GIST: INITIAL THERAPY IN METASTATIC DISEASE

New Horizons GIST Meeting
September 10-12, 2020

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Disclosure

- Research Support (institution):
  - Merck, Bristol Myers Squibb, Novartis, Karyopharm, Boston Biochemical, Deciphera, Genentech, Roche, Pfizer, Medimmune, Eli-Lilly, Boehringer Ingleheim, Entremed/CASI Pharmaceuticals, Amgen, Champions Oncology, Iterion, Blueprint

- Consultancy (paid):
  - Eli Lilly, Boehringer Ingleheim, Merck, Adaptimmune, GSK

- **Slide Credit**
  - **Dr Mark Verrill, Dr Martin Blackstein and Dr Jonathan Trent**

EPIDEMIOLOGY & TREATMENT HISTORY

Gastrointestinal Stromal Tumours (GISTS)

- Part of the spectrum of Soft Tissue Sarcomas
- Distribution:
    - 60% stomach,
    - 30% small bowel,
    - 10% other sites – Oesophagus/Rectum
- Orginate in “stromal” cells in the gut wall.
- Similar gender distribution
- Age range from teens to the 90s
    - peak age around 60 years

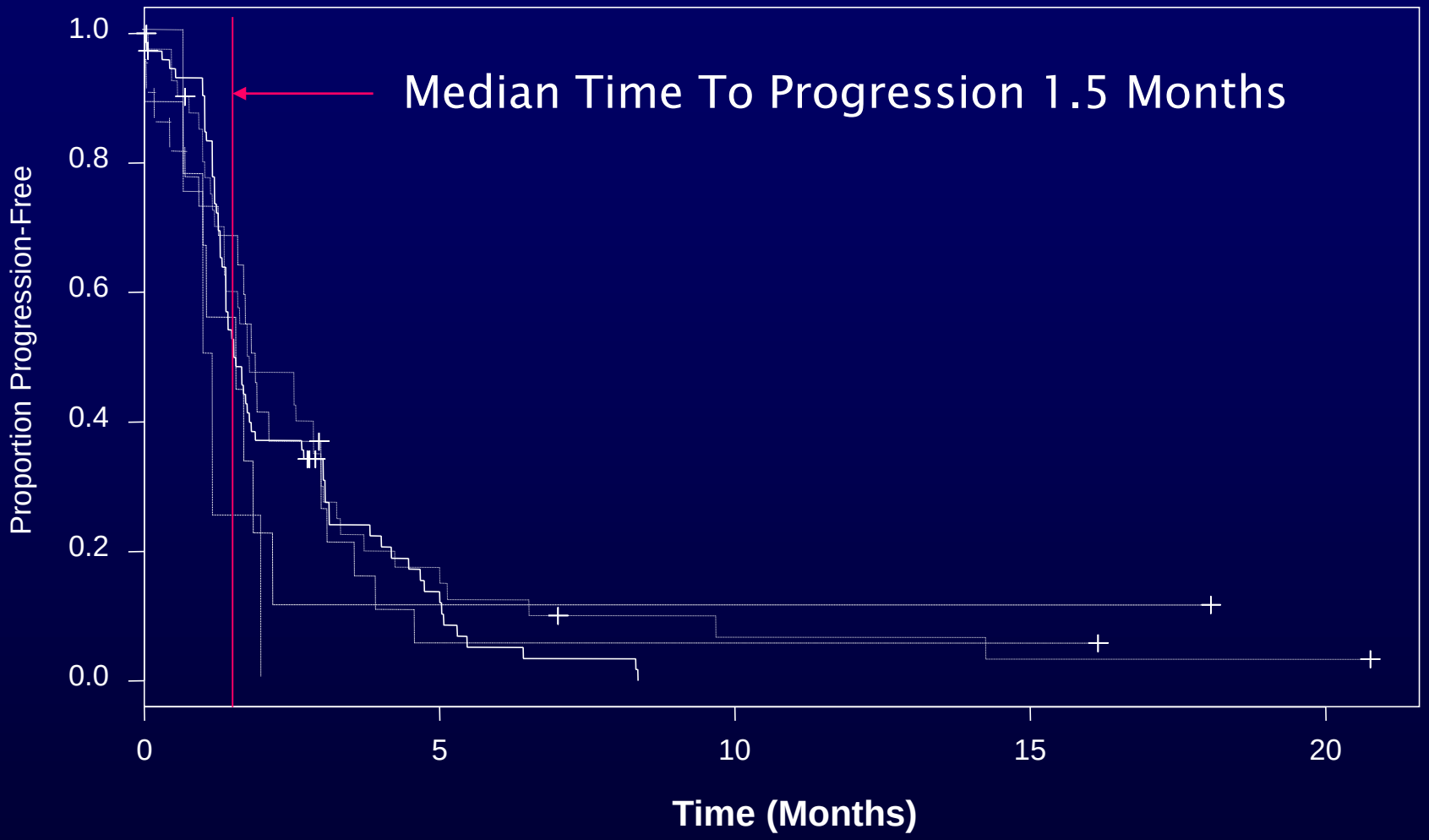
GIST Epidemiology

- Rare
  - Incidence 14.5 per million per year
    - Approximately 450 cases/year in Canada
  - Prevalence 129 per million
- 69% present with symptoms
  - Pain
  - Bleeding
  - Weight loss
- Of remainder, 2/3 incidental, 1/3 autopsy
- In metastatic the setting, liver & peritoneum are the most frequently organs involved.

GIST Treatment

- Treatment of choice for localised disease is surgery
- Many patients suffer relapse, main risk factors:
  - Tumour size (<5cm, 5-10 cm, >10 cm)
  - Mitotic count (<5, 6-10, >10 per 50 hpf)
- Locally advanced & metastatic GIST resistant to cytotoxic chemotherapy and radiotherapy.

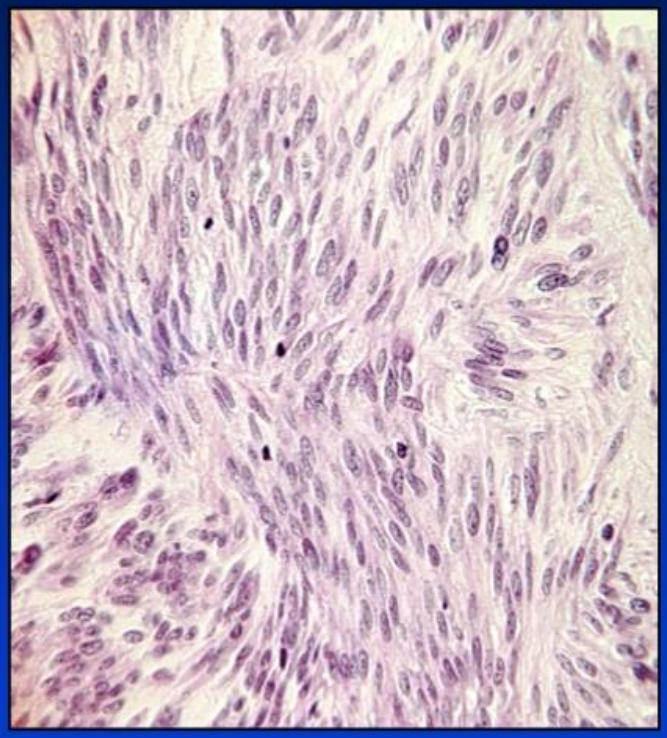
GIST: Outcome in chemo. trials



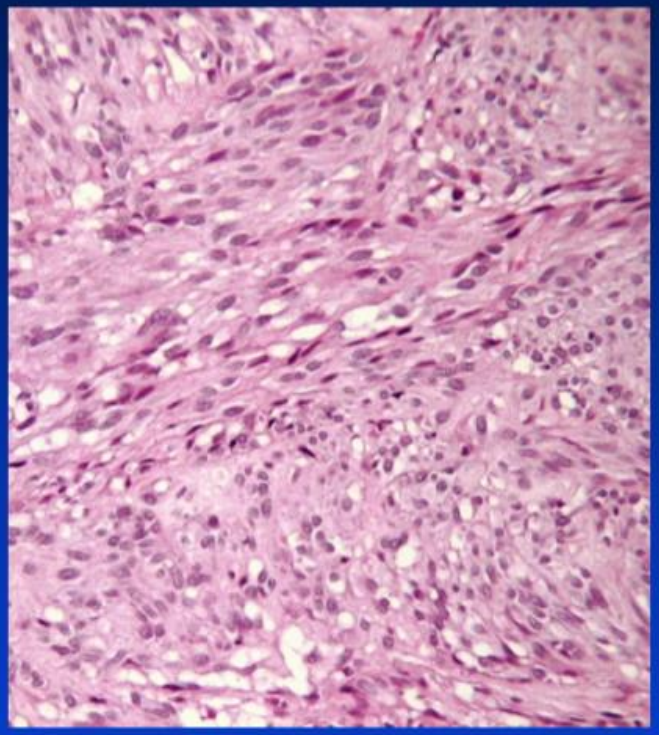
Median Survival for Metastatic/advanced or Non-resectable Disease ~12months

