Molecular Decision-making In GIST Therapy

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GIST Molecular Overview

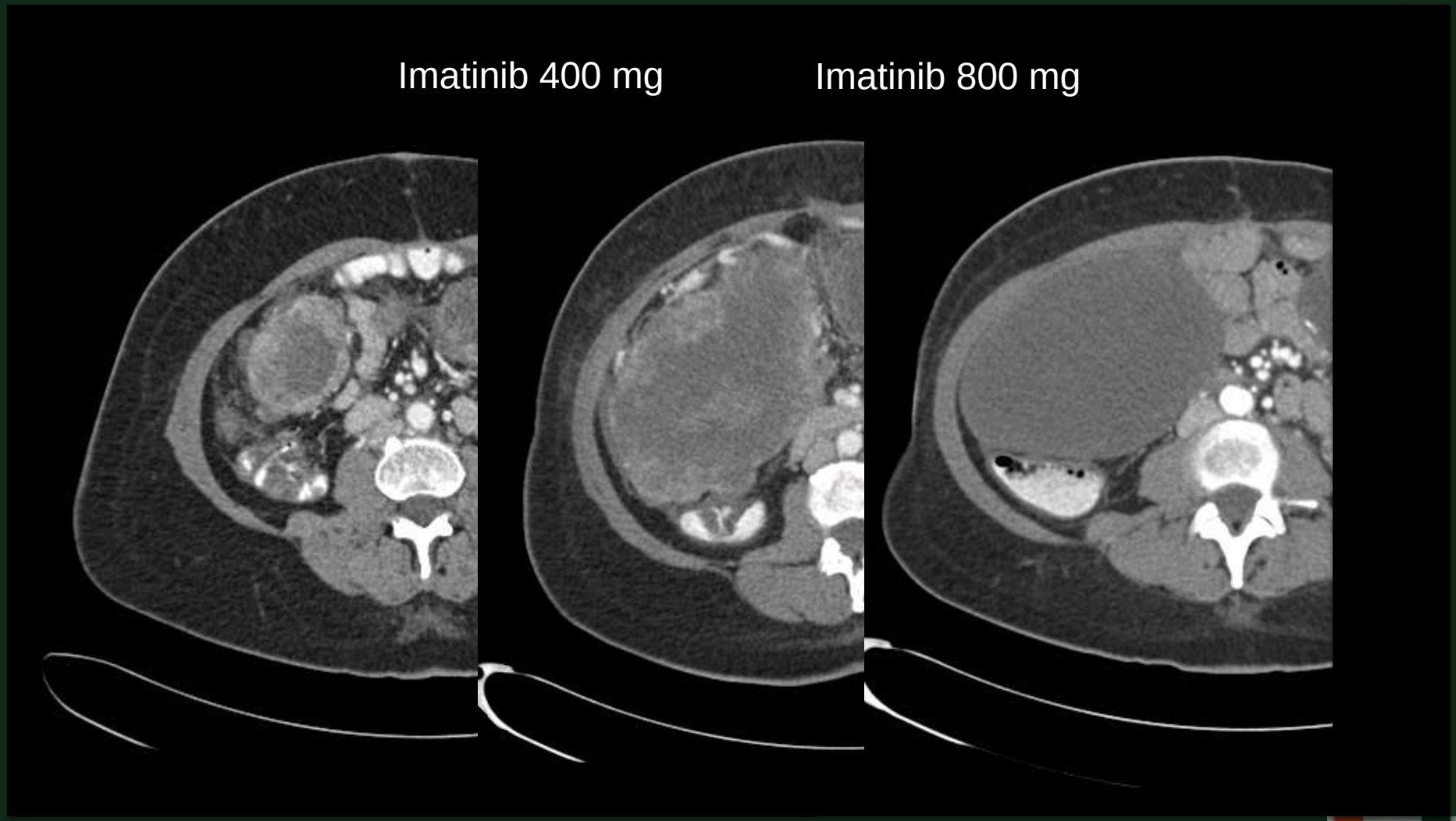
- About 5,000 newly diagnosed GIST patients per year in the US
- Kit mutation ~80% of GISTs
  - Exon 11 (~70%), Exon 9(~10%)
- PDGFR mutation ~10% of GISTs
  - Exon 18 D842V imatinib/sunitinib resistant
- SDH-B deficient
- Raf V600E
- NF-1, Ras
- PI3K
- “wild-type”

Molecular Decision-Making in GIST

- Initial therapy for GIST patients ***requires*** molecular decision-making
  - Kit exon 9
  - PDGFR D842V
  - SDH-B deficiency
  - Raf V600E
  - NF-1, Ras
  - PI3K

