National Comprehensive Cancer Network

Monthly Oncology Tumor Boards

A Multidisciplinary Approach to Individualized Patient Care

Sarcoma

Suzanne George, MD
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July 21, 2016

Moderated by Shannon K. Ryan
Conferences and Meetings Department
National Comprehensive Cancer Network

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Supporters

This educational activity is supported by educational grants from:

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- Please use the Q&A feature on the right-hand portion of your screen for any clinical questions and logistical concerns you have regarding the session. This is the only online method of communicating questions or concerns. Should you need additional assistance please e-mail **education@nccn.org** or call 215-690-0300 and ask to be connected with someone in the NCCN Conferences and Meetings Department.
- While NCCN is pleased to respond to as many questions as possible during this webinar, NCCN will not be able to respond to your individual questions of a clinical nature after the webinar has concluded. We are also not able to offer recommendations on patient care regarding specific cases.
- This webinar features audience polling. When you see a polling slide appear, get ready to vote. Please note that it can take a few moments to collect the results.

Attendance Lists & Registration

- If you are participating with a group of peers, a list of everyone who attended in your group must be submitted within two weeks of the activity in order for the participants to be eligible to receive credit. This list is in addition to individual registration. Attendee lists will not be accepted after two weeks post-activity.
- Lists can be sent to **education@nccn.org** and should contain full contact information for each participant, including first and last name, credentials, mailing address, phone number, and e-mail address.
- If you have not individually registered, please register at: **http://www.cvent.com/d/3fqbck.**

Accreditation Information

Intended Audience

This webinar series is designed to meet the educational needs of oncologists, pathologists, nurses, pharmacists, case managers, and other health care professionals who manage patients with cancer.

Learning Objectives

Following this program, participants should be able to:

- Select an optimal treatment approach and sequence when reviewing potential medical, radiologic, and/or surgical options for treatment of soft-tissue sarcoma.
- Evaluate the clinical evidence base for current and emerging systemic therapies for treating soft-tissue sarcoma.
- Review the data from developing clinical trials in soft tissue sarcoma.

Accreditation Information

Physicians

The National Comprehensive Cancer Network (NCCN) is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

The National Comprehensive Cancer Network designates this live activity for a maximum of 1.0 *AMA PRA Category 1 Credit*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

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Kristina M. Gregory, RN, MSN, OCN, is our lead nurse planner for this educational activity.

Accreditation Information

Pharmacists

Accreditation Statement

National Comprehensive Cancer Network is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education.

Type of Activity: Knowledge

UAN: 0836-0000-16-077-L01-P

Credit Designation: National Comprehensive Cancer Network designates this continuing education activity for 1.0 contact hour (0.1 CEUs) of continuing education credit in states that recognize ACPE accredited providers.

Attention Pharmacists: ACPE and NABP have implemented CPE Monitor as a way to electronically track all ACPE-accredited CPE Units. In order to receive credit for this activity, please enter your six-digit NABP e-profile ID and birth date in the format of MMDD as part of the Overall Evaluation. If you have not already done so, please complete your e-profile at http://www.nabp.net to obtain your NABP e-Profile ID.

To comply with ACPE standards, pharmacists must complete all activity requirements within **30 days** of the live event date.

Accreditation Information

Case Managers

This program has been pre-approved by The Commission for Case Manager Certification to provide continuing education credit to CCM® board certified case managers. The course is approved for 1.0 CE contact hour.

Activity Code: I00022049

Approval Number: 160002841

Accreditation Information

How to Claim Credit:

Within 5 business days after this educational program, you will receive an e-mail with information on how to claim credit for this activity. A statement of credit will be issued only upon completion of the activity evaluation form & immediate post-test within **30 days** of the activity date. A certificate will be electronically generated immediately upon completion of the evaluation.

All credit claiming must be done online through NCCN's continuing education portal at **https://education.nccn.org/node/79158.**

Should you not receive an e-mail within 5 days, please contact us at **education@nccn.org.**

Accreditation Information

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- To meet this requirement, NCCN asks that all participants complete the outcomes measures described below:
  - The post-test and evaluation as indicated in e-mail you will receive within 3-5 business days of the conclusion of this activity. This is required to receive credits or your certificate of completion. You must be registered in advance to receive credits or certificate. Certificates will be generated automatically upon successful completion of this step.
    - There will be a separate WebEx evaluation at the conclusion of this program, which is optional and does not go to NCCN.
  - The follow-up post test (to be sent 30 days after the activity has ended to demonstrate an increase in participant competence)
- NCCN greatly appreciates your compliance with completing the aforementioned post-test and surveys. All of these measures will be available by logging into your account at **http://education.nccn.org**. Reminder e-mails will be sent to the participants via e-mail. If you have any questions or concerns, please e-mail **education@nccn.org.**

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All faculty for this continuing education activity are competent in the subject matter and qualified by experience, training, and/or preparation to the tasks and methods of delivery.

Disclosures

Disclosure of Relevant Financial Relationships

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Faculty Disclosures

The faculty listed below has no relevant financial relationships to disclose:

Chandrajit P. Raut, MD, MSc

The faculty listed below have disclosed the following relevant financial relationships:

Suzanne George, MD
Ariad Pharmaceuticals, Inc: Grant/Research Support
Bayer HealthCare: Grant/Research Support
Blueprint Medicines: Grant/Research Support
Deciphera: Grant/Research Support
Novartis: Grant/Research Support
Pfizer Inc.: Grant/Research Support

NCCN Staff Disclosures

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The activity planning staff listed below has no relevant financial relationships to disclose:

Mark Geisler; Kristina M. Gregory, RN, MSN, OCN; Kristin Kline Hasson; Rose Joyce; Joan S. McClure, MS; Diane McPherson; Melanie Moletzsky; Deborah Moonan, RN, BSN; Lisa Perfidio; Liz Rieder; Shannon K. Ryan; Kathy Smith; Jennifer McCann Weckesser

The NCCN clinical information team listed below, who have reviewed content, has no relevant financial relationships to disclose:

Mary Anne Bergman; Jillian L. Scavone, PhD

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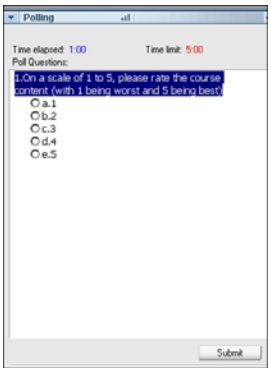
Monthly Oncology Tumor Boards:
A Multidisciplinary Approach to Individualized Patient Care – Sarcoma

Chandrajit P. Raut, MD, MSc
Brigham and Women's Hospital, Dana-Farber Cancer Institute, Harvard Medical School
Suzanne George, MD
Brigham and Women's Hospital, Dana-Farber Cancer Institute, Harvard Medical School

July 21, 2016

Audience Response Question

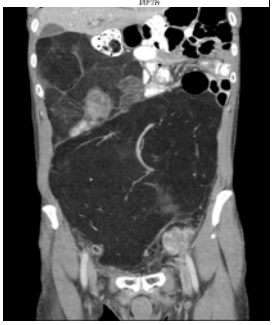
Look for the polling box on right side of your screen, near Q&A box to vote.



It may take a few moments to collect the polling results.

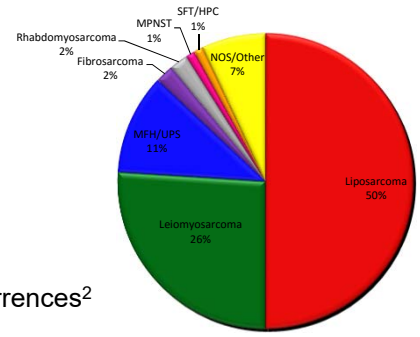
Retroperitoneal Sarcoma

- 15% of all soft tissue sarcomas
  - 1600 new cases per year in the US
  - Median age – mid 60s
  - M:F 1:1
- Frequently asymptomatic until they become large
  - Median size at diagnosis ~15 cm
- > 50% recur locoregionally with surgery alone
- Locoregional recurrence, not distant metastasis, is the leading cause of death



Histology

- 2 most common histologies[1]
  - Liposarcoma
  - Leiomyosarcoma
- Biopsy
  - Core-needle biopsy, not FNA
  - Minimal risk of biopsy site recurrences[2]
- Expert pathology review required[3]
  - Rate of histopathologic discordance – 24%
  - Rate of clinically relevant histopathologic discordance – 16%



[1] Nathan et al. (2009), *Ann Surg*
[2] Wilkinson et al. (2015), *Ann Surg Oncol*
[3] Raut et al. (2011), *JCO suppl abst 10065*

Sarcoma TNM Staging

American Joint Committee on Cancer, 7th ed

Category		Definition
Tumor status		
T0		No evidence of primary tumor
T1		T ≤ 5 cm
	T1a	Superficial
	T1b	Deep (to fascia; RP, abd, pelvis)
T2		T > 5 cm
	T2a	Superficial
	T2b	Deep
Lymph node status		
N0		No regional LN metastases
N1		Regional LN metastases present
Metastasis status		
M0		No distant metastases
M1		Distant metastases present

Only 6% of RPS are < 5 cm*

*Nathan et al. (2010), *Ann Surg*

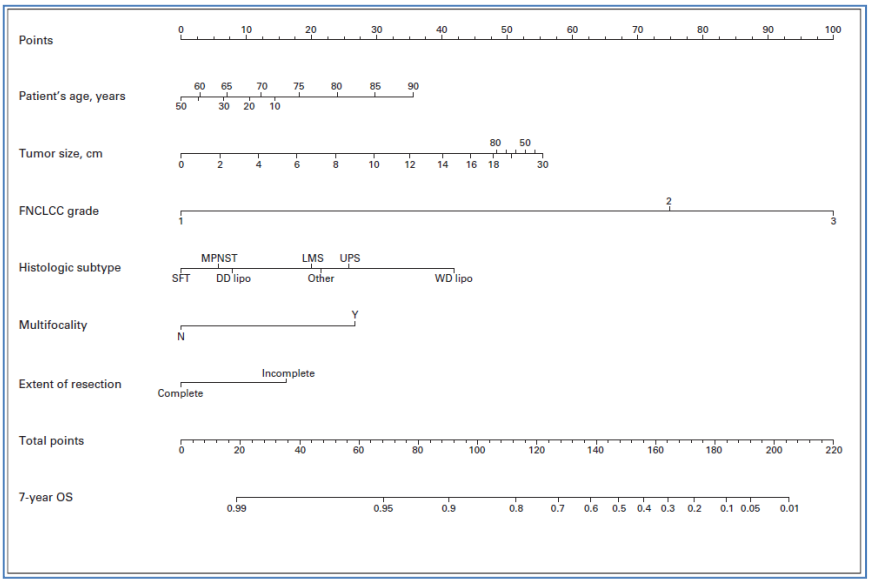
Sarcoma Stage Grouping

American Joint Committee on Cancer, 7th ed

Stage Grouping	Definition			
IA	T1a-b	N0	M0	G1
IB	T2a-b	N0	M0	G1
IIA	T1a-b	N0	M0	G2-3
IIB	T2a-b	N0	M0	G2
III	T2a-b	N0	M0	G3
	Any T	N1	M0	Any G
IV	Any T	Any N	M1	Any G

