

Molecular Aspects of GIST

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Summary of Lecture

1. Historical perspective of GIST
2. KIT/PDGFR α receptor
3. Activating mutations in GIST
4. Clinical implication of Mutational status in Primary/
Resistant GIST
5. Therapeutic strategies in management of
Imatinib/Sunitinib-resistant GIST
6. Wild-Type/ Pediatric/ Hereditary GIST

GIST: A Historical Perspective

Time line

GIST a disease poorly understood

- ? Name
- ? Pathogenesis
- ? Cell of origin
- ? Natural history
- ? Optimal Treatment

1998

2010

Seminal discovery

- Near universal
- Presence of *KIT*
- Mutations are central to pathogenesis of GIST
- Identified a common lineage to Interstitial cells of Cajal

Implication of Finding

- Allows for the accurate diagnosis of GIST
- Provides a compelling rationale to test Imatinib in this disease

GIST: A Historical Perspective

1998

2010

2001: Imatinib (IM) activity reported in a single patient ¹

2004: Phase III Testing of optimal IM dose level ^{5,6}

2003: PDGFRA ⁴

2002: Study B22-22 reported in NEJM ^{2,3}

2006: Efficacy of Sunitinib confirmed in GIST ⁷

¹ Joensuu et al. N Engl J Med. 2001;344(14):1052-6

² Demetri et al. N Engl J Med. 2002;347(7):472- 80

³ Blanke CD et al. J Clin Oncol. 2008;26(4):620- 5

⁴ Science. 2003 Jan 31;299(5607):708-10.

⁵ Verweij J, et al. Lancet. 2004;364(9440):1127- 34

⁶ Blanke CD. J Clin Oncol. 2008;26(4):626-32

⁷ Demetri et al. Lancet. 2006;368(9544):1329-38

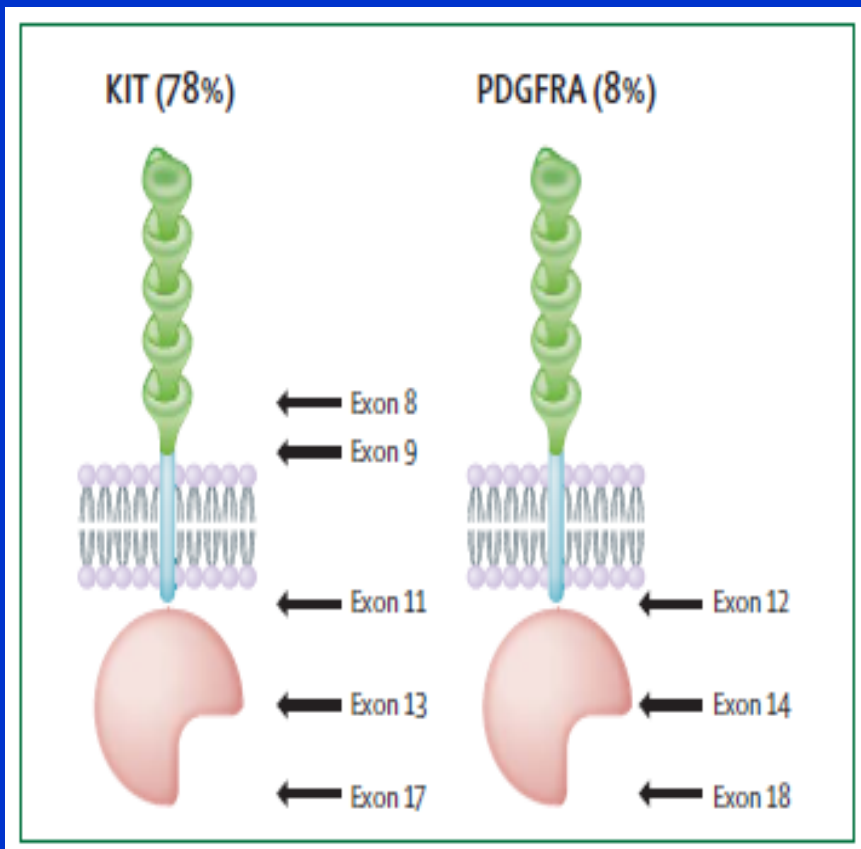
TIME

THERE IS NEW **AMMUNITION**
IN THE WAR AGAINST
CANCER.
THESE ARE THE BULLETS.

Revolutionary new pills like **GLEEVEC**
combat cancer by targeting only the
diseased cells. Is this the breakthrough
we've been waiting for?

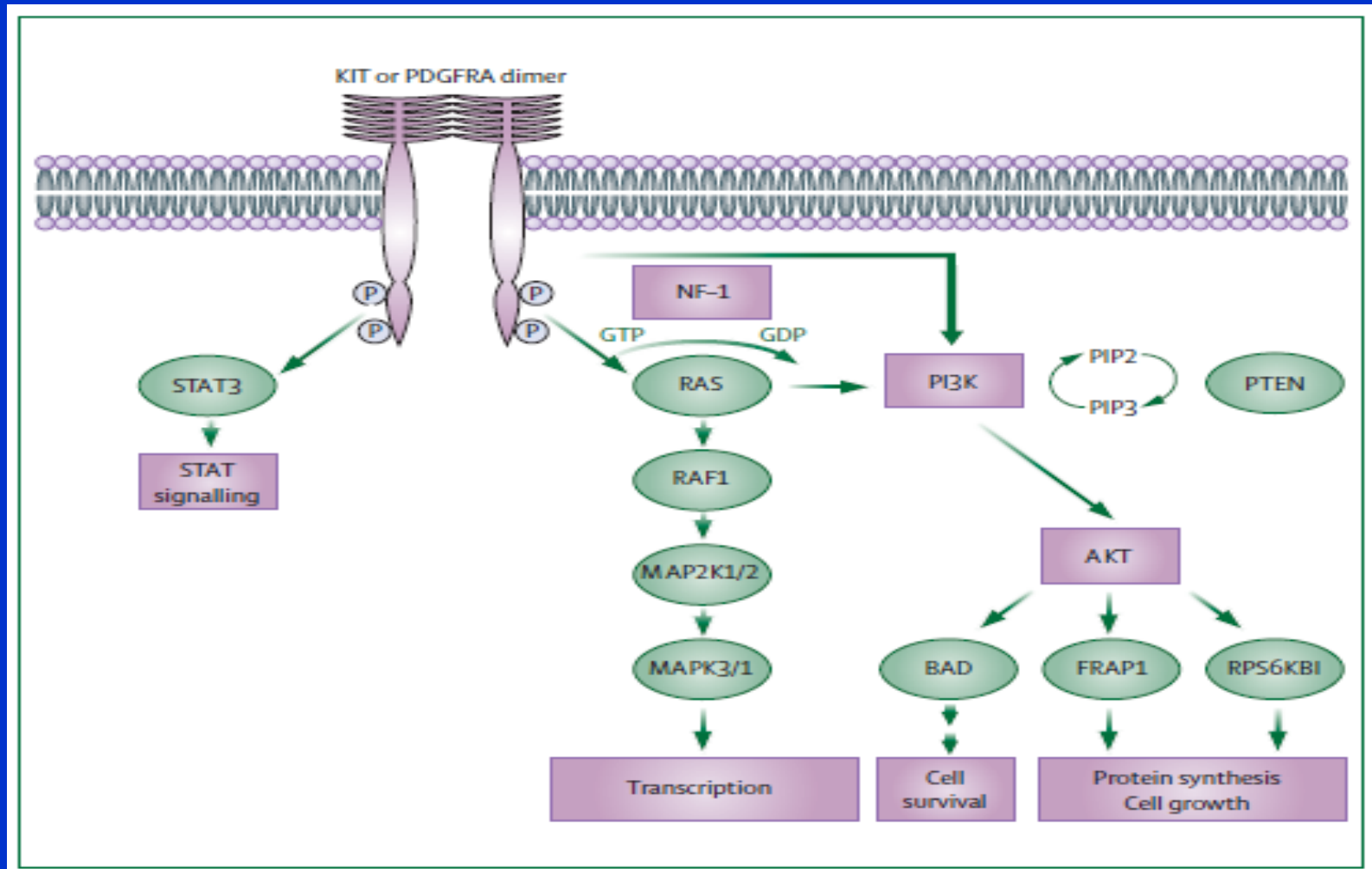


KIT/PDGFRA Receptor



- Tyrosine kinase receptor
 - Extra-cellular component
 - Intra-cellular component
- Ligand: Stem Cell Factor
- Ligand binding results in receptor dimerization
- Activation of downstream pathways