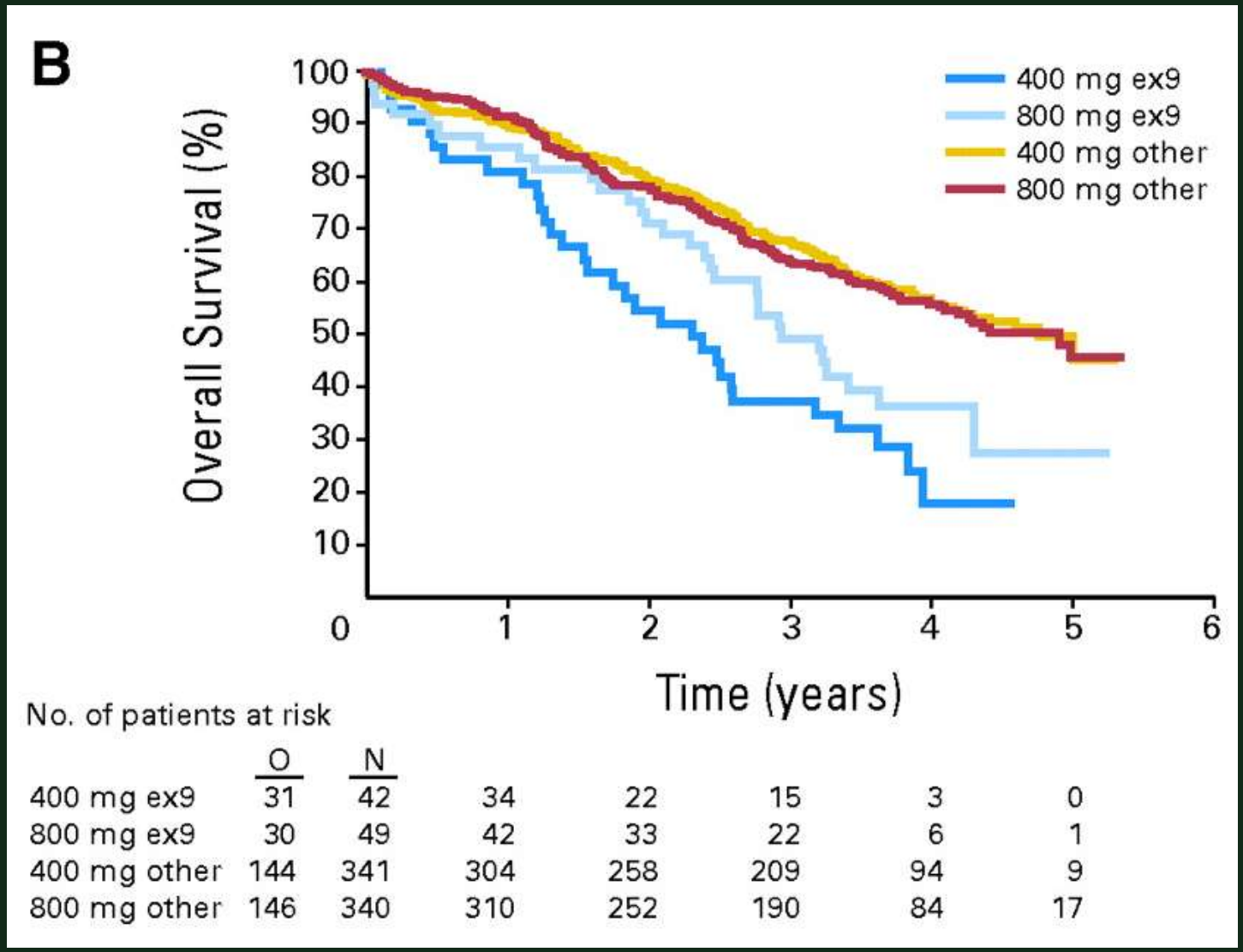
GIST Patient Initial Therapy

KIT Exon 9 Mutation



Initial Imatinib Dose Selection

Kit Exon 9 mutation



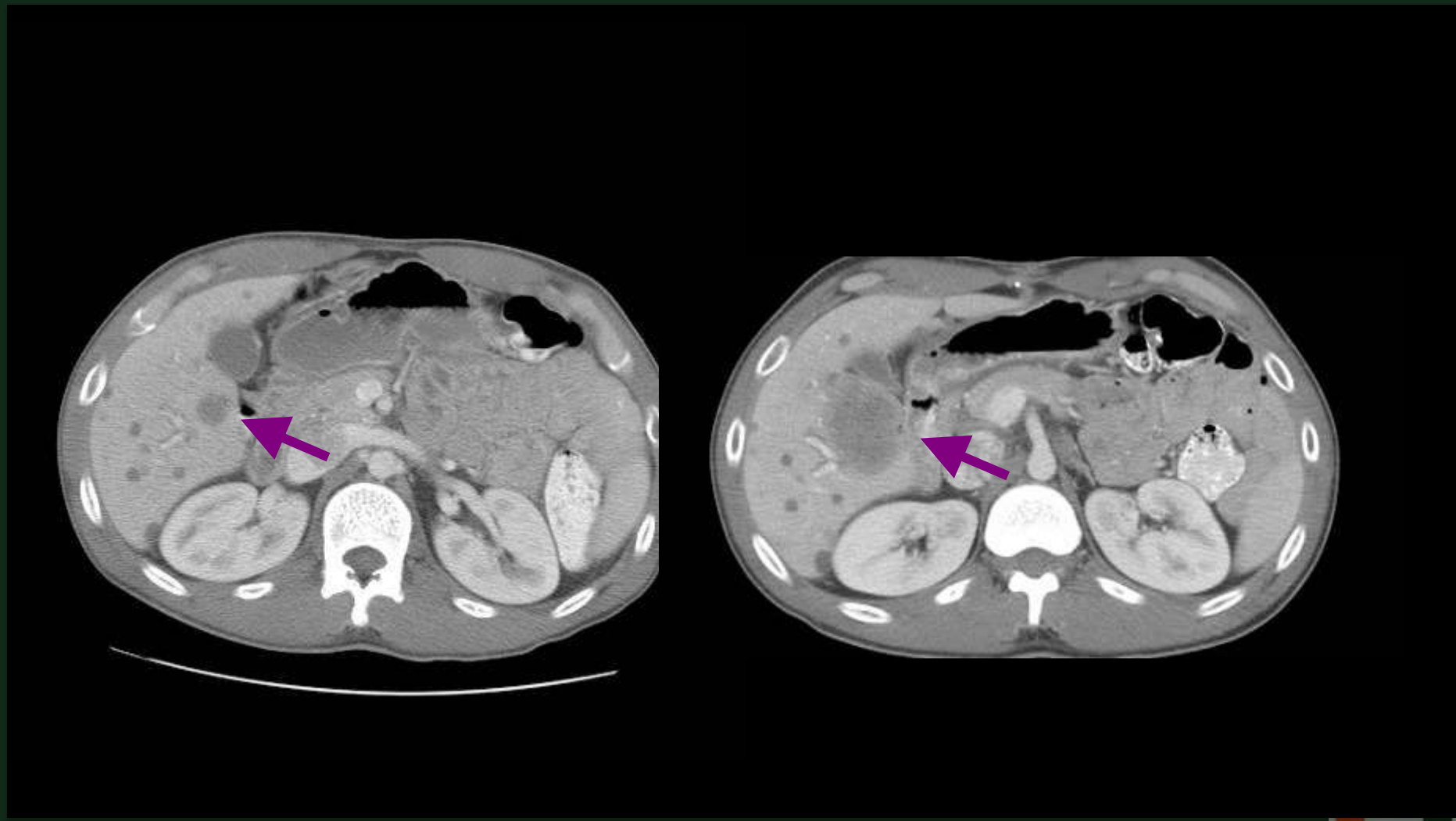
No. of patients at risk

	O	N					
400 mg ex9	31	42	34	22	15	3	0
800 mg ex9	30	49	42	33	22	6	1
400 mg other	144	341	304	258	209	94	9
800 mg other	146	340	310	252	190	84	17

J Clin Oncol. 2010;28:1247.

