-Marie S, et al. *ASCO Educational Book.* 2022;42:885-899.
Cioffi A, Maki RG. *J Clin Oncol*. 2015;33:1849-1854.
Li GZ, Raut CP. *Onco Targets Ther*. 2019;12:5123-5133.

SDH-deficient GIST

- Often sporadic but also found in syndromes (Carney-Stratakis syndrome – germline mutation in SDH B, C, or D subunit)
- Often multifocal
- Most often found in proximal stomach
- Indolent course
- Lymph node involvement
- Poor response to tyrosine kinase inhibitors
- Most common form of GIST in pediatrics
- For unresectable disease, sunitinib, regorafenib, or pazopanib may have benefit

Boikos SA, et al. *JAMA Oncol.* 2016;2(7):922-928.

Treatment of Metastatic Disease

1st Line

- **Imatinib** 400 mg daily
- If KIT exon 9, imatinib 800 mg daily*
- If PDGFRA exon 18, including D842V, **avapritinib** 300 mg daily

*May consider sunitinib if life-threatening adverse effects to imatinib

2nd Line

- **Sunitinib** 50 mg daily x 4 weeks, 2 weeks off OR 37.5 mg daily

OR

- May dose escalate to **imatinib** 800 mg daily as tolerated
- If PDGFRA exon 18, including D842V, **dasatinib**

3rd Line

- **Regorafenib** 160 mg daily

OR

- **Sunitinib** (if not used previously)

4th (and later) Lines

- **Ripretinib** 150 mg daily

OR

- **Regorafenib** (if not used previously)

OR

- Clinical trial

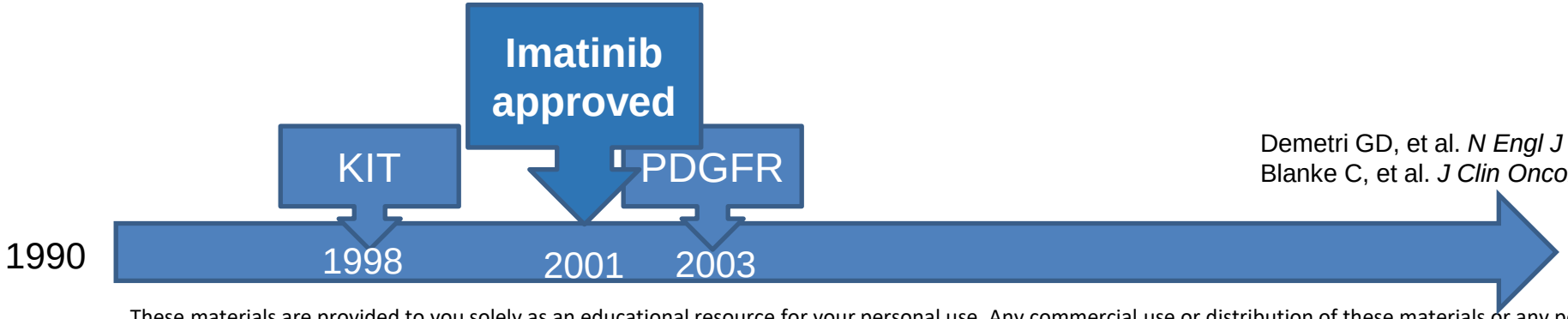
Useful in certain situations: ripretinib dose escalation to 150 mg BID, avapritinib, cabozantinib, pazopanib, sorafenib, nilotinib, dasatinib, everolimus + TKI

Case A

- 56-year-old patient began developing abdominal pain. The next month, the patient presented to the emergency department and a mass with metastases was found on imaging
- Patient diagnosed with GIST via biopsy
  - Pathology was positive for CD34 and DOG1
  - KIT exon 11 mutation found on mutational analysis
- Patient started imatinib 400 mg PO daily 12/26/2014
  - Adverse effects included some loose stools treated with loperamide

Imatinib

- KIT (CD117), ABL, PDGFR-α, CSF-1
- Phase 2 randomized, open-label trial (B2222); median follow-up 63 months; 400 mg and 600 mg
  - Overall response rate 66.7% (Partial response + stable disease)
  - Median time to progression 24 months
  - Median overall survival 57 months
- Dose increases up to 800 mg/d after progression stabilized disease in 30%



Demetri GD, et al. *N Engl J Med*. 2002;347:472-480.
Blanke C, et al. *J Clin Oncol*. 2008;26:620-625.