DIAGNOSIS AND PATHOPHYSIOLOGY

GIST: Pathology

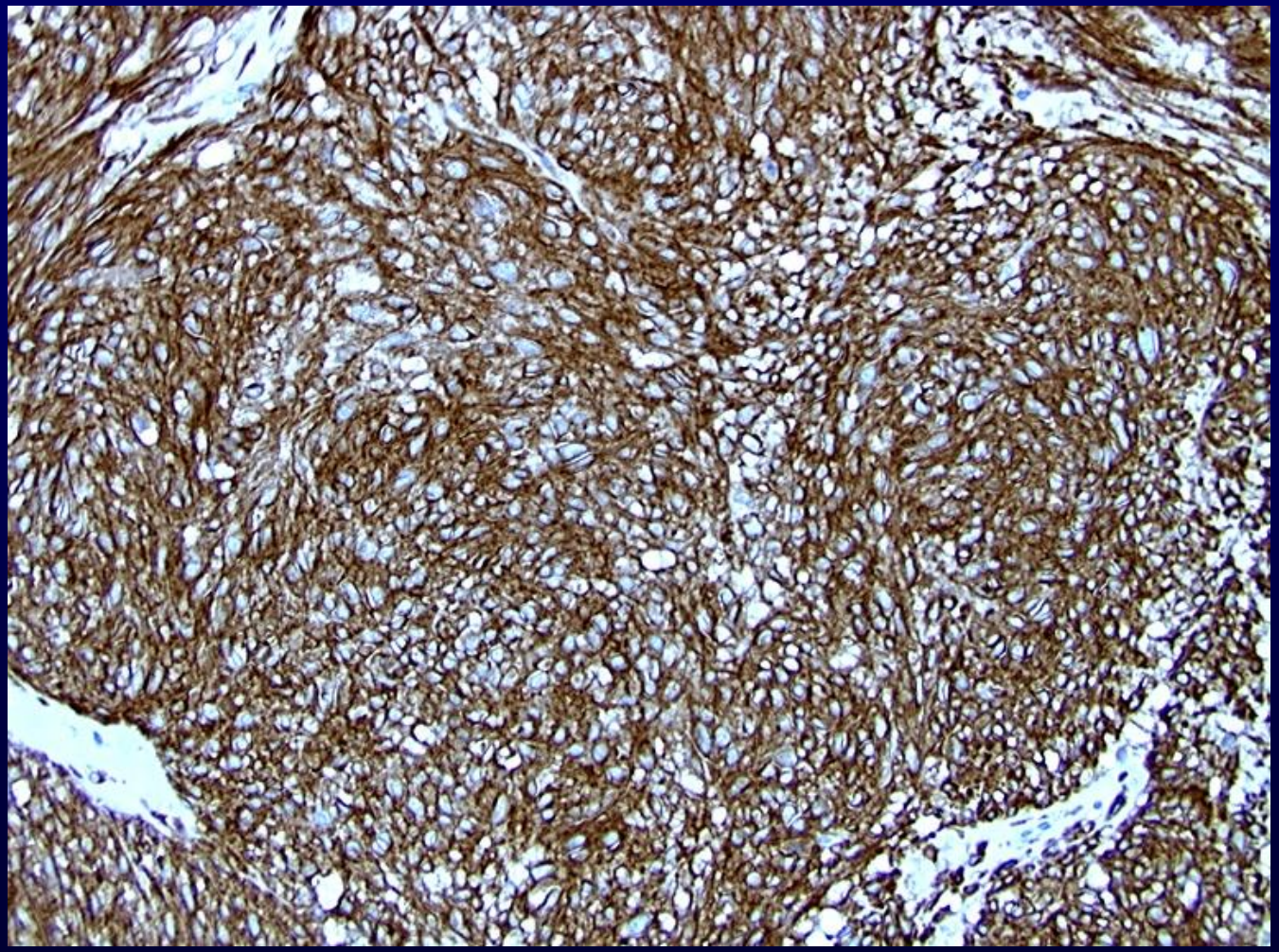


Primary GIST with predominantly spindle-cell morphology



Aggressive ("high grade") GIST with mixed morphology (spindle cell and epitheloid)

GIST: Pathology (IHC)

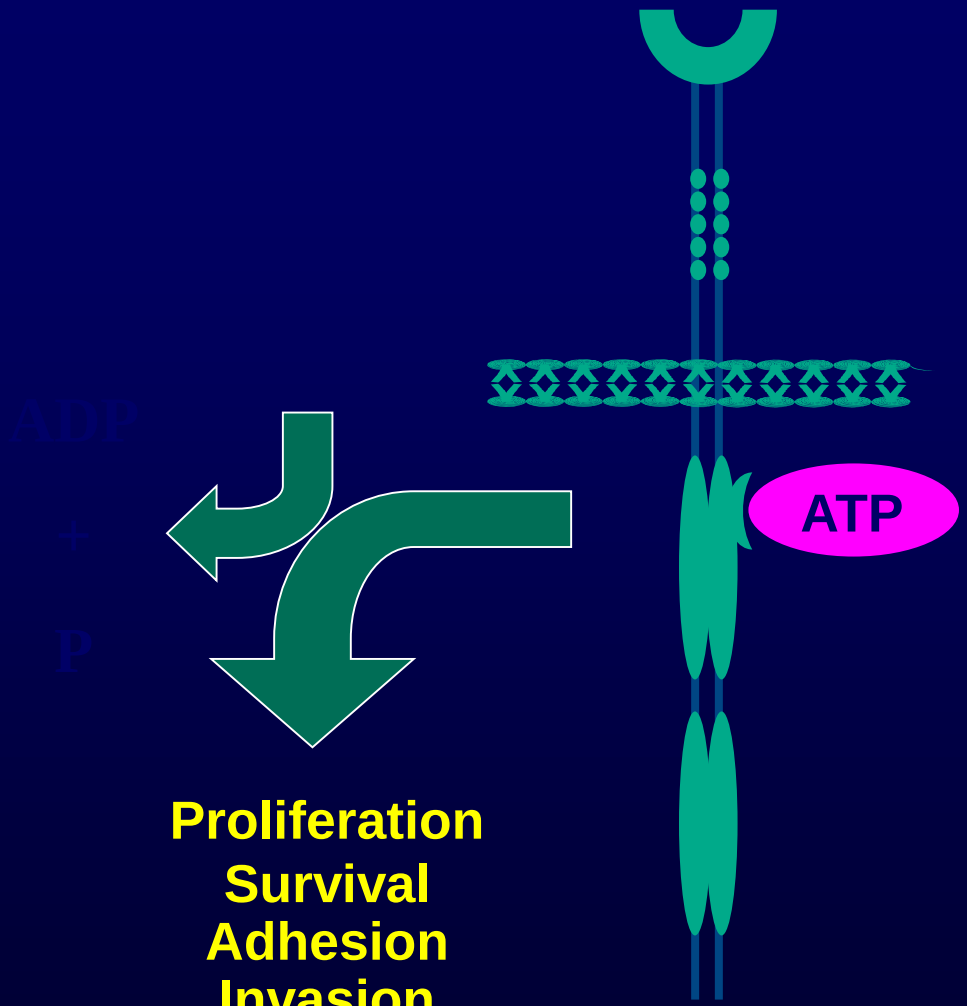


IHC : DOG-1 & CD117/c-Kit +ve

GIST: Tumour Biology

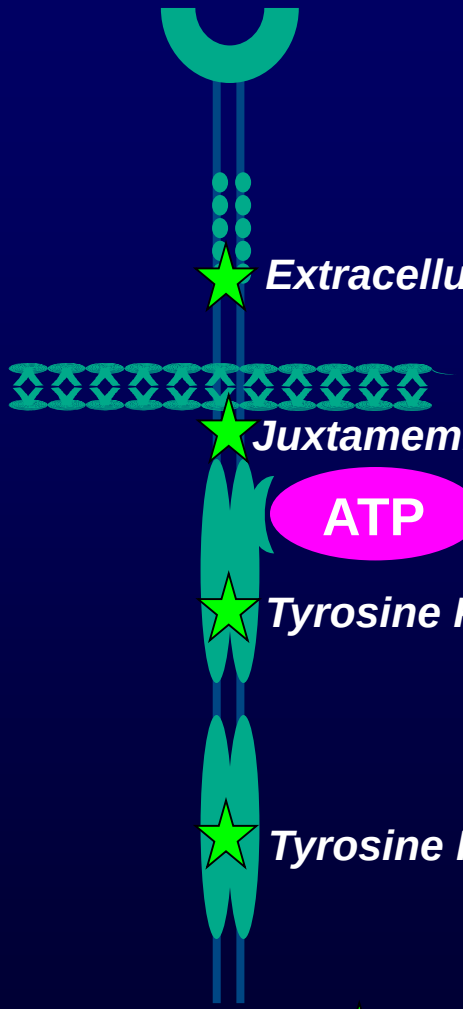
- GIST's are driven by mutations in a cellular growth factor
  - ~90-93% cKIT
  - ~5 % PDGFR
- Mutations are "activating"
- Growth occurs without an external stimulus
- These mutated proteins are the target for specific anti-GIST drugs
- First in class was Imatinib.

Kit Receptor Phenotype



Proliferation
Survival
Adhesion
Invasion
Metastasis
Angiogenesis

Kit Receptor Structure



Extracellular Domain (exon 9, 10.2%)

Juxtamembrane Domain (exon 11, 66.1%)

ATP

Tyrosine Kinase Domain I (exon 13/14, 1.2%)

Tyrosine Kinase Domain II (exon 17, 0.6%)