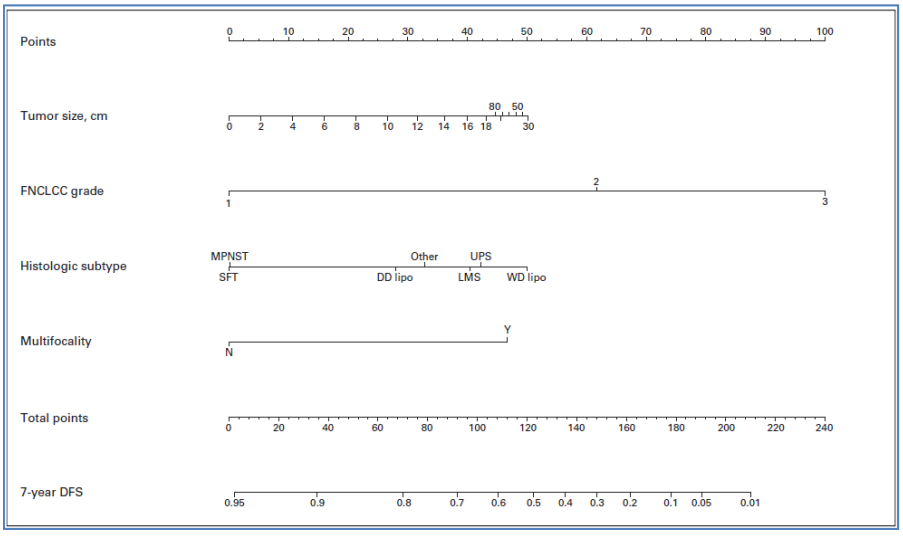
- Omits histology, multifocality, and site of origin
- By stage grouping, only grade distinguishes RPS
- Fails to distinguish patterns of recurrence

Overall Survival

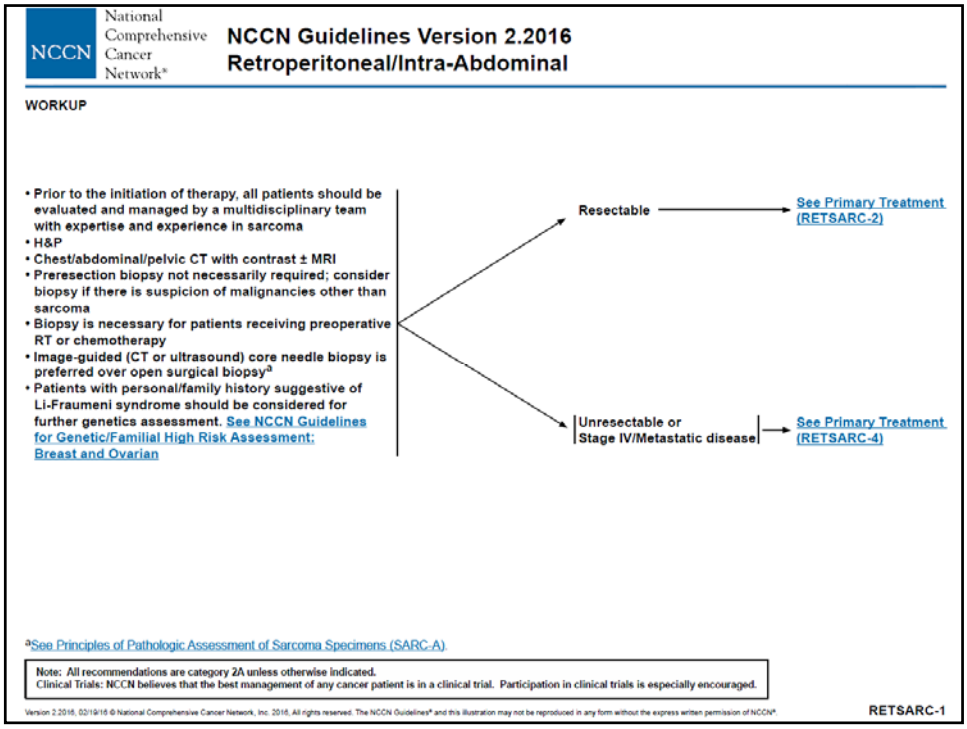


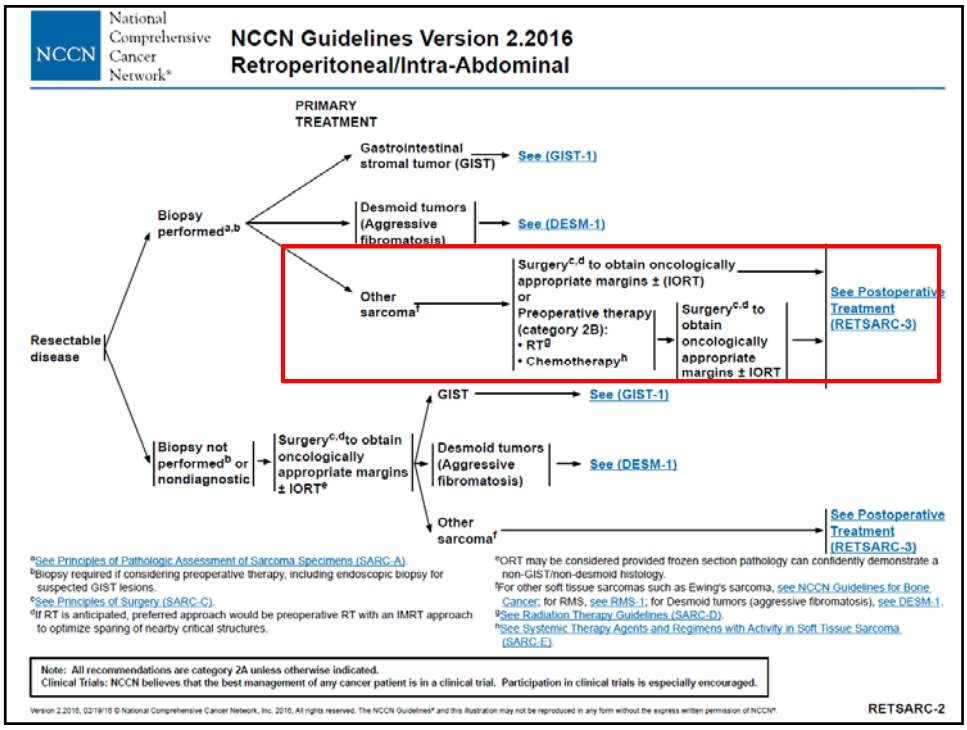
Gronchi et al. (2013), *J Clin Oncol*
Raut et al. (2016), *Cancer*

Disease-Free Survival



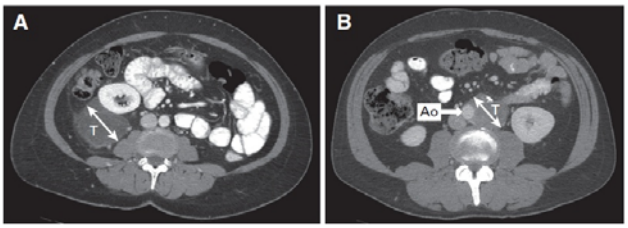
Gronchi et al. (2013), *J Clin Oncol*
Raut et al. (2016), *Cancer*





How Aggressive?

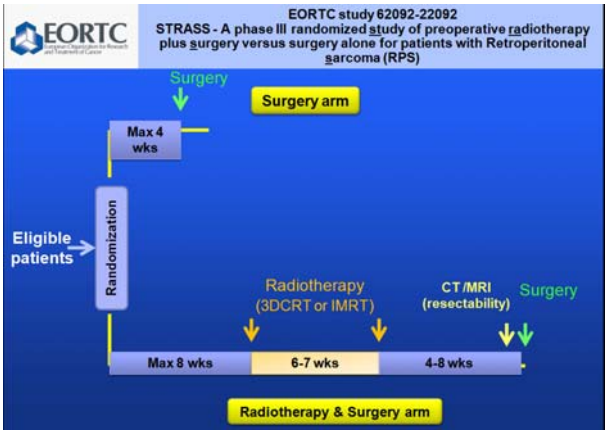
- Dissect just beyond the obvious tumor capsule and risk leaving tumor cells behind?
- More radical surgery removing adjacent un-invaded organs and retroperitoneal tissue?
- Each patient presentation is unique
  - What is a critical margin in one patient may not be so in another patient



Pisters (2009), *J Clin Oncol*

Phase III Preoperative Radiation Trial

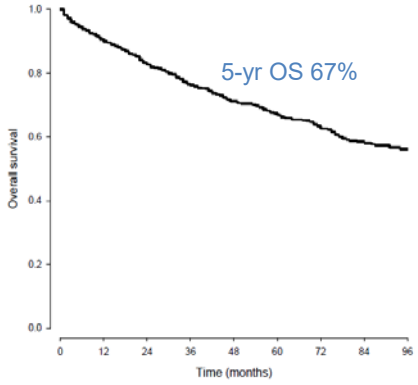
- Preop RT + surgery v. surgery alone
  - Primary resectable RPS
  - No prior RT or surgery
  - No metastases
- Accrual goal = **256**
- Current enrollment = **228**