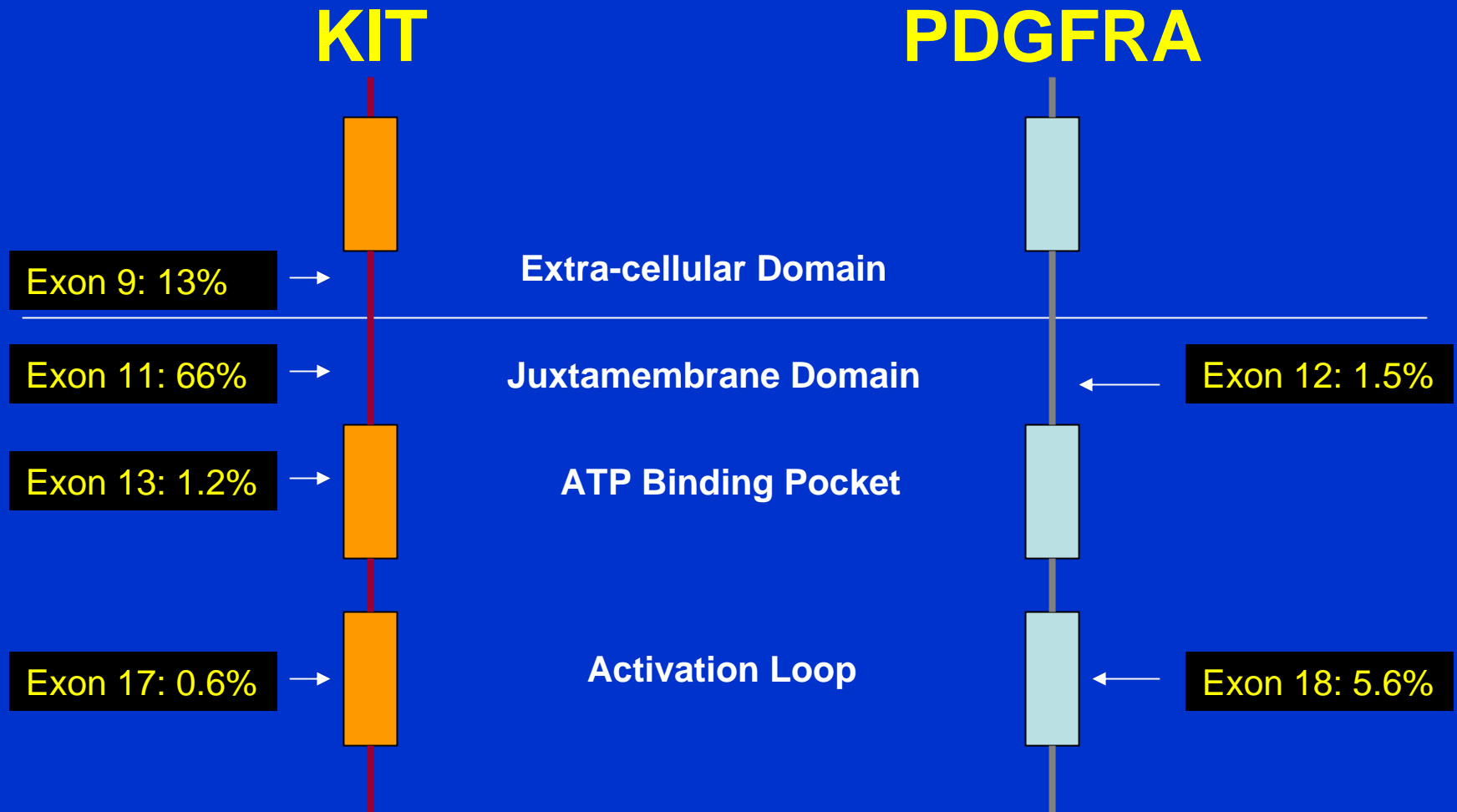
Downstream Pathways of *KIT*/*PDGFRA* Receptor



Pivotal Role of *KIT/PDGFR* Mutation

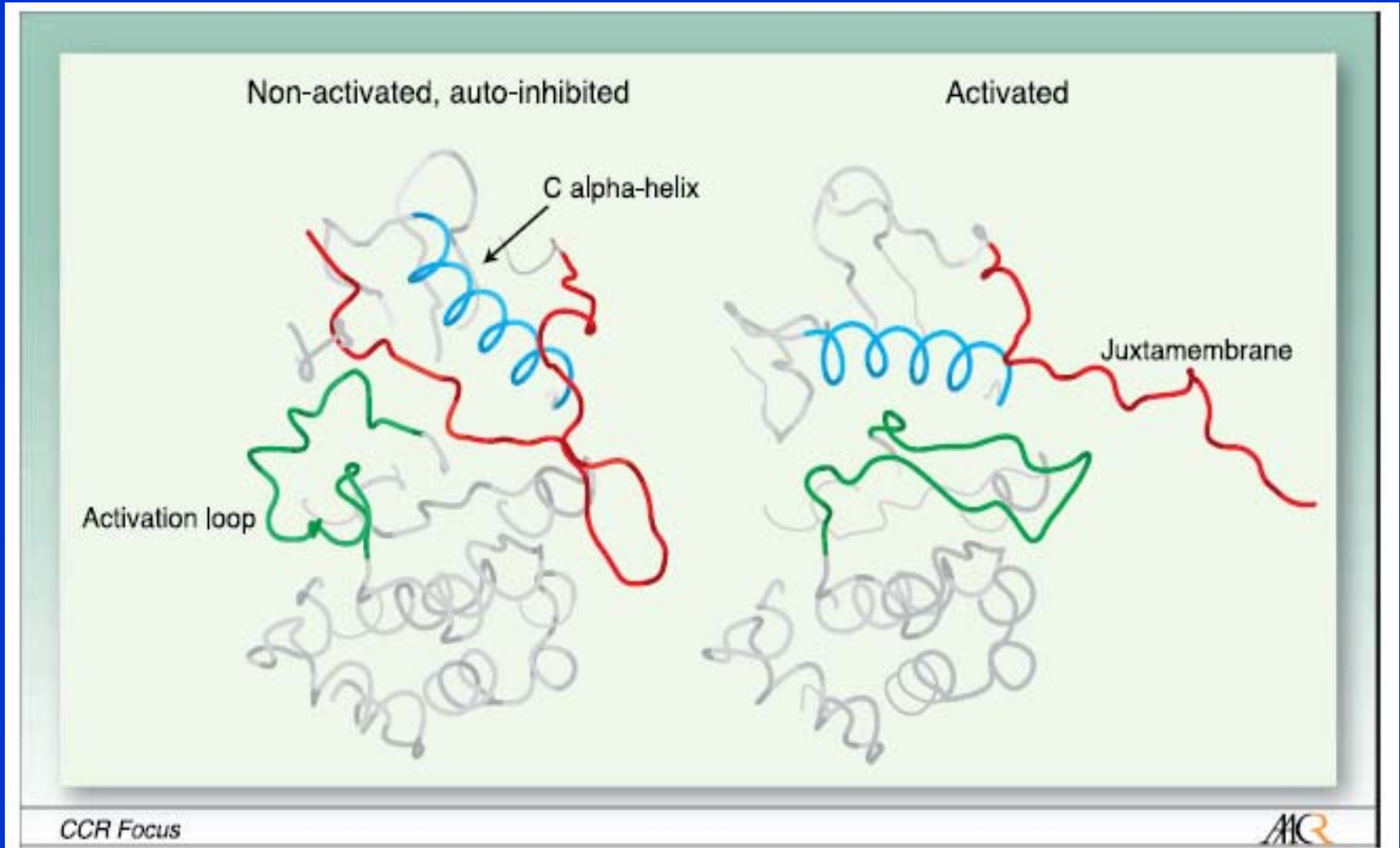
- ***In vitro:*** when expressed mutant kinases demonstrate constitutively activated signaling
- ***In vivo:*** in fresh frozen GIST samples, kinases are phosphorylated indicative of in vivo activity
- ***Mice:*** mice engineered to express mutant forms of *KIT* develop GIST-like tumors
- ***Humans:*** *KIT* mutations are found in earliest form of GIST tumors
- ***Imatinib resistant GIST:*** development of secondary *KIT* mutations (“*KIT*-driven”)