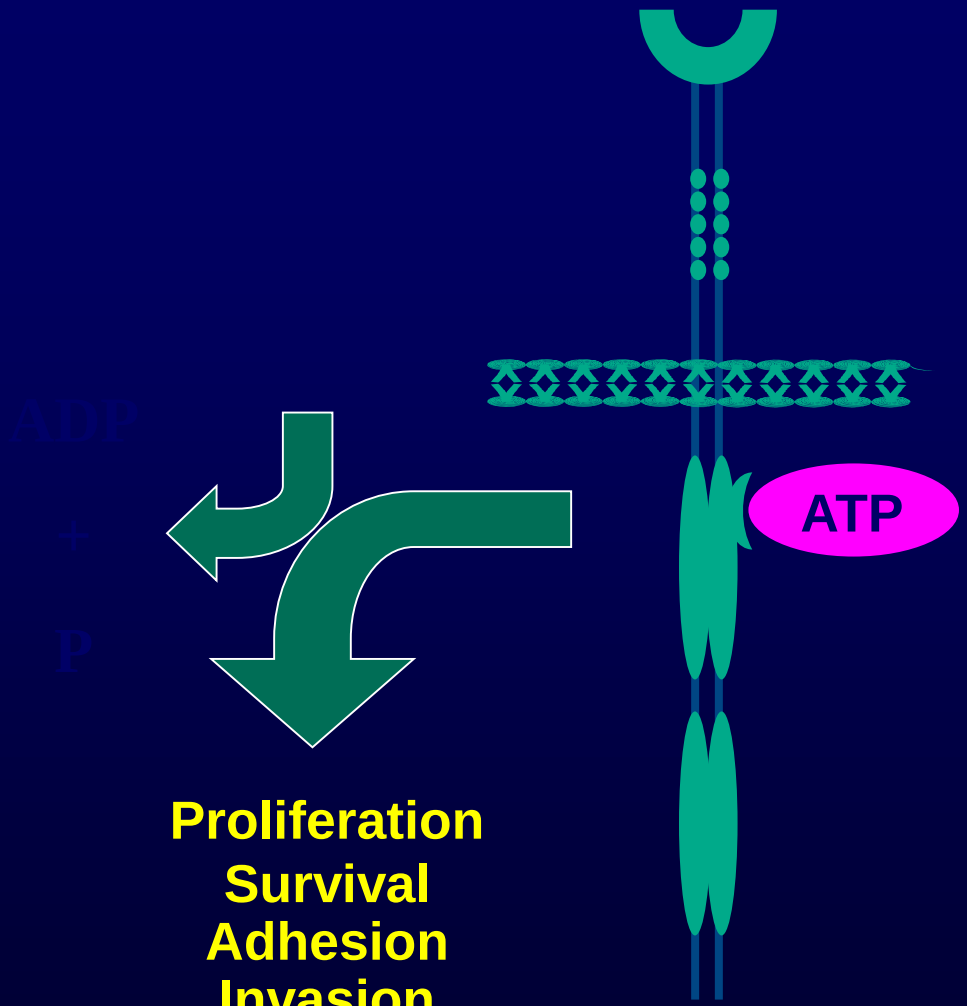
★ = common mutation site

METASTATIC GIST & IMATINIB

Glivec® – Imatinib– STI571

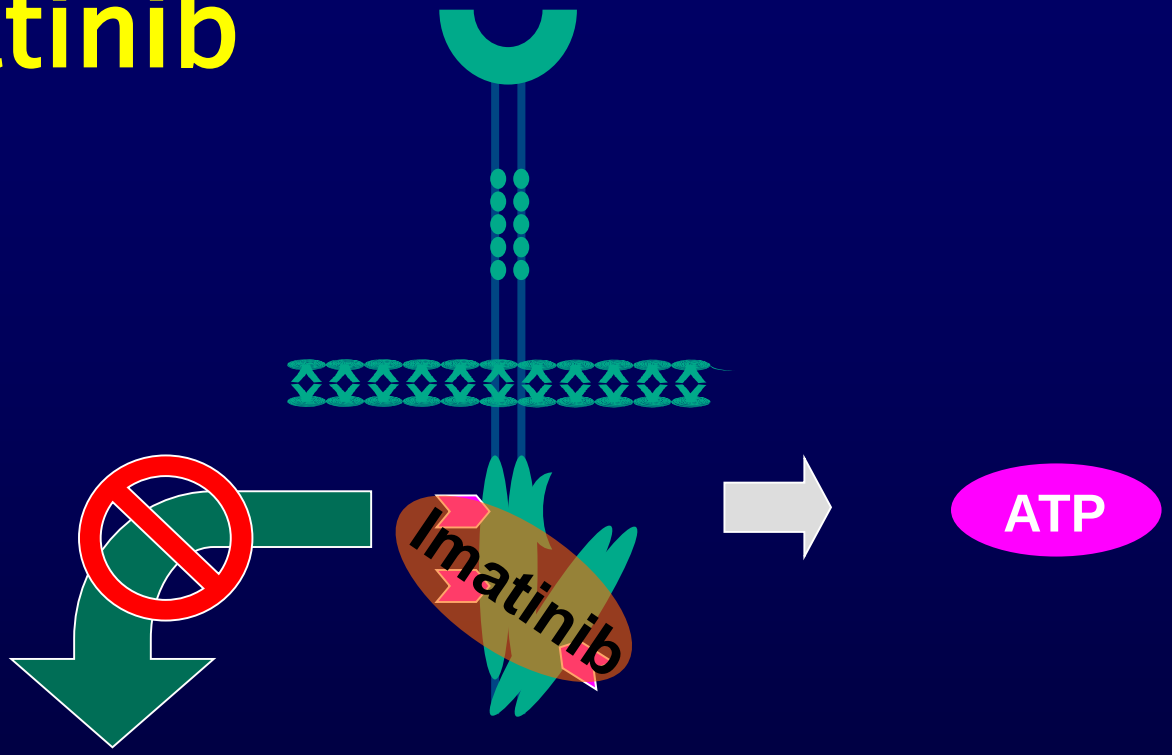
- inhibitor of ABL, BCR-Abl, PDGF and c-KIT
- Based on structure of ATP binding site
- Orally bioavailable
- First in Man June 1998

Kit Receptor Phenotype



Proliferation
Survival
Adhesion
Invasion
Metastasis
Angiogenesis

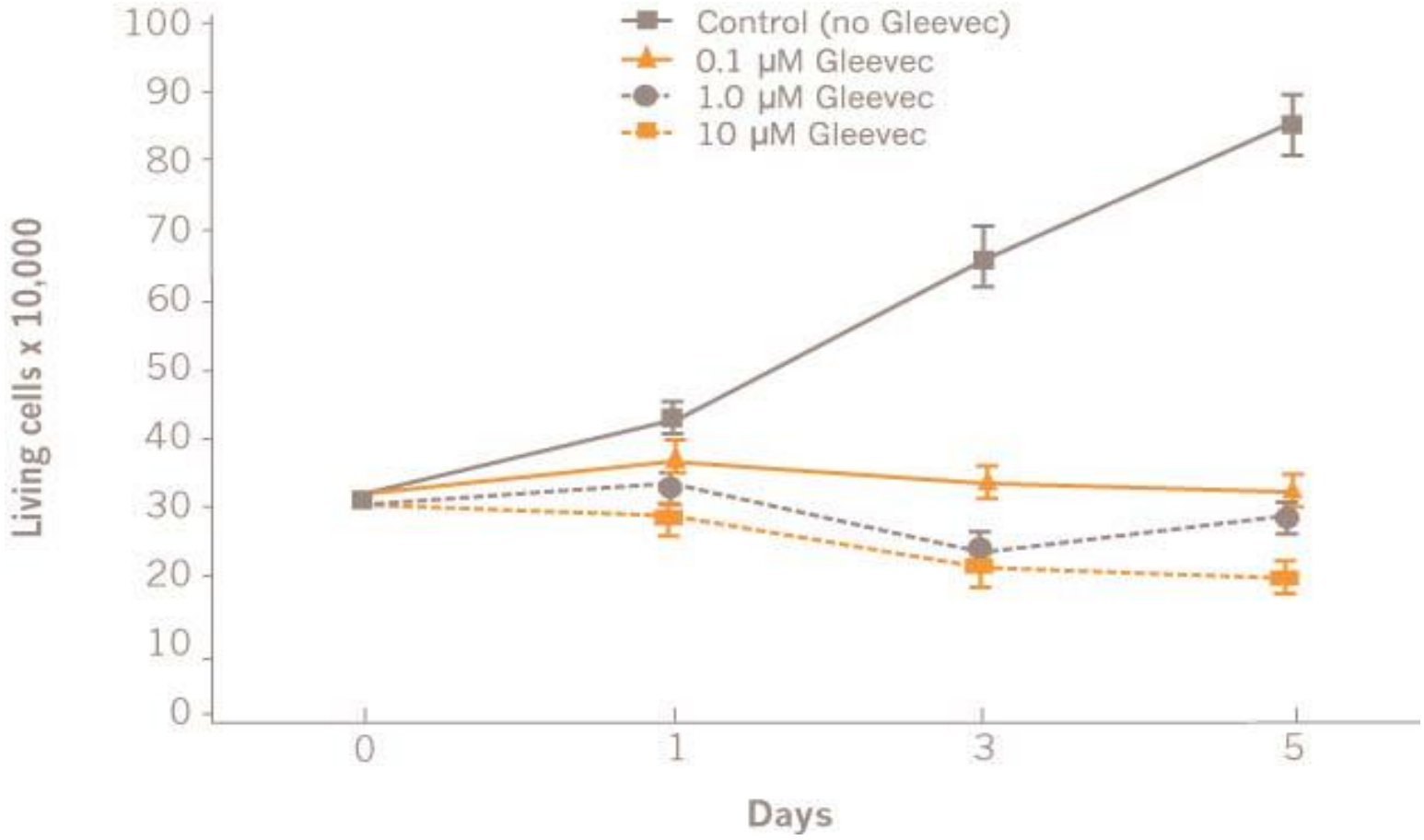
Mechanism of Action of Imatinib



Proliferation
Survival
Adhesion
Invasion
Metastasis
Angiogenesis

= imanitib contact point

Imatinib Inhibition of GIST Cell Proliferation In-*vitro*



Tuveson DT, et al.. Oncogene, 2001;20:5054-5058

EORTC Early Clinical Studies

- Phase I
  - Dose escalation in STS (range 400mg to 1000 mg)
  - 36/40 patients in study had GIST
  - 69% objective response,
  - 81% progression free at a year.
- Phase II
  - 800 mg o.d.
  - 24 patients with GIST, 24 other STS
  - 71% objective response rate in GIST
  - 73% GISTs were progression free at 12 months
- No activity in non-GIST STS
- Few severe or very severe side effects

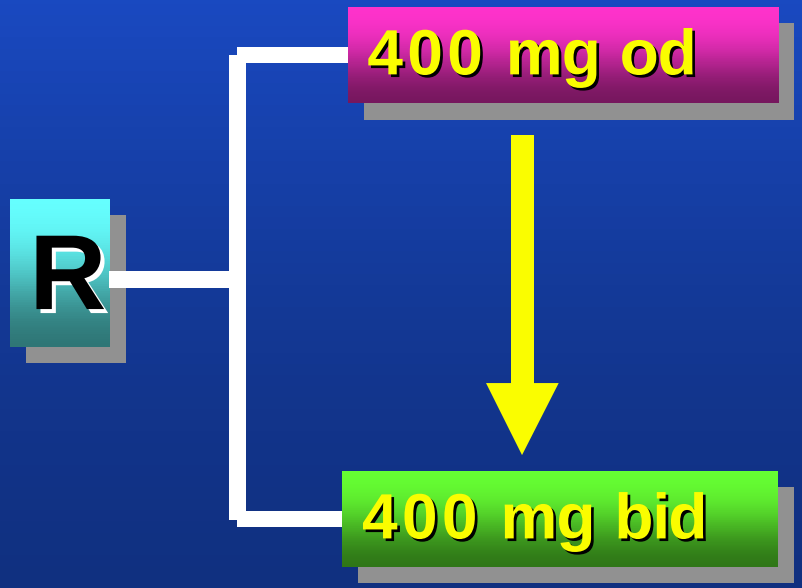
Van Oosterom et al. Lancet - October 2001
Judson et al. Proc ASCO 2002

Phase III Development

- Parallel studies in US & ROW
- Glivec 400 vs 800 mg
- US Study 746 patients in 10 months
  - 57 institutions
- EORTC Study 946 patients, 12 months
  - 56 institutions, 13 countries
- Standard endpoints

