How does biology guide the treatment of sarcoma? GIST

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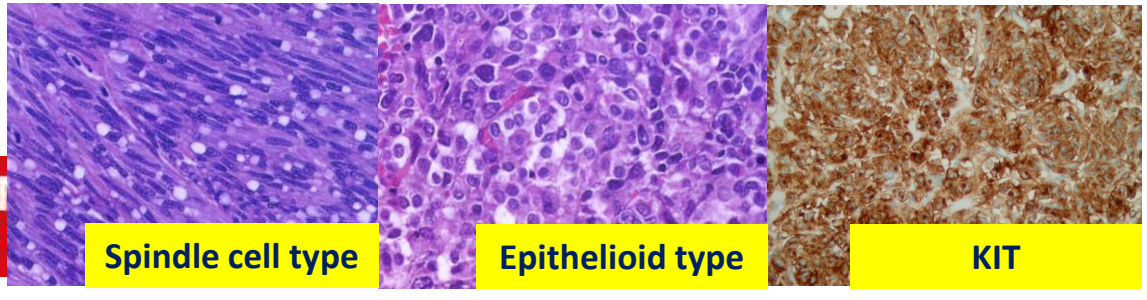
SINGAPORE 2015 ESMO ASIA 18-21 DECEMBER SINGAPORE

COI Disclosure

- Research grants from Novartis and Bayer
- Honoraria from Pfizer, Bayer and Novartis

GIST is potentially malignant mesenchymal tumor in GI

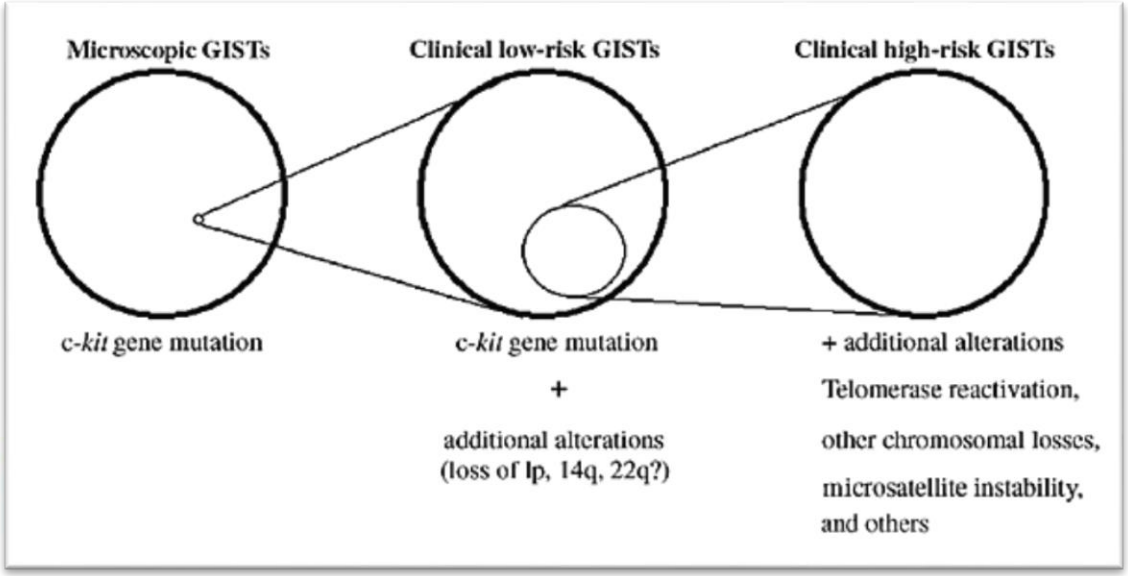
- Spindle cell (70～75%), epithelioid cell (20%) or mixed (5～10%)
- Immunohistochemically positive for KIT (CD117; 95%), DOG1 (95%), CD34(70%)
- Proliferation is mainly driven by either *KIT* or *PDGFRA* mutations (80% or 10%, respectively), and some (10%) may lack these mutations.
- Surgery without lymph node dissection is a mainstay for permanent cure.