Frequency of Primary Mutations in GIST



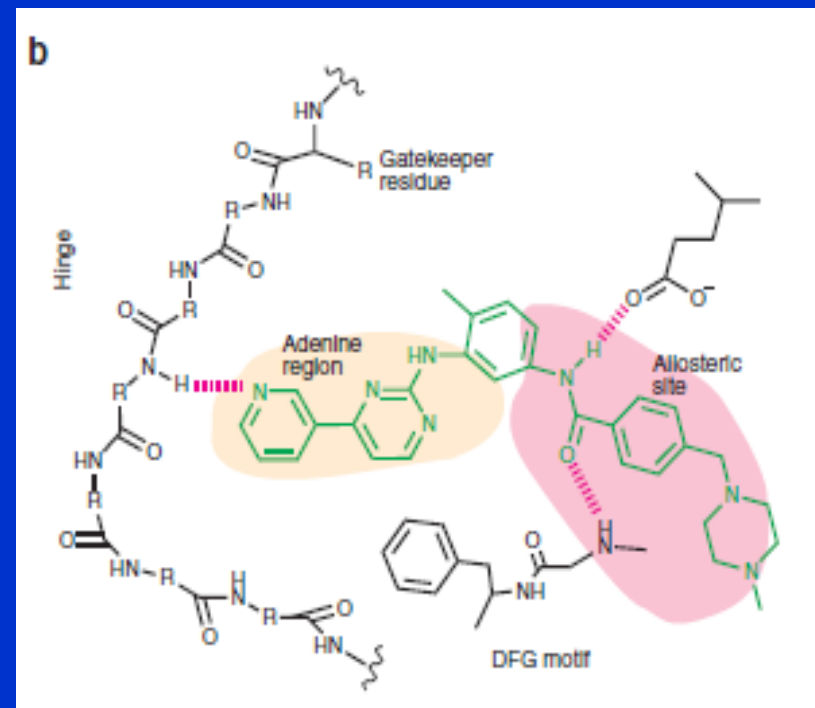
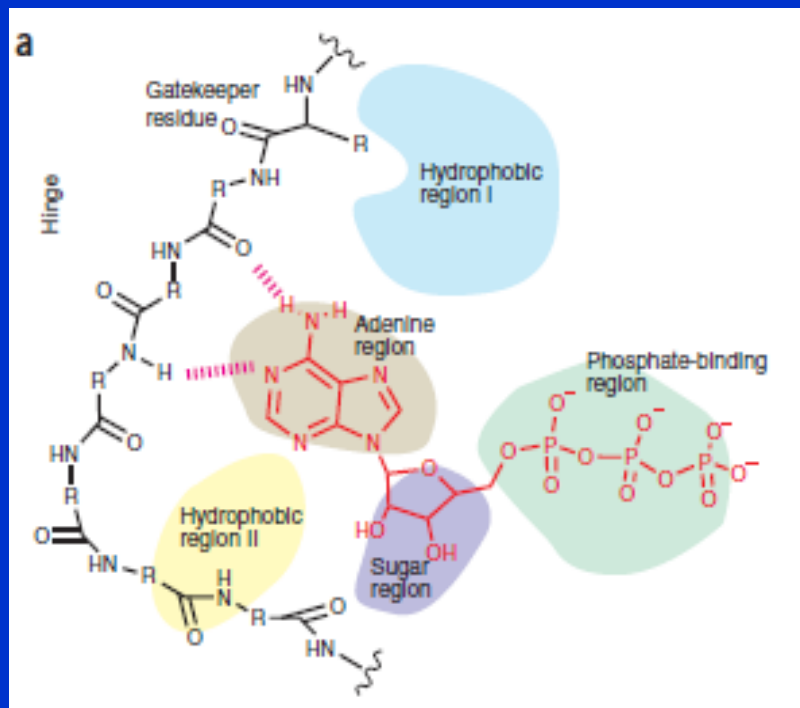
Wild Type for *KIT* and *PDGFRA*: 12%

KIT/PDGFRα Receptor



Imatinib (IM): Type II Kinase Inhibitor

- IM binds to inactive *KIT* conformation (activation loop “out”)¹
- Implication on IM resistance



¹ Mol et al. J Biol Chem. 2004;279(30):31655-63.
Liu and Gray. Nat Chem Biol. 2006;2(7):358-64.