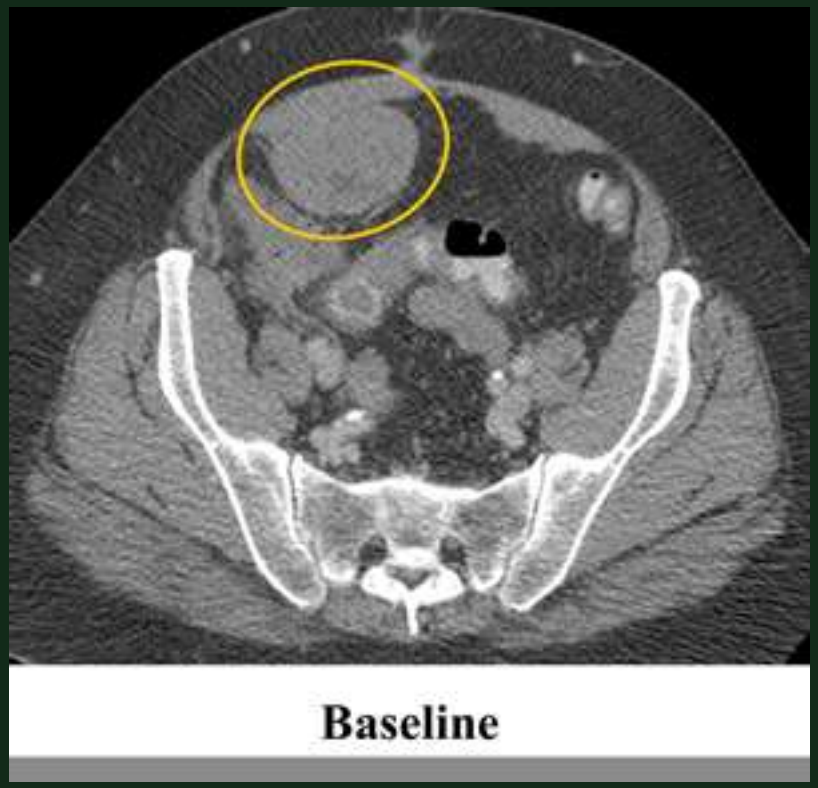
GIST Patient Initial Therapy

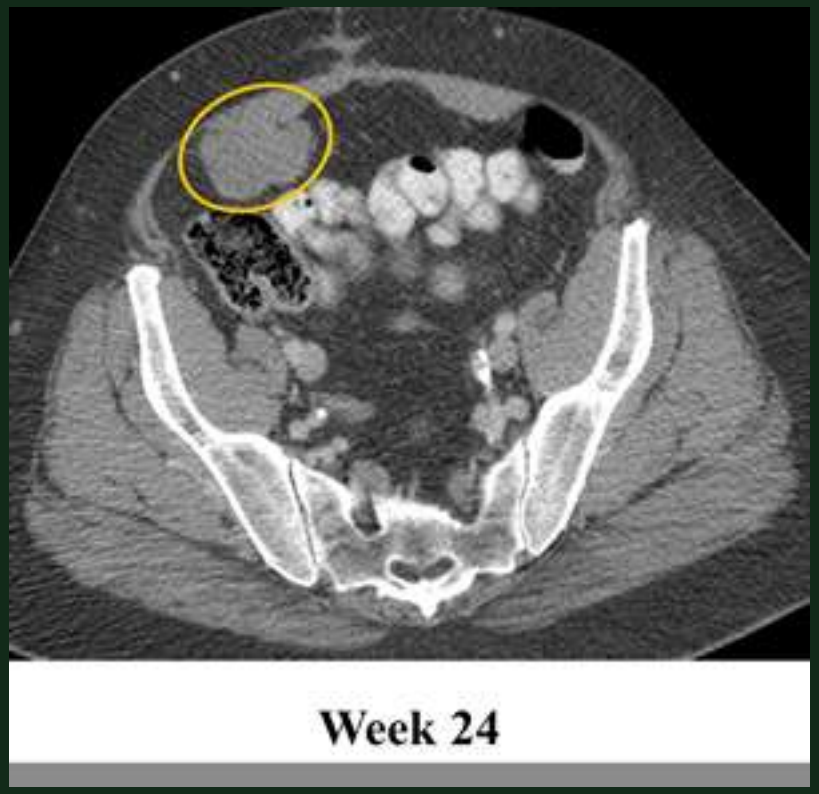
PDGFR D842V Mutation



GIST Patient Initial Therapy

RAF V600E Mutation



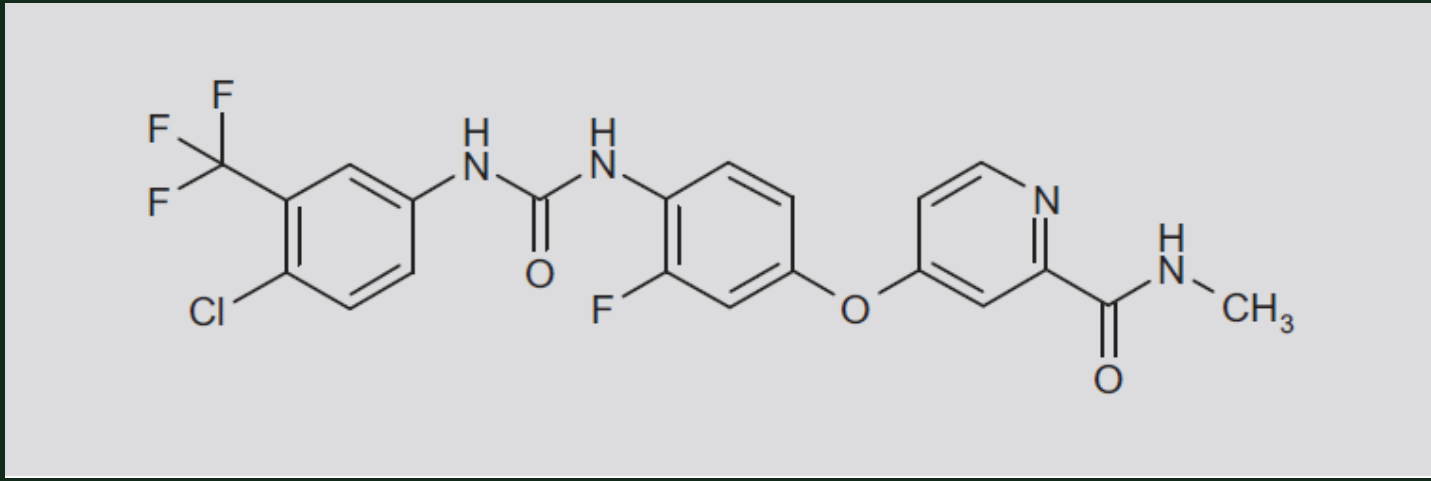


Treatment with RAF inhibitor

Falchook, Trent, Heinrich 2013

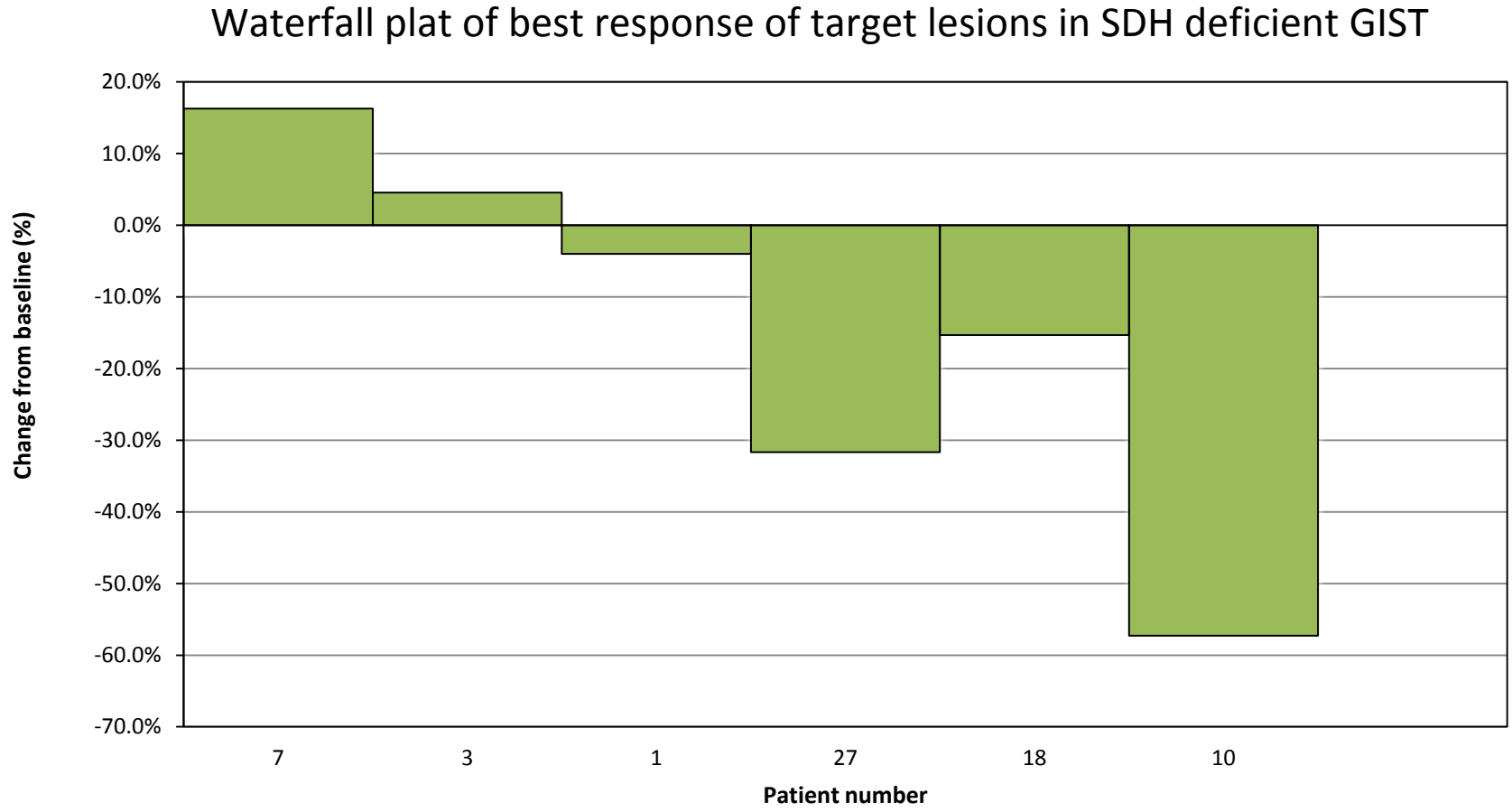
Background - Regorafenib

- Regorafenib (BAY 73-4506) is a structurally distinct oral TKI with inhibitory activity against several kinases including KIT, PDGFRA, FGFR, VEGFR 2,3, TIE-2, and B-RAF.
- Regorafenib is physiologically processed into at least two bioactive metabolites, each with long half-lives (approximately 24 hrs), allowing target kinase inhibition with promising pharmacodynamics



George et al ASCO 2103

Bidimensional response has been observed in SDH-deficient GIST treated with regorafenib



Median age of patients with SDH deficient GIST : 43 yrs (range 25 – 63)

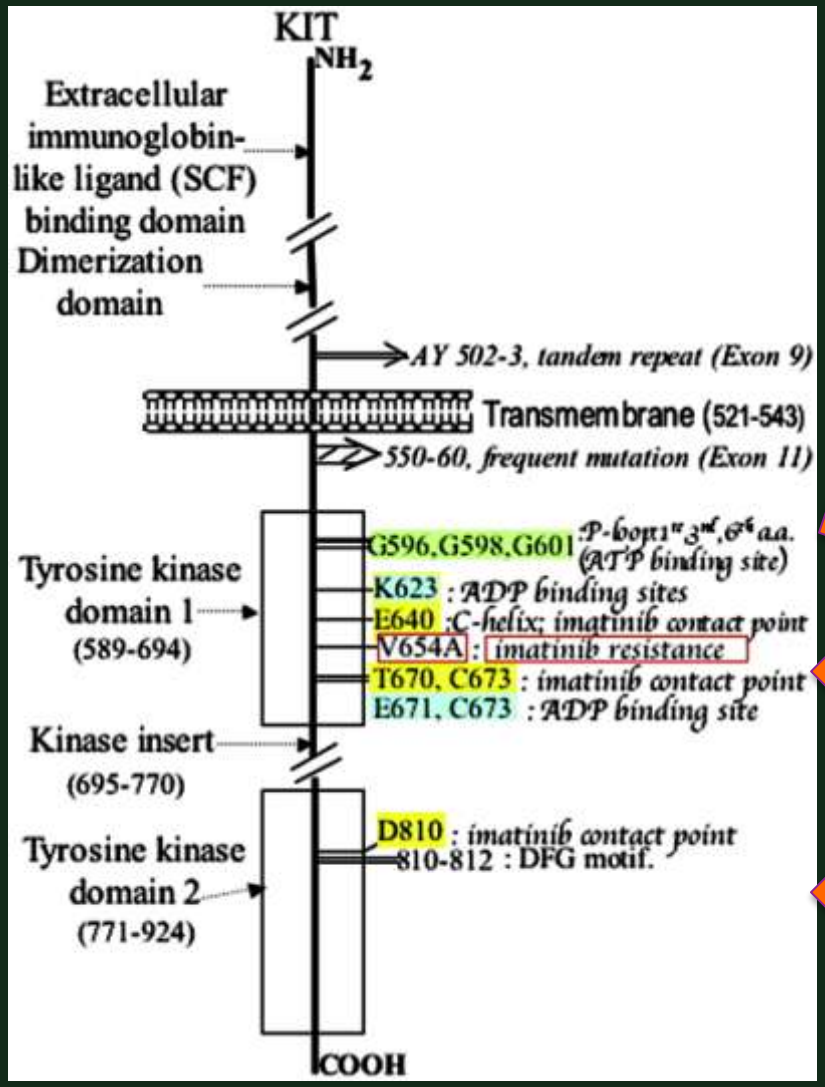
Molecular Decision-Making in GIST

- Initial therapy for GIST patients ***requires*** molecular decision-making
  - Kit exon 9: Imatinib 800mg (or highest tolerated dose)
  - PDGFR D842V: anti-PDGFR trial
  - SDH-B deficiency: Regorafenib ?
  - Raf V600E: Raf inhibitor
  - NF-1, Ras: Raf inhibitor?
  - PI3K: mTOR inhibitor