Drug Plasma Level Monitoring

- Not standard of care
  - High interpatient variability
  - B2222 was defining the mutation locations (exons) and difference between 400 mg, 600 mg, and 800 mg
  - More drugs available now
  - Mutational status has better correlation with efficacy/resistance (exon 9 may need higher dose)
  - Difficult to do within the US reimbursement structure
  - Personalization of medication through dose modification in response to adverse effects allows patients to stay on therapy longer

Clonal Resistance

- Imaging – see loss of vascularity as response, even though tumor size does not change
- Primary resistance – no response to imatinib or resistance within 6 months of stopping imatinib
- Secondary resistance – after 6 months of stopping imatinib
  - Occurs an average of 24 months after starting therapy
  - Typically found in the adenosine triphosphate (ATP)-binding pocket (encoded by exons 13 and 14) or activation loop (A-loop) mutations (encoded by exons 17 and 18)

Antonescu CR, et al. *Clin Cancer Res.* 2005;11:4182-4190.
Kee D, Zalcberg JR. *Ther Adv Med Oncol.* 2012;4(5):255-270.
Gramza AW, et al. *Clin Cancer Res*. 2009;15:7510-7518.

Imatinib at 10 Years

- International study with 56 institutions in 13 countries
  - 400 mg vs 800 mg dose
- Median follow-up 10.9 years
  - PFS 1.7 years (400 mg) and 2 years (800 mg)
  - mOS 3.9 years in both arms
  - 10-year OS 19.4% (400 mg) and 21.5% (800 mg)
- SWOG S0033/CALGB150105 study demonstrated similar outcomes
- For patients that progress on 400 mg dose, can increase to 800 mg daily
  - EORTC study: median PFS 2.76 months
  - SWOG S0033/CALB study: 33% had objective response rate and stable disease

Abbreviations: mOS, median overall survival; PFS, progression-free survival.

Casali PG, et al. *J Clin Oncol.* 2017;35(15):1713-1720. Heinrich MC, et al. *JAMA Oncol.* 2017;3(7):944-952.

Case A Continued

- Three to 4 days after beginning second month of therapy, patient developed a raised, erythematous rash with confluence on arms, upper chest, and back

Adverse Effects of Imatinib
Edema
Dermatitis
Pruritis
Abdominal pain
Diarrhea
Fatigue

Patel S, Reichardt P. *Cancer.* 2021;127:2187-2195.

Imatinib

Dose	400 mg daily, 800 mg daily
Targets	KIT, PDGFR-α
Metabolism	CYP3A4 inhibitor
Adverse effects**	Myelosuppression, dermatologic reactions, edema, fatigue, depression Rare: hepatotoxicity, cardiac failure, GI hemorrhage
Monitoring	CBC weekly x 4 weeks, biweekly x 4 weeks, then periodically; liver enzymes
Fertility	If could become pregnant, use contraception during therapy and for 14 days after last dose*
Other considerations	Warfarin interaction

