# GIST ανωτέρου πεπτικού: Διάγνωση και αντιμετώπιση

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15η Πανελλήνια Εκπαιδευτική Συνάντηση ΕΛΙΓΑΣΤ

"Εξελίξεις στη Γαστρεντερολογία και Ηπατολογία"

Παρασκευή 6 Μαρτίου 2020, Ξενοδοχείο Divani Caravel, Αθήνα

# Επιδημιολογία

- Προέρχονται από τα διάμεσα κύτταρα του  Cajal
- Σπάνιοι όγκοι
- Επίπτωση 1/100000/έτος
- Ελαφρά συχνότεροι στους άνδρες
- 60-65 έτη
- Παιδιατρικοί GIST: διαφορετική κλινική οντότητα

-υπεροχή στα θήλεα,

-απουσία μεταλλάξεων στα KIT/platelet-derived growth factor alpha (PDGFRA),

-succinate dehydrogenase (SDH) enzyme complex,

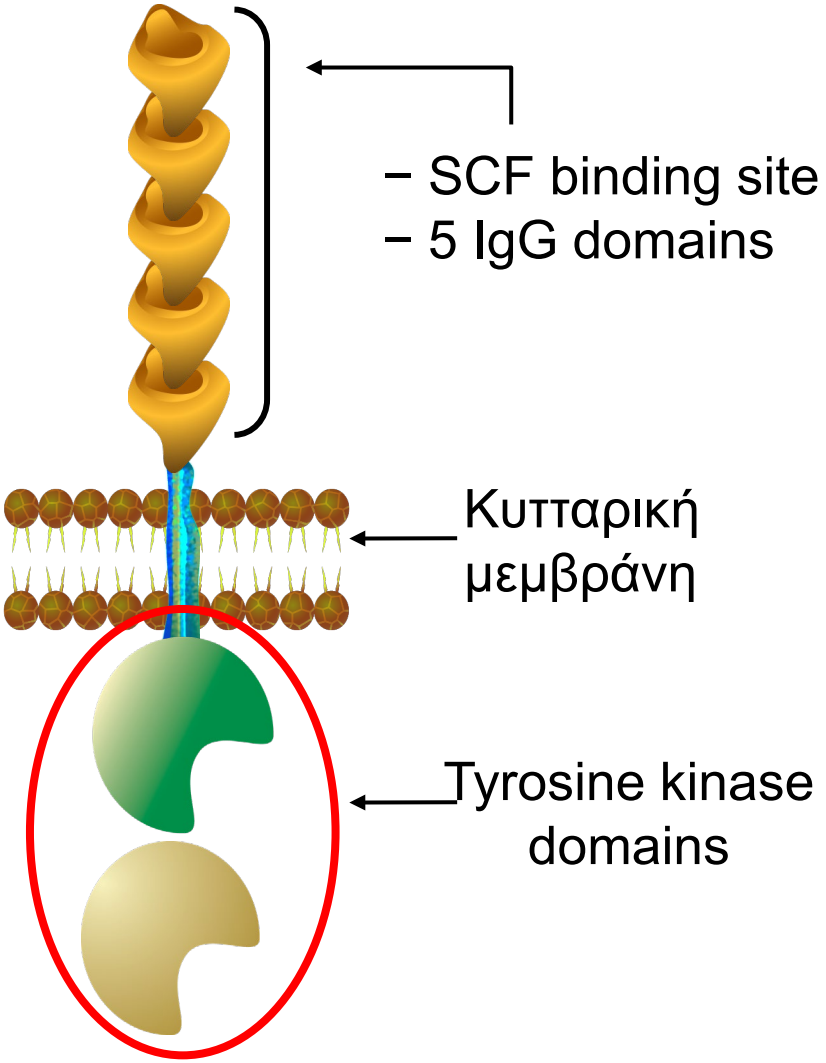
-πολλαπλές εστίες στο στόμαχο

-πιθανές λεμφαδενικές μεταστάσεις

-συσχέτιση με σύνδρομα: τριάδα Carney, Carney-Stratakis, NF1

# GIST

- KIT
  - Διαμεμβρανικός υποδοχέας τυροσινικής κινάσης
  - Κωδικοποίηση από το πρωτοογκογονίδιο KIT
  - Δομική συγγένεια
    - Platelet-derived growth factor receptor (PDGFR)
    - Bcr-Abl



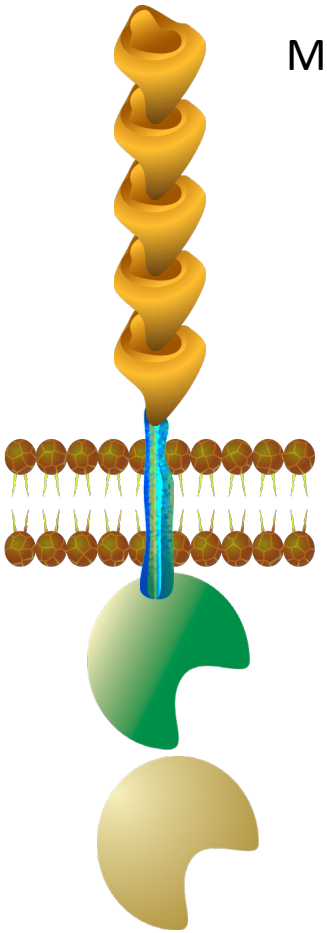

Taylor and Metcalfe. Hematol Oncol Clin North Am 2000

GIST

Μεταλλάξεις KIT και PDGFRA
Καμία μετάλλαξη: ~ 10%

## KIT

Μετάλλαξη: 80%



Exon 9 (10%)