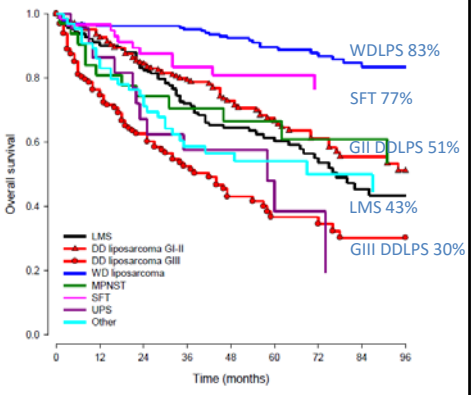


NCT #:01344018

Overall Survival by Histology

1007 patients

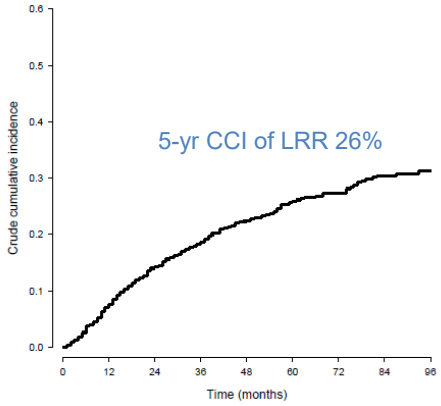


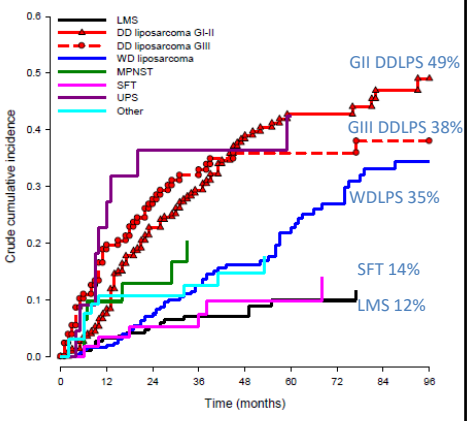


Gronchi et al. (2016), *Ann Surg*

Local Recurrence by Histology

1007 patients

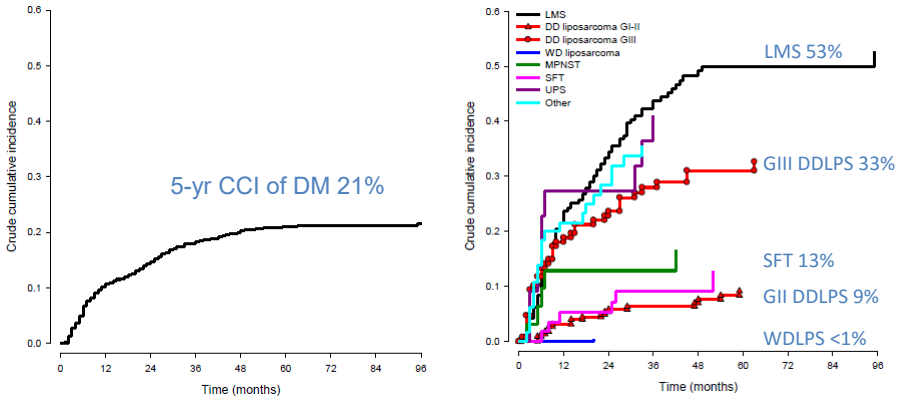




Gronchi et al. (2016), *Ann Surg*

Distant Metastases by Histology

1007 patients

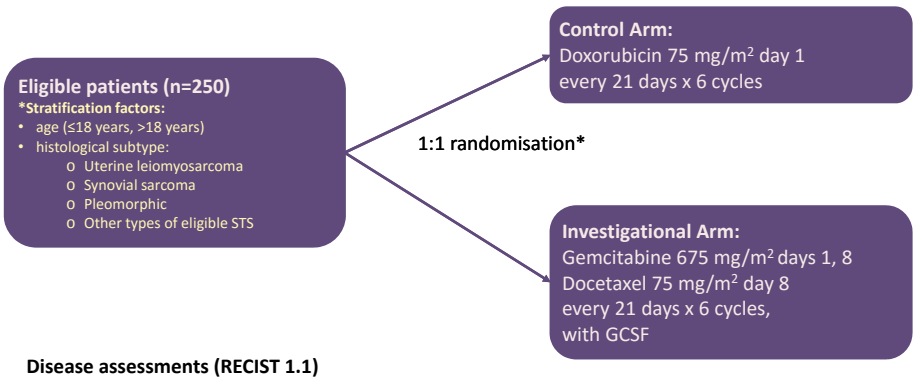


Gronchi et al. (2016), *Ann Surg*

Metastatic Disease: Optimal First Line Approach

- Anthracycline-based therapy
  - Single agent doxorubicin
- Gemcitabine-based therapy
  - Gemcitabine/docetaxel

GeDDiS - Trial Design



Disease assessments (RECIST 1.1) at:
- Baseline
- 12 weeks post randomisation
- 24 weeks post randomisation
- 12 weekly thereafter

Quality of life assessments at:
- Baseline
- 12 weeks post randomisation
- 18 weeks post randomisation
- 24 weeks post-randomisation

Seddon et al, ASCO annual meeting, CTOS annual meeting, 2015

GeDDis - Compliance to Trial Treatment

Reason	Dox (N=129)	GemDoc (N=128)
Total withdrawals during treatment	60 (47%)	80 (63%)
Disease progression	34 (57%)	39 (49%)
Symptomatic deterioration	4 (7%)	3 (4%)
Unacceptable toxicity	1 (2%)	13 (16%)
Serious adverse event	2 (3%)	2 (3%)
Death	5 (8%)	4 (5%)
Other	14 (23%)	19 (11%)

Seddon et al, ASCO annual meeting, CTOS annual meeting, 2015

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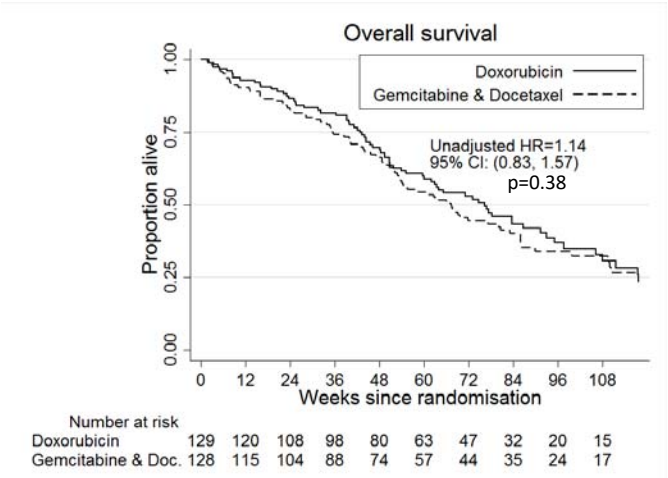
Seddon et al, ASCO annual meeting, CTOS annual meeting, 2015

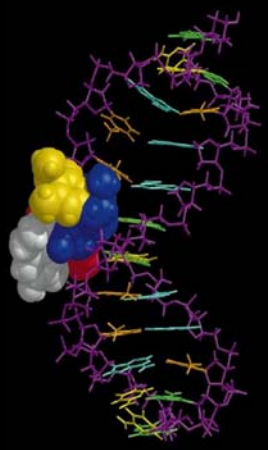
GeDDis- Overall Survival



	Median OS (months)	24 week OS
Dox	17.6	86.8%
GemDoc	15.4	82.6%

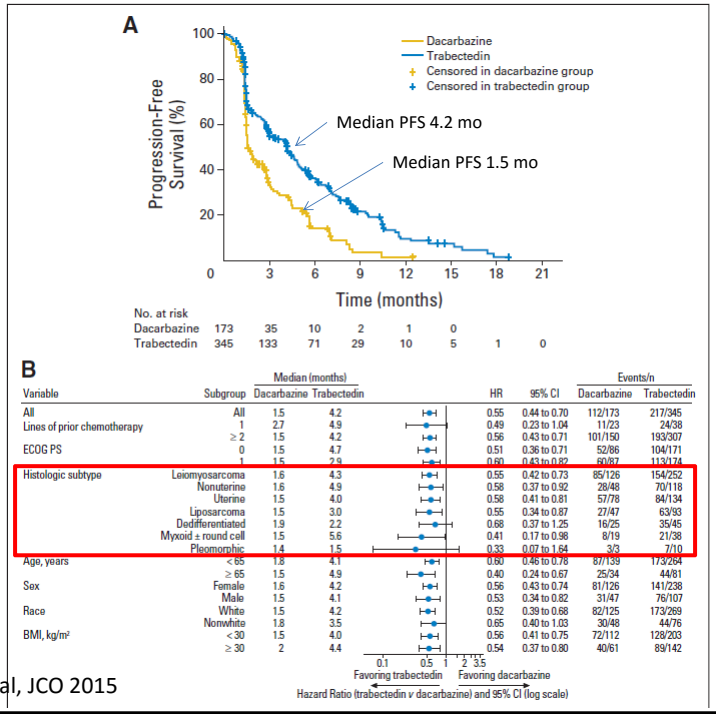
Seddon et al, ASCO annual meeting, CTOS annual meeting, 2015

Trabectedin: Molecular Pharmacology



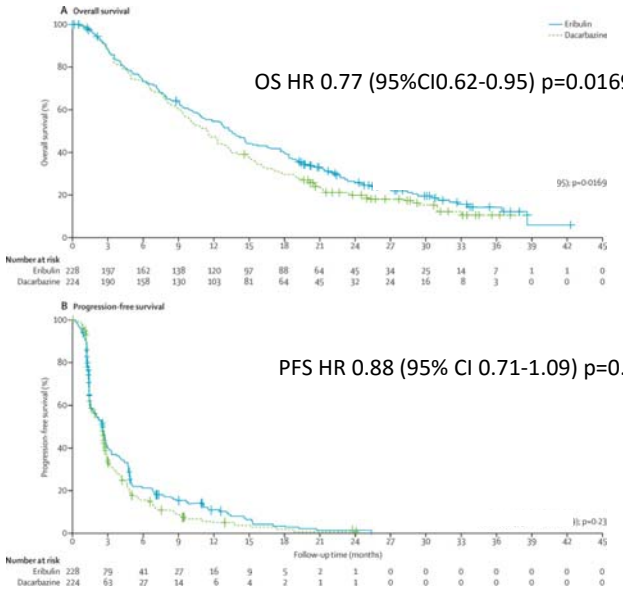
- Binds to DNA minor groove, bending the helix
- Interacts with transcription factors and other DNA binding proteins
- Major activity in myxoid/round cell liposarcoma with TLS/CHOP fusion oncoprotein (DNA binding protein)

Zewail-Foote, et al. *Chemistry & Biology,* 2001.