** Consult package insert for full list of adverse events.

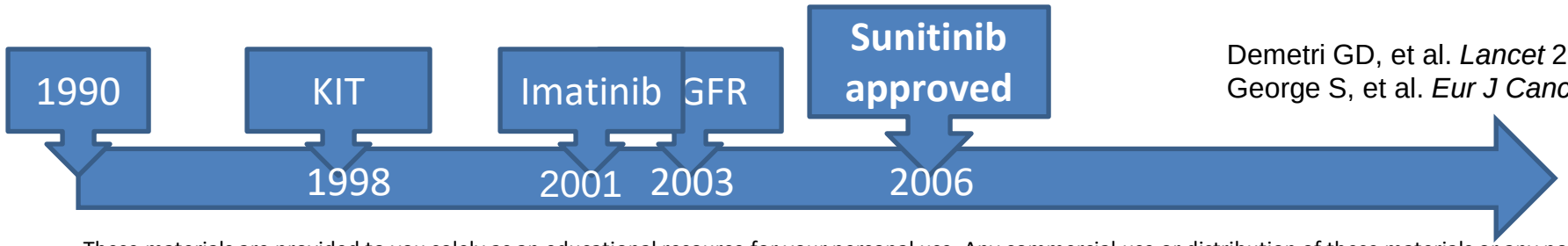
Gleevec. Package insert. Novartis Pharmaceuticals; 2022.

Case A Continued

- Patient was started on sunitinib after progression of disease on imatinib x 6 years
- Calluses at baseline on right hand/fingertips
- Within 2 weeks, patient called describing that the bottom of his feet were burning—“it feels like walking on glass.”

Sunitinib

- Randomized, double-blind, placebo-controlled trial of 312 patients
  - 50 mg PO daily x 4 weeks every 6 weeks
  - Time to tumor progression 6.8 vs 1.6 months
  - Overall survival improved even after crossover
- 37.5 mg PO daily continuous dosing
  - PFS 8.5 months



Demetri GD, et al. *Lancet* 2006;368:1329-1338.
George S, et al. *Eur J Cancer.* 2009;45(11):1959-1968.

Sunitinib

- Therapy after imatinib more toxic
- Providers are slow to advance to next therapy until clear progression is seen
- Median time to tumor progression 6.8 months vs 1.6 months with placebo
- Median PFS of 8.5 months
- Serious adverse effects reported by 20% with sunitinib vs 5% with placebo

Demetri GD, et al. *Lancet.* 2006;368:1329-1338.
Patel S, Reichardt P. *Cancer.* 2021;127:2187-2195.

Sunitinib

Dose	50 mg daily x 4 weeks every 6 weeks or 37.5 mg daily
Targets	PDGFR-α, VEGFR 1-3, FLT3, CSF-1R, RET
Metabolism	CYP3A4
Adverse effects	Fatigue, diarrhea, hand-foot-skin reaction (HFSR), hypertension, neutropenia, lymphopenia, hypothyroidism, QTc prolongation, proteinuria
Monitoring**	Liver enzymes at baseline and with each cycle; urinalysis for proteinuria (baseline and periodic); blood pressure, TSH
Fertility	Use effective contraception if of child-bearing potential during treatment and for at least 4 weeks after last dose; if a partner of child-bearing potential, during and for 7 weeks after last dose
Other considerations	Withhold for ≥ 3 weeks prior to surgery and for at least 2 weeks after with adequate wound healing

** Consult package insert for full list of adverse events.

Sutent. Package insert. Pfizer; 2021.

Hand-Foot-Skin Reaction

- In a 2022 meta-analysis, prophylactic use of urea-based creams
  - 16 randomized controlled trials included
  - Urea-based cream, 54.9% vs 71.4% ($P < 0.00001$)
  - Celecoxib's benefit only seen in capecitabine-induced HFSR
- Urea-based cream has been shown to decrease the incidence and severity of HFSR
- Studies of other topical agents ongoing
- Other recommendations