Molecular Decision-Making in GIST

- Optimal second-line therapy for GIST patients ***requires*** molecular decision-making
  - KIT secondary mutations
    - Exon 13 (ATP binding site)
    - Exon 17 (A-loop)

Secondary Mutations in KIT



ATP/ADP Binding Site (V654)

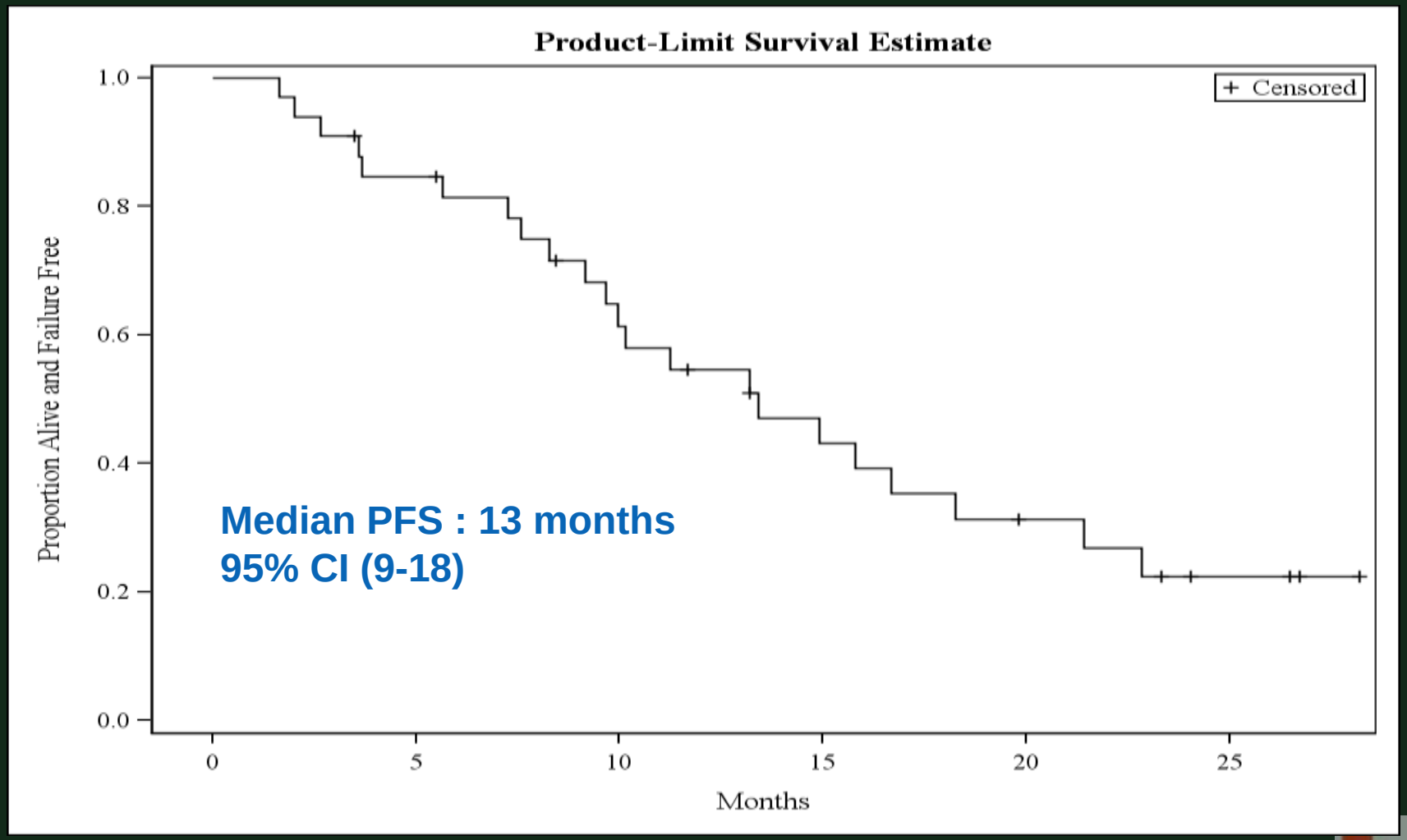
Gate Keeper (T670)

Activation Loop (D820)

Chen, Trent, et al. Cancer Res 2004;64:5913-5919

Regorafenib in Metastatic GIST

Progression-Free Survival



Regorafenib in GIST following failure of IM and SU: Baseline patient characteristics (n=33) Median followup 20 months

	N (% or range)
Median Age, years	56 (25-76)
Female/Male	14 (42)/19 (58)
ECOG PS 0/1	23 (70)/10 (30)
Median number of prior regimens	2 (2-10)
Primary kinase mutation*:	
KIT Exon 11	19
KIT Exon 9	3
Wild type (WT) ** for KIT and PDGFRA	8

*Available for 30 pts. Three pts had insufficient material for analysis

**7 pts were WT for KIT exons 9, 11, 13, 17 and PDGFRA exons 12, 14, 18. Two of 7 pts were also WT for KIT exons 14,15, 16 and 18 (remaining 5 of 7 pts were not tested for these sites of possible mutation)

Regorafenib
exon 17 secondary

Pre-regorafenib secondary mutations	N
Exon 17	7
Exon 18	1
Exon 13	1

Pre-enrollment tumor for secondary mutations was available on 9 study participants

Median PFS for patients with tumor which harbors a known secondary exon 17 mutation : 18 months (95% CI 6-NR)

Summary of secondary exon 17 mutations identified in this patient cohort (n=7)

Case	Primary Mutation	Secondary mutation in exon 17
9	Exon 11 V559A	D820Y
15	Exon 9 Insertion AY502-503	D820Y
19	Exon 11 KPMYEVQW550-557K	D820Y
21	Exon 11 deletion 550-558	N822K
25	Exon 11 W557G	N822K
30	Exon 9 insertion AY502-503	D820Y
31	Exon 11 deletion KPMYEVQ 550-556M	N822K

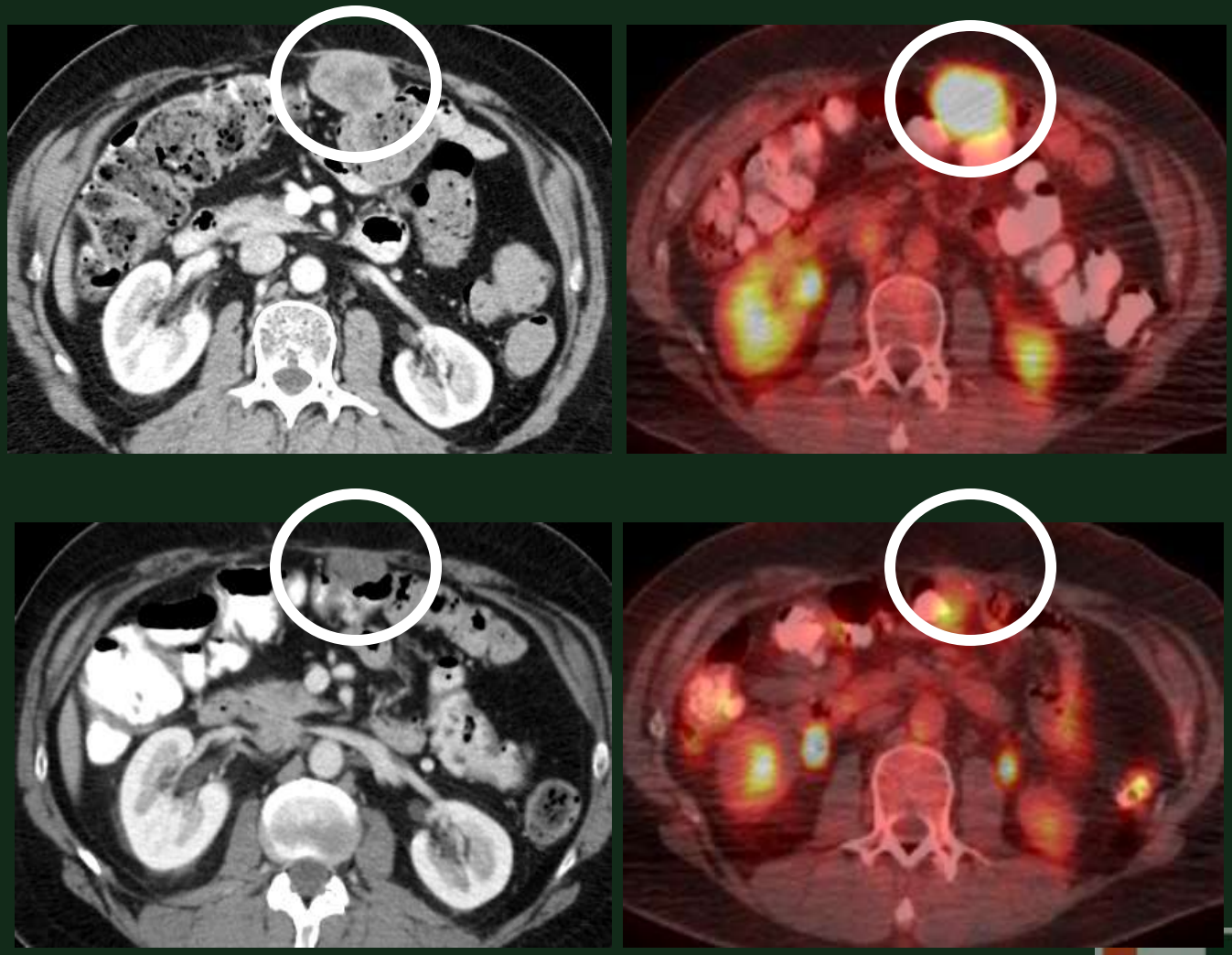
KIT D820Y (exon 17). Radiographic and metabolic response on REGO