Demetri et al, JCO 2015

Eribulin: Modest OS Advantage v. DTIC in "L"-Sarcomas

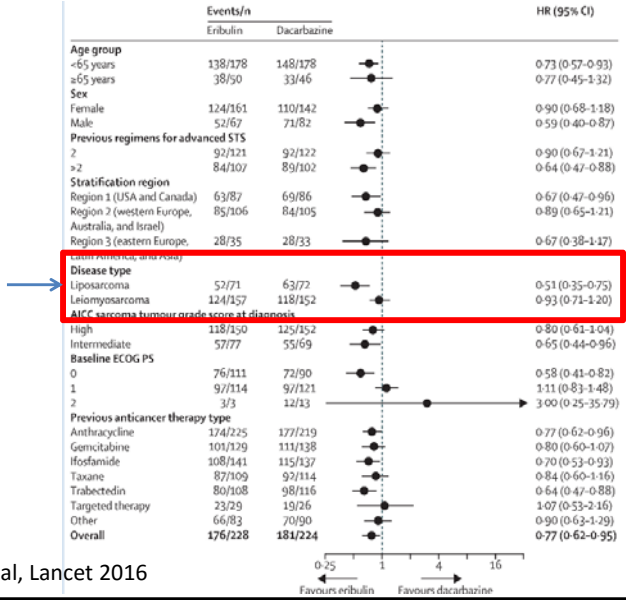


OS HR 0.77 (95%CI0.62-0.95) p=0.0169

PFS HR 0.88 (95% CI 0.71-1.09) p=0.23

Schoffski et al, Lancet 2016

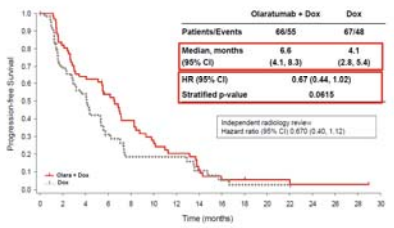
Eribulin v. DTIC: Primary Benefit Seen in Liposarcoma



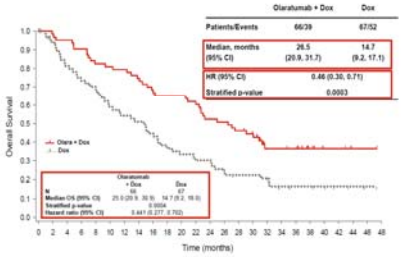
Schoffski et al, Lancet 2016

Olaratumab + Doxorubicin Demonstrated OS Benefit v. Doxorubicin Alone

Progression-Free Survival (ITT) (Phase 2)



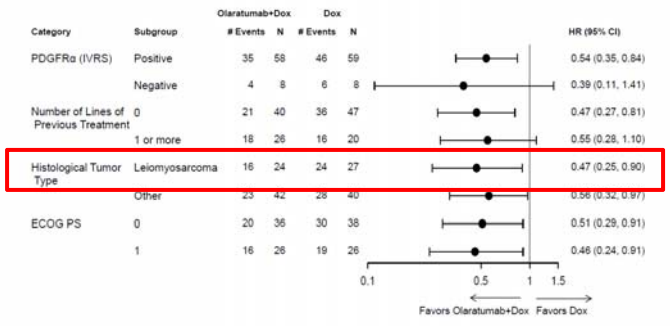
Overall Survival (ITT) (Phase 2)



Tap et al, ASCO 2015

Olaratumab + Doxorubicin in LMS

Overall Survival (ITT) by Stratification Factor (Phase 2)



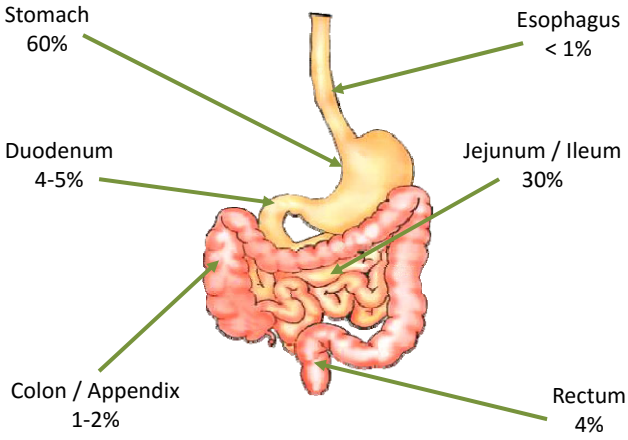
Ongoing Phase III trial – goal to enroll 40% with LMS

Tap et al, ASCO 2015

Gastrointestinal Stromal Tumor

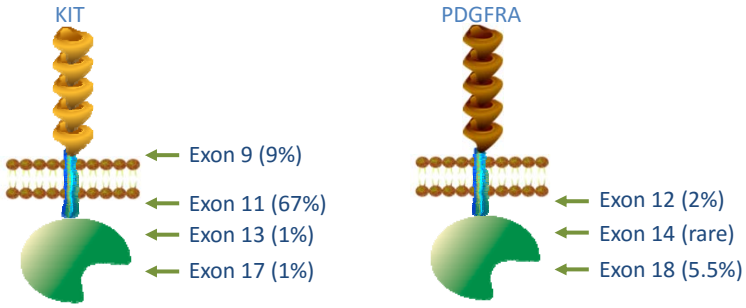
- Most common mesenchymal tumor of GI tract
  - <1% of all GI malignancies
- Clinically relevant incidence
  - 10-20 cases per 1 million population
  - 3000-4000 cases per year in the US
- Arise from interstitial cells of Cajal (pacemaker cell for intestinal peristalsis)

Distribution by Site



Pathologic Mutations

- > 80% - activating mutations of *KIT* proto-oncogene
  - *KIT* encodes the KIT receptor tyrosine kinase (TK)
- 8% - mutations of another TK gene, *platelet-derived growth factor α (PDGRFA)*

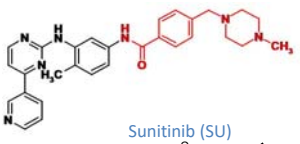


Corless and Heinrich (2008), *Ann Rev Pathol*

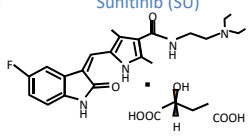
Tyrosine Kinase Inhibitors

- Identification of effective KIT tyrosine kinase inhibitors (TKI)
  - Imatinib mesylate – selective
  - Sunitinib malate – multi-targeted
  - Regorafenib – multi-targeted
- Key characteristics
  - Relatively safe
  - Well-tolerated
  - Orally available
- FDA-approved

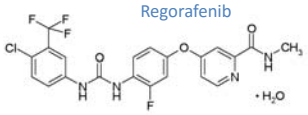
Imatinib (IM)

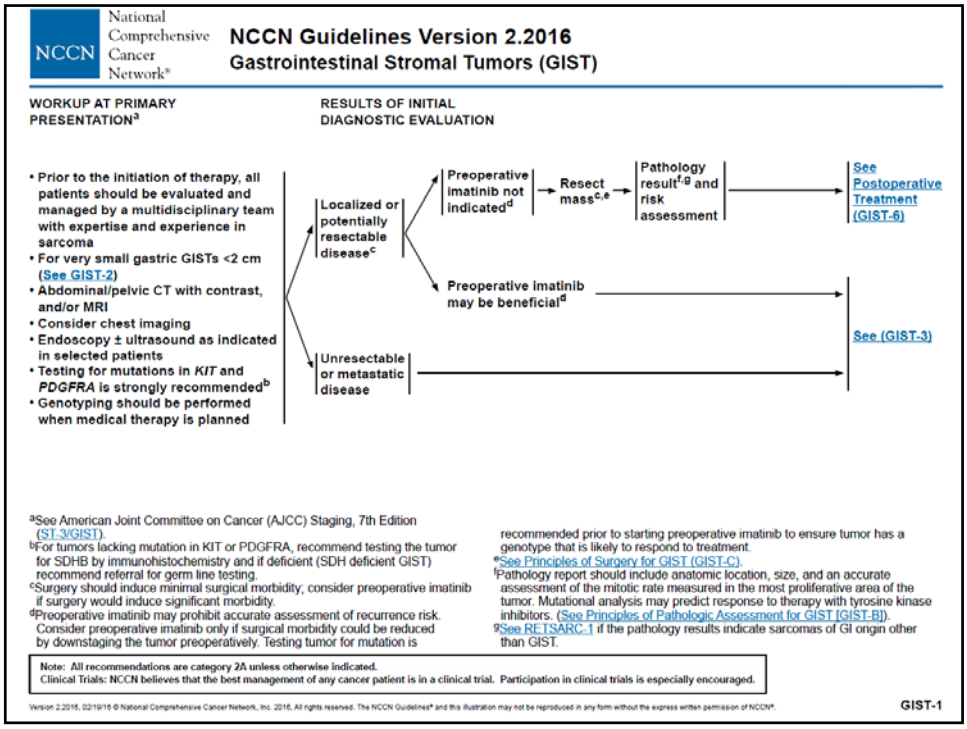


Sunitinib (SU)



Regorafenib



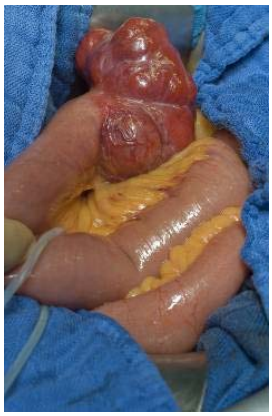


Surgery

- Surgery is the principal treatment and only curative therapy for localized, resectable primary disease

Surgery: Technique

- R0 resection
- Laparoscopic resections when feasible
  - Data mostly for gastric GISTs
  - Follow-up < 5 yrs
- Extensive resections when necessary
- Gentle handling – soft, friable tumors
- Thorough abdominal exploration
- Lymphadenectomy not indicated