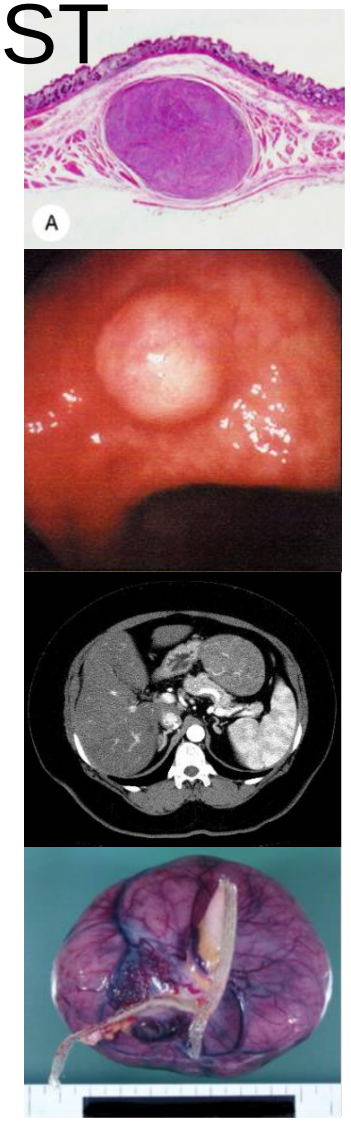


Frequency of clinical GIST & microGIST

- ✓microGIST 1~3/10
- ✓Found at health examination ~1/1,000
- ✓Clinical GIST ~1/100,000
- ✓*KIT* mutations were seen in most microGISTs
- ✓Gastric GISTs less than 2 cm without high risk features may not always be indicated for surgery

(NCCN, ESMO guidelines)





Hedenbro JL. Surg Endosc 1991

Kawanowa K. Hum Pathol 2006

Corless CL. Am J Pathol 2002

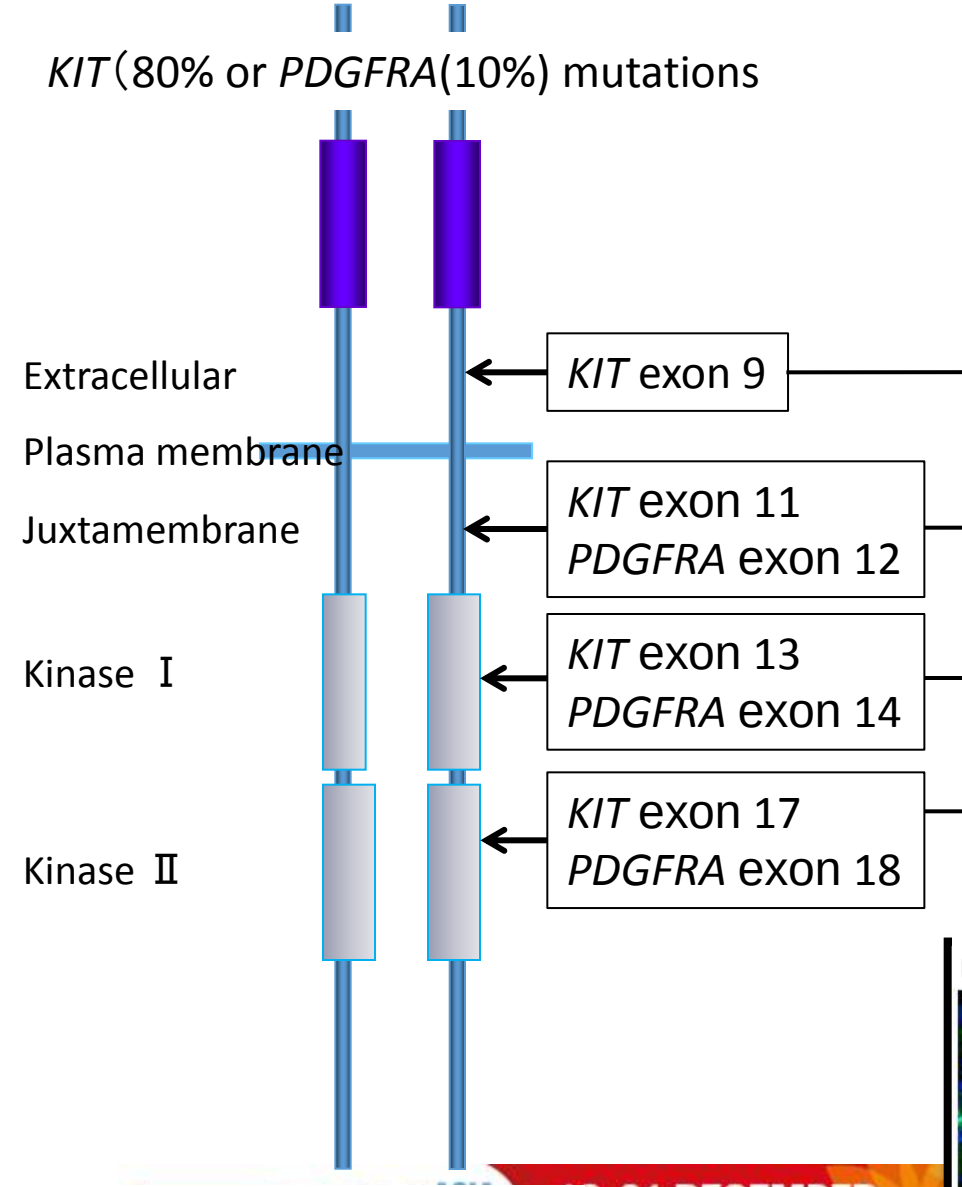
Rossi S. Am J Surg Pathol. 2011

Nishida T. Gastric Cancer 2008

Mutations in GISTs and KIT activation

KIT（80% or *PDGFRA*(10%) mutations

GIST without mutations in *KIT* and *PDGFRA*
(wild type GIST：10%)：imatinib-resistant