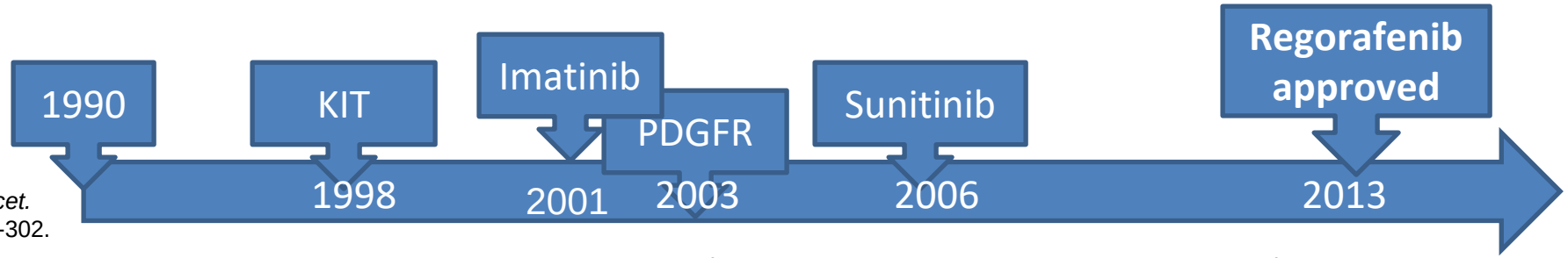
Pandy JGP, et al. *Support Care Cancer.* 2022;30(11):8655-8666.
Ren Z, et al. *J Clin Oncol.* 2015;33:894-900.
Lee YS, et al. *Eur J Cancer.* 2020;140:19-27.
Lan TC, et al. *Cancer Nurs.* 2022;45(5):378-386.

Case A Continued

- Despite dose reductions and dermatology consult, the HFSR was not tolerable
- The patient was placed on regorafenib 160 mg PO daily x 21 days every 28 days
- At follow-up visit, patient had no nausea, vomiting, constipation, oral sensitivity, rash, HFSR
- Experienced hoarse voice and hand calluses, skin that burned a little where it was dry, some fatigue

Regorafenib

- KIT, RET, RAF1, BRAF, VEGFR1-3, PDGFR-α
- Dose: 160 mg PO daily D1-21 every 28 days
- Greater activity against exon 17 to 18 secondary KIT mutations
- Phase 3, randomized, placebo-controlled trial with crossover after progression on placebo
  - 240 patients: median PFS 4.8 vs 0.9 months



Demetri GD, et al. *Lancet.* 2013;26;381(9863)295-302.

Regorafenib

- Dose modifications 72% in regorafenib arm vs 25.8% with placebo
  - Discontinuation rates were similar (6.1% vs 7.6%)
- In retrospective analysis, 20% had discontinued therapy due to adverse effects but had never been dose reduced
- Appropriate monitoring and treatment of associated adverse effects affects continuation on therapy

Regorafenib Adverse Effects
Hand-foot-skin reaction
Fatigue
Hypertension
Hypophosphatemia
Diarrhea
Hypothyroidism

Patel SR, Reichardt P. *Cancer.* 2021;127:2187-2195. Demetri GD, et al. *Lancet.* 2013;26;381(9863):295-302. Grothey A, et al. *Oncologist.* 2014;19:669-680. Chamberlain F, et al. *Clin Sarcoma Res.* 2020;10:1.

Regorafenib

Dose	160 mg daily days 1-21 every 28 days
Targets	KIT, RET, BRAF, VEGF 1-3, PDGFR-α
Metabolism	CYP3A4, UGT1A9, BCRP inhibitor
Adverse effects**	Hand-foot-skin reaction, fatigue, hypertension, hypophosphatemia, diarrhea, hypothyroidism, dysphonia, GI/abdominal pain
Monitoring	Liver enzymes at baseline every 2 weeks x 2 months, then monthly; blood pressure; CBC
Fertility	Use contraception during therapy and for at least 2 months following therapy if of childbearing potential or have a partner that is
Other considerations	Withhold ≥ 2 weeks prior and for at least 2 weeks after major surgery and adequate wound healing occurs

** Consult package insert for full list of adverse events.

Stivarga. Package insert. Bayer Healthcare Pharmaceuticals, Inc; 2012.

