Canadian Life Raft Group

GIST updates

Cheng-Han Lee

chenghan@mail.ubc.ca

Department of Pathology and Laboratory Medicine

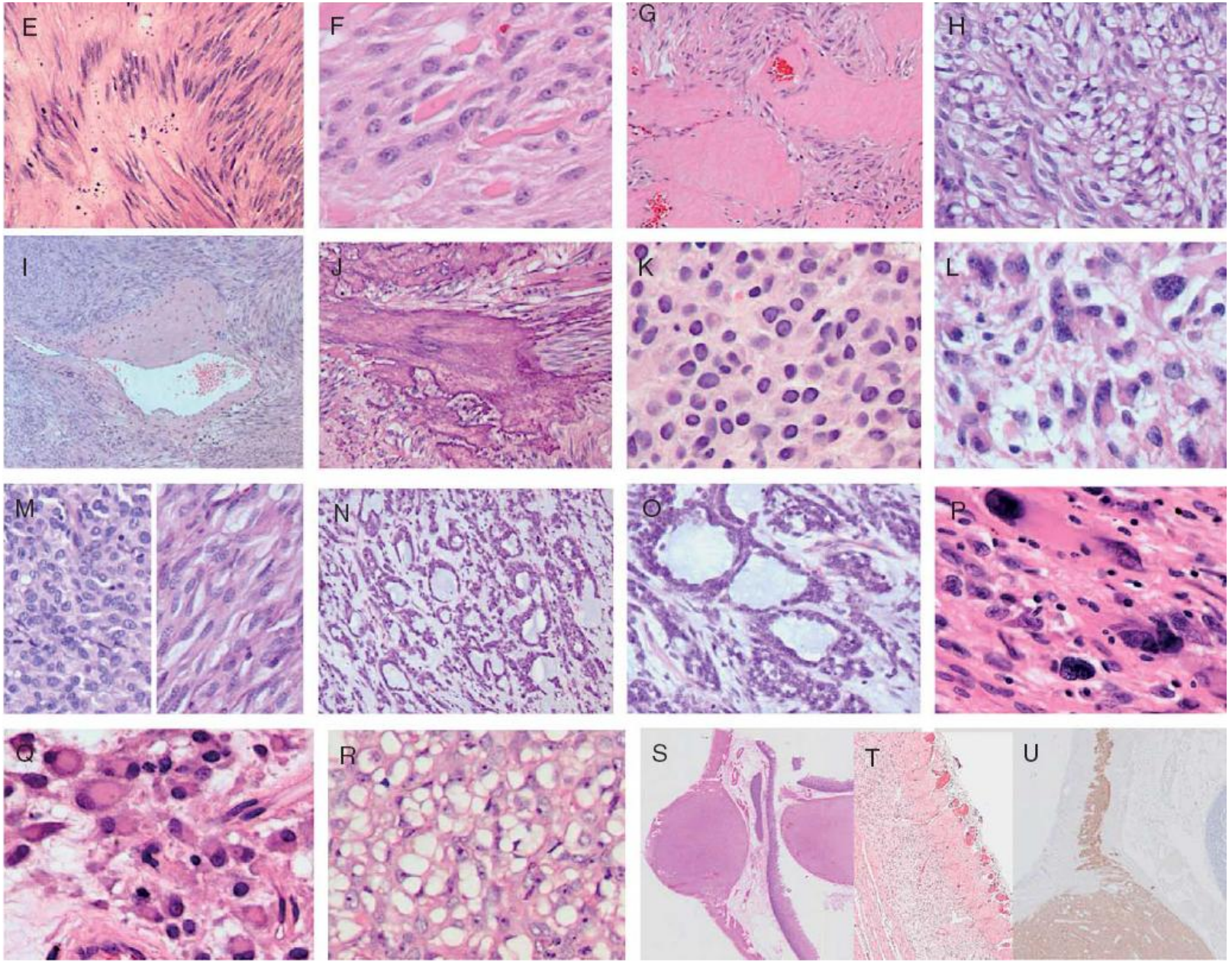
Vancouver CoastalHealth

UBC THE UNIVERSITY OF BRITISH COLUMBIA

Outline

- Diagnosis of GIST in pathology
- Diagnostic and predictive genetic markers in GIST
- Secondary resistance mutations
- Emerging therapies