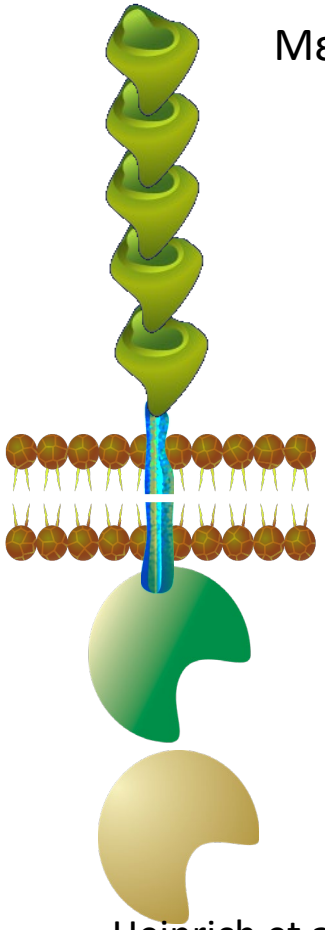
Exon 11 (75%)

Exon 13 (1%)

Exon 17 (1%)

## PDGFRA

Μετάλλαξη: 5-8%



Κυτταρική μεμβράνη

Exon 12 (1%)

Exon 14 (<1%)

Κυτταρόπλασμα

Exon 18 (6%)

Heinrich et al. Hum Pathol. 2002
Corless et al. Proc Am Assoc Cancer Res. 2003

# GIST

- Διάγνωση
  - Ενδοσκόπηση
  - Ενδοσκοπικό υπερηχογράφημα (EUS)
  - Αξονική τομογραφία, μαγνητική τομογραφία (CT, MRI)
  - Τομογραφία εκπομπής ποζιτρονίων (PET-CT)
  - Ιστολογική εξέταση

# GIST
# Ενδοσκόπηση

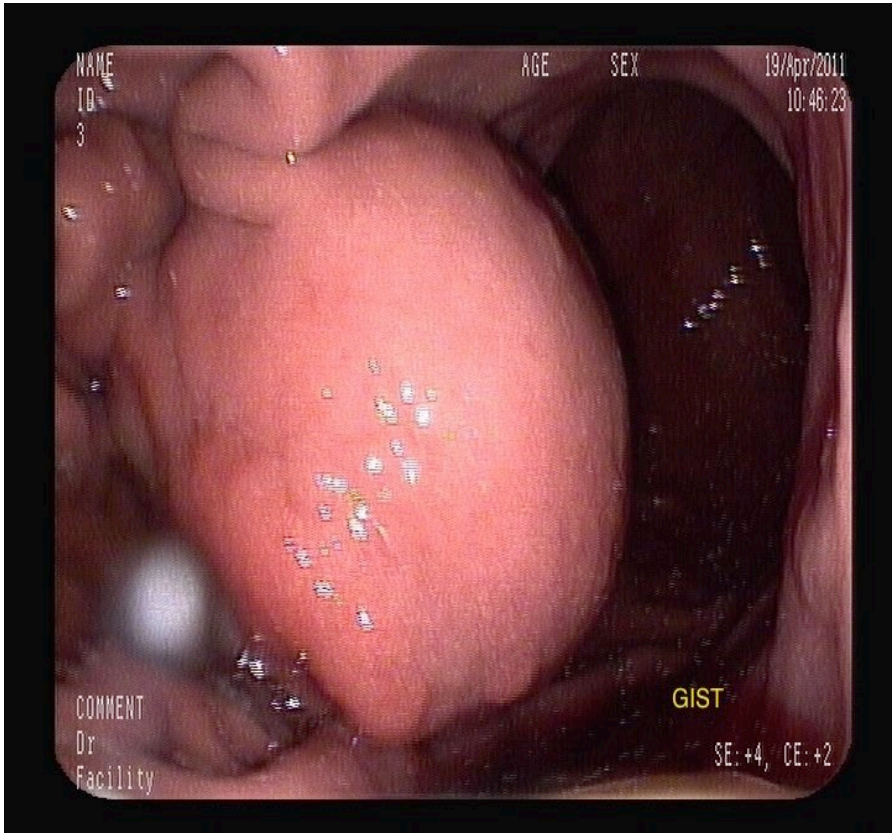
- Ενδοσκόπηση
  - Υποεπιθηλιακοί όγκοι: 1/300 ενδοσκοπήσεις
  - Στόμαχος (60-70%), παχύ έντερο (5%), οισοφάγος (< 5%)
  - Ομαλά όρια, ενδοαυλική προβολή, φυσιολογικός βλεννογόνος
  - Κεντρική εξέλκωση (σπανίως)
  - Πλειοψηφία < 2 cm
- Λήψη βιοψιών
  - Λαβίδα βιοψίας: Συνήθως αρνητικές
  - EUS-FNA
    - Μη ακριβής προσδιορισμός μιτωτικού δείκτη