Primary Mutational Status & Imatinib

- Randomized phase II Imatinib 400mg vs 600mg daily¹

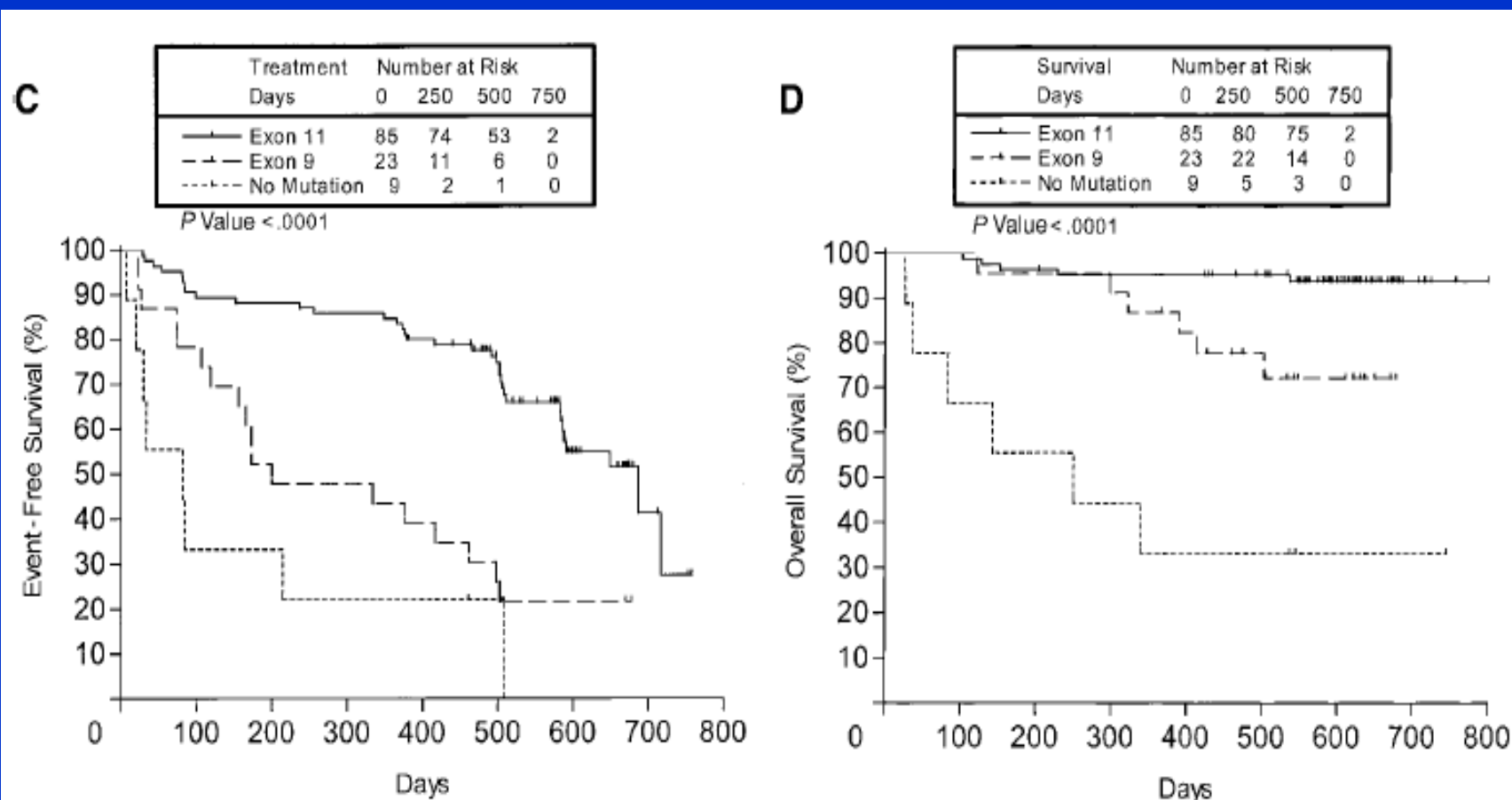
Figure 1: Imatinib 400mg vs 600mg daily¹

	<i>KIT</i> Ex 11	<i>KIT</i> Ex 9	Wild Type
Partial Response	84%	48%	0%
		P=0.0006	P<0.0001
Event Free Survival	687 days	200 days	82 days

¹ Demetri et al. N Engl J Med. 2002;347(7):472-80

² Heinrich et al. J Clin Oncol. 2003;21(23):4342-9

Primary Mutational Status & Imatinib



Primary Ex 9 Mutation & Imatinib

PFS	Median Estimate (mths)			3yr estimate		HR	P-value
	N	400mg	800mg	400mg	800mg		
All <i>KIT</i> Ex9 mutant	91	6.0	19.1	5%	17%	0.58	0.017
EU-AUS	59	4.2	19.4	0%	25%	0.43	0.0023
North American	32	9.4	16.8	14%	6%	0.99	0.97

Imatinib Resistance

- Imatinib Resistance
 - **Primary Resistance**
(within 3-6 mths of starting imatinib)
 - **Secondary Resistance**
(typically 2 years from starting imatinib)

Primary Imatinib (IM) Resistance

- 10% of GIST pts
- Observed in all genotypes
- More common in:
 1. ***KIT* ex 9 mutants**
 2. ***PDGRA* ex18 (D842V)**
 3. ***KIT/PDGRA* wild-type**

Primary Imatinib (IM) Resistance

1. *KIT* ex 9 mutants

- Inadequate dosing
- May be overcome with higher IM doses

2. *PDGFRA* ex18 (D842V)

- Activation loop mutation
- Active receptor conformation impeding IM binding

3. *KIT/PDGRA* wild-type

- Other molecular events including BRAF mutations

V600E *BRAF* mutations are alternative early molecular events in a subset of *KIT/PDGFR*A wild-type gastrointestinal stromal tumours

A Agaimy,¹ L M Terracciano,² S Dirnhofer,² L Tornillo,² A Foerster,² A Hartmann,¹
M P Bihl²

- 69 GIST samples
 - 39 KIT/ 2 PDGFRA
 - 28 WT
- BRAF mutations 7% wild-type; 0% in mutant GISTs

Secondary Imatinib (IM) Resistance

Mechanism of Secondary Resistance

1. Emergence of resistant mutants
2. Other molecular events including
 - KIT amplification
 - Insulin-like growth factor-1 receptor (IGF-1R) over-expression
 - Drug efflux pumps
 - Pharmacological mechanisms