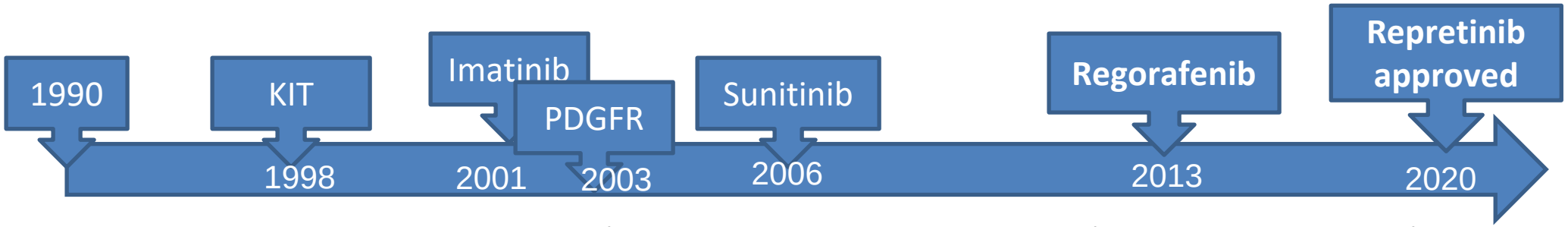
Case A Continued

- Patient had further progression of their disease after 15 months on therapy
- Patient started ripretinib
  - Had constipation; used senna and docusate with little effect
  - Mild hypertension
- After about 6 weeks, patient developed a drug rash with little pruritic bumps on arms, legs, and torso
  - Foot beginning to become sore, as with previous experience with HFSR

Ripretinib

- INVICTUS study
- International, double-blind, randomized, placebo-controlled trial
- All patients had documented progression or intolerance to imatinib, sunitinib, and regorafenib
- Median progression-free survival 6.3 months vs 1 month with placebo
- Dose escalation to 150 mg BID after daily treatment
  - Median PFS 3.7 months

Blay JY, et al. *Lancet Oncol.* 2020;21(7):923-934.
Zalcberg JR, et al. *Oncologist.* 2021;26:e2053-2060.



Ripretinib

- 6% of patients had adverse effects that led to dose reductions
- 5% discontinued the study due to adverse effects
- Safety profile similar with 150 mg daily and twice daily
- Patient reported quality of life was not impacted
  - Alopecia and HFSR did not worsen over time

Ripretinib Adverse Effects
Alopecia
Myalgia/muscle spasms
Nausea
Fatigue
Hand-foot-skin reaction
Diarrhea

Patel SR, Reichardt P. *Cancer.* 2021;127:2187-2195. Heinrich MC, et al. *J Clin Oncol.* 2020;38(suppl):11535. George S, et al. *J Clin Oncol.* 2020;38(suppl):11539. Blay JY, et al. *Lancet Oncol.* 2020;21(7):923-934.

Ripretinib

Dose	150 mg PO daily*
Targets	KIT, PDGFRα, PDGFRb, VEGFR2, TIE2, BRAF
Metabolism	CYP3A4, p-glycoprotein, and BCRP substrates
Adverse effects**	Arthralgias/myalgias, hypertension, hand-foot-skin reaction, alopecia Rare - skin cancer
Monitoring	LVEF baseline and as clinically indicated, blood pressure
Fertility	Contraception during therapy and for at least 1 week after if of child-bearing potential or have a partner that is
Other considerations	Withhold 1 week prior and for at least 2 weeks after surgery; limit sun exposure during and for at least 1 week after stopping therapy.

** Consult package insert for full list of adverse events.

Qinlock. Package insert. Deciphera Pharmaceuticals; 2022.