# GIST
# EUS

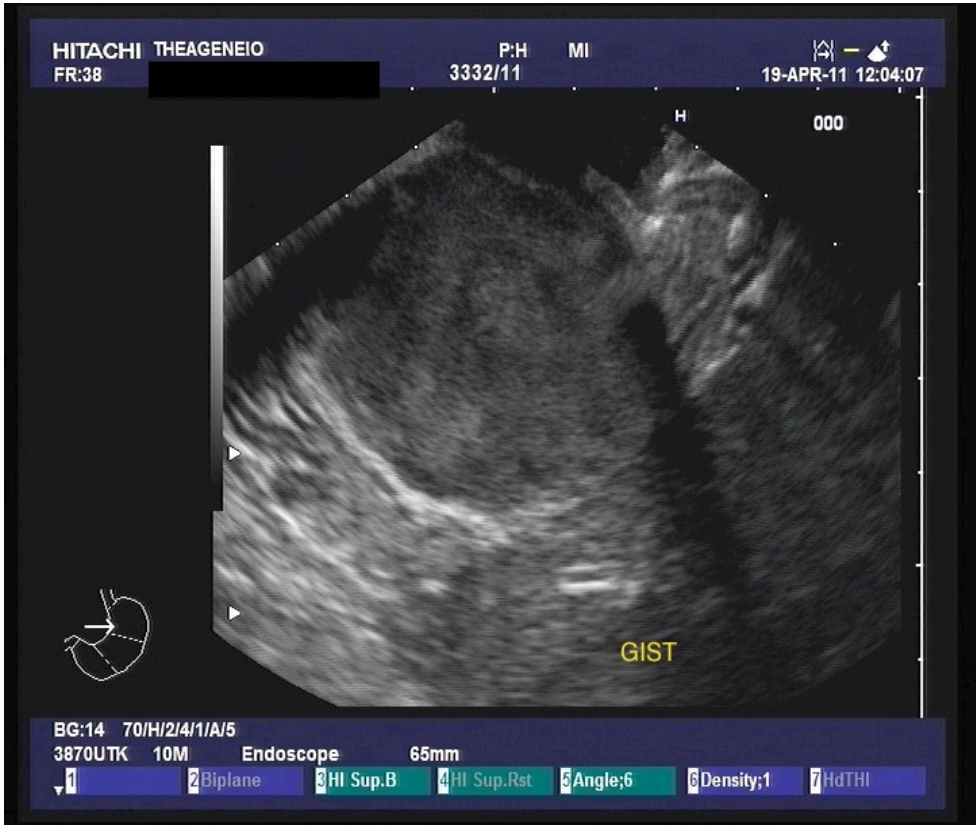
- Μέτρηση διαστάσεων
- Στιβάδα προέλευσης
- Υποηχοϊκή, ομοιογενής αλλοίωση
- Σημεία κακοήθειας:
  - > 3 cm, ανώμαλα όρια
  - Υπερηχογενείς εστίες, κυστικές αλλοιώσεις, ανομοιογένεια, εξέλκωση
- Λήψη κυτταρικού υλικού / βιοψίας