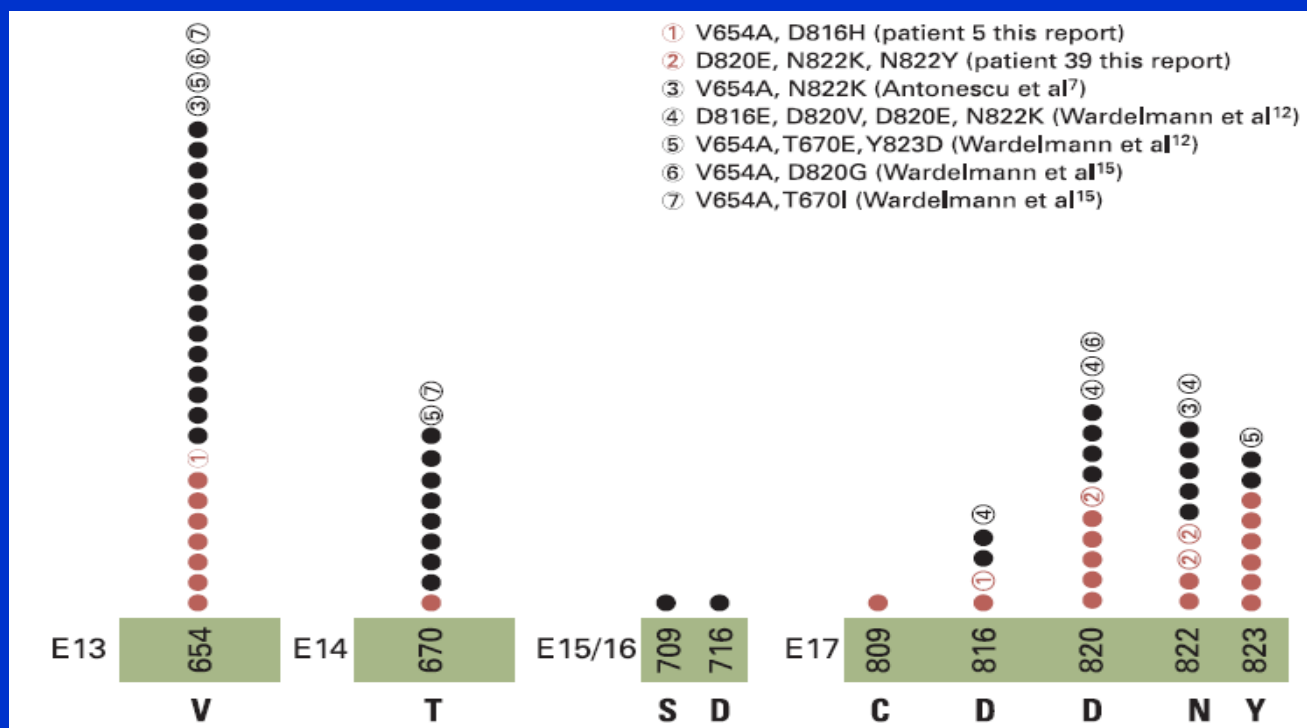
Secondary Mutations

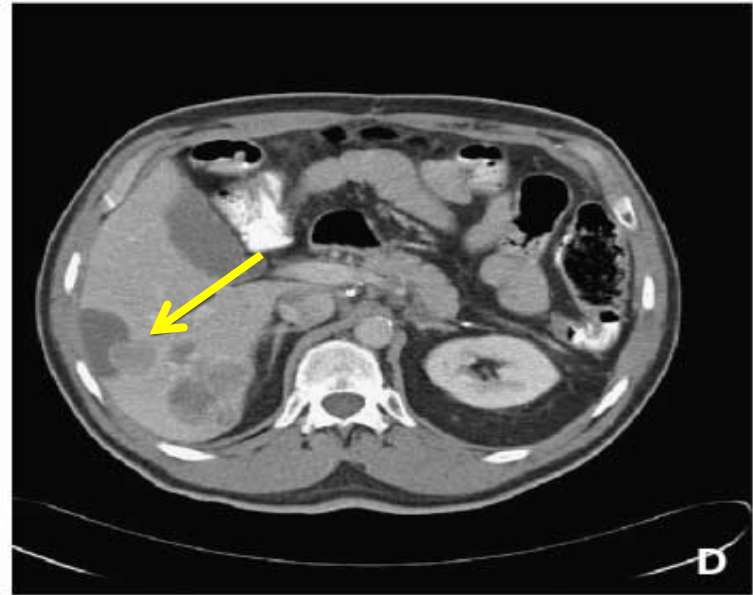
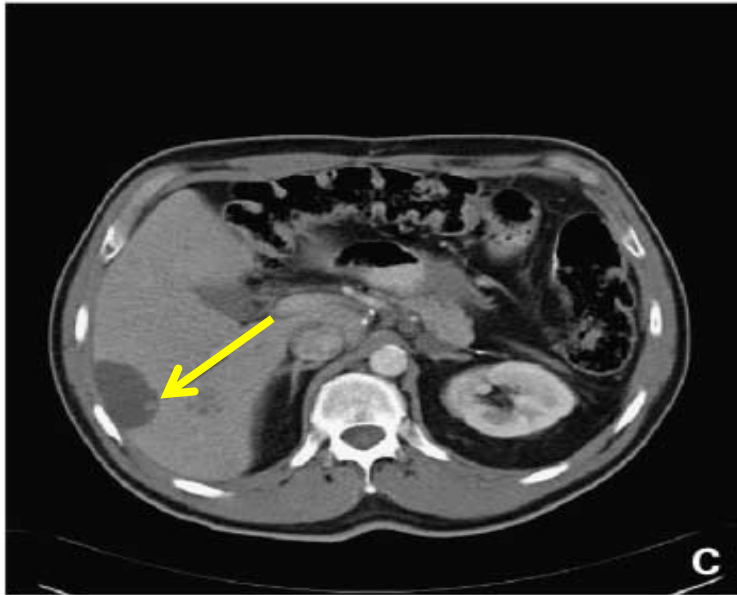
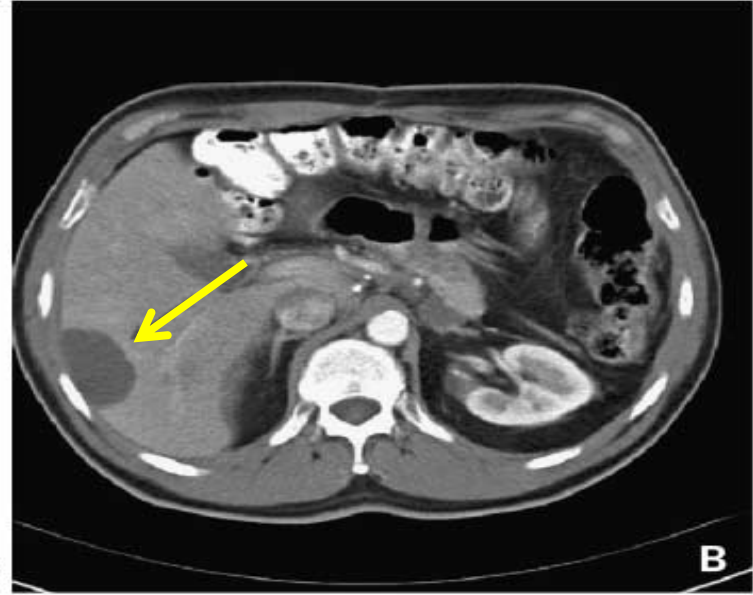
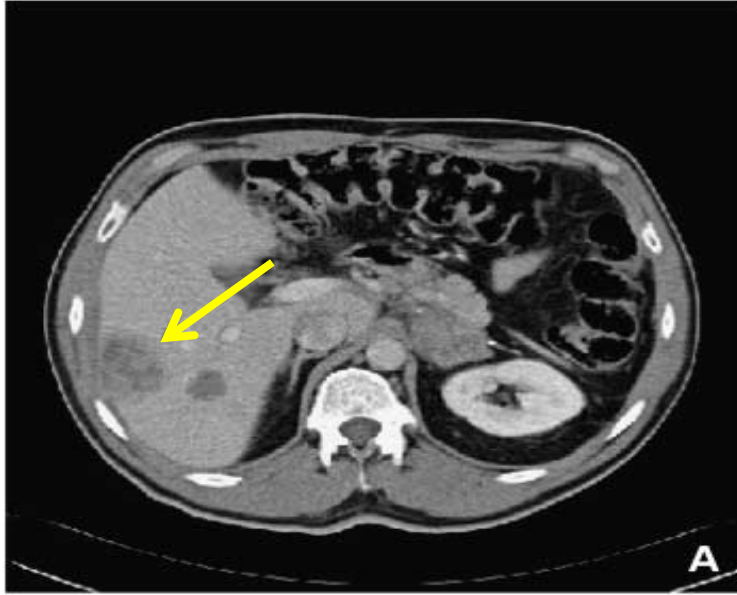
- Levels of activated *KIT* in IM-resistant GIST similar to untreated GIST
- Secondary *KIT/ PDGFRA* mutations found in primary *KIT/ PDGFRA* mutants respectively
- No secondary mutations noted in WT GISTs