Surgery: Margins

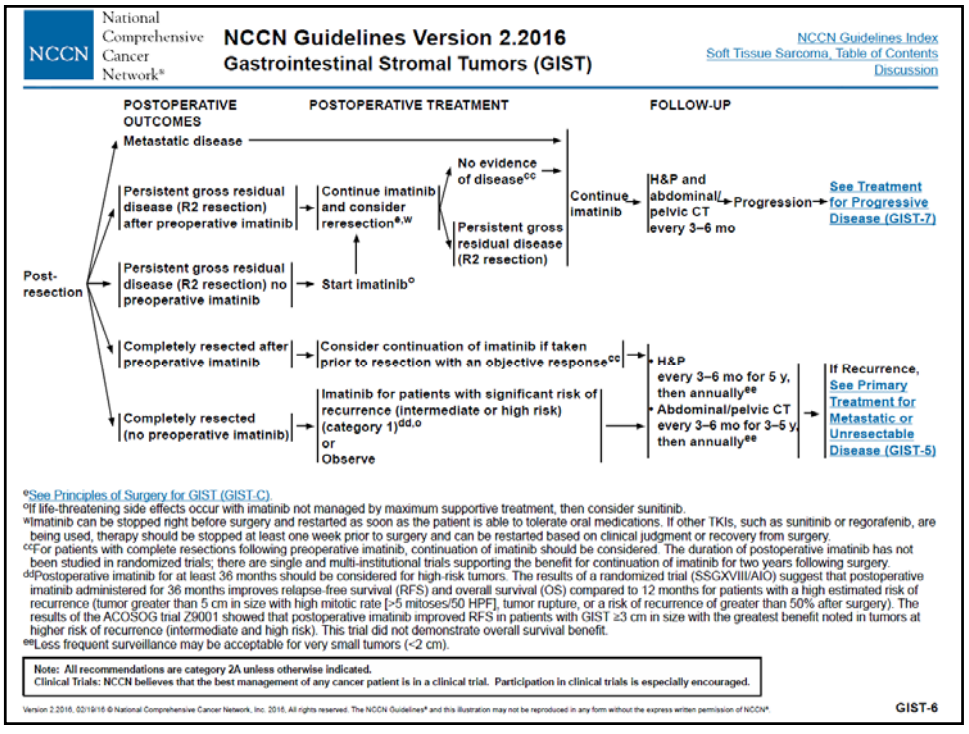
- No apparent benefit to wide margins (unlike adenocarcinomas or other sarcomas)
- No role for enucleation or endoscopic mucosal resection due to involvement of muscularis propria
- Adjacent organs
  - Primary tumors may displace adjacent structures, but are rarely invasive into surrounding organs
  - *En bloc* multi-organ resection may be necessary to achieve negative margins, especially with recurrent disease

Risk for Recurrence

Tumor Parameters		% Pts with Progressive Disease			
Size	Mitotic Count	Stomach	Duodenum	Jejunum / Ileum	Rectum
≤ 2 cm	≤ 5 per 50 HPFs	0	0	0	0
> 2, ≤ 5 cm		1.9	8.3	4.3	8.5
> 5, ≤ 10 cm		3.6	} 34	24	} 57
> 10 cm		12		52	
≤ 2 cm	> 5 per 50 HPF	0*	*	50*	54
> 2, ≤ 5 cm		16	50	73	52
> 5, ≤ 10 cm		55	} 86	85	} 71
> 10 cm		86		90	

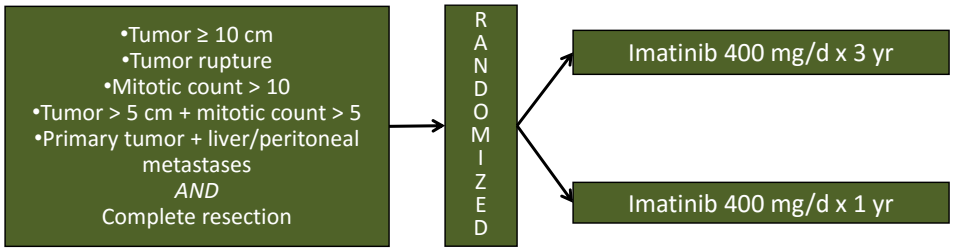
* Too few cases

Miettinen and Lasota (2006), *Sem Diag Pathol*



Adjuvant Imatinib – 3 Years

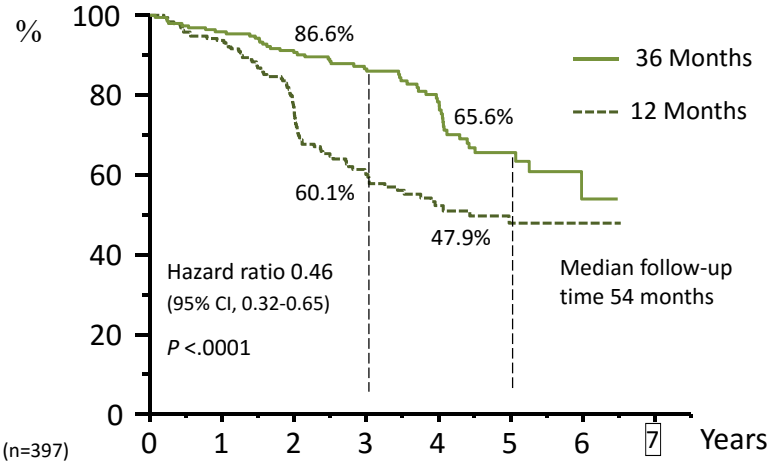
SSG XVIII/AIO



N=397

Joensuu et al. (2012), *JAMA*

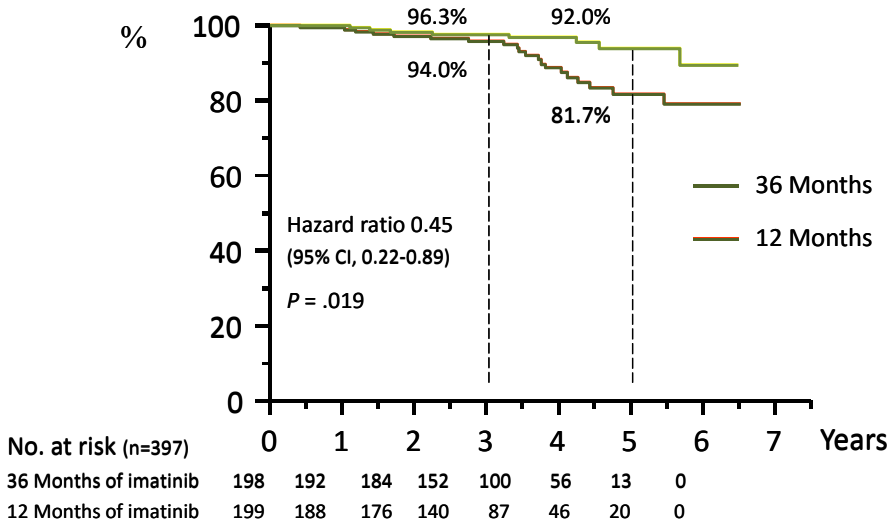
Recurrence-Free Survival



No. at risk (n=397)								
36 Months of imatinib	198	184	173	133	82	39	8	0
12 Months of imatinib	199	177	137	88	49	27	10	0

Joensuu et al. (2012), *JAMA*

Overall Survival



Joensuu et al. (2012), *JAMA*

PERSIST5

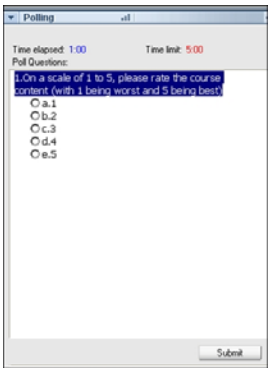
Post-resection **E**valuation of **R**ecurrence-free **S**urvival for gastro**I**ntestinal **S**tromal **T**umors with **5** years of adjuvant imatinib

- Phase II trial
- Accrual
  - Target – 85 pts
  - Enrolled – 91 pts
- Eligibility criteria
  - Primary, non-metastatic KIT+ GIST
  - Significant risk of recurrence
    Any site ≥ 2 cm + mitotic count ≥ 5/50 HPF **–OR–**
    Non-gastric primary ≥ 5 cm
  - R0 resection

NCT#: 00867113

Audience Response Question

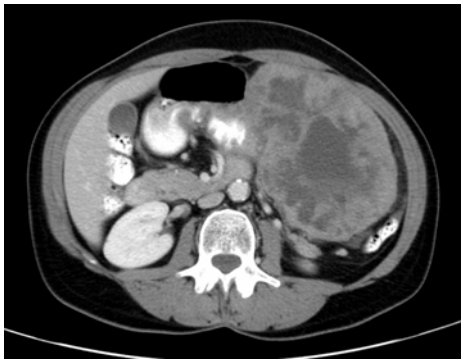
Look for the polling box on right side of your screen, near Q&A box to vote.



It may take a few moments to collect the polling results.

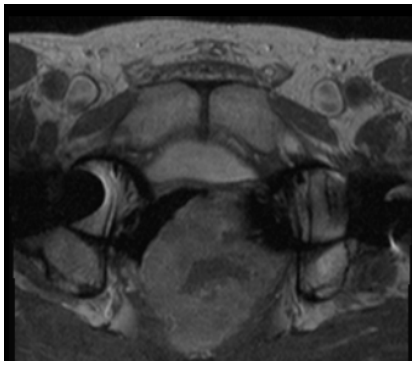
Case 3

- 61 YO woman
  - Abdominal pain
- CT:
  - 18 x 13 x 10 cm mass
- CT-guided biopsy
  - GIST



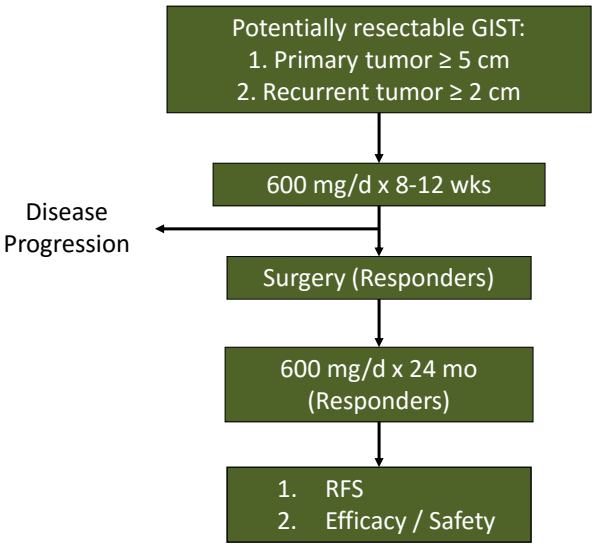
Case 4

- 68 YO man
  - Constipation
- Rectal exam: large palpable mass
- MRI
  - 9.5 cm rectal mass
- Endorectal biopsy
  - GIST