Many different appearances of GIST



Adv Anat Pathol 2007;14:261–285

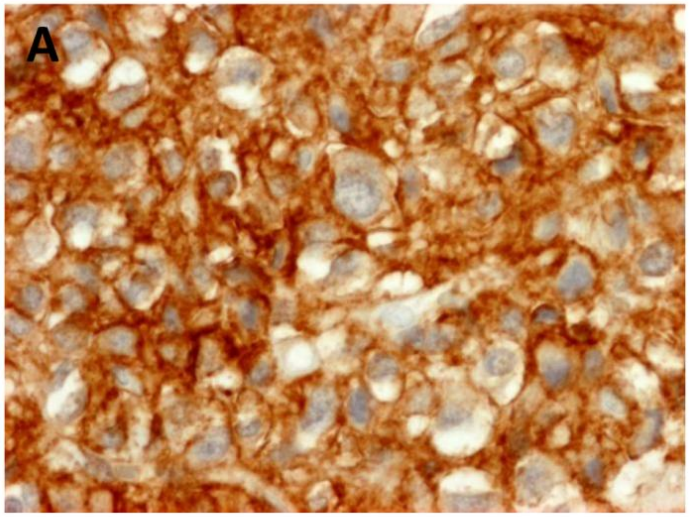
Diagnostic immunomarkers in GIST

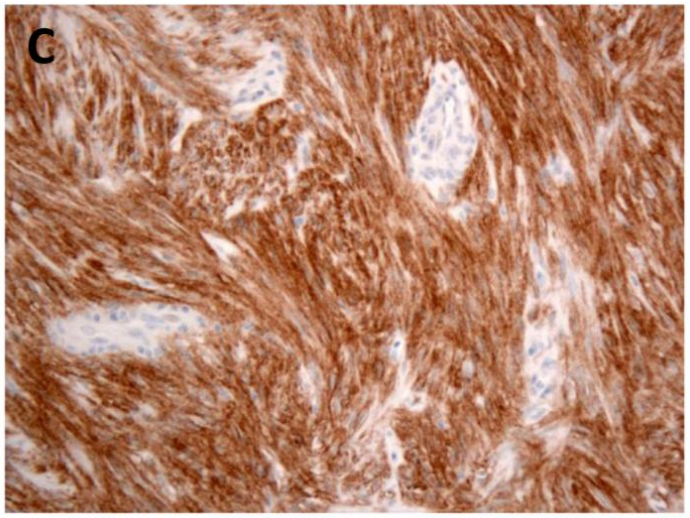
Positive markers

- **KIT (CD117)**
- **ANO1 (DOG1)**
- **CD34**
- PRKCQ
- CA2
- PROM1 (CD113)