# Διάγνωση GIST

Ενδοσκόπηση




EUS

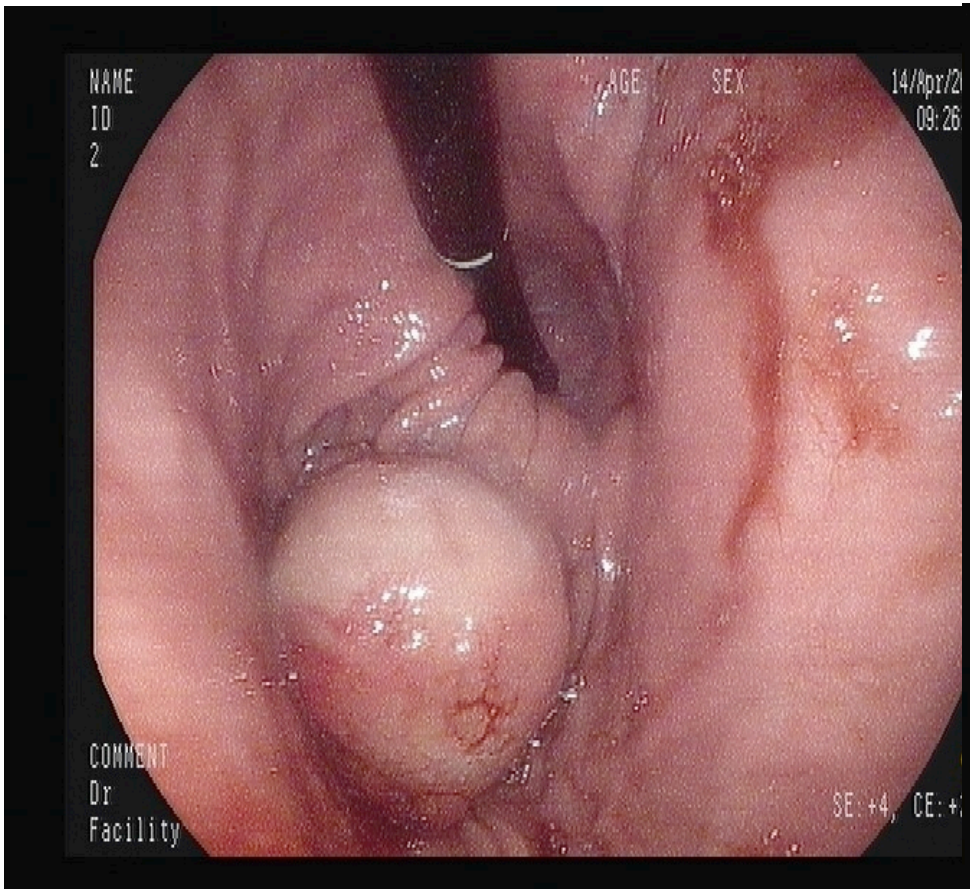



Ενδοσκοπικό Εργαστήριο Α.Ν.Θ. Θεαγένειο

# Διάγνωση GIST

Ενδοσκόπηση

EUS




GIST: Proposed guidelines for assessing the malignant potential

A. Gastric GI stromal tumors

B. Small-intestine GI stromal tumors

**A**

| Tumor size | Mitotic rate | Predicted biologic behavior |
|---|---|---|
| ≤2 cm | ≤5 mitoses/50 HPF<br>>5 mitoses/50 HPF | Metastasis rate or tumor-related mortality: 0 metastasis rate or tumor-related mortality: <4% |
| >2 cm ≤5 cm | >5 mitoses/50 HPF | Metastasis rate or tumor-related mortality: 16% |
| >2 cm ≤10 cm | ≤5 mitoses/50 HPF | Metastasis rate or tumor-related mortality: <4% |
| >5 cm ≤10 cm | >5 mitoses/50 HPF | Metastasis rate or tumor-related mortality: 55% |
| >10 cm | ≤5 mitoses/50 HPF | Metastasis rate or tumor-related mortality: 12% |
| >10 cm | >5 mitoses/50 HPF | Metastasis rate or tumor-related mortality: 86% |

**B**

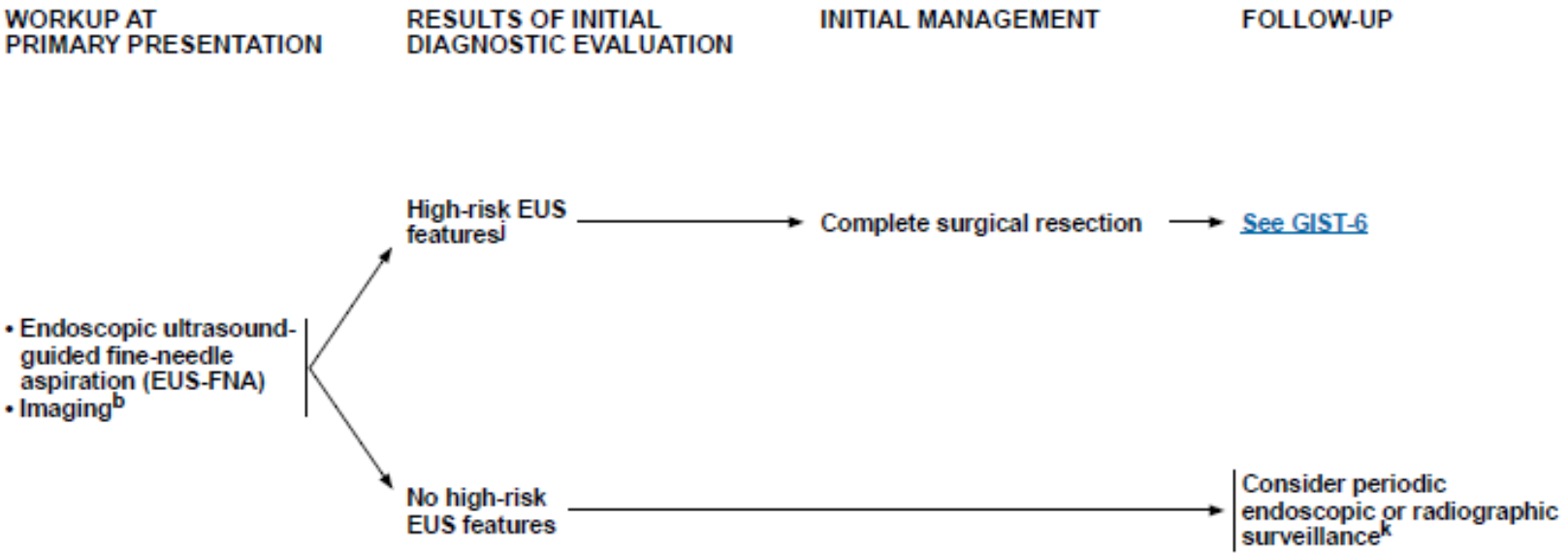
| Tumor size | Mitotic rate | Predicted biologic behavior |
|---|---|---|
| ≤2 cm | ≤5 mitoses/50 HPF | Metastasis rate or tumor-related mortality: 0 |
| >2 cm ≤5 cm | <5 mitoses/50 HPF | Metastasis rate or tumor-related mortality: 2% |
| >2 cm ≤5 cm | >5 mitoses/50 HPF | Metastasis rate or tumor-related mortality: 73% |
| >5 cm ≤10 cm | ≤5 mitoses/50 HPF | Metastasis rate or tumor-related mortality: 25% |
| >5 cm ≤10 cm | >5 mitoses/50 HPF | Metastasis rate or tumor-related mortality: 85% |
| >10 cm | >5 mitoses/50 HPF | Metastasis rate or tumor-related mortality: 50%-90% |