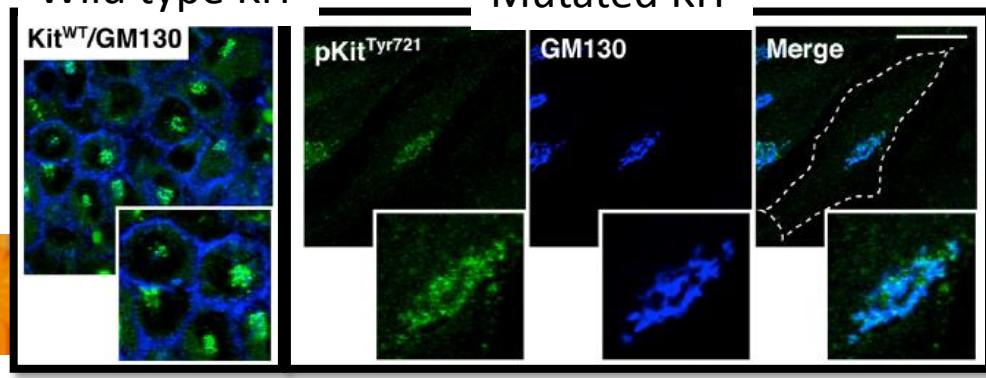
KIT exon 9 — Less sensitive to imatinib

KIT exon 11
PDGFRA exon 12 — Sensitive to imatinib

KIT exon 13
PDGFRA exon 14 — Sensitive to imatinib

KIT exon 17
PDGFRA exon 18 — Some mutations (eg. D842V) are resistant to imatinib

Wild type KIT　　Mutated KIT



Corless C Nat Rev Cancer. 2011
Nishida T. Gastric Cancer 2015

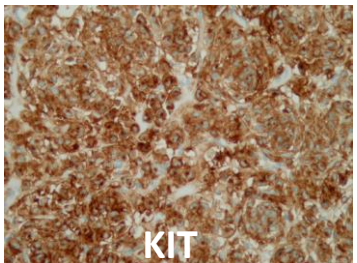
Wild-type GIST and mutations

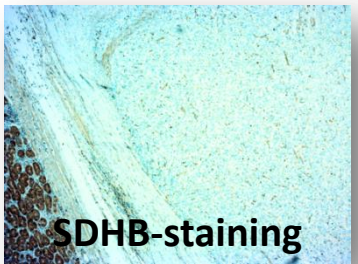
Wild type GIST (10%) is GIST without mutations in the *KIT* and *PDGFRA* genes. Wild type GIST usually express the KIT protein and are KIT-positive in immunohistochemistry.

Alteration	Estimated Frequency	**Imatinib activity**	References
NF1 mutation (NF type I)	1~2%	**insensitive**	Andersson et al. *Am J Surg Pathol*. 2005 Nishida T. J Gastroenterol 2015
BRAF mutation	rare	**prob. insensitive**	Agaram et al. *Genes Chrom Cancer*. 2008 Agaimy et al. J Clin Pathol 2009
KRAS or *NRAS* mutation	rare	**prob. insensitive**	Heinrich and Corless, unpublished
SDHA, SDHB, SDHC or *SDHD* mutation (Carney-Stratakis)	~1%	**prob. insensitive**	SDHB negative in IH Janeway et al. *PNAS*. 2011 Pantaleo et al. J Natl Cancer Inst. 2011
Loss of SDHB expression* (probably post-transcriptional)	<1%	**prob. insensitive**	SDHB negative in IH Janeway et al. *PNAS*. 2011

Carney-Stratakis syndrome: association of GIST and paraganglioma From Christopher Corless, Oregon Health & Science University

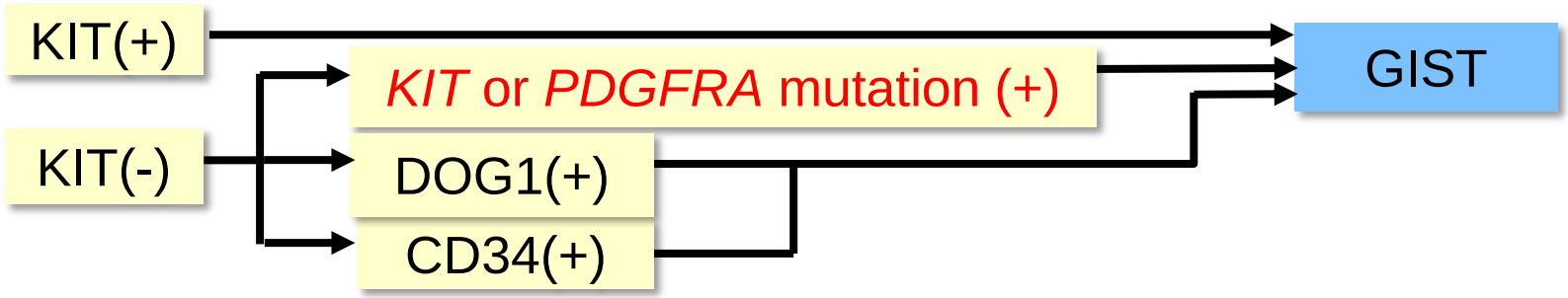
*: Carney triad: GIST, paraganglioma, pulmonary chondroma