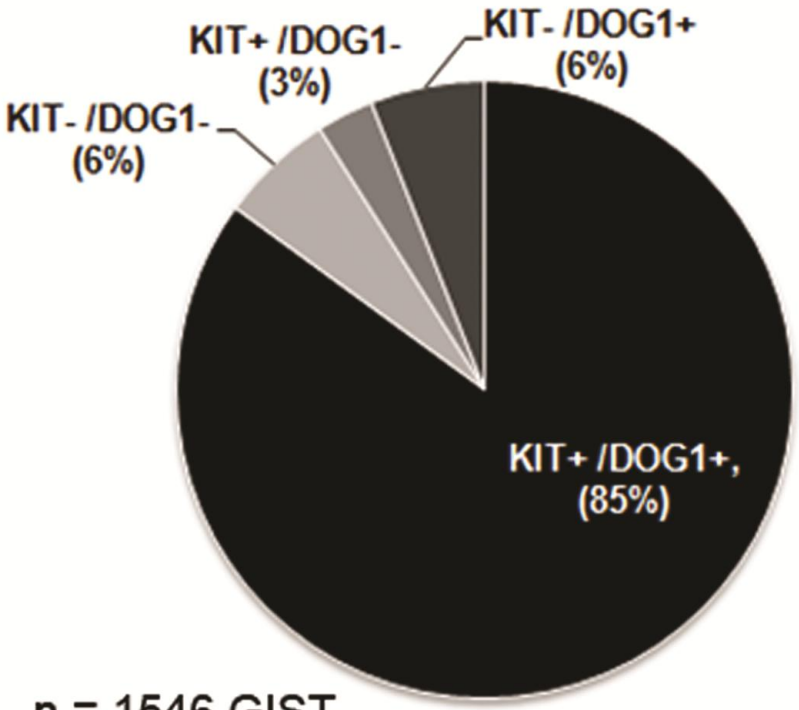
Negative marker

- Desmin





	DOG1.1	KIT	CD34	DOG1.1/KIT/CD34
KIT ex 11 (n=207)	180/197 (91%)	158/196 (81%)	129/200 (65%)	183/189 (97%)
KIT ex 9 (n=20)	16/16 (100%)	17/19 (89%)	10/18 (61%)	15/15 (100%)
KIT ex 13 (n=6)	4/5 (80%)	5/6 (83%)	3/6 (50%)	5/5 (100%)
PDGFRa ex 18 (n=26)	18/23 (78%)	3/24 (13%)	8/26 (31%)	18/22 (82%)
PDGFRa ex 12 (n=7)	5/5 (100%)	0/7 (0%)	1/6 (17%)	5/5 (100%)