Von Mehren et al. NCCN 2018

# GIST
# Βιοψία

- EUS-FNA > διαδερμική βιοψία (αιμορραγία, διασπορά κυττάρων)
- Αναγκαιότητα: Χαρακτηριστικά όγκου, έκταση νόσου
- Επιβεβαίωση διάγνωσης (απαραίτητη πριν τη χορήγηση θεραπείας)
- Προσδιορισμός γενετικών μεταλλάξεων
- Μεταστατική νόσος: CT κατευθυνόμενη βιοψία

## APPROACH TO PATIENTS WITH VERY SMALL GASTRIC GISTS (<2 CM)[i]




[b] See Principles of Imaging (SARC-A).
[i] Adapted with permission from Sepe PS, Brugge WR. A guide for the diagnosis and management of gastrointestinal stromal cell tumors. Nat Rev Gastroenterol Hepatol 2009;6:363-371. All recommendations for this algorithm are category 2B.
[j] Possible high-risk EUS features include irregular border, cystic spaces, ulceration, echogenic foci, and heterogeneity.
[k] Endoscopic ultrasonography surveillance should only be considered after a thorough discussion with the patient regarding the risks and benefits. Evans J, Chandrasekhara V, Chatahadi, KV, et al. The role of endoscopy in the management of premalignant and malignant conditions of the stomach. Gastrointest Endosc 2015;82(1):1-8.

**Note: All recommendations are category 2A unless otherwise indicated.**
**Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.**