Baseline

Pre-REGO biopsy

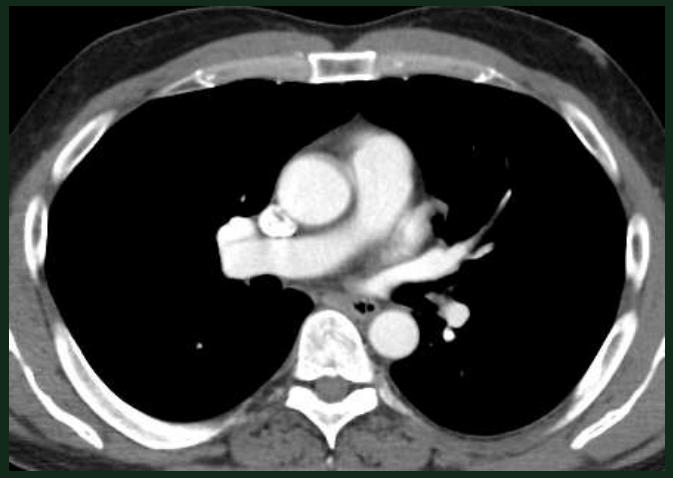
KIT ex 11 + ex 17 (D820Y)

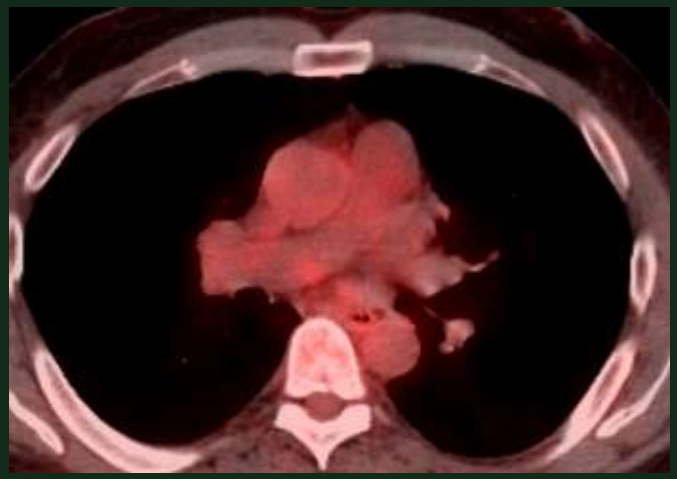
C4D21



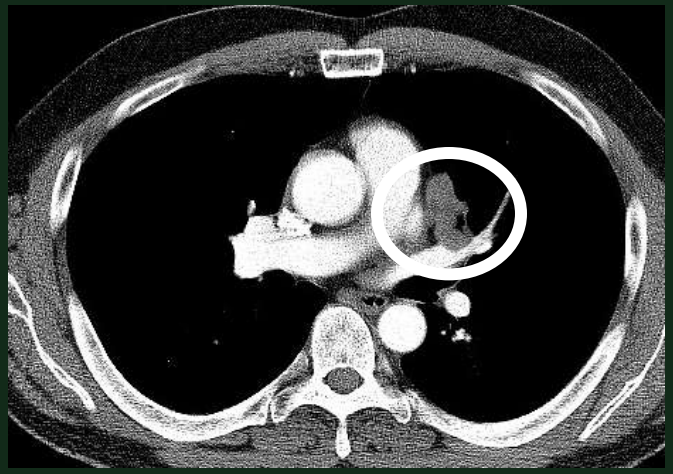
KIT V654A (exon 13). Radiographic and metabolic progression on REGO

Baseline





C12D21

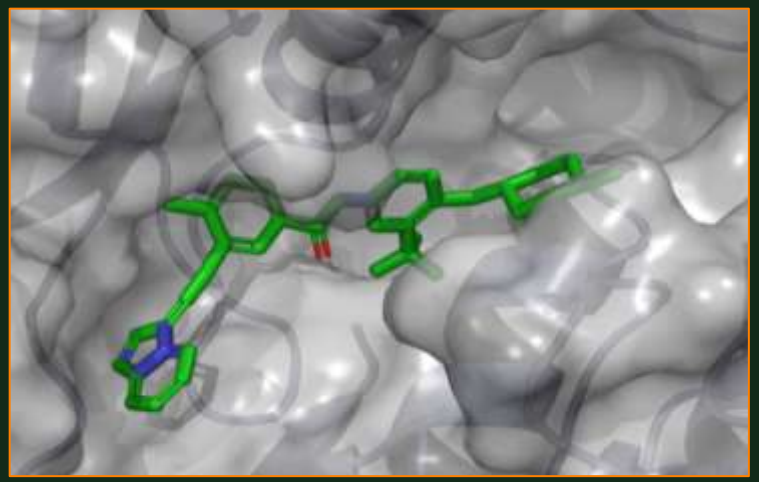


KIT ex 11 + Ex 13 (V654A)

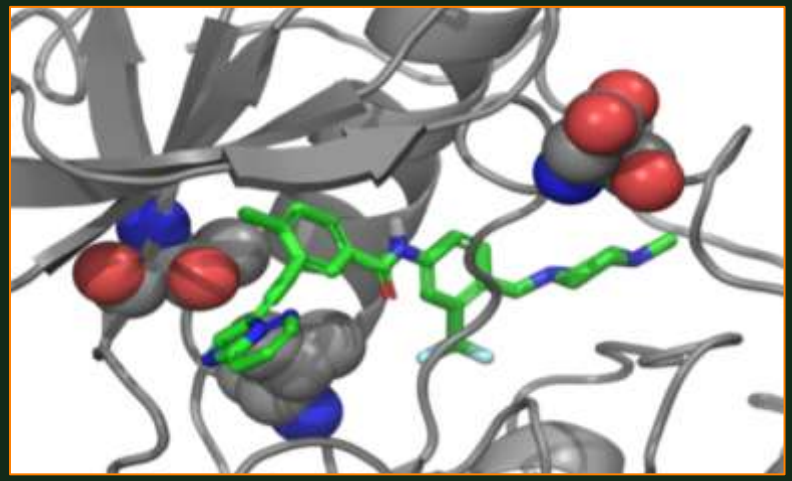
Use of ponatinib to inhibit kinase mutations associated with drug-resistant GIST