Study design

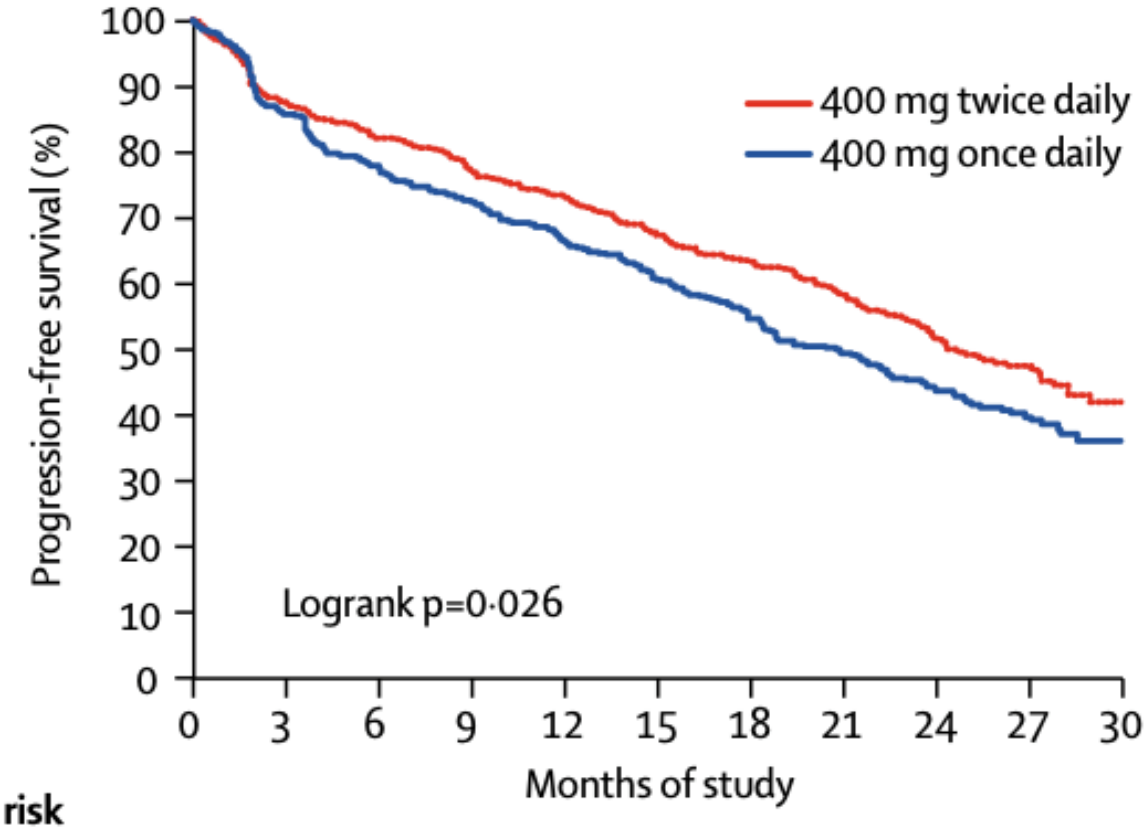
- Patients with advanced GIST
- Randomization :
  - 400 mg / day - cross over to 800 mg / day after PD
  - 800 mg / day (400 mg bid)



Response to treatment

	400 mg	800 mg
CR	26 (5.6 %)	18 (3.9 %)
PR	206 (44.7 %)	218 (47.2 %)
NC	151 (32.7 %)	154 (33.3 %)
PD	45 (9.8 %)	32 (6.9 %)
E.Dth - PD	8 (1.7 %)	5 (1.1 %)
E.Dth - Tox	1 (0.2 %)	1 (0.2 %)
E. Dth. - Other	2 (0.4 %)	---
Uneval / Miss.	22 (4.7 %)	34 (7.4 %)

EORTC Phase III – PFS

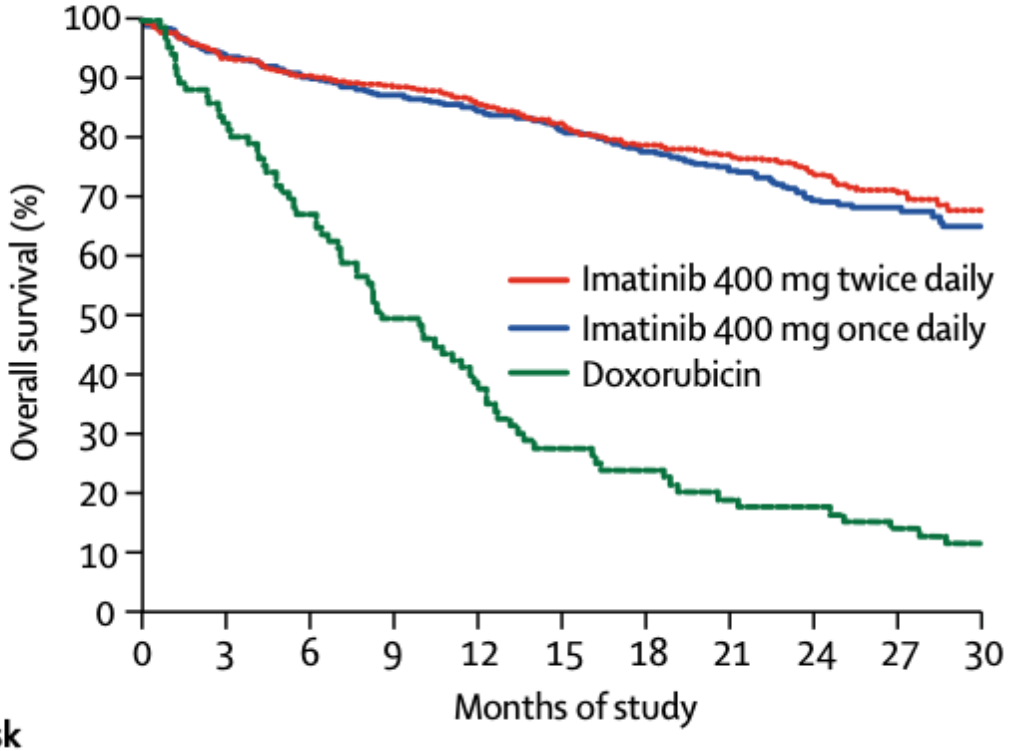


Number at risk

400 mg once daily	473	404	366	338	307	270	228	184	127	71	25
400 mg twice daily	473	414	388	365	343	300	266	218	147	96	39

Verweij, et al 2004

EORTC Phase III – OS Benefit



Number at risk						
Imatinib 400 mg once daily	473	423	387	315	192	49
Imatinib 400 mg twice daily	473	427	399	323	201	51
Doxorubicin	86	57	31	19	14	8

Verweij, et al 2004

Clinical Trials of Imatinib in GIST

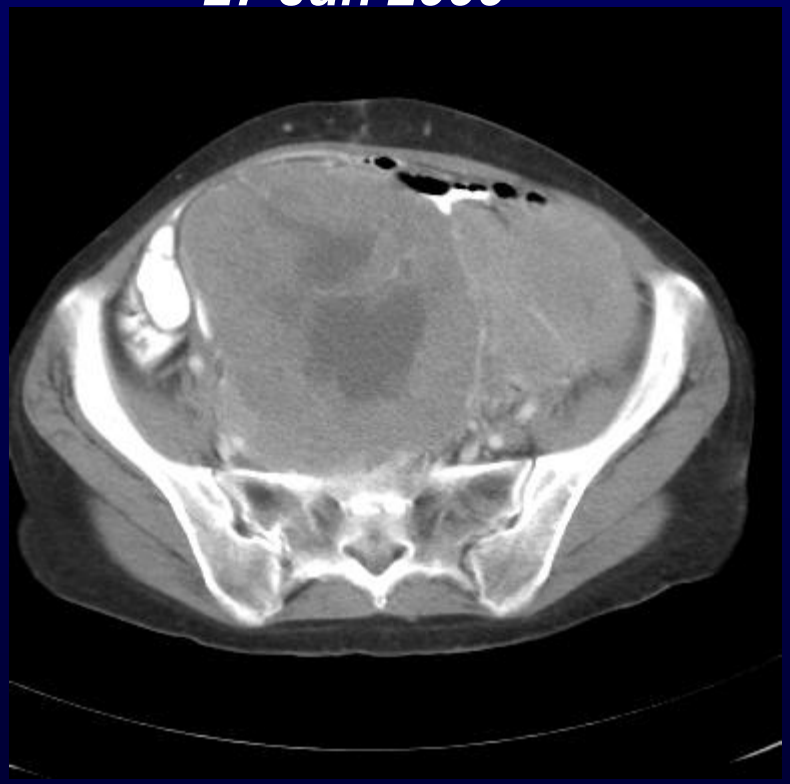
Study	Phase	N	OR	CR	PR	SD	PD	OS (2 yr)	TTP (median)	PFS
van Oosterom, 2001	I	36	53%	0%	53%	36%	11%	-	-	-
von Mehren, 2002	II	147	63%	0%	63%	19%	12%	-	72 wks	-
Verweij, 2003	II	27	71%	4%	67%	18%	11%	-	-	73% (1 yr)
Rankin, 2004	III	746								
-400 mg daily			48%	3%	45%	-	-	78%	-	50% (2 yr)
-800 mg daily			48%	3%	45%	-	-	73%	-	53% (2 yr)
Verweij, 2004	III	946								
-400 mg daily			50%	5%	45%	32%	13%	69%	-	44% (2 yr)
-800 mg daily			54%	6%	48%	32%	9%	74%	-	52% (2 yr)

Courtesy Dejka Araujo, M.D.

PEARLS ON IMATINIB RESPONSE

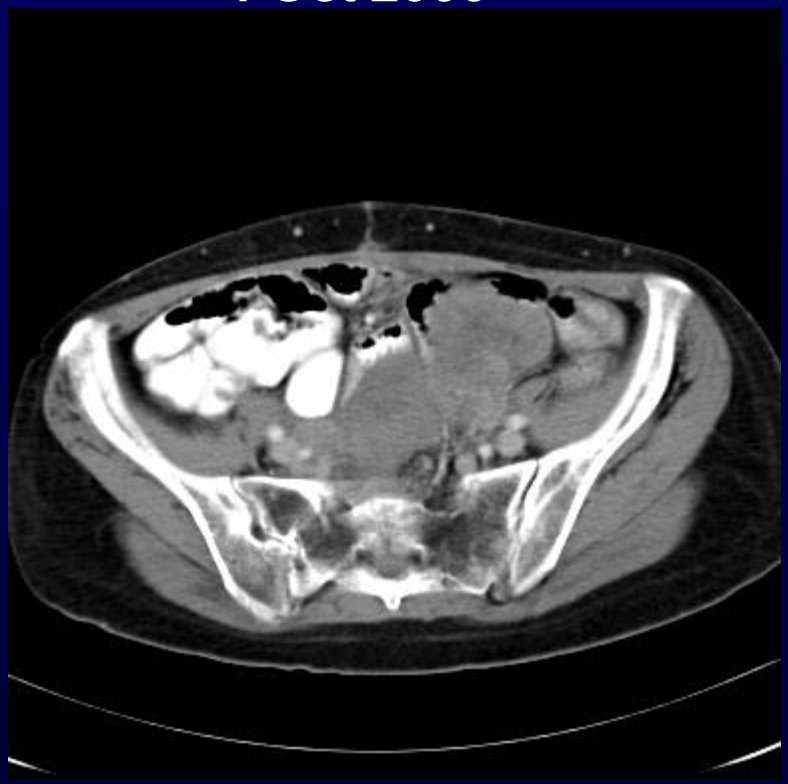
Example of CT Response after 3 months of Imatinib