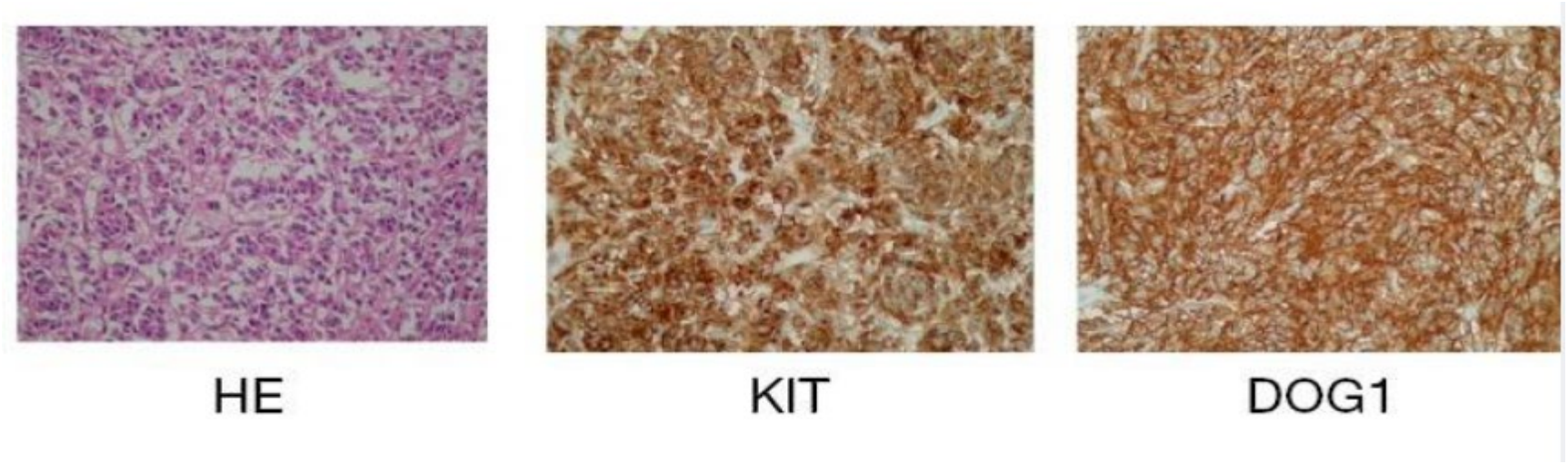




Λαζαράκη Γ, Υποεπιθηλιακοί όγκοι στομάχου, Φεβρουάριος 2020

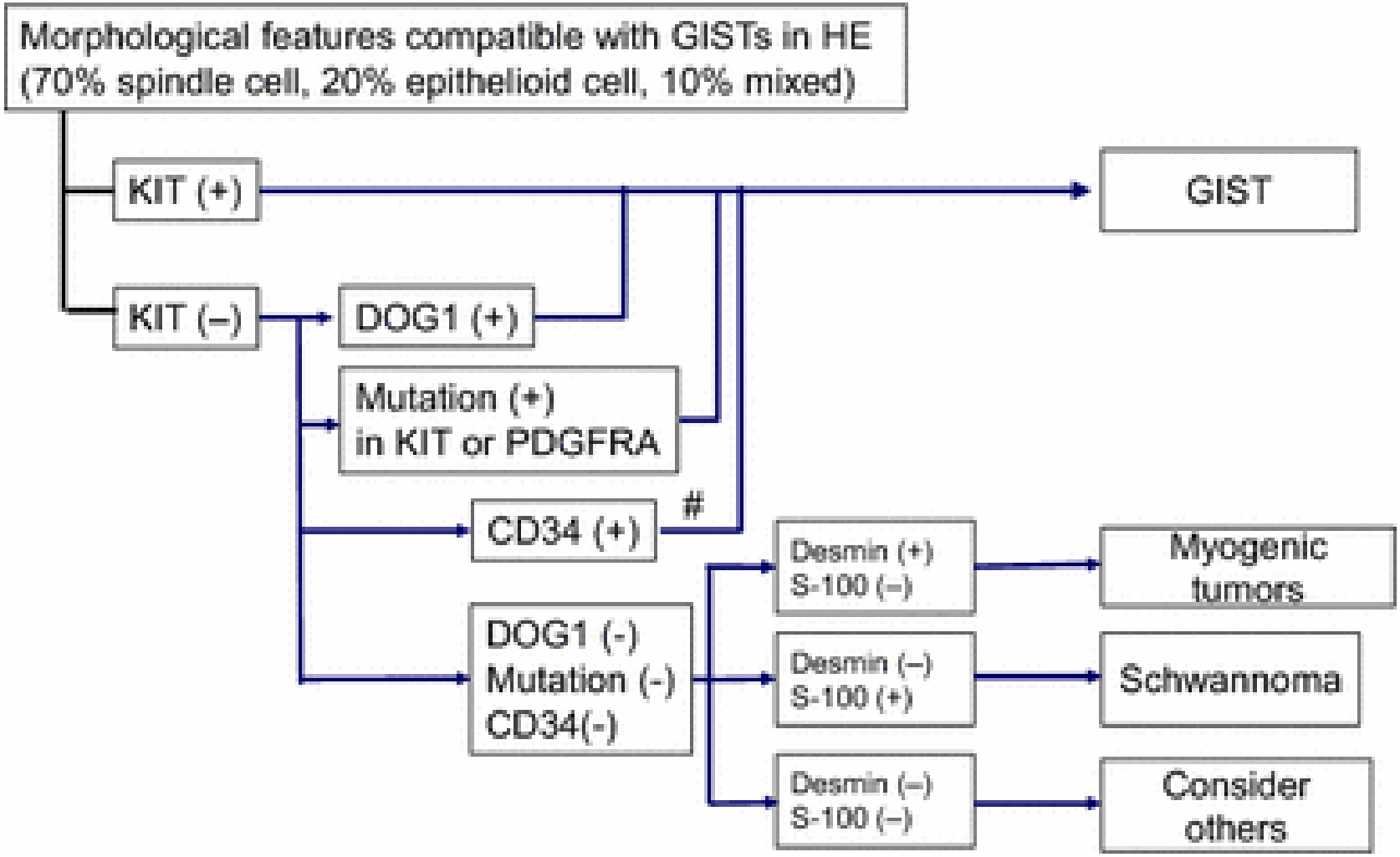
# GIST
# Διάγνωση

- Μορφολογία κυττάρων: ατρακτοειδή (70), επιθηλιοειδή(20%), μικτή
- Ανοσοϊστοχημεία
  - CD117
  - DOG1: Διάγνωση CD117-αρνητικών GIST
- Μιτωτικός δείκτης (ανά $5mm^2$ = 50 HPF)