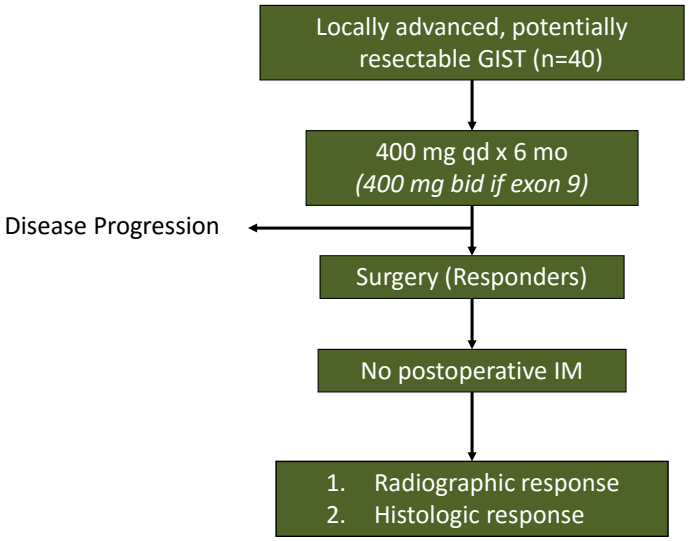
Neoadjuvant IM

RTOG 0132



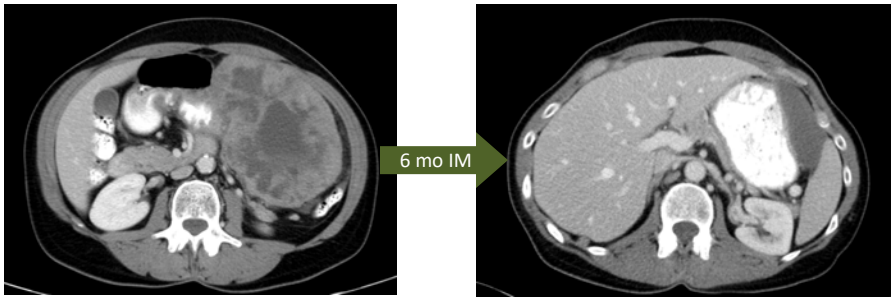
Eisenberg et al. (2008), *J Surg Oncol*

Apollon (Munich): Phase II



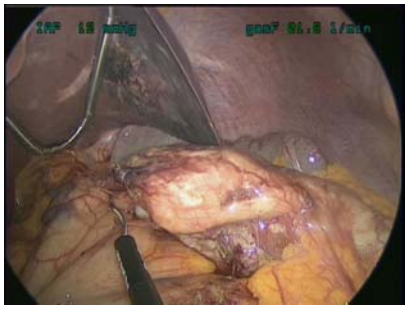
Case 3

- Neoadjuvant imatinib 400 mg qd x 6 mo
- CT: 11 cm maximal diameter (cranio-caudal)



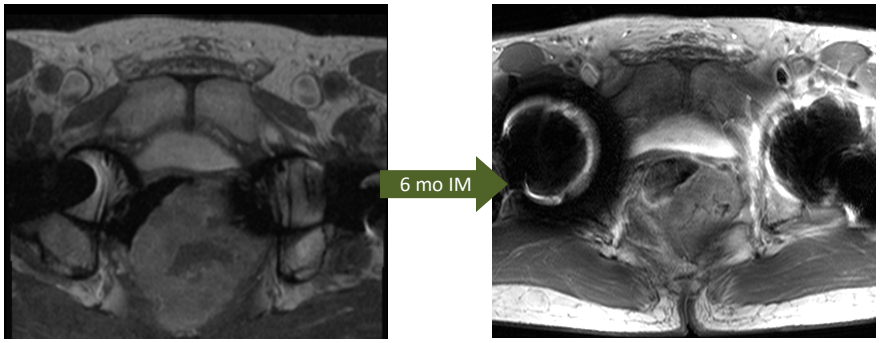
Case 3

- OR: laparoscopic partial gastrectomy
- Pathology:
  - Primary gastric GIST
  - 10.0 cm
  - Extensive hyalinization
  - Negative margins



Case 3: Large Rectal GIST

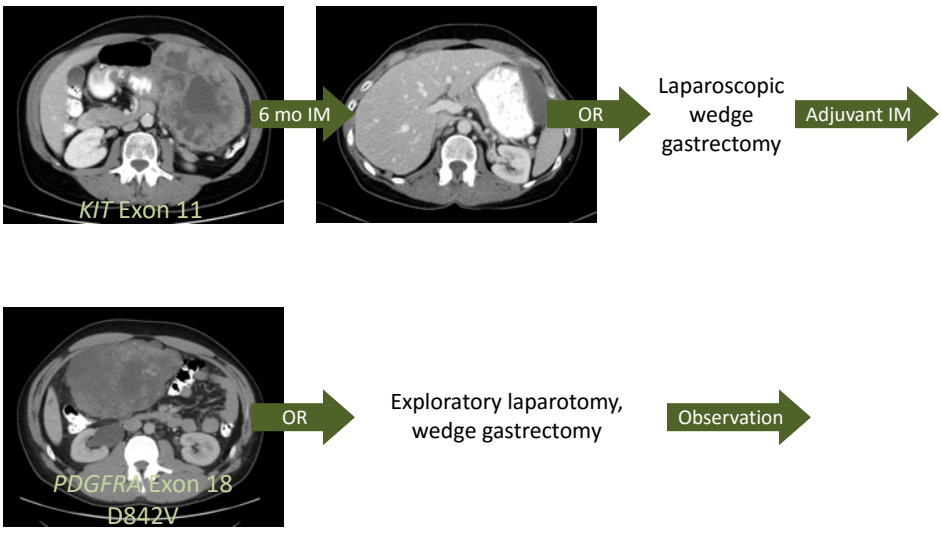
- Neoadjuvant imatinib 400 mg qd x 6 mo
- MRI: 6.1 cm maximal diameter

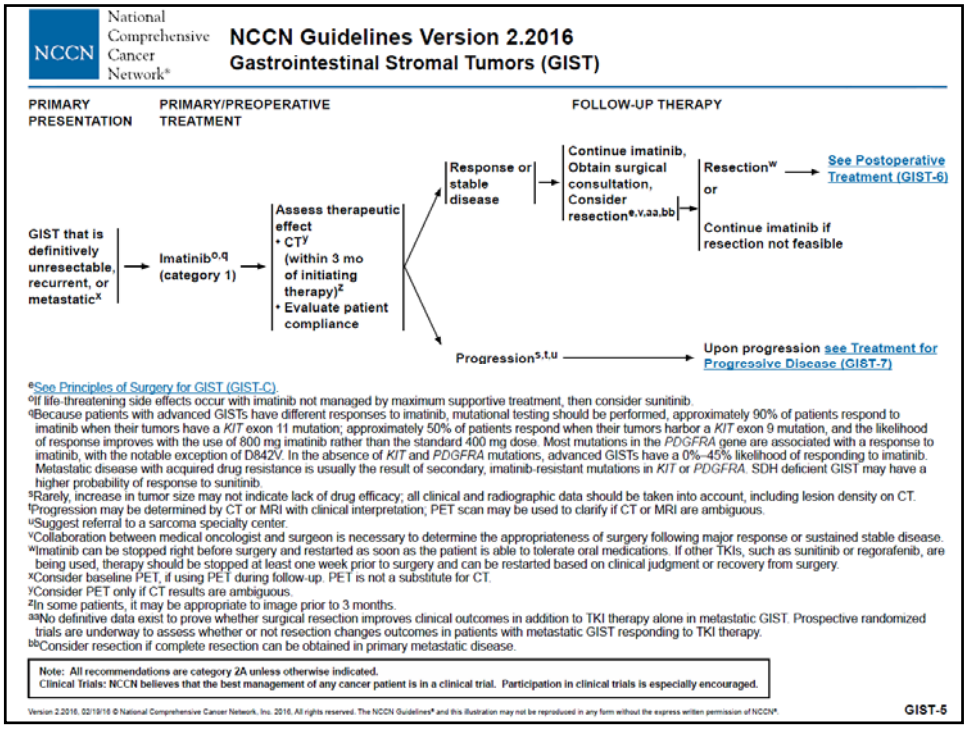


Case 4

- OR: transansal resection
- Pathology:
  - Primary rectal GIST
  - 6.1 cm
  - No mitotic activity
  - Negative mucosal margins
  - Closest radial margins 1mm

Treatment Influenced by Mutation





GIST Metastases

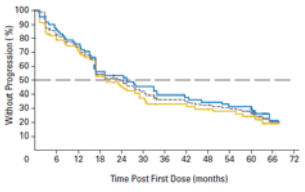
- Most common sites
  - Liver
  - Peritoneum
- Local recurrences rare
- Other sites (lung, soft tissue) rare, usually only in the late stages of the disease
  - Nodal metastases are exceedingly rare

Rationale for Surgery

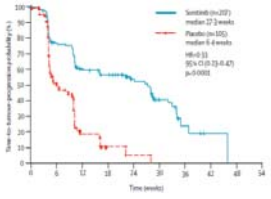
- Advent of targeted TKI therapy has altered the treatment paradigm for metastatic GIST
- 3 observations support consideration of surgery:
  1. Durable periods of partial response or stable disease on imatinib (IM)
  2. Pathologic complete responses rare
  3. Response to IM not maintained indefinitely

Progression on TKI Therapy

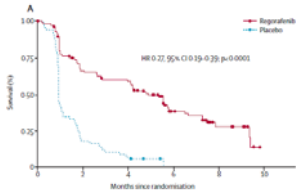
Imatinib	Sunitinib	Regorafenib
24 months	6.8 months	4.8 months



Blanke et al (2008), *J Clin Oncol*



Demetri et al (2006), *Lancet*



Demetri et al (2013), *Lancet*

Does Surgery Improve Survival?