	Primary IM Resistance	Secondary IM Resistance
Secondary Mutations	10%	67%

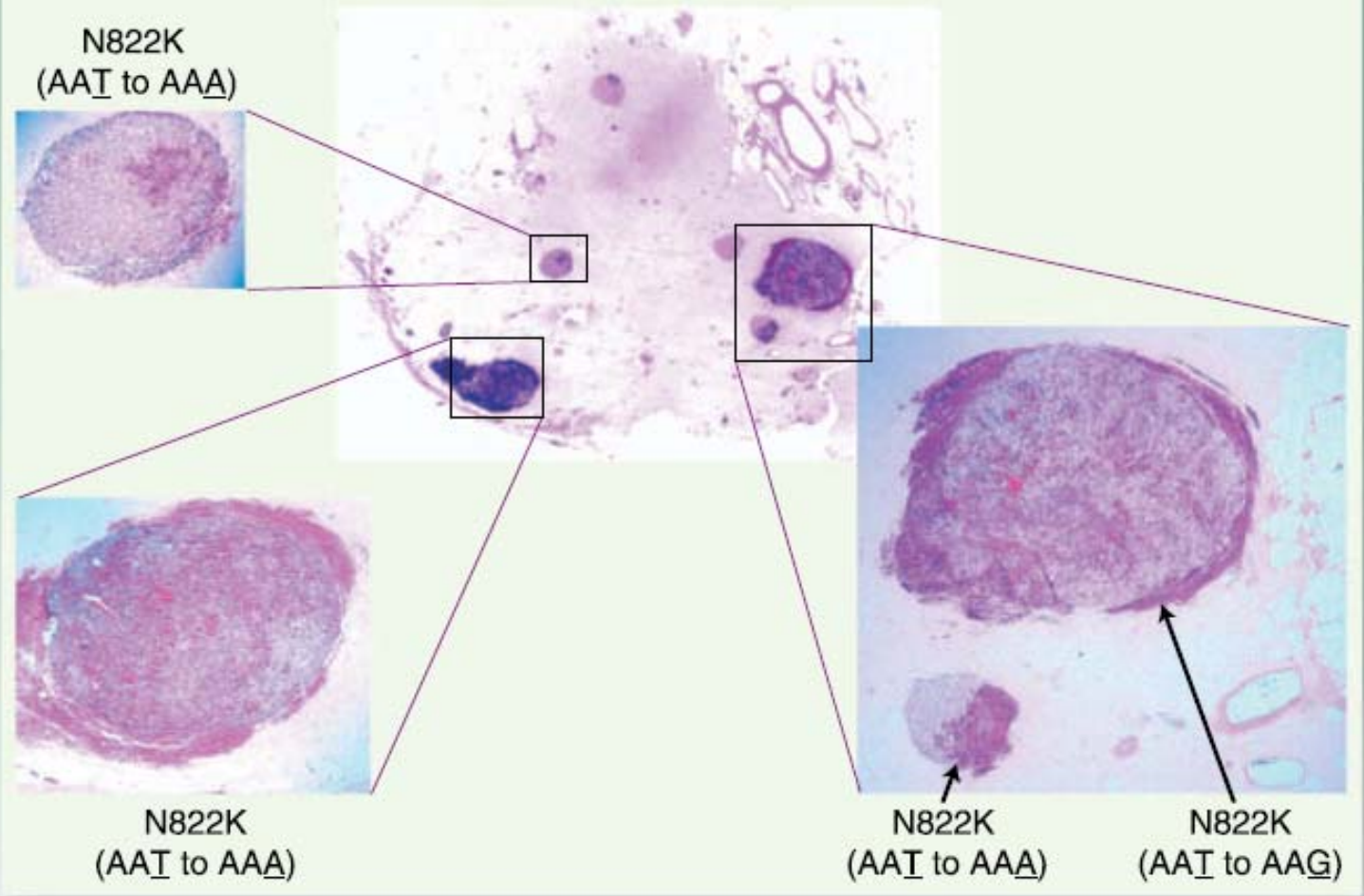
Secondary Mutations

- Non-randomly distributed
 - ATP binding pocket (Ex 13/14)
 - Kinase activation loop (Ex 17/18)





Multi-focal, clonal resistance

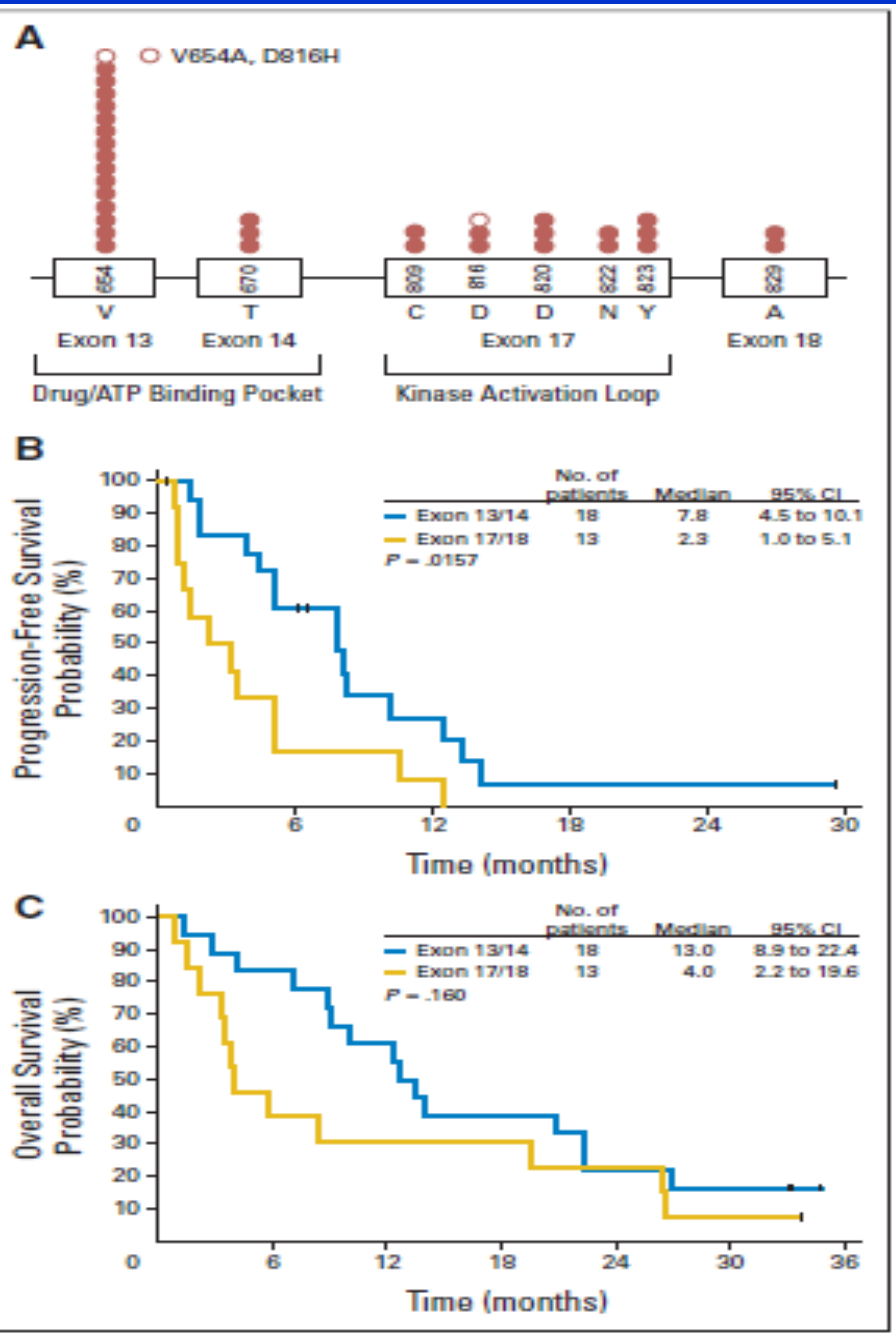


2nd Line Sunitinib Therapy

- Approved for 2nd line treatment¹
- Median PFS 7 mths
- PFS and OS ^{1,2}
 - Primary Exon 9 and WT superior to Ex 11
- Implication of Genotype on drug activity