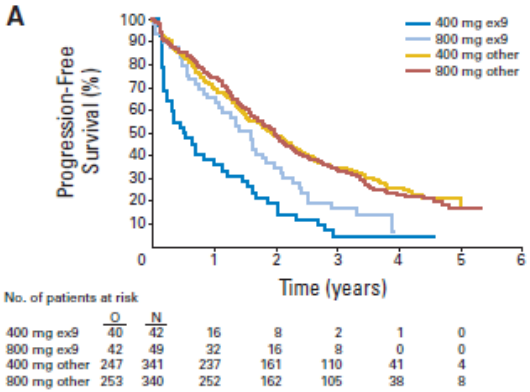


Clinical importance of mutation research in GIST

- Diagnosis of GIST, esp., KIT-negative GIST



- Biomarker of TKI therapy



MetaGIST group J Clin Oncol 2010

- Potential prognostic factor (controversial)

Corless CL. J Clin Oncol 2014
Joensuu H. J Clin Oncol 2015
Wozniak A, Clin Cancer Res 2014
Yan L. Sci Rep 2015

Prognostic factors after complete resection

- Mitosis (/50HPF) or (/5mm^2)
- Tumor Size (cm)
- Location (Gastric vs non-gastric)
- Tumor Rupture
- Genotype (controversial)

High risk GISTs may require multidisciplinary treatment

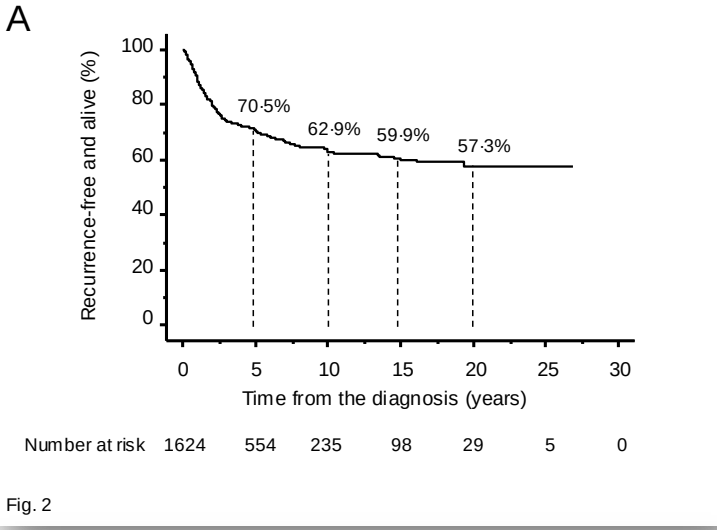
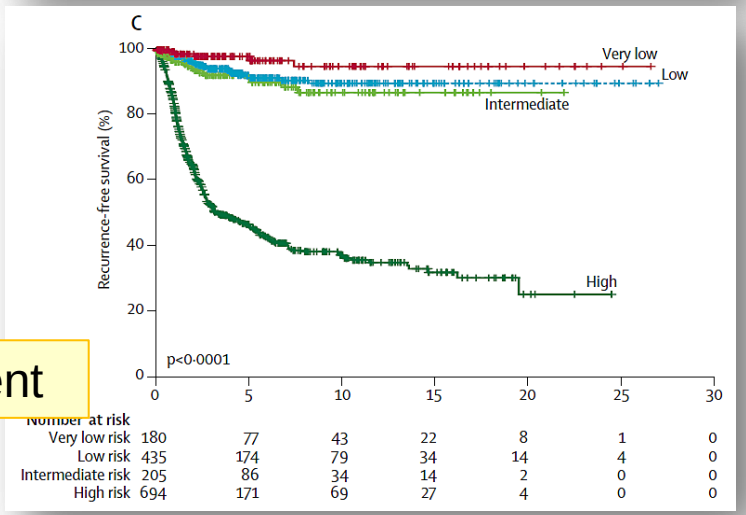