Ponatinib Binds Kit In The Presence Of Resistance Mutations

Ponatinib/ KIT co-crystal structure



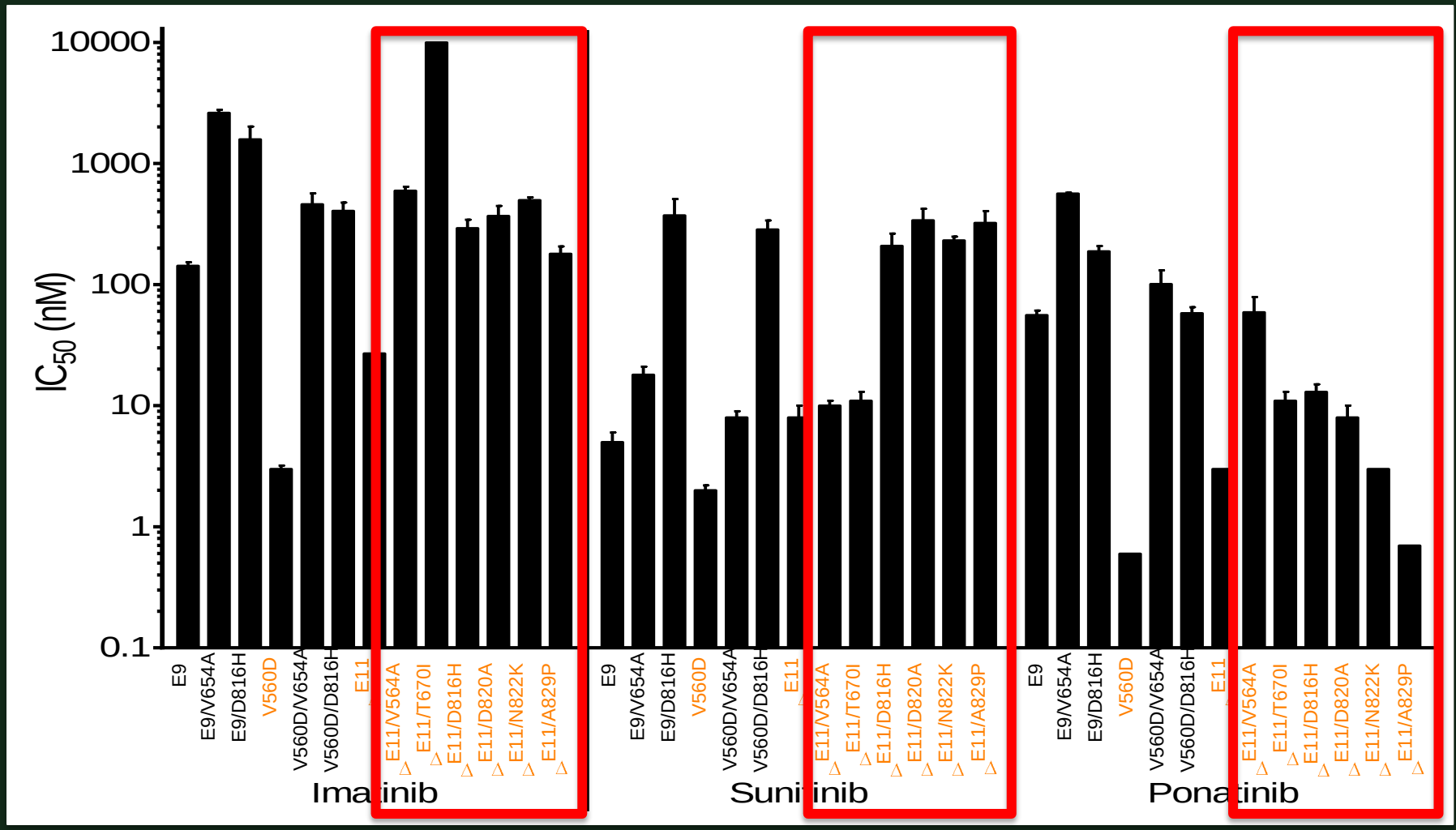
Ponatinib binds the inactive conformation deep in the ATP binding pocket



Ponatinib binding can tolerate key KIT resistance mutations

Heinrich et al ASCO 2013

Differential Activity of TKIs



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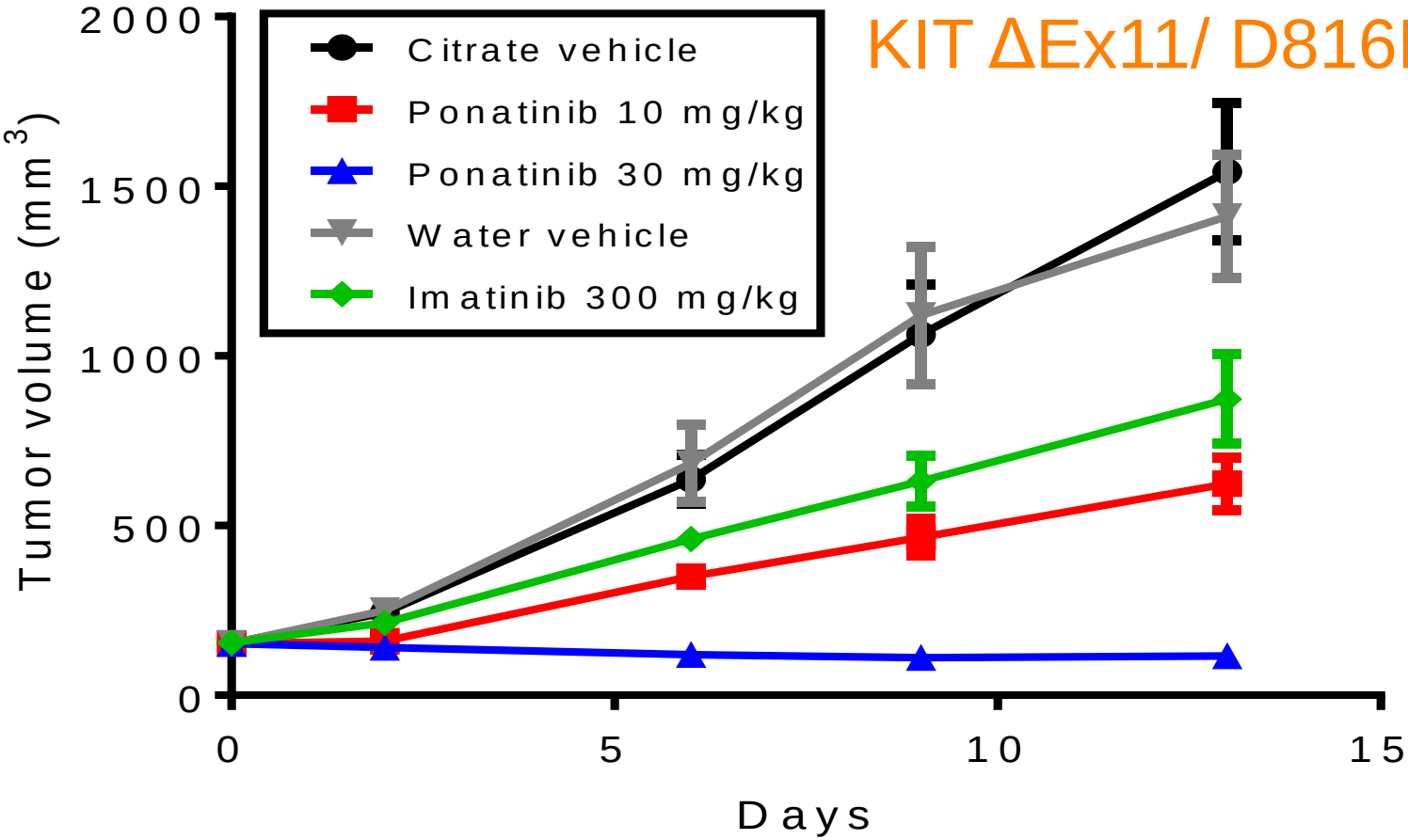
Ponatinib Potently Inhibits Secondary Mutants In A-Loop