PDGFRa ex 14 (n=1)	0/1 (0%)	0/1 (0%)	0/1 (0%)	0/1 (0%)
WT (n=39)	33/37 (89%)	29/35 (83%)	20/38 (53%)	31/33 (94%)
Unknown (n=141)	112/139 (81%)	104/138 (75%)	81/133 (61%)	118/133 (89%)



n = 1546 GIST

Am J Surg Pathol. 2008 Feb;32(2):210-8.

Adv Anat Pathol. 2010 May;17(3):222-32

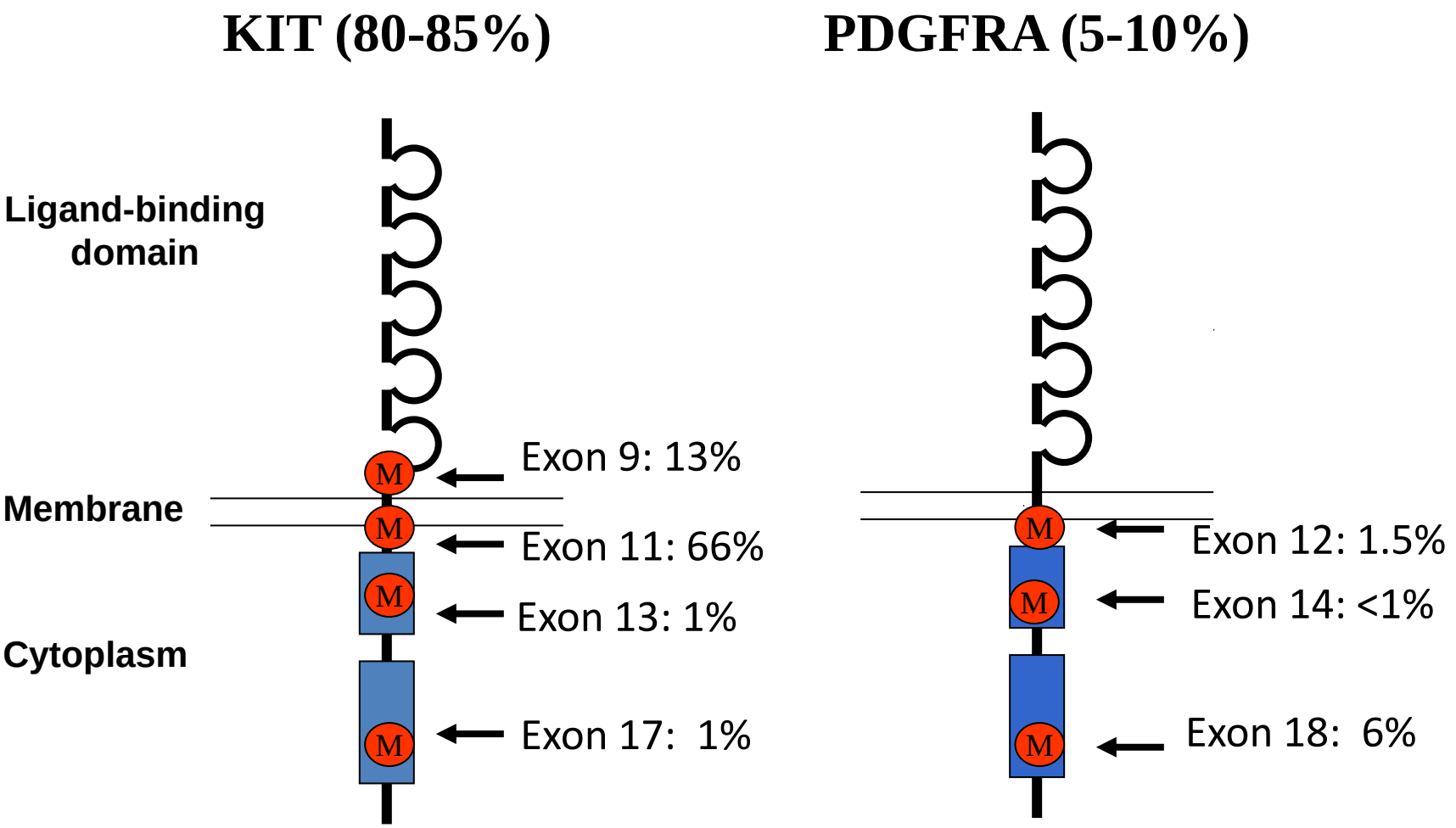
Mitotic index as an indicator for malignancy risk in GIST