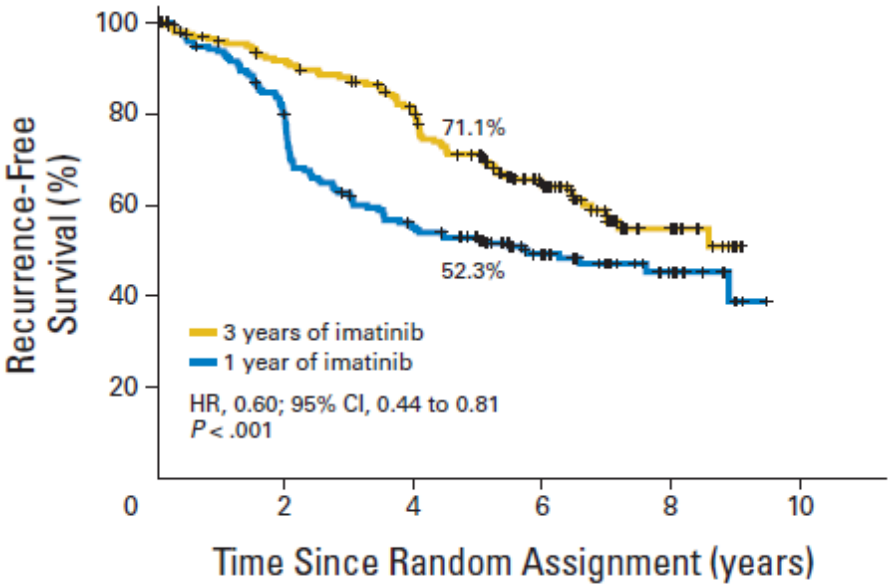
Fig. 2



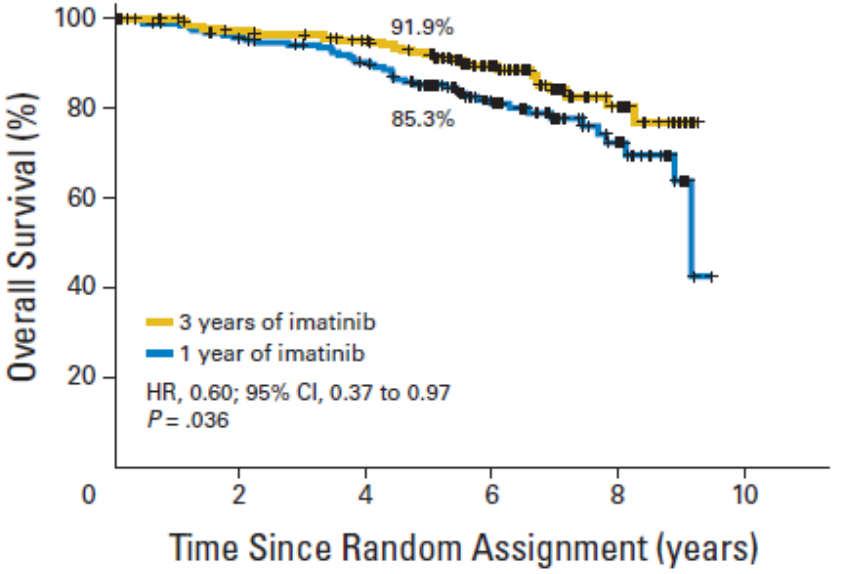
Joenssu H. Lancet Oncol 2011
Rutkowski P. Eur J Surg Oncol. 2011
Yanagimoto Y. Gastric Cancer 2014

Adjuvant therapy for high risk GIST patients
SSGXVIII RFS & OS（ITT）

RFS



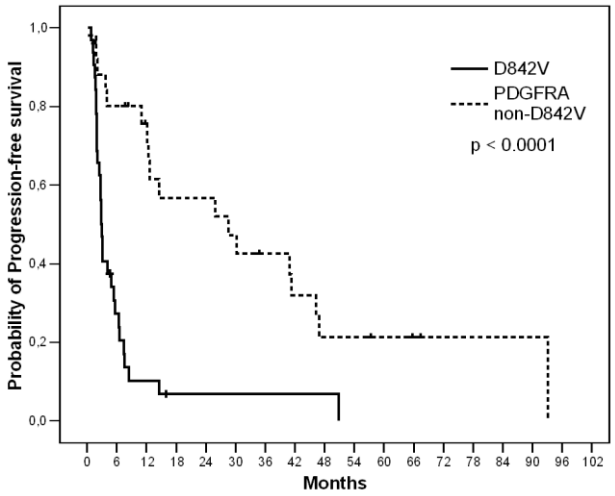
OS



Joensuu H. JAMA. 2012
Joensuu H. J Clin Oncol 2015

Recommendations in Adjuvant Therapy

- Indication：High risk GIST
- Duration: 3 years (at least)
- Genotype is important
  - *PDGFRA D842V* is resistant to imatinib
  - Wild-type GISTs are insensitive to imatinib
  - *KIT* exon 9 mutation may require higher dose
- For recurrences：
  - During adjuvant：sunitinib
  - After adjuvant：re-challenge of imatinib