- Surgery + imatinib *versus* imatinib alone
- Phase III trials – closed due to poor accrual
  - China – 41/210 pts
  - EORTC – 12/350 pts

Surgery for Metastatic GIST on TKI Therapy

Author (Year)	TKI	No. Pts	Responsive to TKI (%)	Unifocal Progression on TKI (%)	Multifocal Progression on TKI (%)	R0/R1 (%)
Raut (2006)	*IM/SU*	69	33	47	20	83
Rutkowski (2006)	*IM*	32	75	NA	25	81
Bonvalot (2006)	*IM*	22	91	5	NA	68
DeMatteo (2007)	*IM*	40	50	33	17	80
Andtbacka (2007)	*IM*	35	46	NA	17	31
Gronchi (2007)	*IM*	38	71	21	8	82
Sym (2008)	*IM*	34	71	9	21	65
Raut (2010)	*SU*	50	86	NA	14	50
Bauer (2014)	*IM*	239	NA	NA	NA	79
Rubió-Casadevall (2015)	*IM*	47	57	NA	43	62

Presented at the Connective Tissue Oncology Society Annual Meeting, November 2015

Surgery for Metastatic Gastrointestinal Stromal Tumors on Tyrosine Kinase Inhibitor Therapy: A Multicenter Analysis

Mark Fairweather, MD[1*], Vinod Balachandran, MD[2*], George Li, MD[1], Monica Bertagnolli, MD[1], Cristina Antonescu, MD[3], Samuel Singer, MD[2], Ronald DeMatteo, MD[2#], Chandrajit Raut, MD[1#]

[*]co-first/[#]last authors

[1] Department of Surgery, Brigham and Women's Hospital, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA

Departments of [2]Surgery and [3]Pathology, Memorial Sloan-Kettering Cancer Center, New York, NY

BWH BRIGHAM AND WOMEN'S HOSPITAL

Memorial Sloan-Kettering Cancer Center

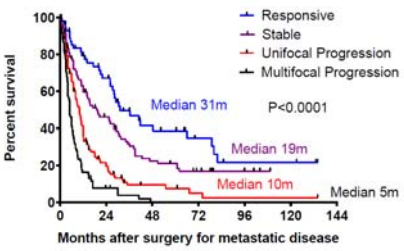
Multicenter Analysis

- Identified patients with metastatic GIST treated with TKI therapy and cytoreductive surgery
  - April 2001 – February 2014
  - **323** patients undergoing **400** operations
- Radiographic response at time of surgery
  - Responsive disease
  - Stable disease
  - Unifocal progression
  - Multifocal progression

Fairweather, et al. Connective Tissue Oncology Society Annual Meeting, Nov 2015. Paper 034. 2306514.

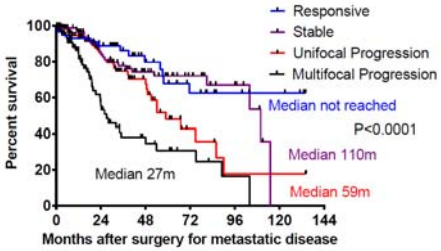
Radiographic Response

Progression-Free Survival



Median PFS 11 mo

Overall Survival



Median OS 86 mo

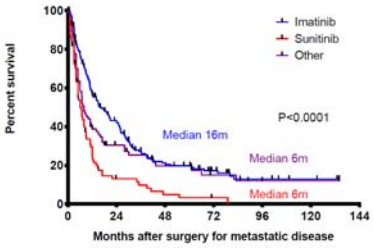
323 pts, 400 operations

Radiographic response at time of surgery is predictive of PFS and OS

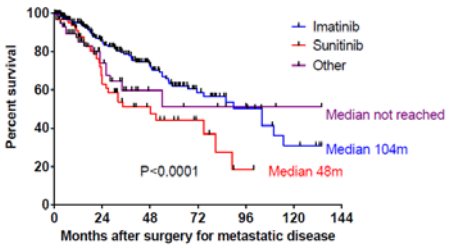
Fairweather, et al. Connective Tissue Oncology Society Annual Meeting, Nov 2015. Paper 034. 2306514.

Tyrosine Kinase Inhibitor

Progression-Free Survival



Overall Survival



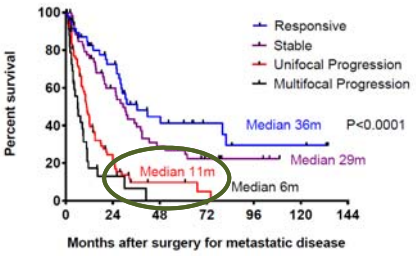
323 pts, 400 operations

Type of TKI at time of surgery is predictive of PFS and OS

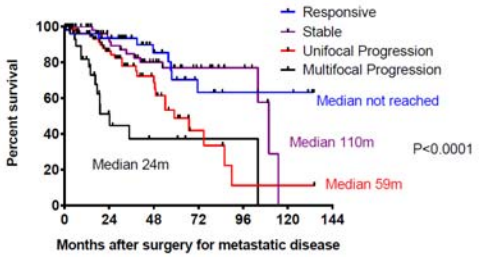
Fairweather, et al. Connective Tissue Oncology Society Annual Meeting, Nov 2015. Paper 034. 2306514.

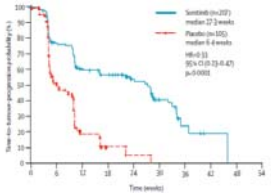
Imatinib

Progression-Free Survival



Overall Survival





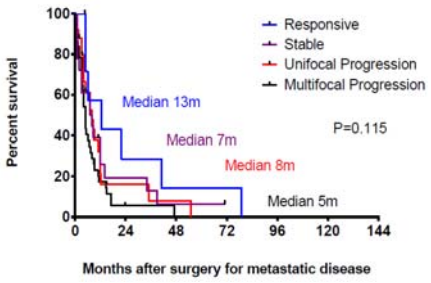
Radiographic response on imatinib at time of surgery is predictive of PFS

Multifocal progression on imatinib at time of surgery is associated with worse OS

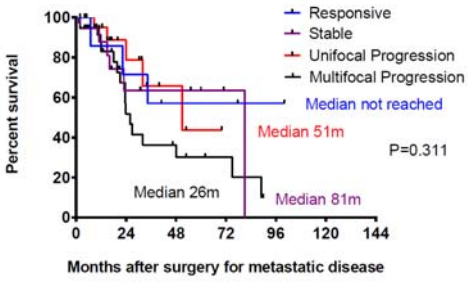
Fairweather, et al. Connective Tissue Oncology Society Annual Meeting, Nov 2015. Paper 034. 2306514.

Sunitinib

Progression-Free Survival



Overall Survival



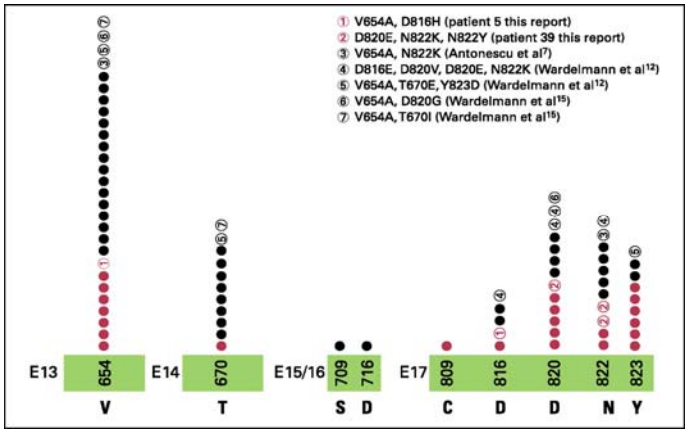
93 operations

*Radiographic response on sunitinib at time of surgery is **not predictive** of PFS or OS*

Fairweather, et al. Connective Tissue Oncology Society Annual Meeting, Nov 2015. Paper 034. 2306514.

Despite these dramatic results – resistance to imatinib remains a major challenge in the advance disease setting

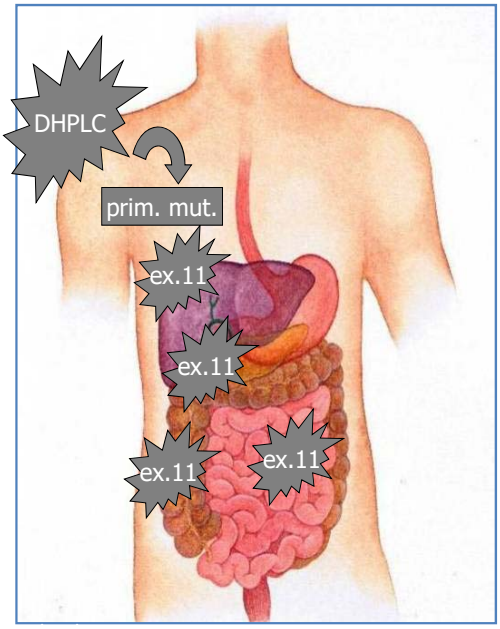
TKI Sensitivity Varies Based on Location of Mutation



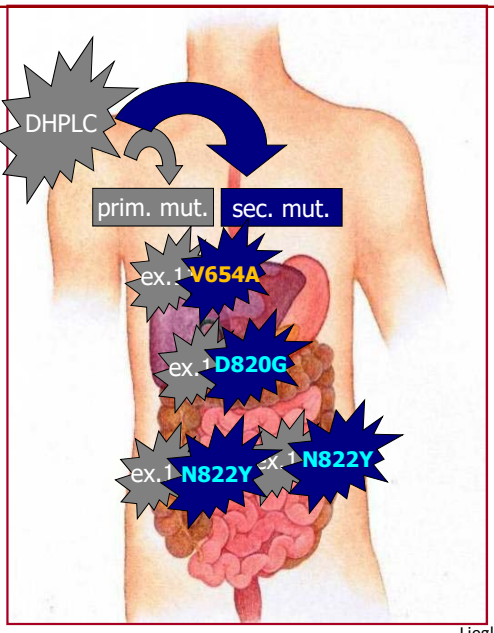
Courtesy of J. Fletcher

Modified from Heinrich et al. JCO 2006, JCO 2008

Progression on Imatinib: KIT Exon 11 Primary Mutation



GIST Progression on Imatinib: Mutational Heterogeneity



Drug/ATP binding pocket
Sunitinib sensitive

Kinase activation loop

Courtesy of J. Fletcher

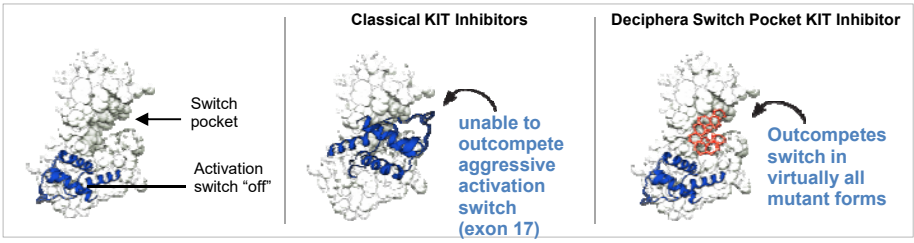
Liegl et al. J Pathol. 2008 Sep;216(1):64-74

Could Alternation of Current TKIs Optimize Disease Control?