¹Demetri et al. Lancet. 2006;368(9544):1329-38

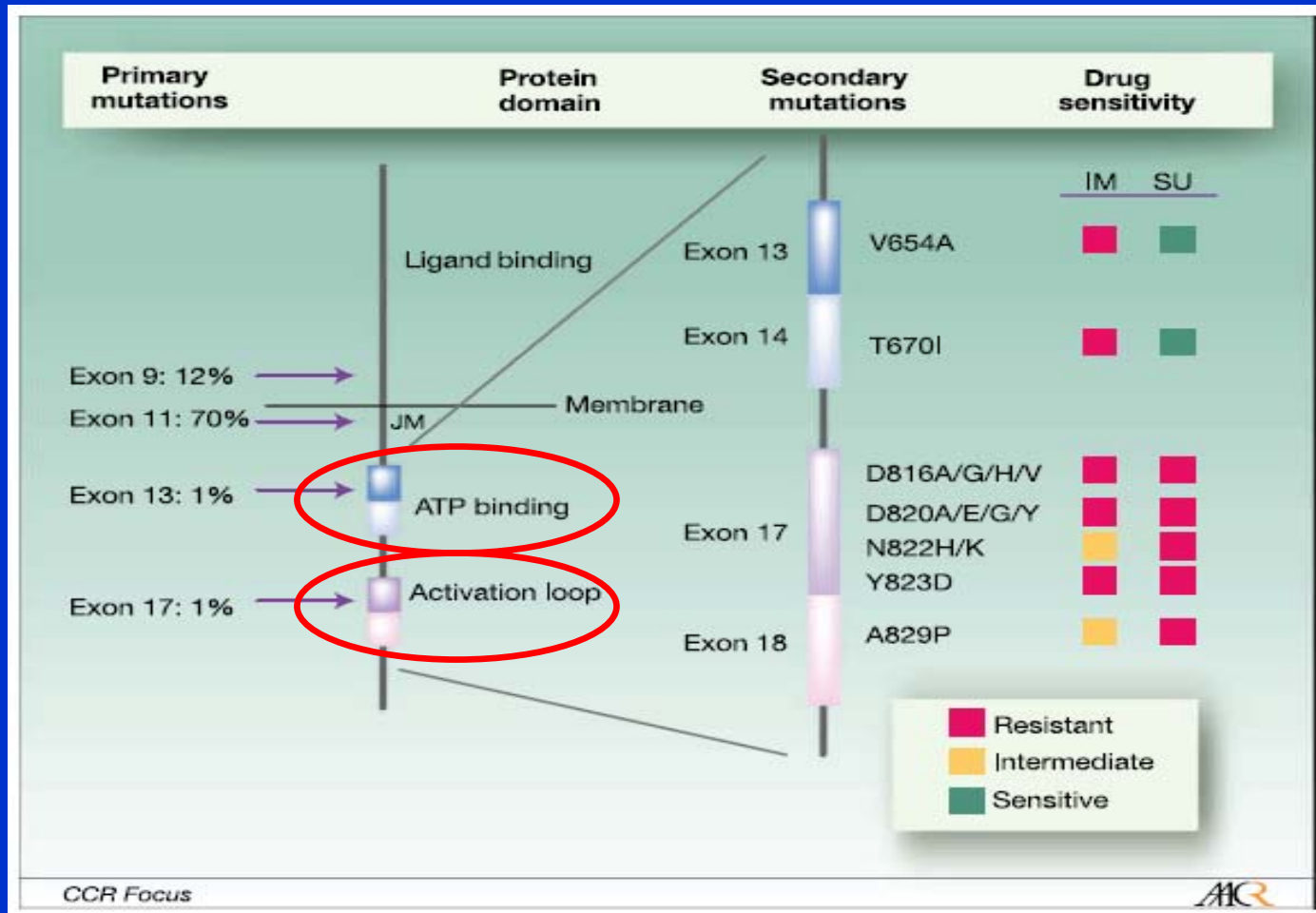
²Heinrich et al. J Clin Oncol. 2008;26:5352-59



Secondary mutations

- Ex13/14
- Ex17/18

Impact of Secondary *KIT* Mutations on Therapeutic Outcome to Sunitinib (SU)



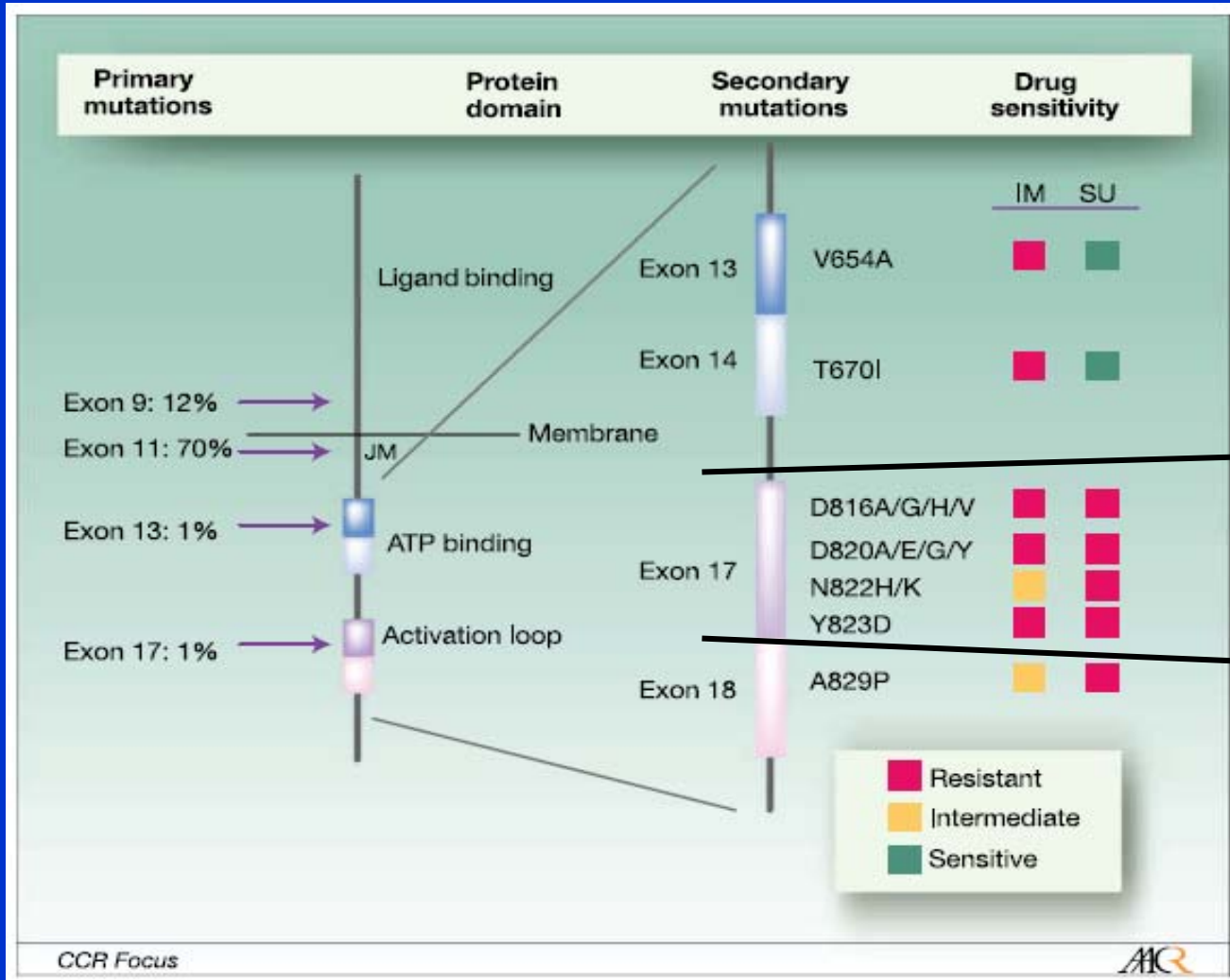
Sorafenib (SOR) in IM/SU-Resistant GIST

- Recently SOR has demonstrated activity in IM/SU-resistant GIST
- University of Chicago Consortium Phase II¹
 - 13% PR
 - 5 mth median PFS
- European retrospective series²
 - 4th line after IM, SU and Nilotinib
 - 5 mth median PFS