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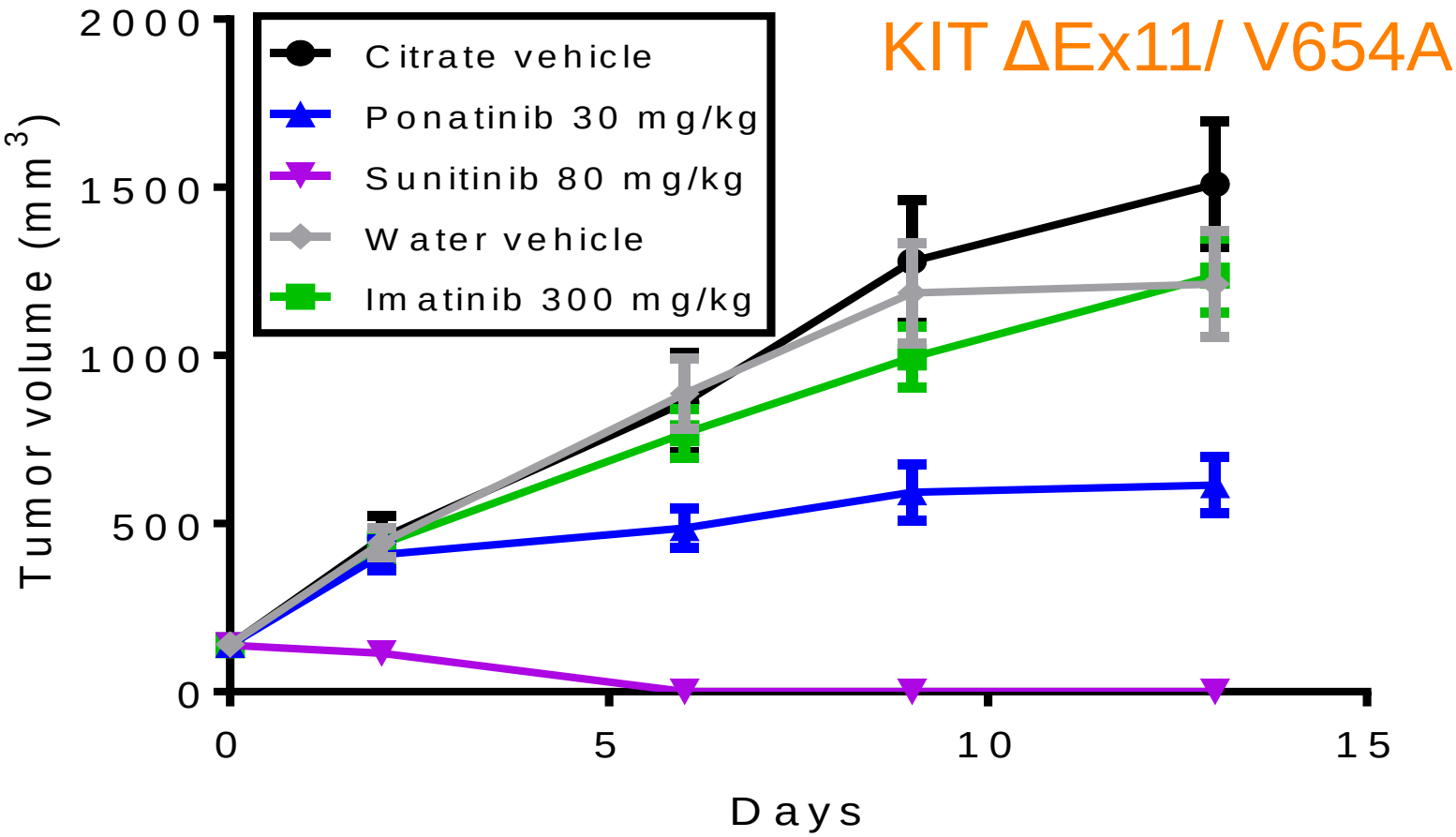
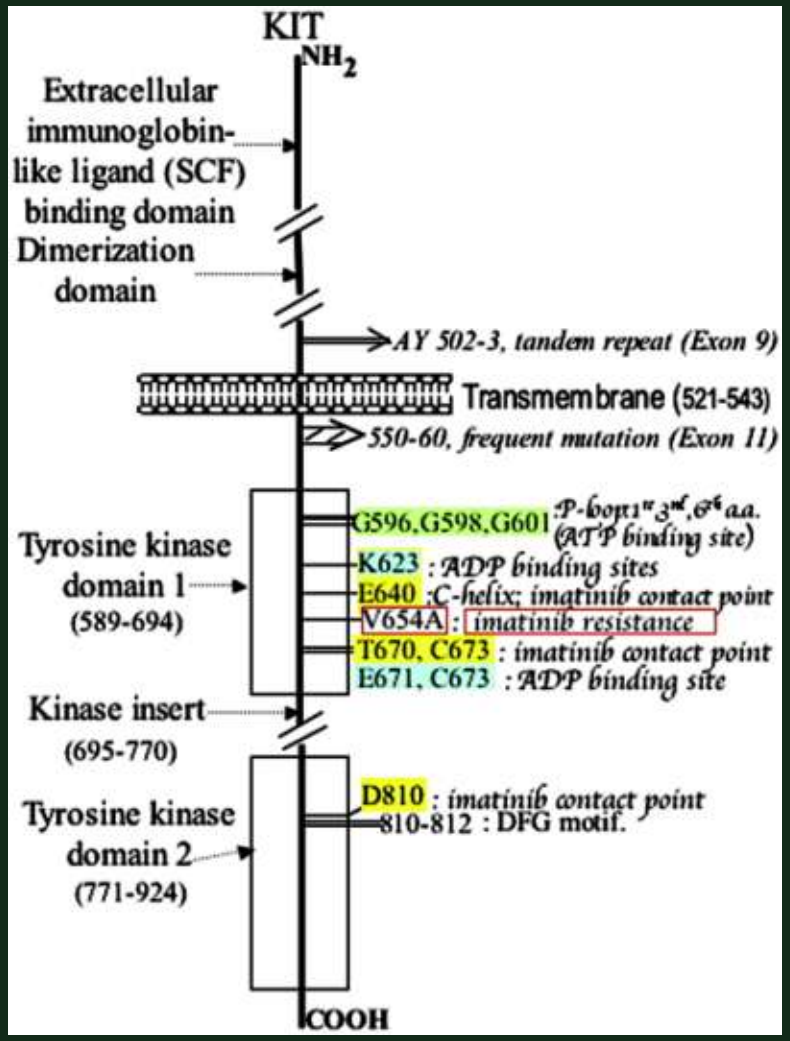
Sunitinib Superior If Secondary Mutation Is In ATP-binding Site



Conclusions

- Ponatinib is clearly active against GIST cell lines including those with secondary mutations in Exon 17 (A-loop) and Exon 14 (Gate Keeper)
- Ponatinib is superior to other TKIs in terms of IC50 in GIST cell lines except those with Exon 13 (V654 ATP binding site) secondary mutation
- Clinical trial in resistant GIST is warranted

Secondary Mutations in KIT



ATP/ADP Binding Site (V654)

Gate Keeper (T670)

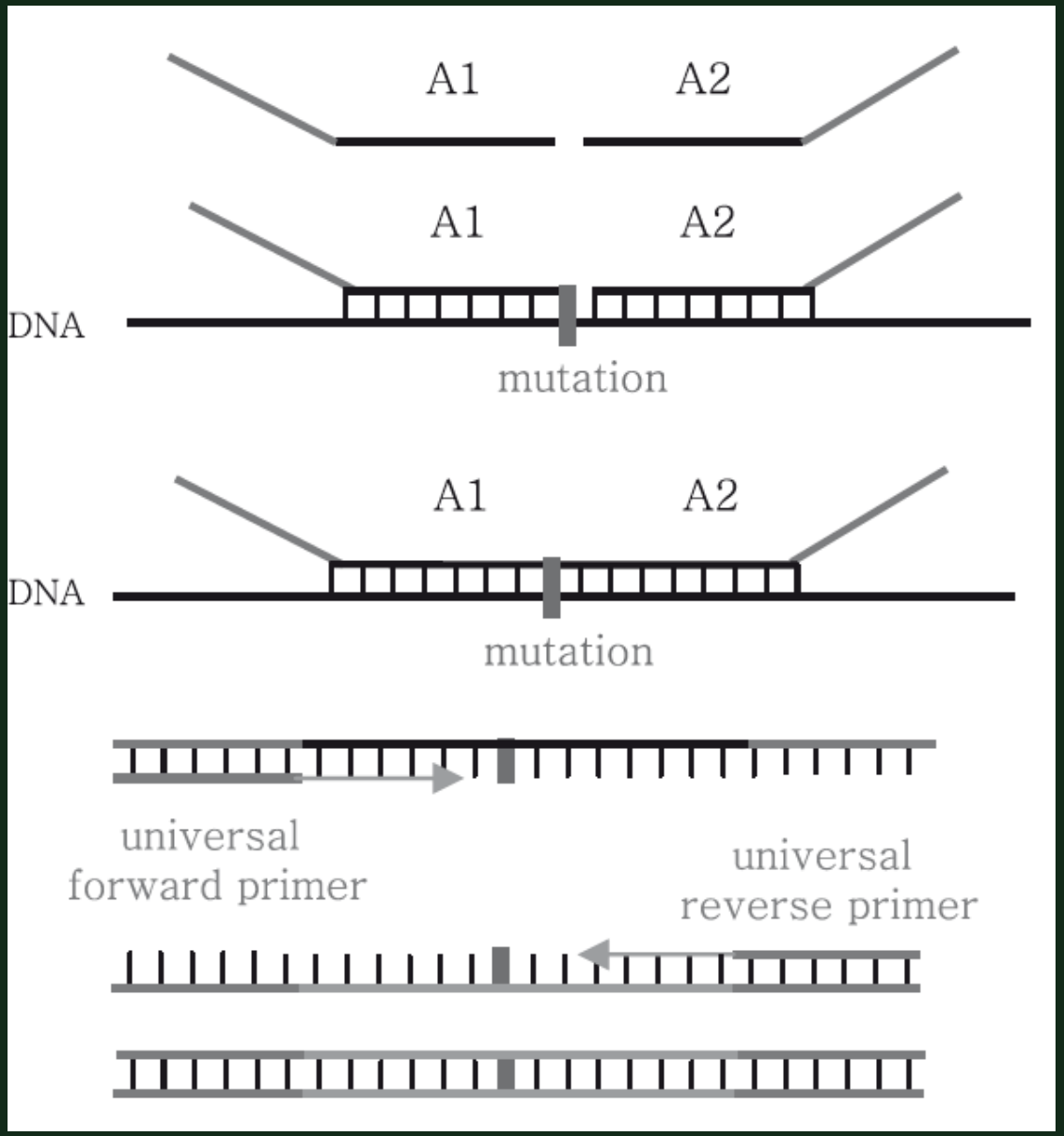
Activation Loop (D820)