ESMO Guidelines. Ann Oncol 2018

# Pathological diagnosis of GIST by immunohistochemistry and genotyping



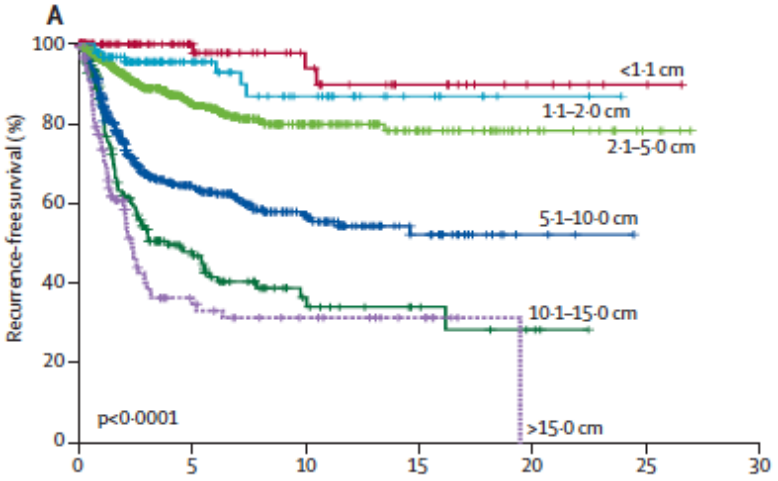

Nishida et al. Gastric Cancer 2015

# Κίνδυνος υποτροπής (Τροποποιημένα κριτήρια NIH)

| Risk category | Tumor size (cm) | Mititic index (per 50 HPF) | Primary tumor site |
|---|---|---|---|
| Very low | < 2,0 | ≤ 5 | Any |
| Low | 2,1 to 5 | ≤ 5 | Any |
| Intermediate | 2,1 to 5 | > 5 | Gastric |
| | < 5,0 | 6 to 10 | Any |
| | 5,1 to 10 | ≤ 5 | Gastric |
| High | Any | Any | Tumor rupture |
| | > 10 | Any | Any |
| | Any | > 10 | Any |
| | > 5 | > 5 | Any |
| | 2,1 to 5 | >5 | Non gastric |
| | 5,1 to 10 | ≤ 5 | Non gastric |

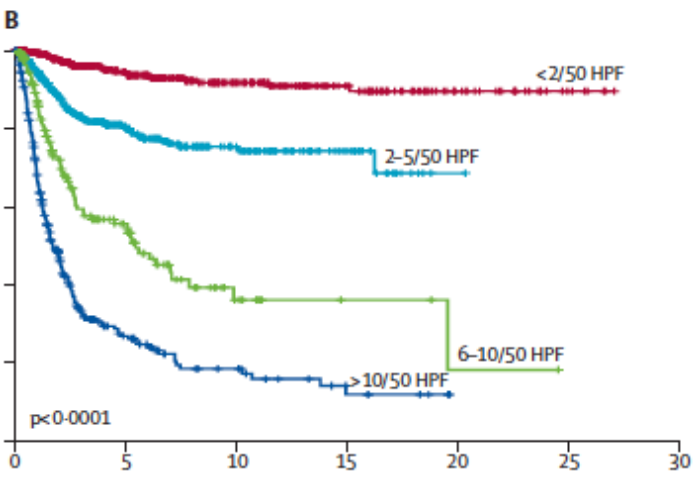
Joensuu H. Hum Pathol 2008

# Risk of recurrence of gastrointestinal stromal tumour after surgery: an analysis of pooled population-based cohorts




Number at risk

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| ≤1·0 cm | 94 | 14 | 4 | 0 | 0 | 0 | 0 |
| 1·1–2·0 cm | 114 | 41 | 23 | 8 | 2 | 0 | 0 |
| 2·1–5·0 cm | 586 | 226 | 88 | 39 | 15 | 4 | 0 |
| 5·1–10·0 cm | 491 | 159 | 68 | 23 | 3 | 0 | 0 |
| 10·1–15·0 cm | 176 | 47 | 14 | 7 | 3 | 0 | 0 |
| >15·0 cm | 115 | 22 | 13 | 7 | 0 | 0 | 0 |

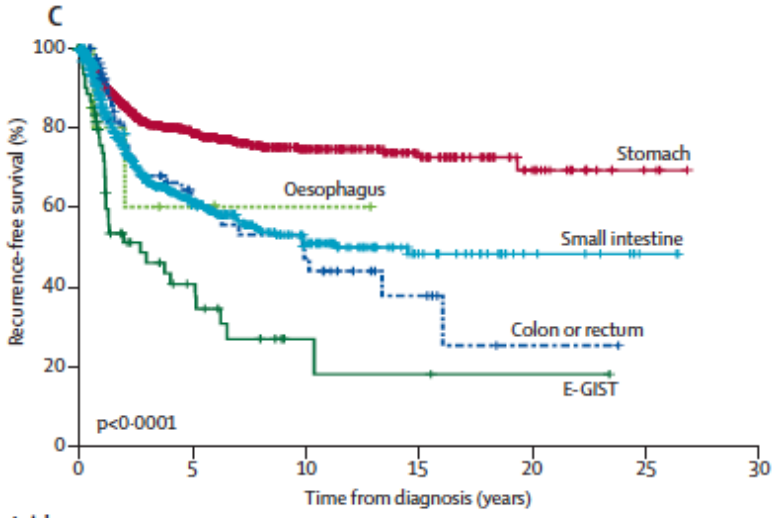



Number at risk

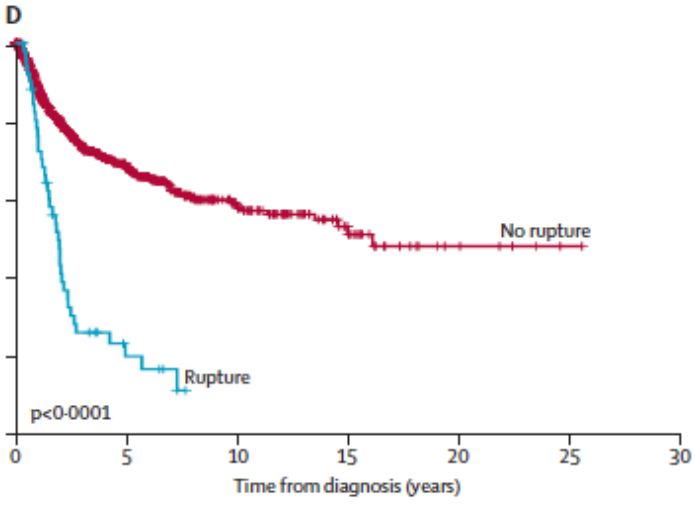
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| <2 per 50 HPF | 545 | 254 | 134 | 65 | 26 | 5 | 0 |
| 2–5 per 50 HPF | 491 | 164 | 68 | 23 | 1 | 0 | 0 |
| 6–10 per 50 HPF | 167 | 45 | 10 | 3 | 1 | 0 | 0 |
| >10 per 50 HPF | 290 | 42 | 15 | 6 | 0 | 0 | 0 |