¹ Wiebe et al. J Clin Oncol 26: 2008 (May 20 suppl; abstr 10502)

² Reichardt et al J Clin Oncol 27:15s, 2009 (suppl; abstr 10564)

Sorafenib (SOR) in IM/SU-Resistant GIST



Preclinical Studies

SOR vs IM

SOR vs SU



Greater Potency



Equivalent

Challenges in the Management of IM/SU-resistant GIST

- Heterogeneous population
- Clonal evolution of secondary mutations

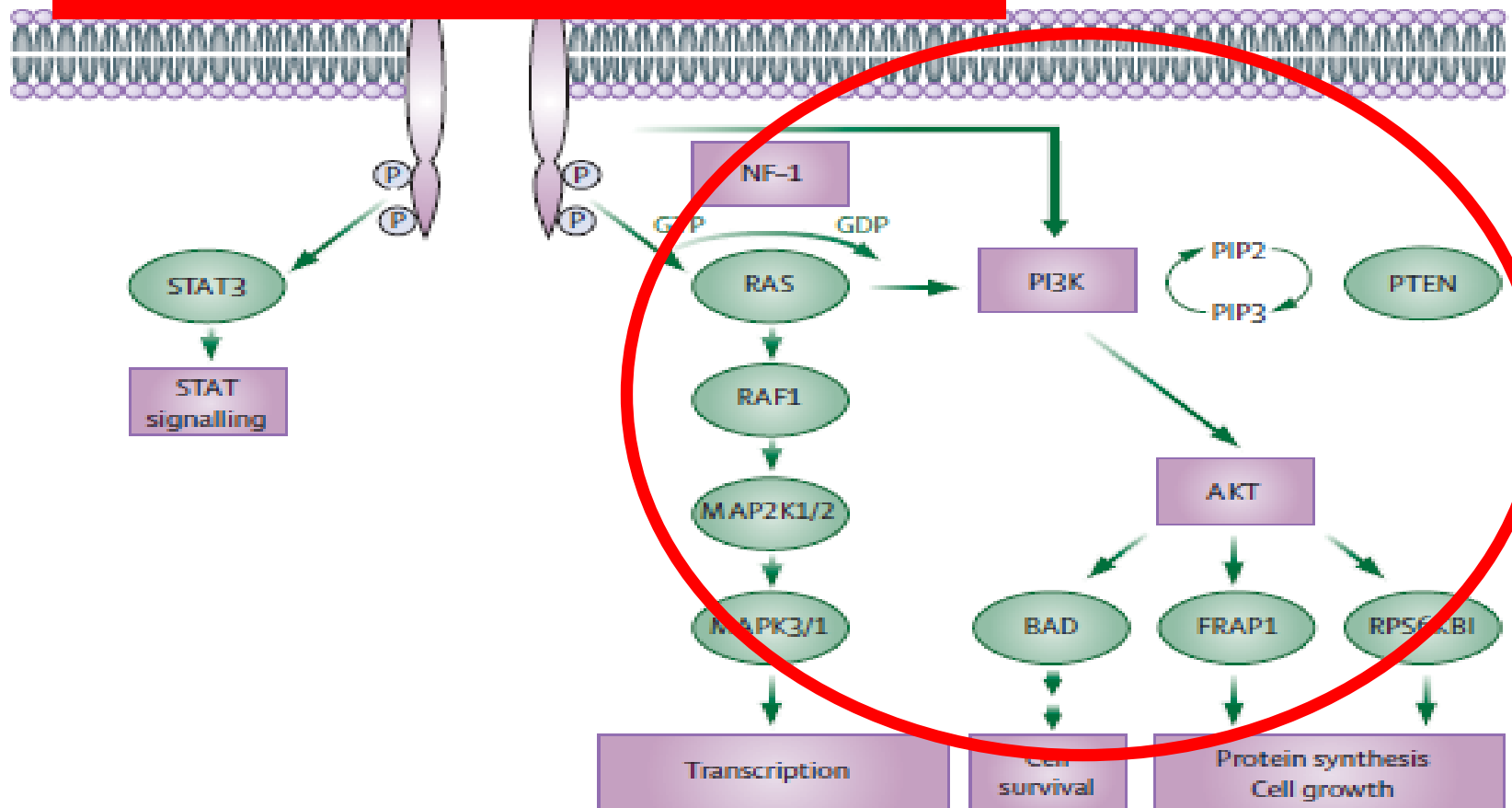
Strategies in the Management of IM/SU-resistant GIST

IM dose Escalation

FRA dimer

Novel small molecule TKI

Heat Shock Protein-90 inhibitors



Wild Type (WT) GIST

- About **12%** of GIST ¹
- **Insulin-like growth factor-1 receptor** (IGF-1R) over-expressed in both adult and pediatric WT GIST ^{2,3}
- IGF-1R amplification detected at higher frequency in WT compared to mutant GIST ²
- Aberrant IGF-1R expression may be associated with pathogenesis of WT GISTs
- Small proportion (**7%**) WT GIST may harbor activating **BRAF mutations**⁴

¹ Corless et al. J Clin Oncol. 2004;22(18):3813-25

² Tarn et al. Proc Natl Acad Sci U S A. 2008;105(24):8387-92

³ Corless et al. J Clin Oncol (Meeting Abstracts). 2009;27:10506

⁴ Agaram et al. *Genes Chromosomes Cancer*. 2008;47(10):853-9

Pediatric GIST

- Rare, about 1-2% of all GIST cases ¹
- Express KIT and display high level of KIT activation
- Relative absence of *KIT/PDGFR*A mutations, 15% vs 85% in adult GISTs ^{2,3}
- Distinct gene-expression signatures ³
- In vitro and small series suggest sunitinib and other TKIs may be more active than IM ^{3,4}

¹ Miettinen et al. Am J Surg Pathol. 2005;29(10):1373-81

² Janeway et al. Cancer Res. 2007;67(19):9084-8

³ Agaram et al. Clin Cancer Res. 2008;14(10):3204-15

⁴ Janeway et al. Pediatr Blood Cancer. 2009;52(7):767-71.

Hereditary GIST

Neurofibromatosis Type-1 associated GIST Hereditary GIST

- Autosomal dominant (AD) disease
- Germline mutations in *KIT*

Carney-Stratakis Syndrome

- Mutation in *NF-1* gene which encodes for Neurofibromin
- Multi-focal GIST

- Neurofibromin negative regulator of RAS signaling
- May be associated with cutaneous/ mucous membrane hyperpigmentation, urticaria pigmentosa, mastocytosis
- Comprise of GIST and paraganglioma

- Respond to IM
- GIST typically multi-focal
- Large study on-going
- Majority of cases WT for *KIT/PDGFR*

- Linked to Succinate dehydrogenase deficiency (SDHD)

Conclusion

- GIST is a heterogeneous disease
- *KIT/PDGFRA* mutations are central to the pathogenesis of this disease
- Primary and Secondary mutations play major roles in response and resistance to therapy
- GIST serves as a model for drug development in cancer therapeutics

Thank You!