Chen, Trent, et al. Cancer Res 2004;64:5913-5919

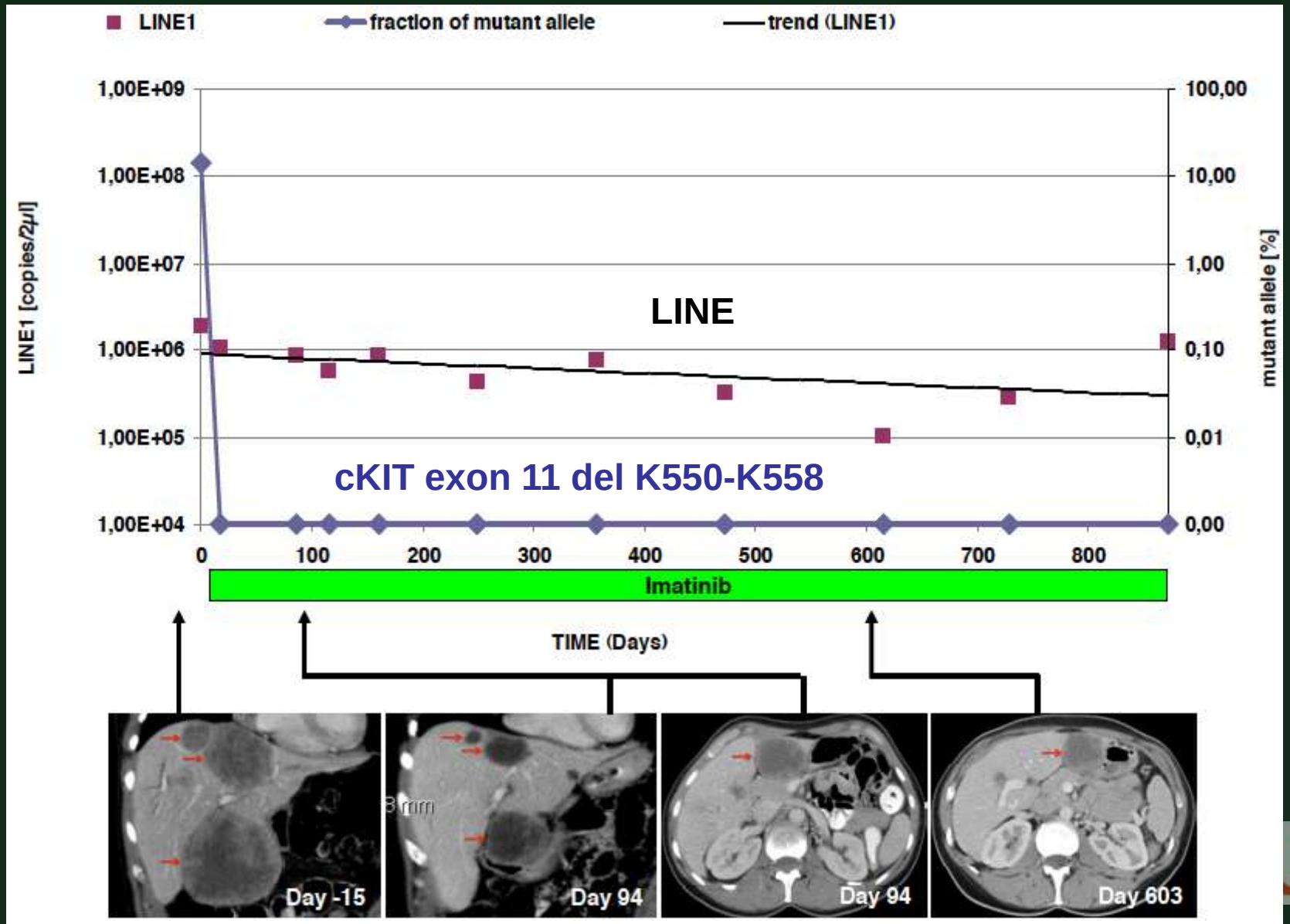
Detection of mutant free circulating tumor DNA in the plasma of patients with gastrointestinal stromal tumor (GIST) harboring activating mutations of ckit or pdgfra

Bubnoff et al ASCO 2013

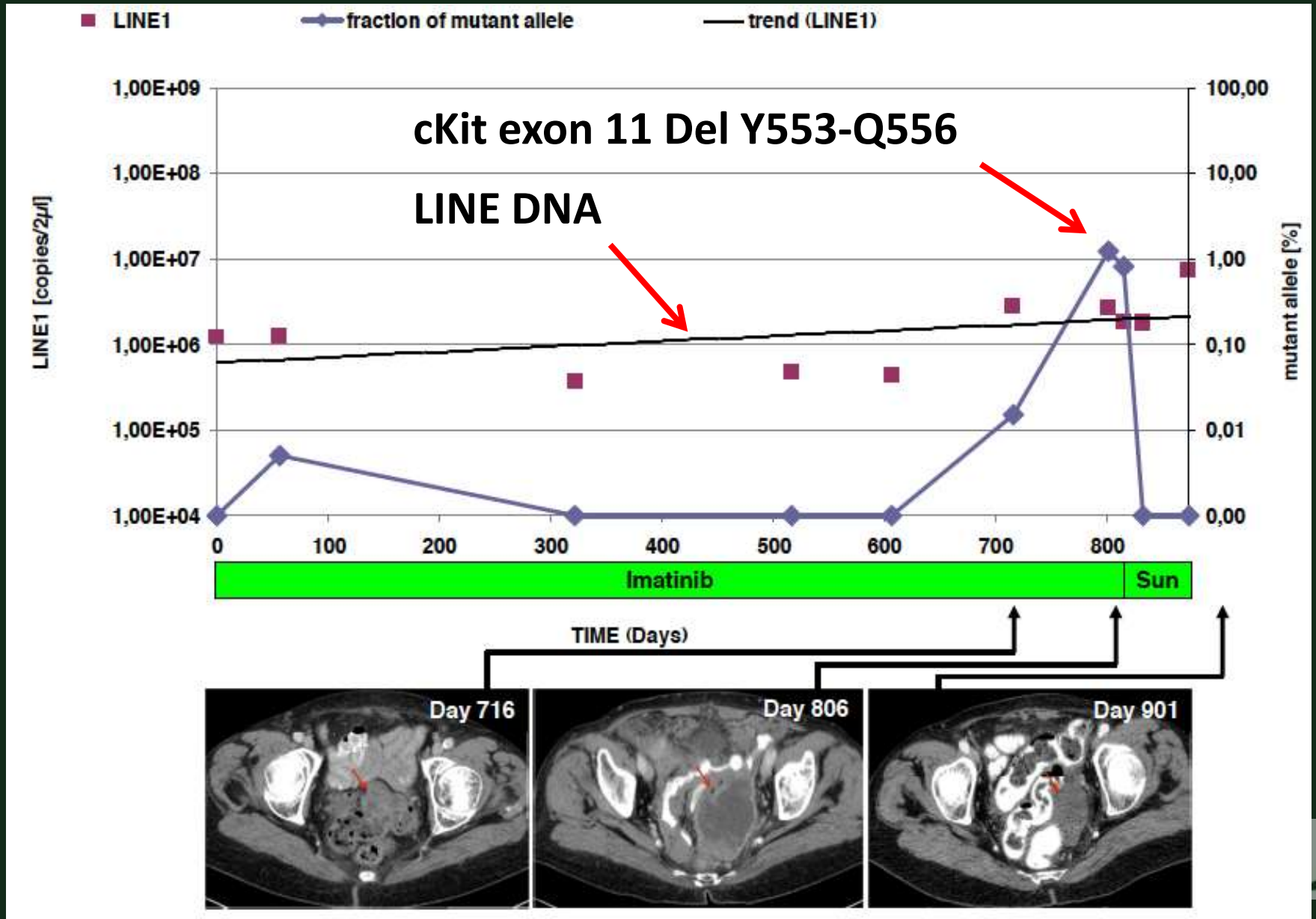
Ligation-PCR



Rapid Decrease of mutant fcDNA: Predictive for response

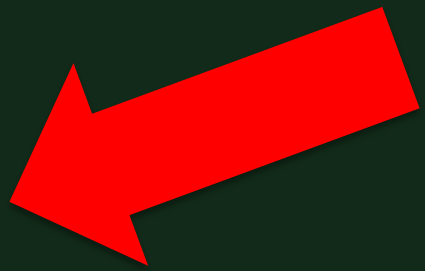


GIST: Progression and response: *Transient* increase of mutant fcDNA in Plasma



Detection of Tumor fcDNA in GIST
Results

- 15/38 pts had positive mutant fcDNA
- pts. with active disease: 9/18 positive
- pts. in CR according to Miettinen risk of relapse
  - HR: 5/14 positive
  - MR: 1/3 positive
  - LR/NA: 0/3 positive



Conclusions

- fcDNA is detectable in plasma from GIST patients
- Improved sensitivity may allow early detection of progression and identification of specific secondary mutations allowing drug selection
- May have a role in further stratifying intermediate to low risk GIST patients for adjuvant imatinib therapy

Molecular Decision-Making in GIST

- Optimal therapy for GIST patients ***requires*** molecular decision-making
  - Kit exon 9
  - PDGFR D842V
  - SDH-B deficiency
  - Raf V600E
  - NF-1, Ras
  - PI3K
  - KIT secondary mutations
    - Exon 13 (ATP binding site)
    - Exon 17 (A-loop)

Molecular Decision-Making in GIST

Optimal therapy for GIST patients ***requires*** molecular decision-making

- Kit exon 9: Imatinib 800mg (or tolerated dose)
- PDGFR D842V: anti-PDGFR trial
- SDH-B deficiency: Regorafenib ?
- Raf V600E: Raf inhibitor
- NF-1, Ras: Raf inhibitor?
- PI3K: mTOR inhibitor
- KIT secondary mutations
  - Exon 13 (ATP binding site): Sunitinib 37.5 mg daily
  - Exon 17 (A-loop): Ponatinib?

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