27 Jun 2000



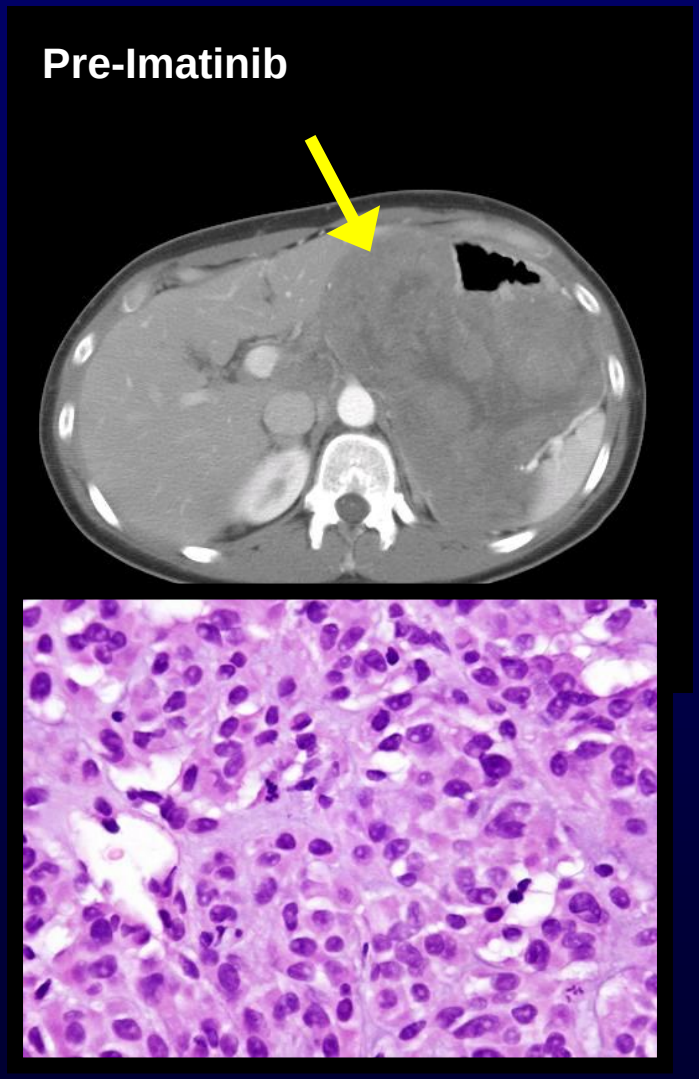
Before Imatinib

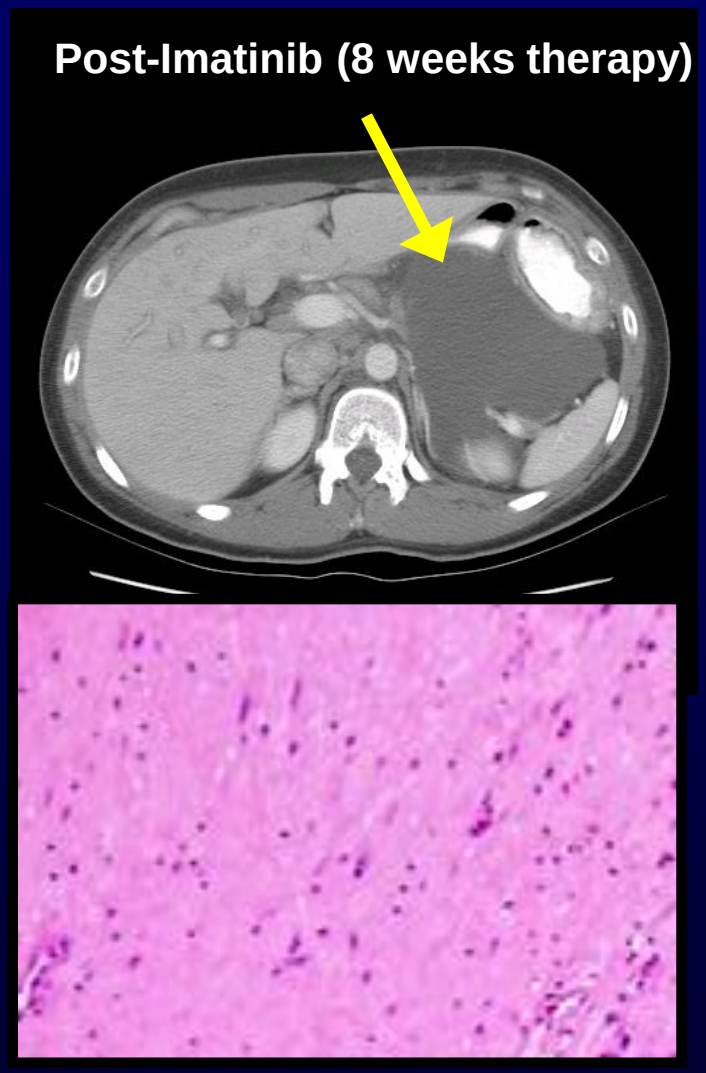
4 Oct 2000



After Imatinib

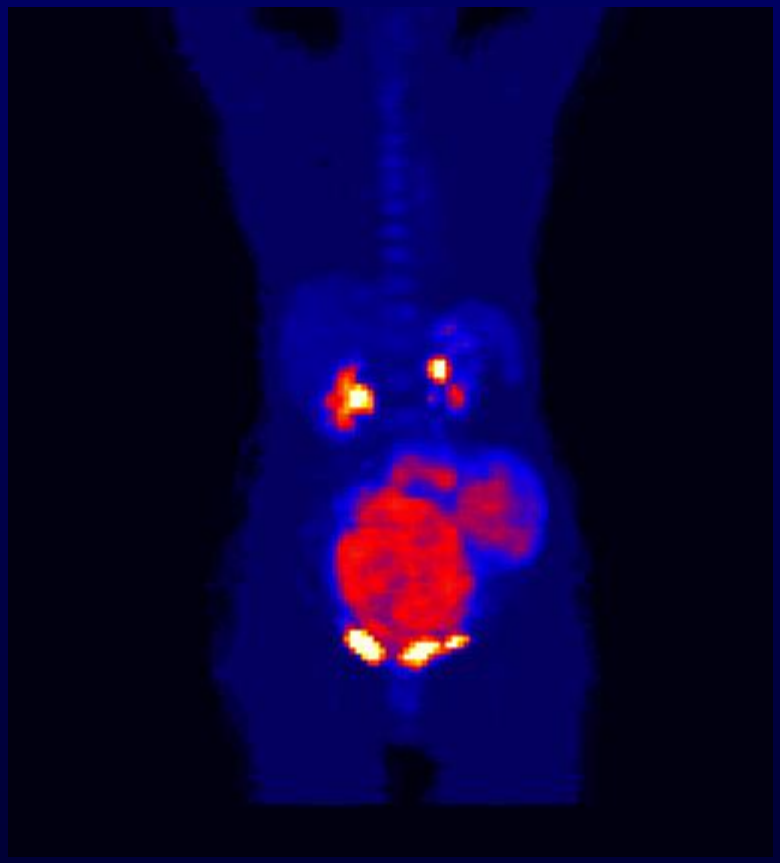
GIST Response



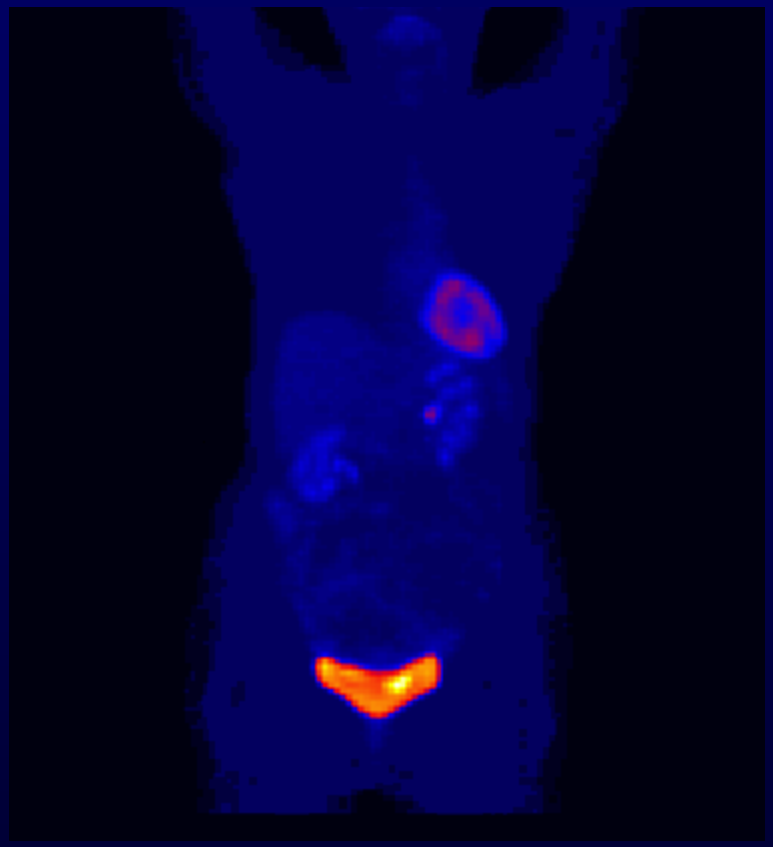


Courtesy Jon Trent and Alex Lazar

Example of FDG-PET Response at 1 month



Before Imatinib



After Imatinib

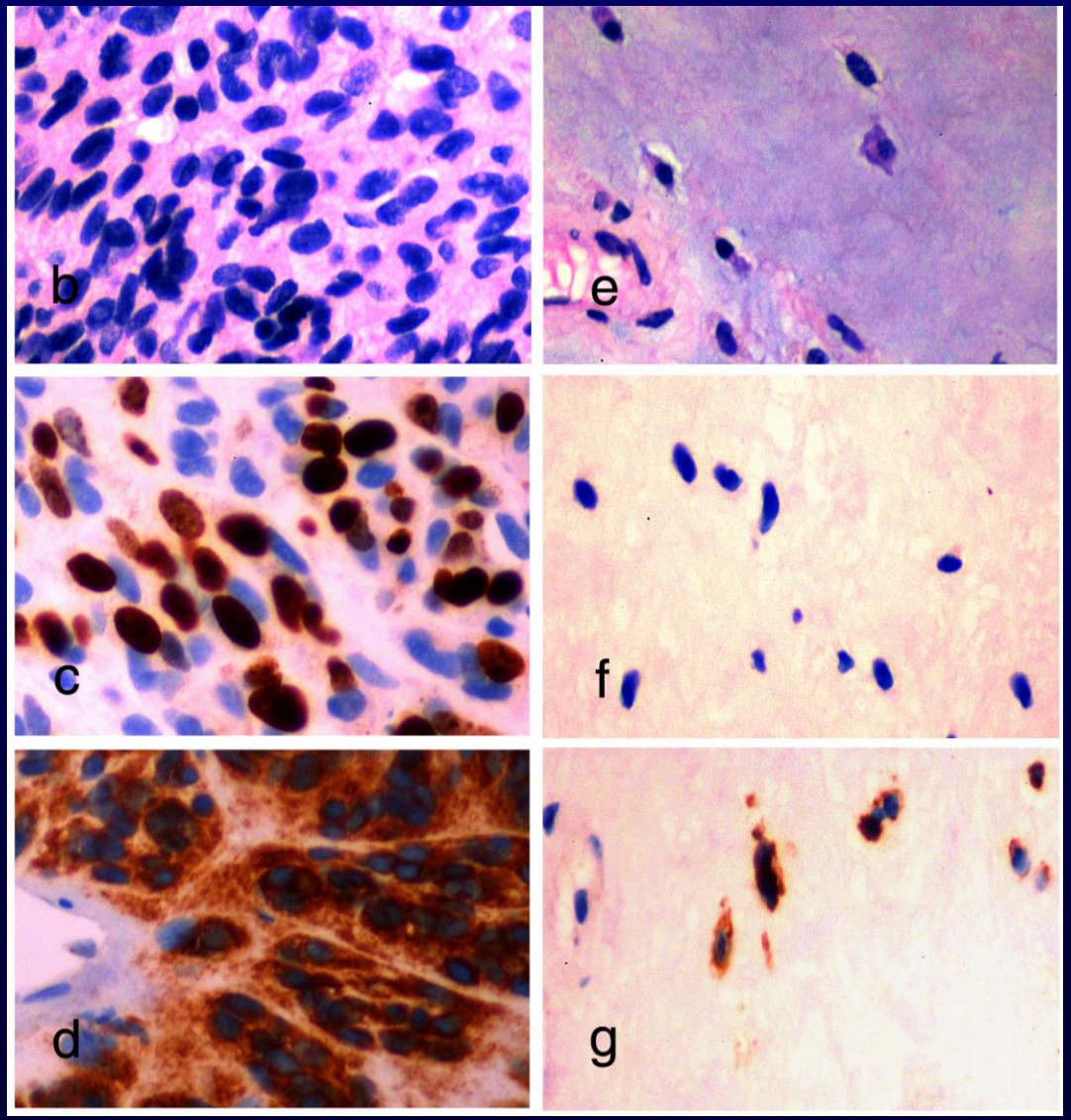
Tumor Biopsy Before Glivec

Tumor Biopsy After Glivec

H+E

Ki-67

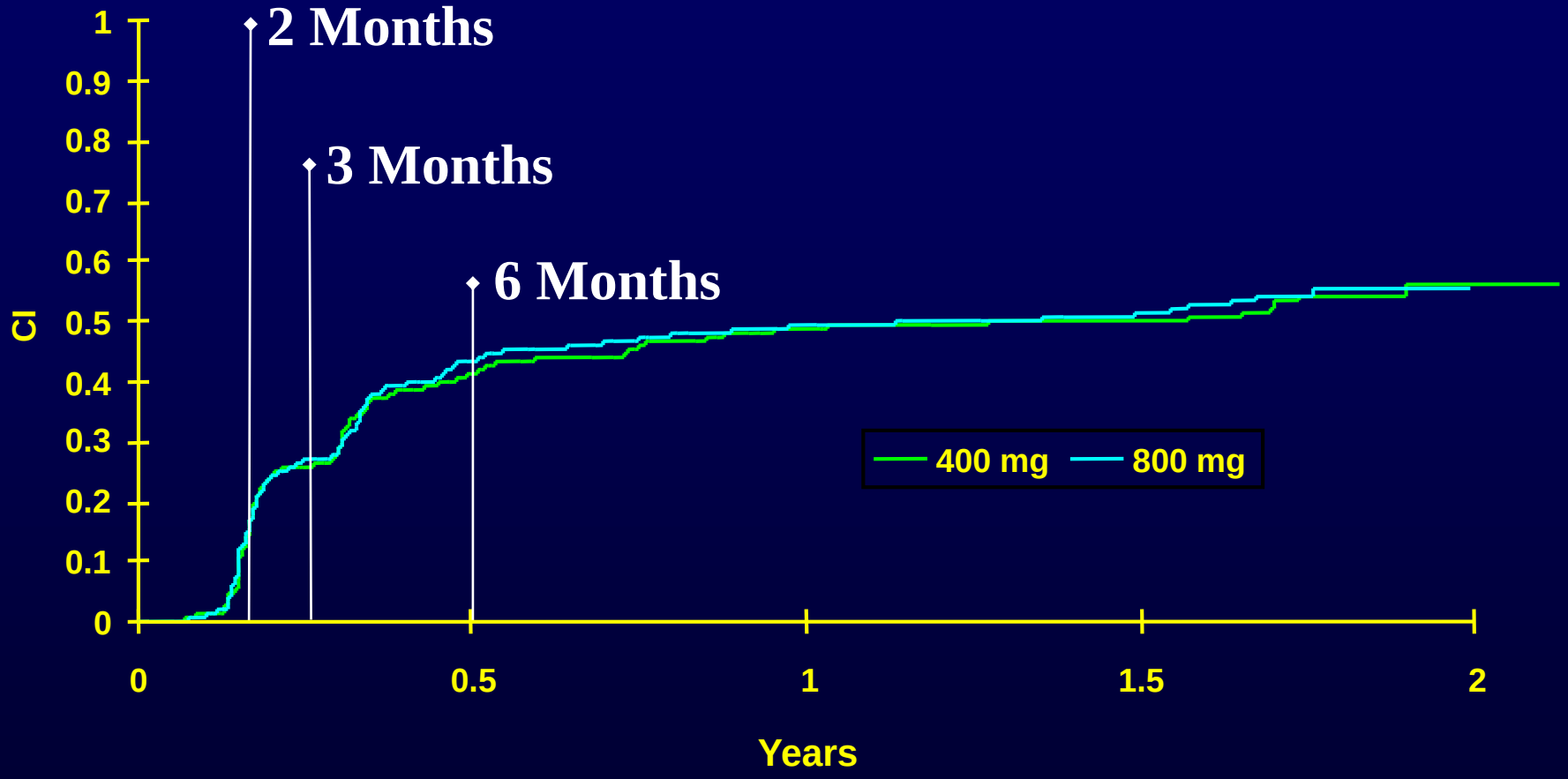
CD117