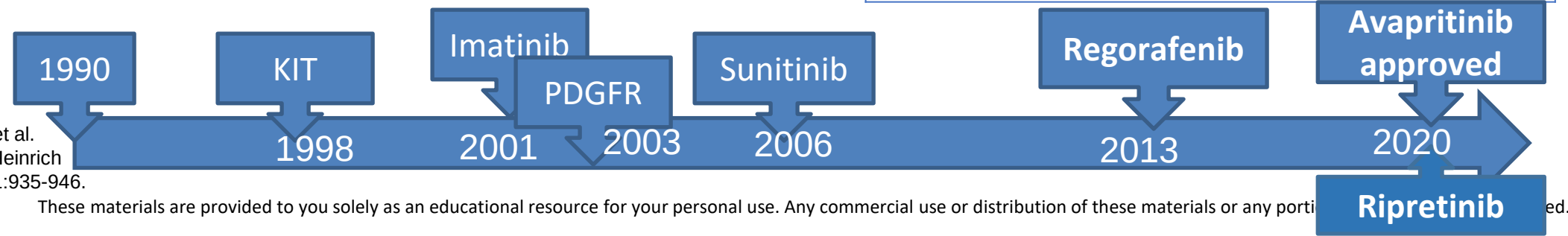
Case A Continued

- After 5 months, patient experienced progression of disease
- Adverse effects on therapy included intermittent loose stools, fatigue, and hypertension
- Escalation of ripretinib to 150 mg PO BID

Avapritinib

- Patients with D842V mutations
  - Median PFS 34 months
  - Median OS not reached
  - Overall response rate 91%
  - Median duration of response 27.6 months
- Dose reductions in 64.5% of patients with exon 18 mutations
  - 49.6% in those in 4+ lines of therapy

Avapritinib Adverse Effects
Nausea/vomiting
Diarrhea
Decreased appetite
Fatigue
Anemia
Cognitive dysfunction
Periorbital edema



Jones RL, et al. *Eur J Cancer.* 2021;145:132-142. Joseph CP, et al. *Oncologist.* 2021;26:e622-631. Heinrich MC, et al. *Lancet Oncol.* 2020;21:935-946.

Cognitive Effects with Avapritinib

- Dose modification recommendations
- Memory impairment, confusion, dizziness, fatigue, speech disturbance, and hallucination **“is common with use”**

Central nervous system toxicity, 58%

- Cognitive dysfunction
  - 41-48%, grade 3/4, 4%
- Dizziness, 20-22%
- Fatigue 61%, grade ≥3, 9%
- Memory impairment, 26-29%
- Mood disorder, 13%

Joseph CP, et al. *Oncologist.* 2021;26:e622-e631.

Avapritinib

Dose	300 mg PO daily
Targets	PDGFRα exon 18 (D842V)
Metabolism	CYP3A4 substrate
Adverse effects**	Edema (periorbital, peripheral, facial), diarrhea, nausea/vomiting, cognitive dysfunction*
Monitoring	Cognitive effects* Intracranial bleeding in patients with aneurysm or previous history of intracranial bleeding or cerebrovascular accident
Fertility	Contraception during and for at least 6 weeks after last dose if of child-bearing potential or have a partner that is
Other considerations	Moderate-to-high emetic potential

** Consult package insert for full list of adverse events.

Ayvakit. Package insert. Blueprint Medicines Corp; 2021.

Efficacy of GIST Therapies

	Imatinib	Sunitinib	Regorafenib	Ripretinib	Avapritinib
Treatment line	1st	2nd	3rd	4th or more	Any
ORR (%)	68.1	6.8	4.5	9.4	91.0
SD, 12 weeks (%)	15.6	53.0	53.0	47.0	98.0
mPFS (mo)	24.0	5.6	4.8	6.3	34.0

Abbreviations: mPFS, median progression-free survival; ORR, overall response rate; SD, stable disease.

ASCO Educational Book. 2022;42:885-899.