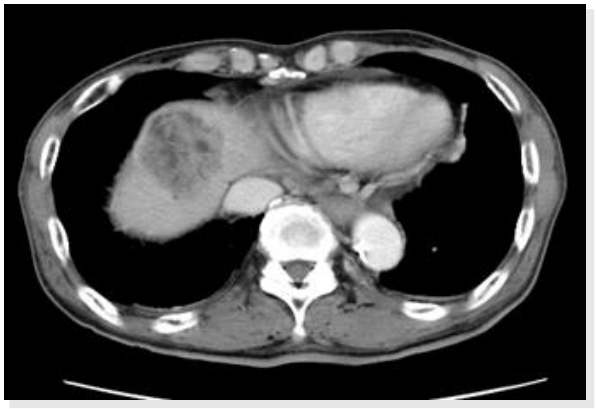
Cassier PA *et al., Clin Cancer Res*., 2012

	Best Response after IM Rechallenge			RR (%)
Responses at stop IM	CR or PR	SD	PD	
CR	15	4	0	79
PR	12	9	2	52
SD	4	5	0	44

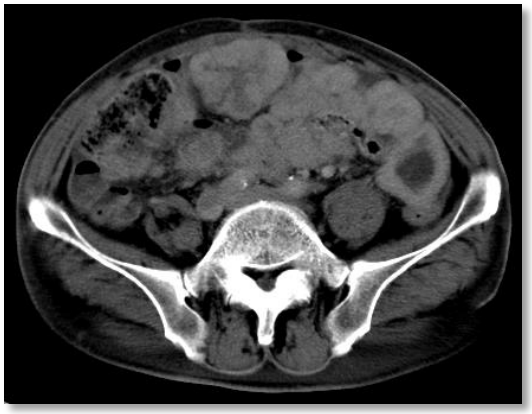
Patrikidou A et al. Ann Oncol 2013

Recurrence and Metastasis of GIST

Initial recurrences and metastasis of GIST mostly occurred in the abdominal cavity