H. Joennsuu, et al NEJM 344:1052-1056

Time to PR by RECIST

Cumulative incidence of CT responses



Verweij et al, ASCO 2003

GIST Evaluation

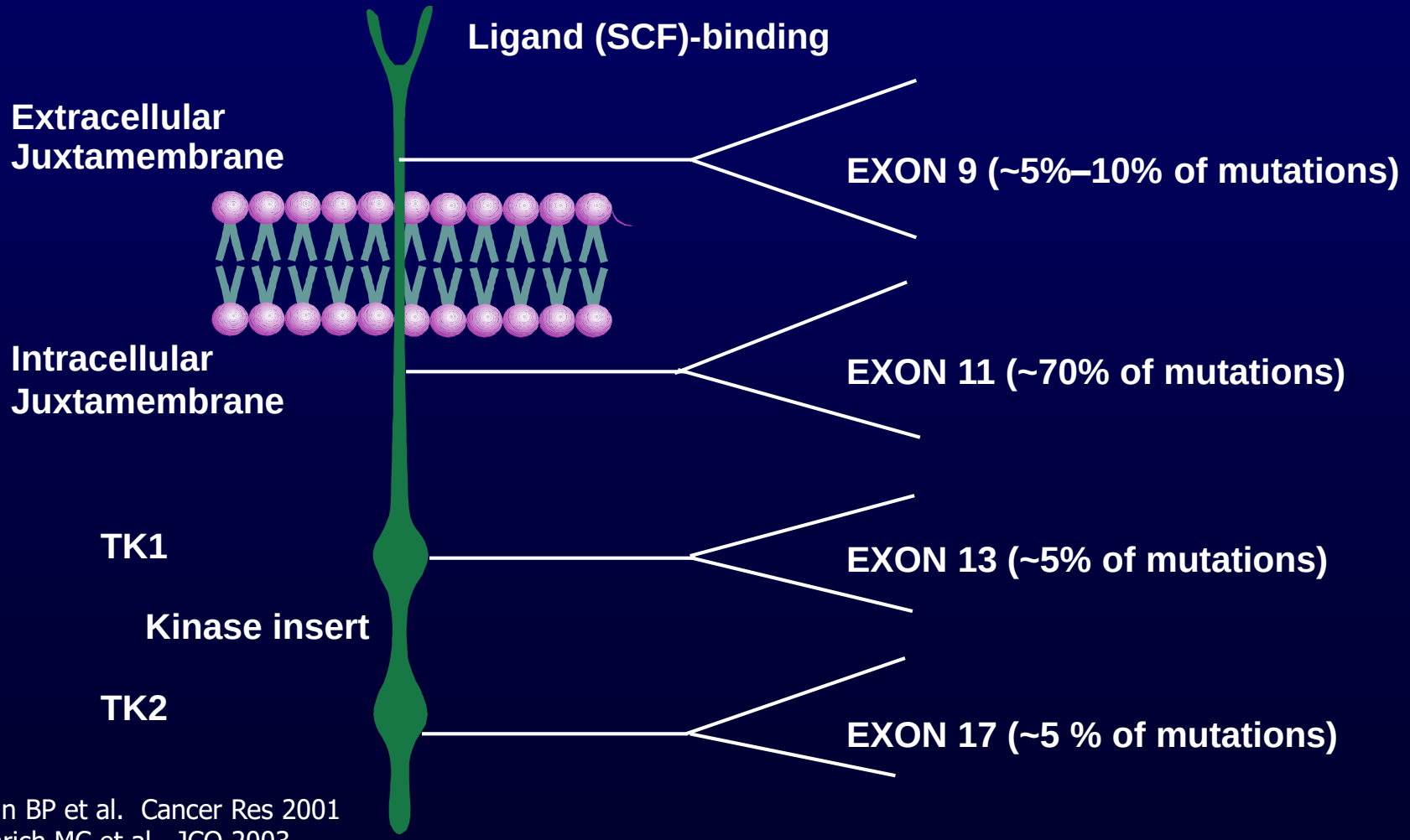
- Every 2-3 months (extend over time)
- History and Physical Examination
- Laboratory Testing
- Abdominal/pelvic CT with contrast
  - Recommended for diagnosis and staging
  - Also useful for assessing common sites of metastasis (eg, liver, peritoneum)
- ^{18}FDG-PET
- MRI with gadolinium

^{18}FDG-PET=fluorine-18-fluorodeoxyglucose positron emission tomography.