Table 1 Risk Stratification of Primary GIST by Mitotic Index, Size, and Site*

Tumor Parameters		Risk of Progressive Disease* (%)			
Mitotic Index	Size	Gastric	Duodenum	Jejunum/Ileum	Rectum
≤ 5 per 50 hpf	≤ 2 cm	None (0%)	None (0%)	None (0%)	None (0%)
≤ 5 per 50 hpf	> 2 ≤ 5 cm	Very low (1.9%)	Low (4.3%)	Low (8.3%)	Low (8.5%)
≤ 5 per 50 hpf	> 5 ≤ 10 cm	Low (3.6%)	Moderate (24%)	(Insuff. data)	(Insuff. data)
≤ 5 per 50 hpf	> 10 cm	Moderate (10%)	High (52%)	High (34%)	High (57%)
> 5 per 50 hpf	≤ 2 cm	None†	High†	(Insuff. data)	High (54%)
> 5 per 50 hpf	> 2 ≤ 5 cm	Moderate (16%)	High (73%)	High (50%)	High (52%)
> 5 per 50 hpf	> 5 ≤ 10 cm	High (55%)	High (85%)	(Insuff. data)	(Insuff. data)
> 5 per 50 hpf	> 10 cm	High (86%)	High (90%)	High (86%)	High (71%)