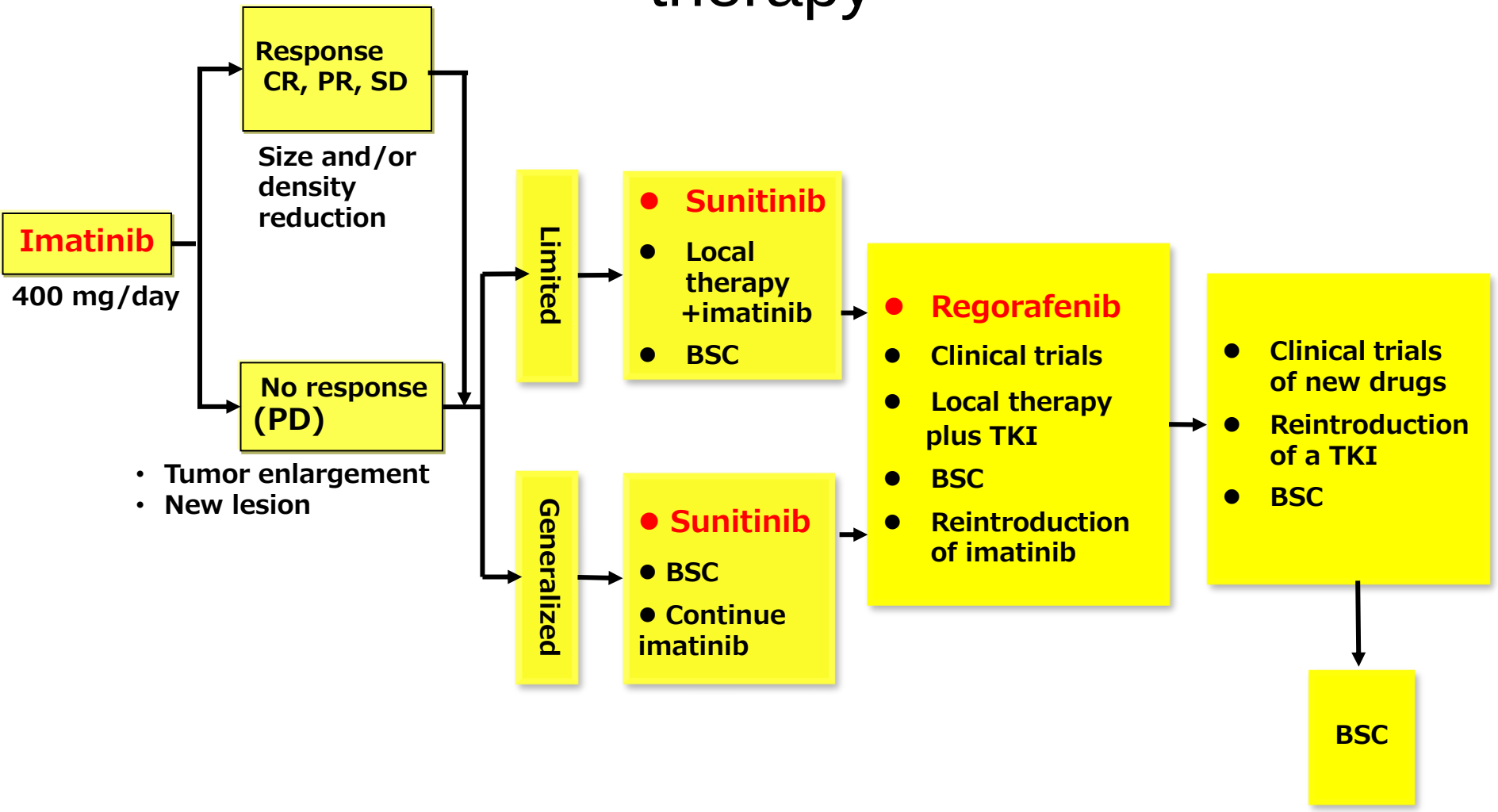


Liver metastasis
（usually multiple）



Peritoneal recurrence
（multiple）

Treatment of metastatic/recurrent GIST is medical therapy

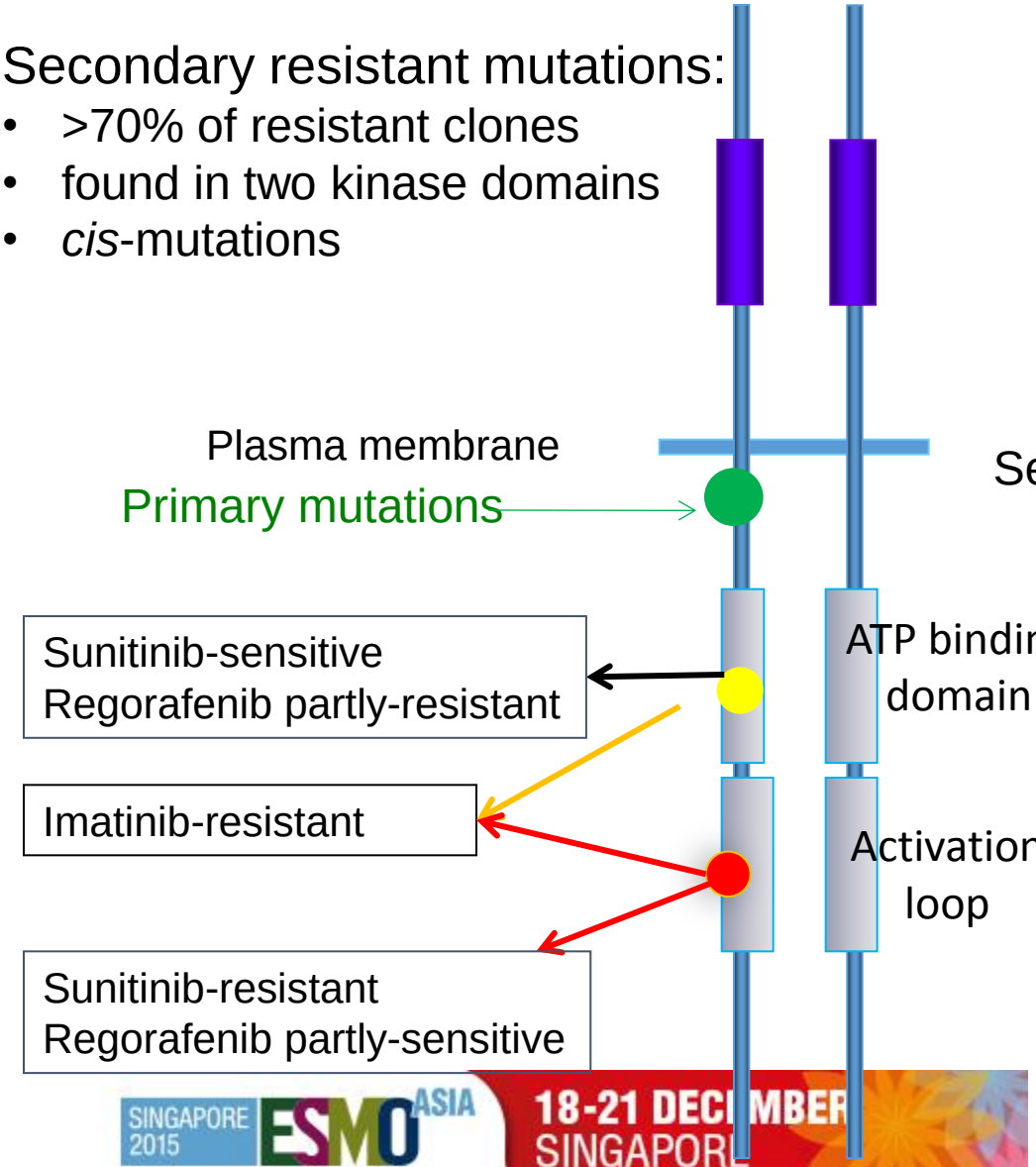


Modified with
Japanese GIST Clinical Practice Guideline ver.3
NCCN guidelines and
ESMO Guidelines

Acquired resistant mutations in kinase domains are major causes of imatinib-resistance

Secondary resistant mutations:

- >70% of resistant clones
- found in two kinase domains
- *cis*-mutations



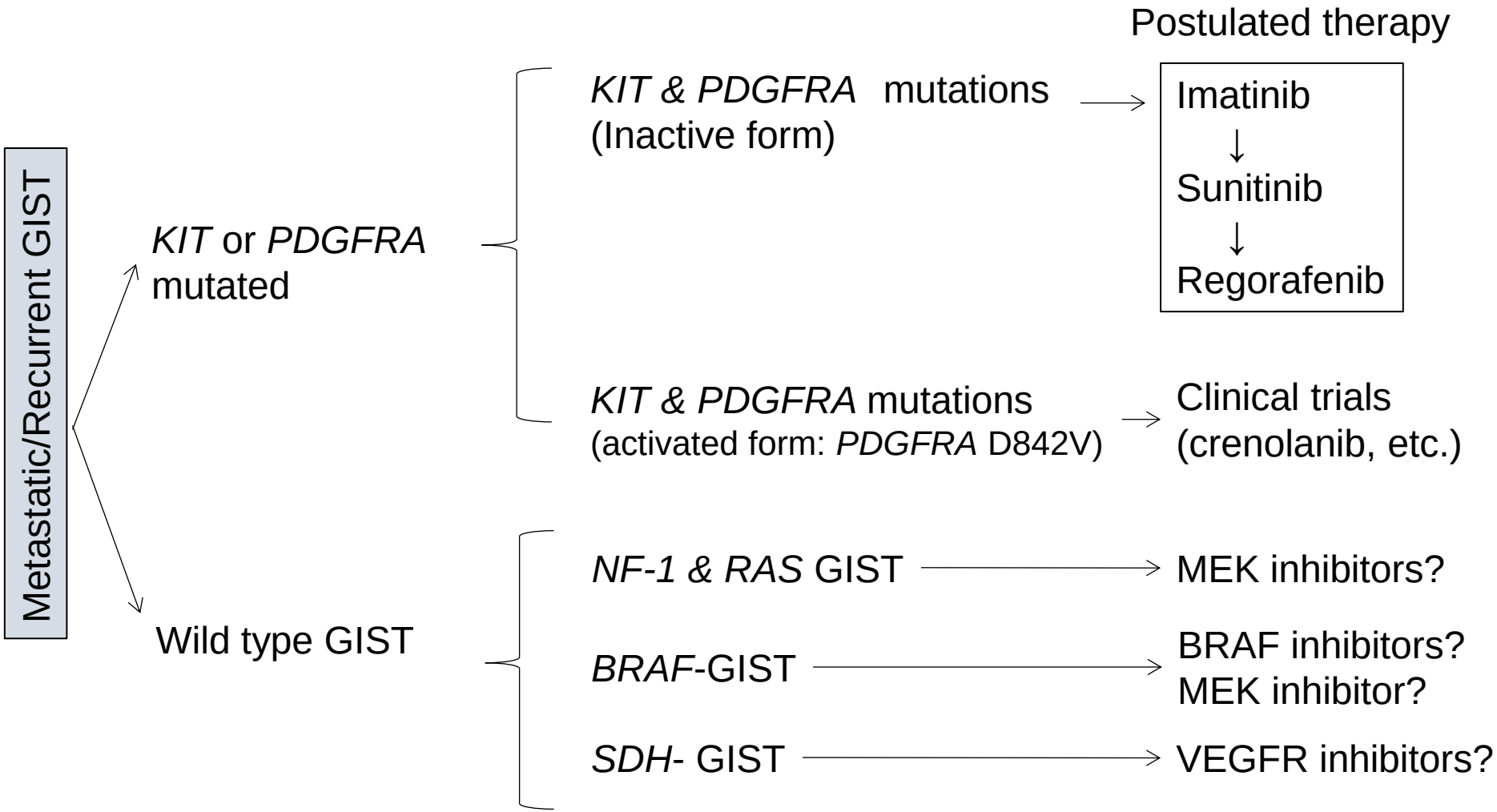
Resistant
Intermediate
Sentitive

Drug sensitivity

Secondary mutations	IM	SU	Reg
V654A	■	■	■
T670I	■	■	■
D816A/G/H/V	■	■	■
D820A/E/G/Y	■	■	■
N822H/K	■	■	■
Y823D	■	■	■
A829P	■	■	□

George S JCO 2012
Corless C. Nat Rev Cancer 2011
Nishida T. Gastric Cancer 2015 Epub

Perspectives of genotype-guided treatment strategy for metastatic/recurrent GIST



Nishida T. Expert Opin Pharma 2014

SUMMARY

- GIST is a potentially malignant tumor in GI and is frequently accompanied with *KIT* or *PDGFRA* mutations.
- Genotyping is important in the diagnosis and treatment with target agents.
- Target therapy with imatinib, sunitinib or regorafenib is indicated for metastatic/recurrent GIST, although permanent cure could be obtained only by R0 surgery.
- In future, genotype-guided treatment strategy would be preferable for metastatic/recurrent GIST.

Thank you for kind attention

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