McAulliffe et al, *Annals of Surg Onc* 2009;16(4):910-9; Van den Abbeele. *Oncologist*. 2008;13:8.

ARE ALL KIT MUTATIONS EQUAL?
IMATINIB DOSING CONSIDERATIONS……..

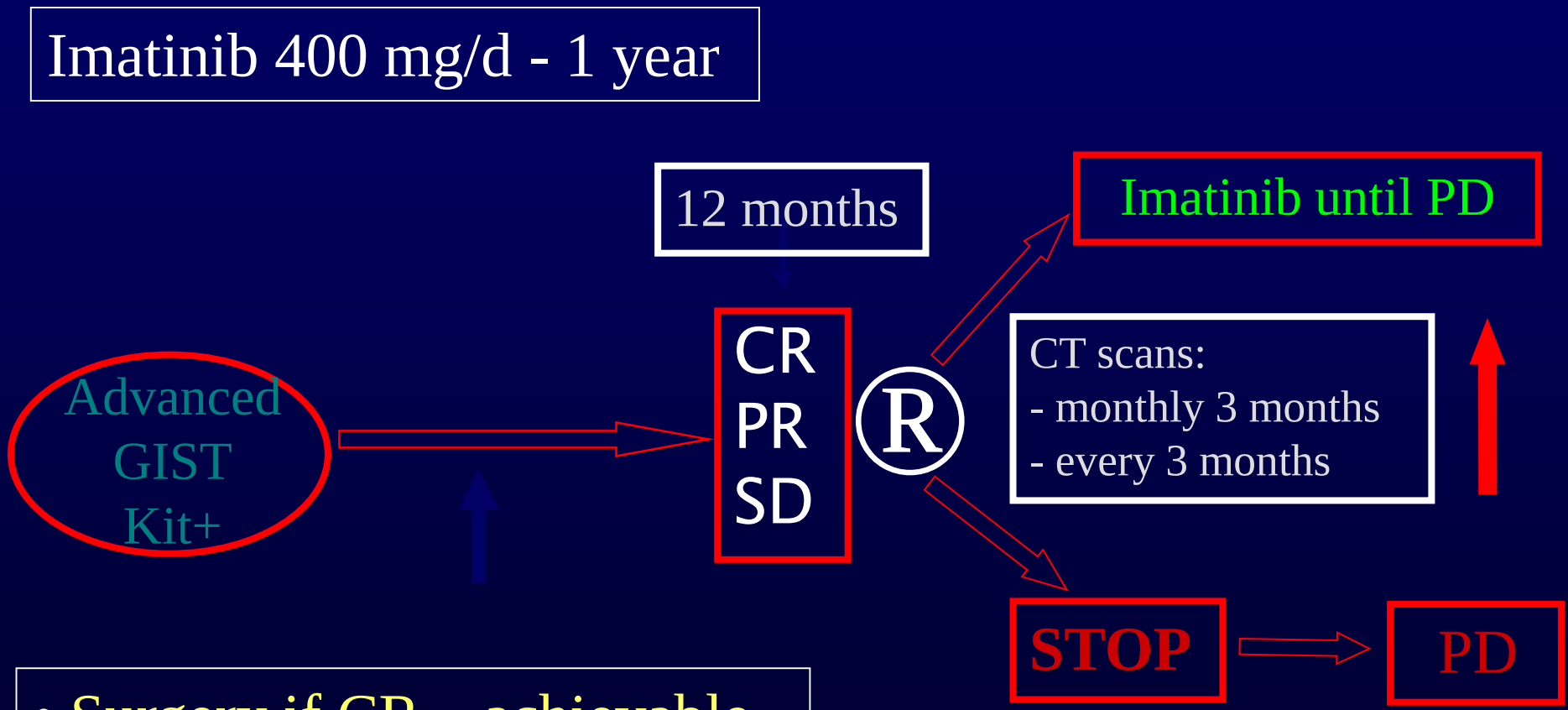
KIT gain-of-function mutations in GISTs[19,20]



19. Rubin BP et al. Cancer Res 2001
20. Heinrich MC et al. JCO 2003

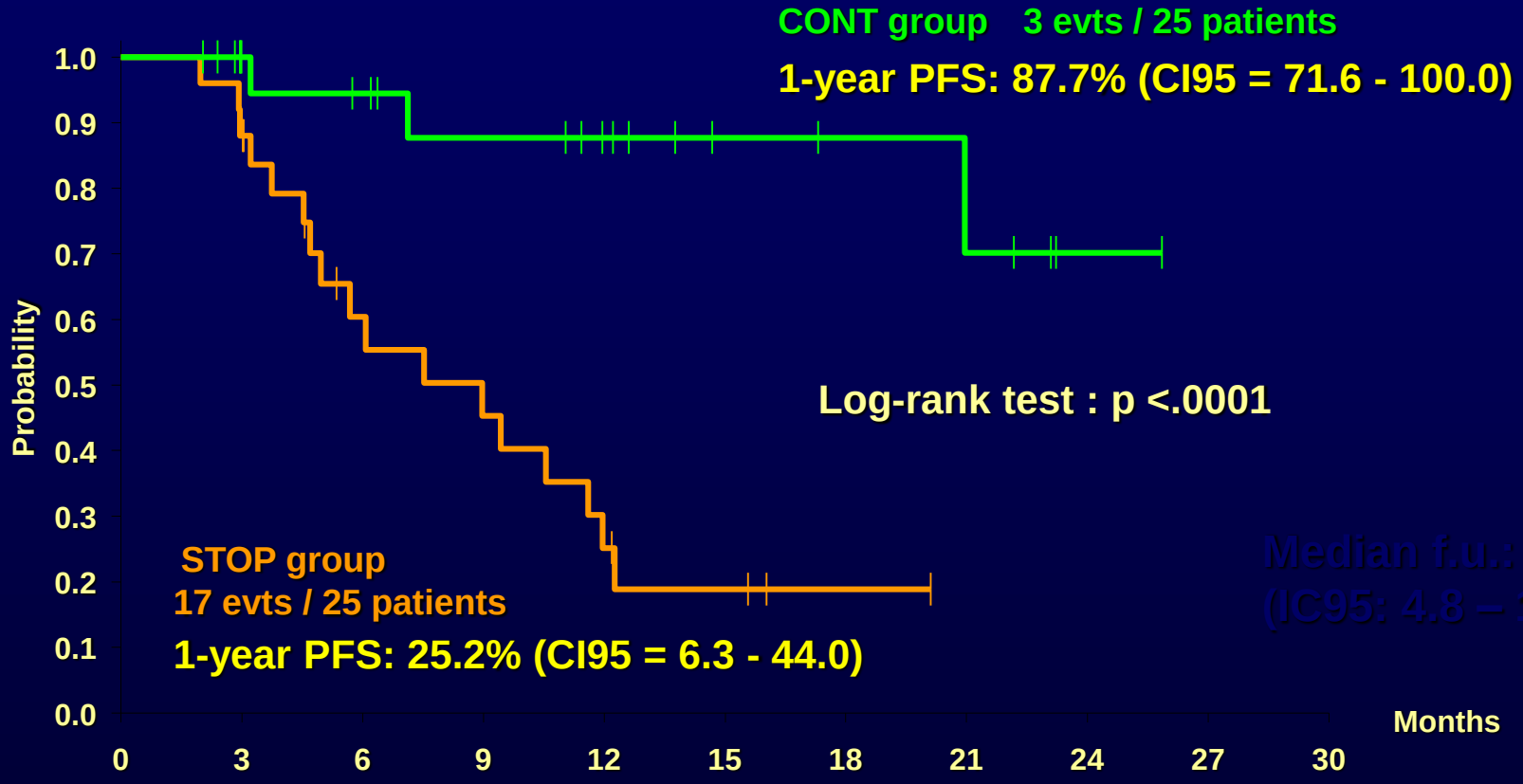
HOW LONG TREATMENT WITH IMATINIB?

French Sarcoma Group: BFR14 Study design



LeCesne et al. ECCO 2005, Abs 713

BFR14 3-yr randomization Progression Free Survival

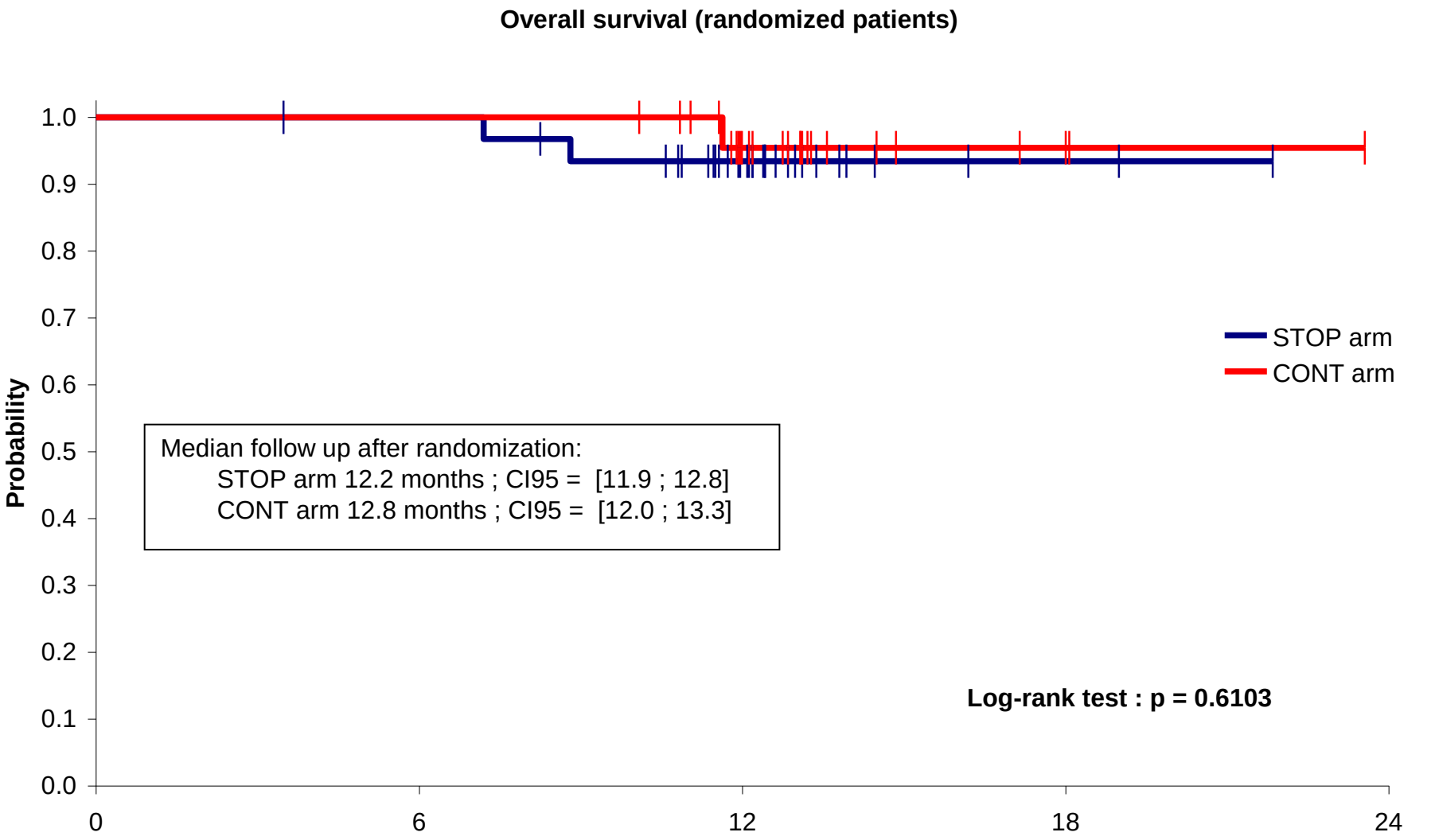


Rate of PD in STOP group

at 6 months: 40%
at 9 months: 55%
at 1 year: 75%

Updated sept 07, ECCO 14

Overall Survival in randomized patients



LeCesne et al. ECCO 2005, Abs 713

IMATINIB TOXICITIES & DOSE MANAGEMENT

How to take imatinib…..