J Natl Compr Canc Netw. 2007 Jul;5 Suppl 2:S1-29

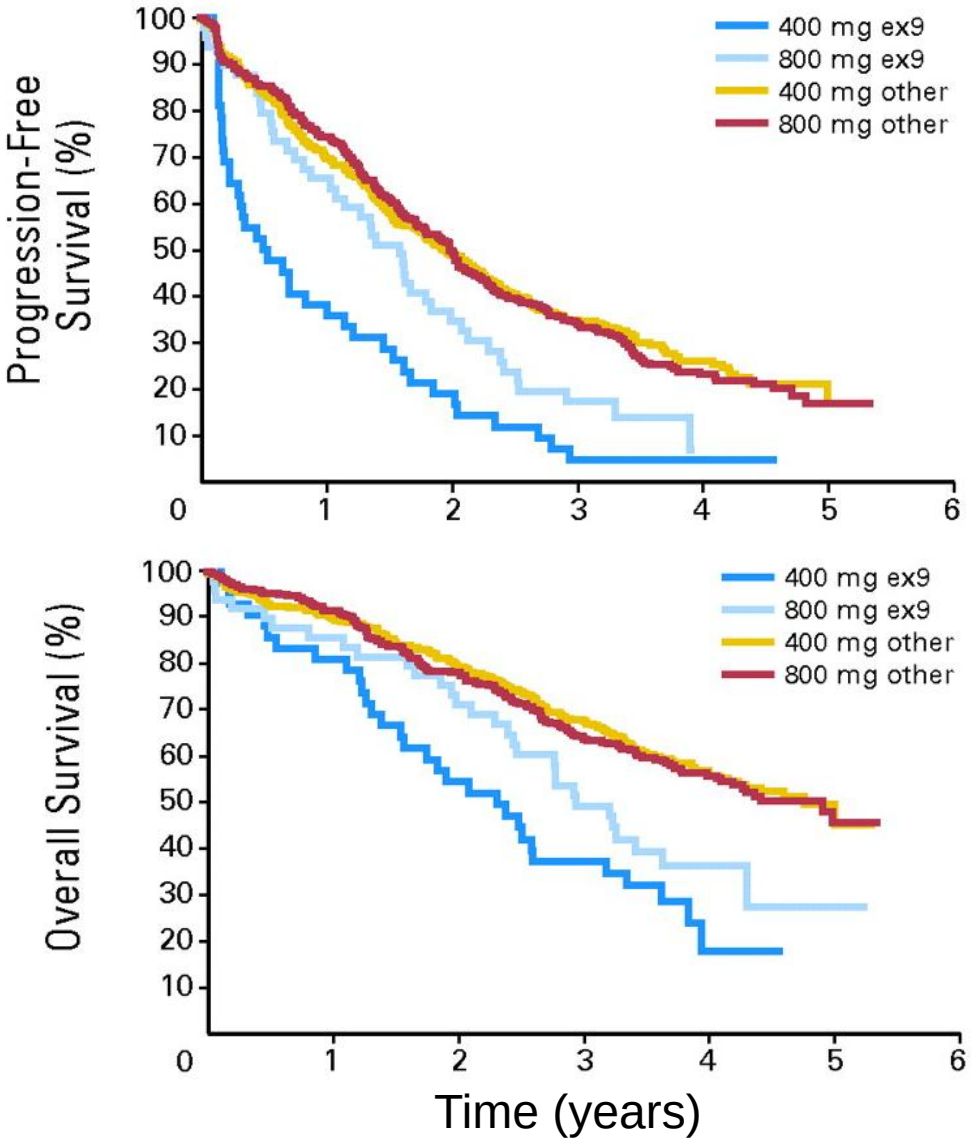
Genetic markers in GIST



Kinase genotype and response to imatinib

	EORTC phase I/II (n=37)	B2222 phase II (n=127)	EORTC AustralAsian phase III (n=363)	SWOG S0033 /CALGB 150105 phase III(n=397)	Overall Average
Objective response					
KIT exon 11	83% (n=24)	83% (n=85)	70% (n=248)	64% (n=283)	69% (n=640)
KIT exon 9	25% (n=4)	48% (n=23)	35% (n=58)	38% (n=32)	38% (n=117)
No mutation	33% (n=6)	0% (n=9)	25% (n=52)	37% (n=67)	30% (n=128)
Progressive disease					
KIT exon 11	4%	5%	3%	NR	4%
KIT exon 9	0%	17%	17%	NR	16%
No mutation	33%	56%	19%	NR	25%

Kinase genotype and optimal imatinib dose



J Clin Oncol. 2010 Mar 1;28(7):1247-53.