Other Tyrosine Kinase Inhibitors

	Line of therapy	ORR (%)	mPFS
Avapritinib	3rd or 4th	17	4.2
Cabozantinib	3rd	14	5.5
Dasatinib	2nd or more	4	2.9
Dovitinib	3rd or more	3-5	3.6-4.6
Masitinib	2nd	N/A	3.7
Nilotinib	3rd or more	0-10	2-3.7
Pazopanib	2nd or more, 3rd/4th	0-3	2.9-4.5
Ponatinib	2nd or more	8	4.3
Sorafenib	2nd or more, 3rd or more	13	4.9-5.2

ASCO Educational Book. 2022;42:885-899.

Ongoing Research

- CGT9486 (bezuclastinib)
  - Type 1 KIT inhibitor
  - Phase 1b/2a nonrandomized trial
  - Low-dose CGT9486 (≤500 mg), high-dose CGT9486 (1000 mg), and CGT9486 + sunitinib (25 or 37.5 mg daily)
    - PFS 1.74 months, 5.75 months, 12.1 months for all pts (n = 15)
    - 11.6 months for pts previously treated with sunitinib (n = 9)
    - After 3 or more therapies (n = 9), mPFS 11 months (compared with ripretinib 6.3 months mPFS)
- Cabozantinib
- KIT inhibitors
- Rogaratinib

Wagner AJ, et al. *JAMA Oncol.* 2021;7(9):1343-1350.

Adherence

- Factors affecting adherence
  - Age >51 years
  - Female
  - High number of concomitant medications
  - Complications with patients' therapy or disease
  - Treatment-related adverse events
  - Increased healthcare costs
- Patients and physicians both overestimate adherence to therapy
- Significant impact on clinical outcomes
  - Mean total health care costs $71,126 for patients with poor adherence (<70%) compared with $38,062 for those with good adherence (≥90%)
  - Mean inpatient length of stay 29.9 days for those with poor adherence vs 3.4 days with good adherence

Blay JY, et al. *Cancer Treat Rev.* 2014;40:242-247.
Mazzeo F, et al. *Anticancer Res.* 2011;31(4):1407-1409.

Adherence

- To improve adherence
  - Manage adverse effects
    - One study found that patients were more likely to skip doses if they experienced heart failure, serious infection, diarrhea, or nausea; least likely cause for skipped doses, edema
  - Patient support programs
  - Improved communication
- Encourage patient to keep a diary
- Follow up on adverse effects and adherence at clinic visits/telephone calls

Blay JY, et al. *Cancer Treat Rev.* 2014;40:242-247.

Adherence

- Elderly (n = 36) vs nonelderly (n = 162)
  - Both groups started imatinib equally
  - Drug-related toxicity causing discontinuation of imatinib 32.7% vs 5.1% in nonelderly
  - mPFS = 24 months in elderly vs 33 months in nonelderly
  - mOS = 34 months in elderly vs 59 months in nonelderly

Farag S, et al. *Eur J Cancer.* 2017;86:318-323.

Patient Education

- Initial teaching with clinic team (MD, APP, ONN, PharmD)
- Early check-in phone call and/or clinic visits
  - Several points of contact to reinforce knowledge
- Team-based approach to treatment of adverse effects
  - Includes referral to appropriate clinics: dermatology, cardiology, oral medicine, endocrinology, nephrology, hepatology, etc
- Oral Chemotherapy Education
  - Collaboration among 4 organizations: NCODA, ONS, HOPA, ACCC
  - www.oralchemoedsheets.com

Abbreviations: ACCC, Association of Community Cancer Centers; HOPA, Hematology/Oncology Pharmacy Association; NCODA, National Community Oncology Dispensing Association; ONS, Oncology Nursing Society.

Summary

- Additional drugs being added to the armamentarium for GIST therapy
- Resistance is close behind
- Evolving understanding of resistance patterns
- New mechanisms being explored, especially in SDH-deficiency
- Best use of current therapies are to maximize tolerability by addressing adverse effects to extend duration of therapy

Thank you!