Ongoing Phase Ib in TKI refractory GIST:

- ✓ Rapid alternation regimen might minimize toxic effects.
- ✓ Alternation of complementary drugs increases the spectrum of effective inhibition of IM-resistant clones.
- ✓ Embedded correlatives evaluating cf DNA – noninvasive assessment of KIT genomic profile

Future Approaches Aim to Inhibit KIT Broadly: Switch Pocket Technology – DCC-2618

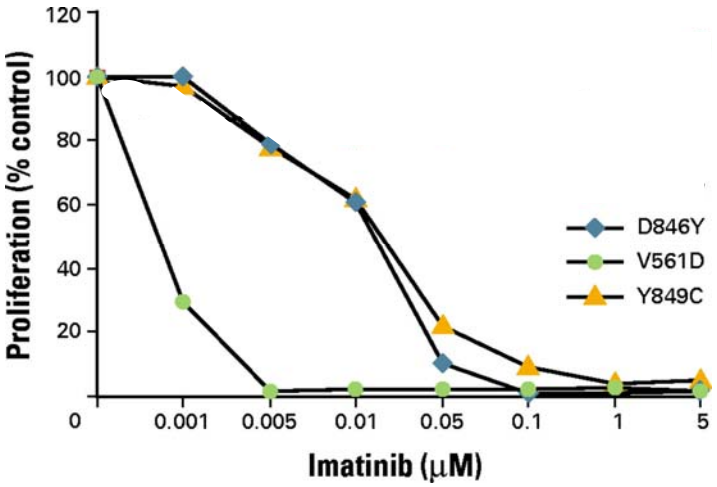


Compared to Type I or classical Type II kinase inhibitors, KIT switch pocket inhibitor DCC-2618:

- Binds potently and durably to KIT and PDGFRα
- Inhibits wild-type and virtually all mutant forms of KIT in preclinical models

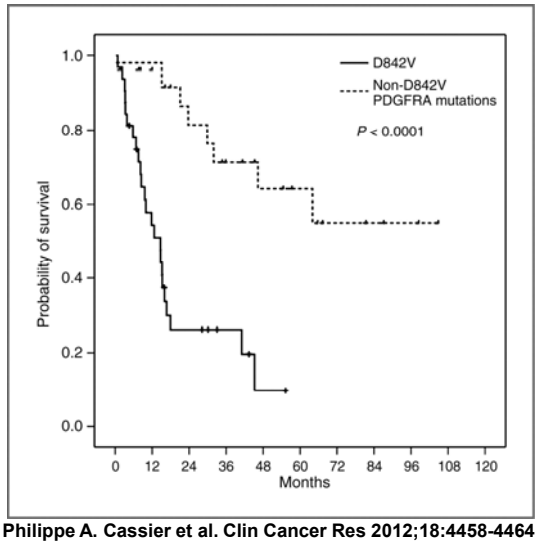
Smith et al, AACR Annual Meeting April 2015, abstract 2690

Most PDGFRA Mutations are Imatinib Sensitive



Corless C L et al. JCO 2005;23:5357-5364

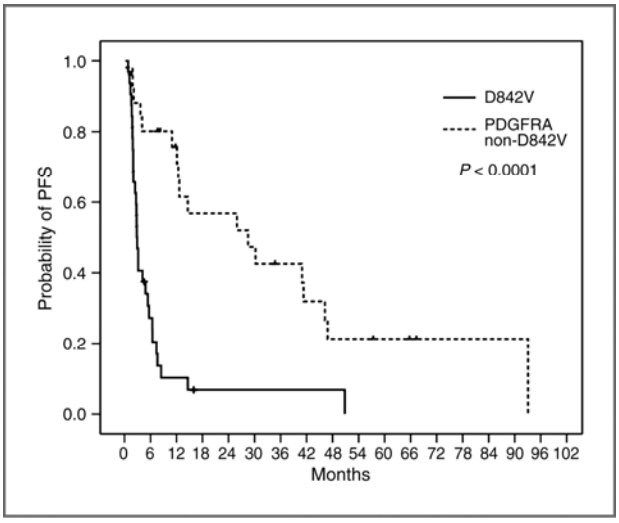
OS of Patients with Advanced GIST According to Type of PDGFRA Mutation



Philippe A. Cassier et al. Clin Cancer Res 2012;18:4458-4464

Clinical Cancer Research

PFS of Patients with Advanced PDGFRA-Mutant GISTs on 1st-Line Imatinib According to Type of PDGFRA Mutation

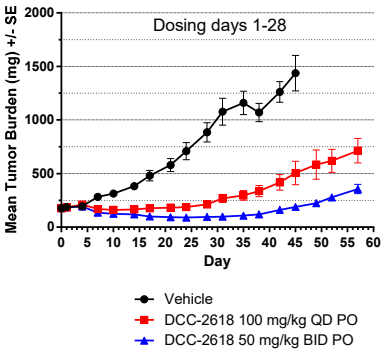


Philippe A. Cassier et al. Clin Cancer Res 2012;18:4458-4464

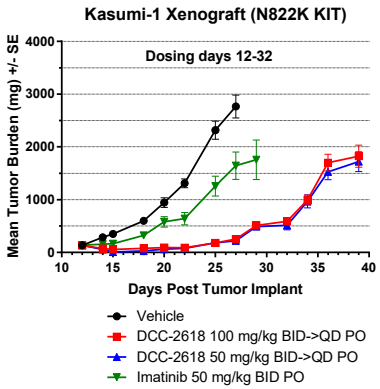
Clinical Cancer Research

DCC-2618 Inhibits Growth *In Vivo* of Exon11/Exon 17 Mutant KIT-Driven Tumor Models

DCC-2618 results in tumor regression in refractory GIST Exon 17 Y823D xenograft



DCC-2618 inhibits >90% growth of Exon 17 N822K Mutant AML Cancer Model

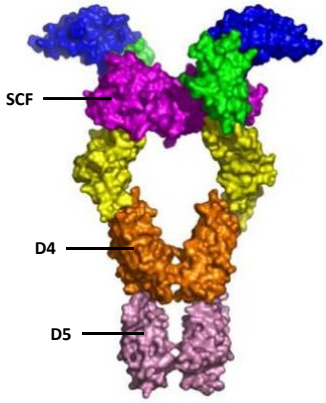


*ED_{90} Efficacy - Cmax ~597 ng/mL; AUC ~5,000 ng*h/mL @ 100 mg/kg/day

Smith et al, AACR Annual Meeting April 2015, abstract 2690

KTN0158 has a Unique Mechanism of Action

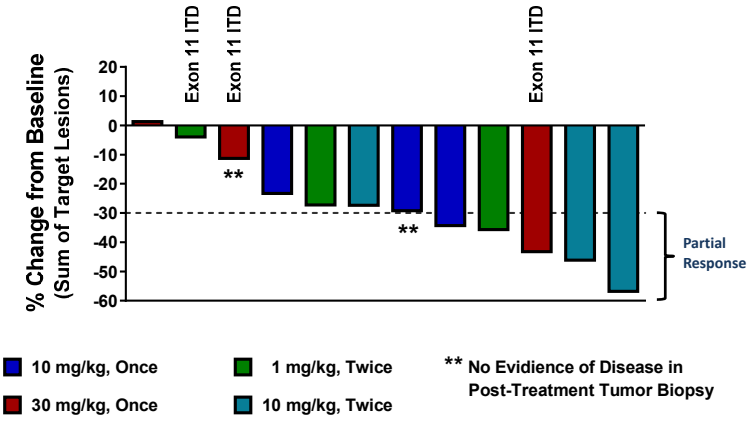
KIT bound to Its Ligand SCF



- Homotypic interactions between the KIT D4 and D5 domains are critical for receptor activation
- KTN0158 binds to D4 and blocks dimerization and ligand binding
- KTN0158 does not have agonist activity

Adapted from: Yuzawa, S., Schlessinger, J. *et al.* (2007). *Cell*. 130: 323-334.

KTN0158 has Anti-tumor Activity in Mast Cell Tumors in Dogs

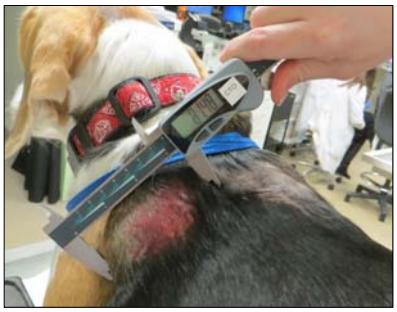


All dogs treated with KTN0158 experienced clinical benefit regardless of KIT mutation status

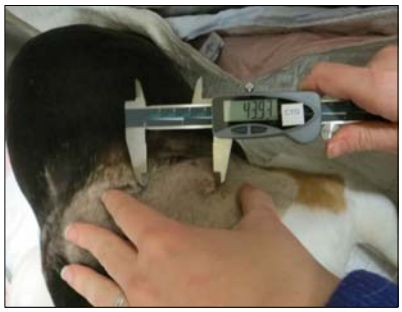
The Ohio State University College of Veterinary Medicine

London, et al. Mol Cancer Ther December 2015 14; C167

KTN0158 Dog Mast Cell Tumor Study
Partial Response to Treatment



Day 1



Day 15

Change in Tumor: - 46.1%

The Ohio State University College of Veterinary Medicine

London, et al. Mol Cancer Ther December 2015 14; C167

Thank you

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Q&A SESSION

Please use the Q&A feature on the right-hand portion of your screen to submit clinical questions to the speakers.

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