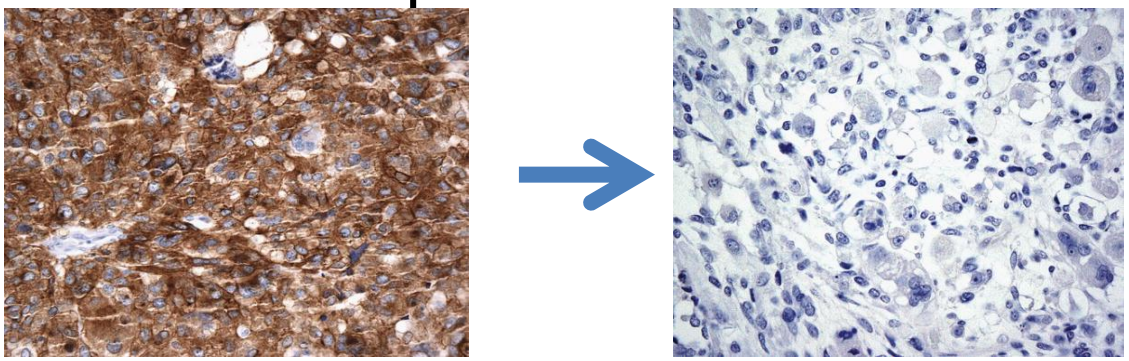
Primary resistance to imatinib

- 10-20% of GIST patients

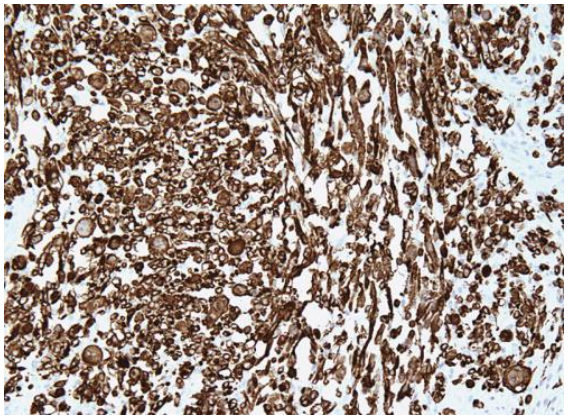
- Relates to KIT/PDGFRA mutational profile
  - A subset of *KIT* exon 9 cases
  - *PDGFRA* exon 18 D842V mutant
  - Majority of wild-type GISTs:

Dynamic nature of GIST markers under imatinib therapy

- Immunomarkers
  - Loss of KIT expression



  - Expression of new markers (i.e. desmin)



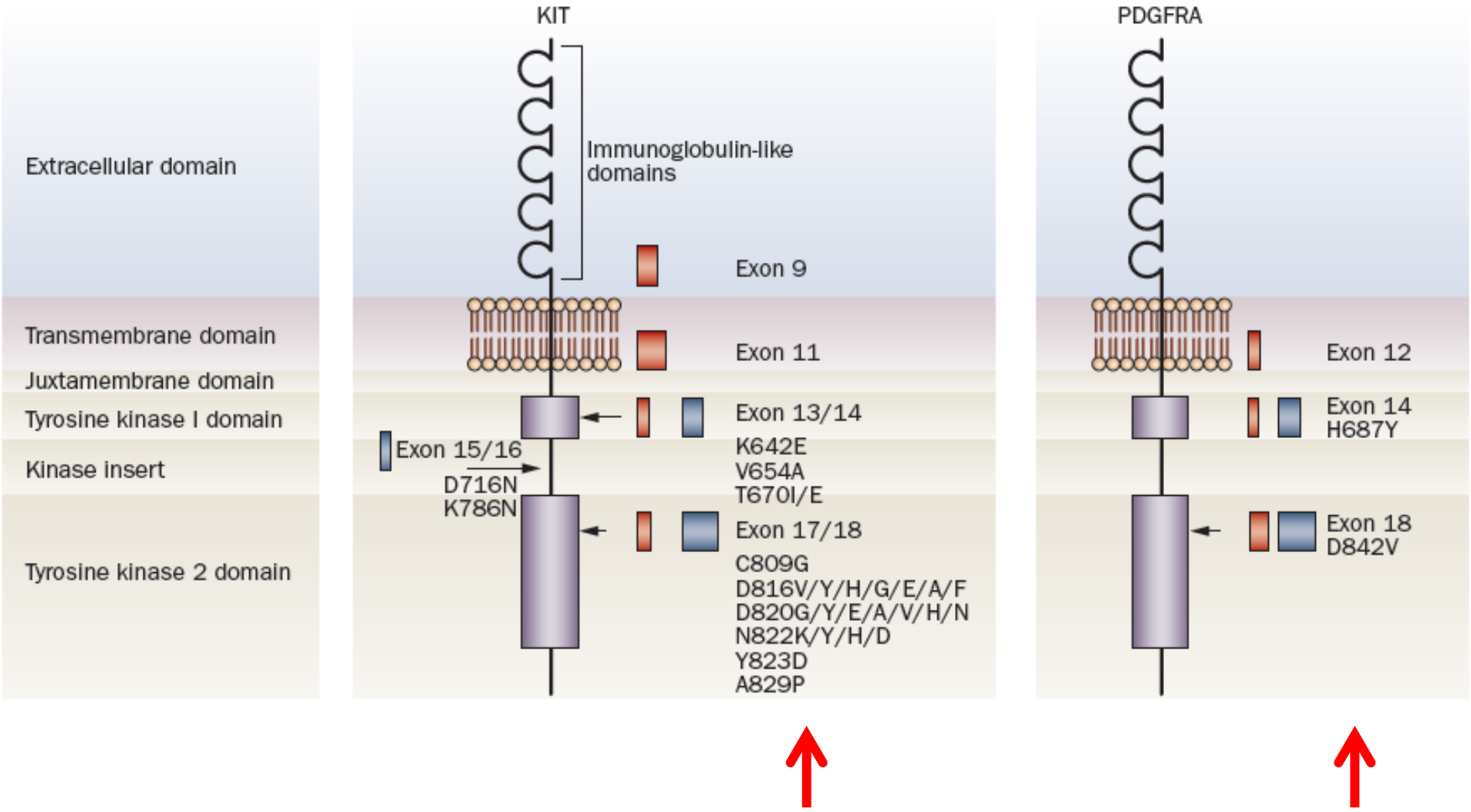
Am J Surg Pathol. 2009 Feb;33(2):218-26.