- Tablet 400mg and 100mg strengths
- Take with meal once daily with large glass or water and meal

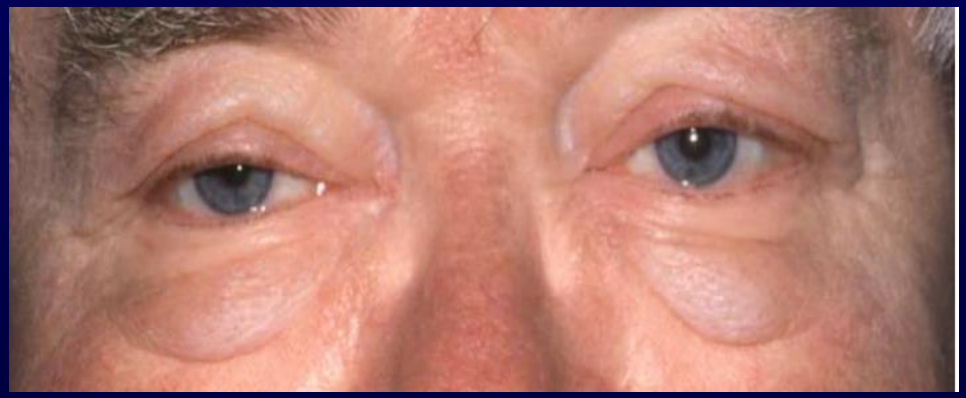
- Imatinib is metabolized via the P450 pathway – mainly mediated by CYP3A4 and CYP3A5.
  - Interactions with other drugs possible. Please double check with your physician and pharmacy.

Side effects profile at 400mg

Frequency of side effects (400 mg/day dose)

Symptom	Any grade %	Grade 3 or 4 %
Anemia	89	7
Oedema	71	2
Fatigue	68	6
Pleuritic pain	51	4
Nausea	49	3
Diarrhoea	48	2
Leucopenia	43	3
Granulocytopenia	41	7
Rash	27	2
Vomiting	26	3
Anorexia	26	2
Myalgia	24	0
Pruritus	16	1
Constipation	16	1

Derived from Verweij et al 2004.



Side effects: 400 vs. 800 mg

Toxic Event	Adjusted *p*–Value
Edema	<0.001
Anemia	<0.001
Rash	<0.001
Fatigue	<0.001
Nausea	<0.001
Hemorrhage	<0.001
Diarrhea	0.0026
Dyspnea	0.036
Pleuritic Pain	0.053

Verweij et al, 2004

Interruptions and Reductions of Therapy

	400 mg	800 mg
Treatment Interruption	40%	64%
-Hematologic	6%	7%
-Non-Heme	23%	43%
Dose Reduction	16%	60%
-Hematologic	2%	4%
-Non-heme	10%	42%

Intergroup Phase III Study of Imatinib in Advanced GIST

Dose Reduction	400 mg (376 pts)	800 mg (370 pts)	800 mg X-Over
1	10%	44%	16%
2	7%	26%	5%
3	2%	11%	0%
4	1%	4%	0%

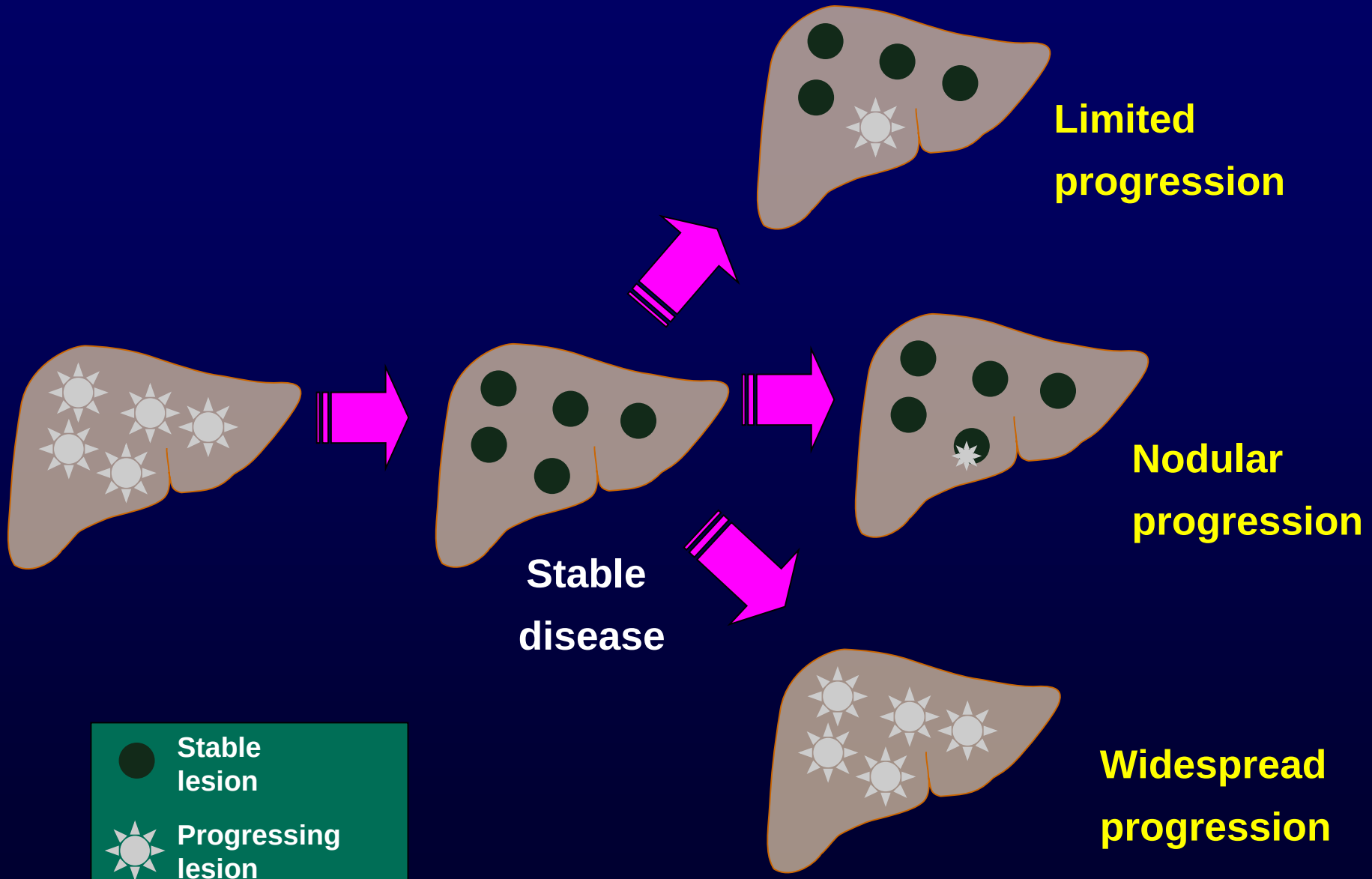
Dilco et al, ASCO 2005

Selected Toxicities Management

- GI- taking dosing nocte, antiemetic, anti-diarrhea meds, split dosing.
- Cramps/myalgia – fluid intake, salt supplements, tonic, anagesics
- Rash – topical meds
- If high grade toxicities/intolerable despite supportive mx – will need dose hold/change

DISEASE PROGRESSION BEYOND IMATINIB

Type of Progression



Therapy by Type of Progression

- Limited or Nodular Progression
  - Hepatic Artery Chemoembolization
  - Hepatic Radio-frequency Catheter Ablation
  - Surgical Resection
  - Radiation Therapy (esophageal or rectal)
- Widespread progression
  - Increase Imatinib to 800 mg daily
  - Sunitinib/Regorafenib/Repiretinib/Clinical Trial

OFF LABEL DRUG USE & NON KIT MUTATIONS

GIST : Off-Label

Class	Agent	Trial Phase	Results
KIT Inhibitors	Sorafenib	II	PR=13%, SD=58% PFS=5 months
	Dasatinib	II	PR=22%, SD=24% PFS= 2 months
	Nilotinib	I/II/III	PR=10%, SD=37% PFS=3 months
	Pazopanib	II	PazoGIST, PFS-1.9 months
	Ponatinib	II	Exon 11 CBR 37%, PFS 4.3 months
	Axitinib	ND	ND

GIST : Off-Label Non Kit Mutations

- PDGFR D842V: anti-PDGFR trial (***avapritinib***, crenolanib)
- SDH deficiency: sunitinib or regorafenib
- Raf V600E: Raf inhibitor
- NF-1, Ras: Raf or Mek inhibitor
- PI3K: mTOR inhibitor
- IGF-1R expressing – IGF-1R inhibitor trial
- TRK fusion – LOXO-101 NTRK inhibitor inhibitors
- KIT resistance mutations
  - Exon 13 (ATP binding site): sunitinib 37.5 mg daily, Ripretinib
  - Exon 17 (A-loop): regorafenib 120 mg daily, ripretinib

Take Home Messages

- Imatinib remains 1st line therapy in metastatic GIST for most patients
  - Certainty in diagnosis and mutational testing imperative
  - Dose escalation of imatinib are needed in certain circumstances
  - Treatment till widespread progression is the preferred therapy strategy
- Although generally tolerable…
  - Treatment breaks/dose reductions of imatinib may be needed

Thank you

UHN Princess Margaret Cancer Centre
University Health Network

MOUNT SINAI HOSPITAL
Joseph and Wolf Lebovic Health Complex

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