Secondary resistance

Mechanism of secondary resistance

- KIT-dependent
  - **New KIT/PDGFR mutations**
    - Emergence of multi-clonal resistance mutation (acquired and/or intrinsically hard-wired)
  - Genetic amplification of KIT/PDGFRA
- KIT-independence*
  - Activation of downstream pathway(s)
  - Activation of other receptor tyrosine kinase (i.e. AXL)

Secondary imatinib resistance mutations



Nat Rev Clin Oncol. 2011 Mar;8(3):161-70.

Intra-tumoral heterogeneity in resistance mechanisms

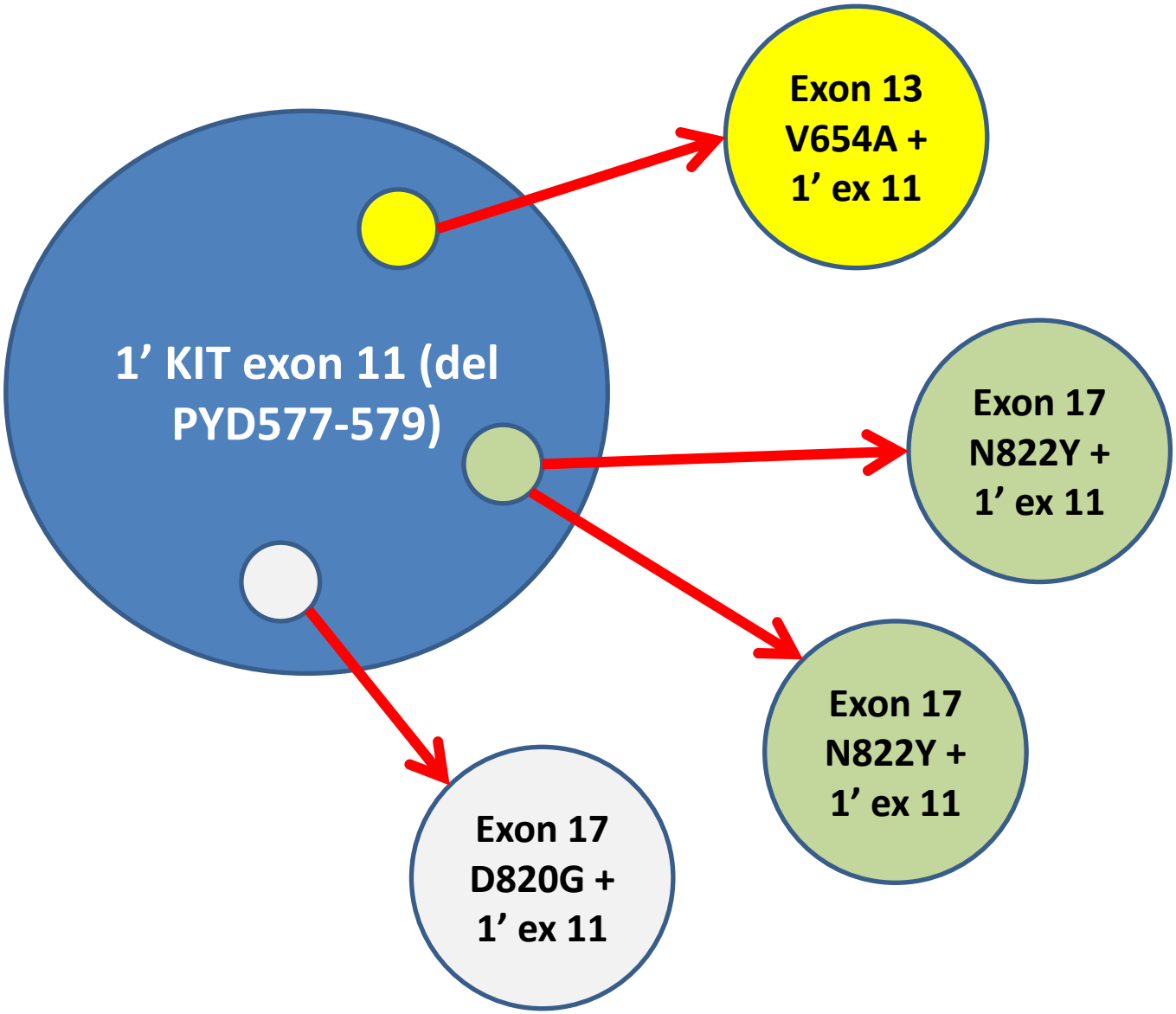
- The secondary mutations clustered in the ATP binding pocket and kinase catalytic regions of KIT.

- 9/11 (83%), had secondary drug-resistant KIT mutations, including six (67%) with two to five different secondary mutations in separate metastases

- These secondary resistance mutation show varying *in vitro* sensitivity to second generation RTK inhibitors (but none works against all secondary resistance mutations)

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

Heterogeneity in secondary imatinib-resistant mutations



Alternative targets in GIST treatment

Drug name	Company	Phase of development
Drugs that inhibit HSP90 resulting in the proteasomal degradation of oncogenic client proteins		
IPI-504 (retaspimycin)	Infinity Pharmaceuticals in conjunction with MedImmune (Astra Zeneca)	Phase III trial was suspended due to safety concerns
STA-9090	Synta Pharmaceuticals Corp.	Phase II
BIIB021	Biogen Idec	Phase II
BIIB028	Biogen Idec	Phase I
SNX-5422	Serenex	Phase I
XL888	Exelixis	Phase I
AUY922	Novartis	Phase I
AT13387	Astex Therapeutics	Phase I
Drug that inhibits the targeted proteolysis via the 26S proteasome		
Bortezomib (Velcade)	Millenium Pharmaceuticals	Currently in combination trials
Drugs that inhibit mTOR		
Everolimus (RAD001)	Novartis	Phase II
Ridaforolimus (Deforolimus, AP23573)	Ariad Pharmaceuticals	Phase III
Drug that inhibits PI3K and mTOR		
PF-04691502	Pfizer Oncology	Phase I
Drugs that deacetylate by histone deacetylase inhibitors, leading to an accumulation of both hyperacetylated histones and transcription factors		
Vorinostat (Zolinza, SAHA)	Patheon, Inc. (Merck)	Phase I
CUDC101	Curis, Inc.	Phase I
Panobinostat	Novartis	Phase I

Nat Rev Clin Oncol. 2011 Mar;8(3):161-70.

Targeting tumor microenvironment in GIST