Joensuu H et al. Lancet Oncol 2012

# Risk of recurrence of gastrointestinal stromal tumour after surgery: an analysis of pooled population-based cohorts



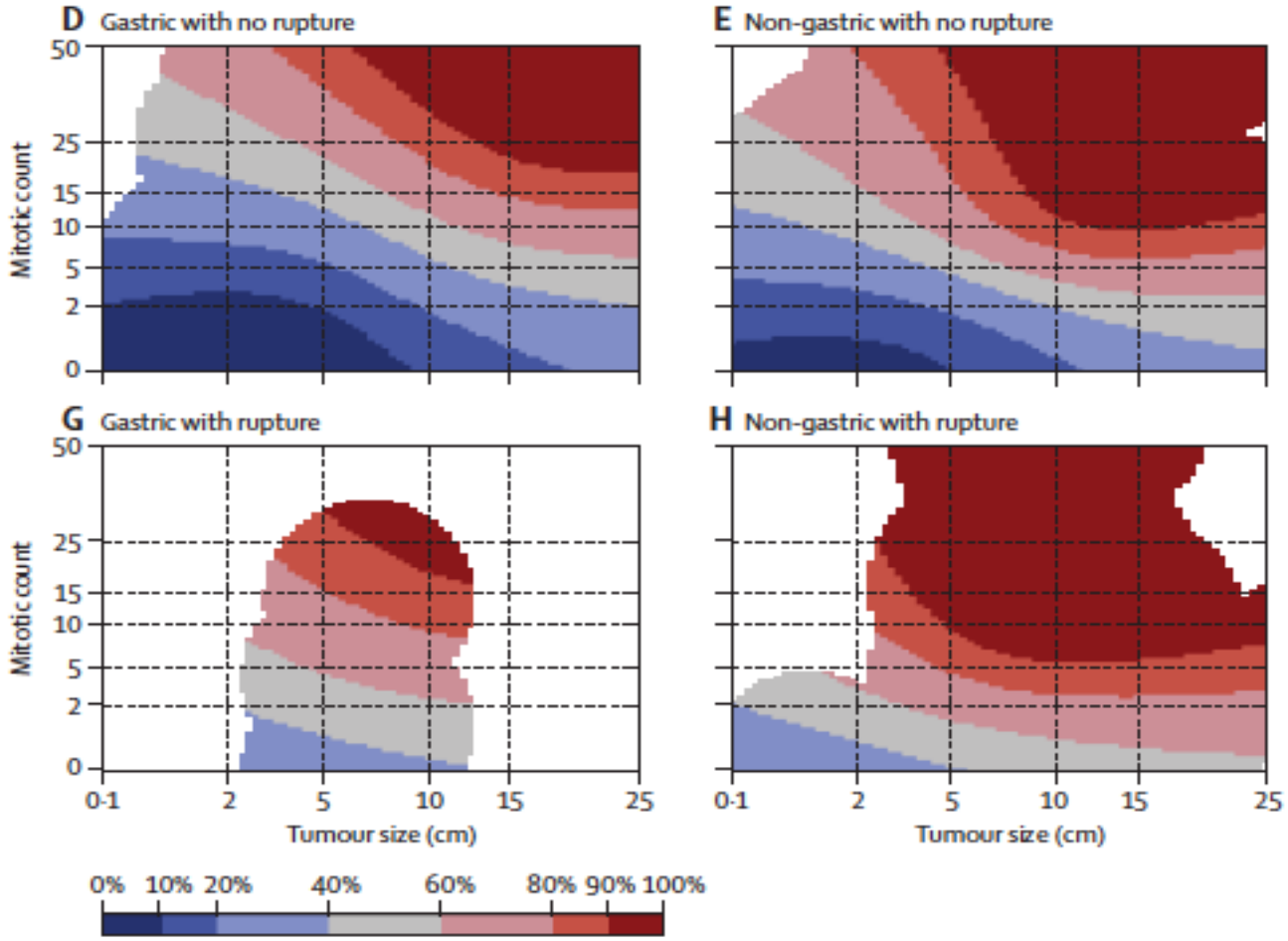

| Number at risk | | | | | | | |
|---|---|---|---|---|---|---|---|
| Stomach | 956 | 345 | 146 | 64 | 19 | 3 | 0 |
| Small intestine | 515 | 162 | 70 | 26 | 8 | 2 | 0 |
| Oesophagus | 8 | 2 | 2 | 0 | 0 | 0 | 0 |
| Colon or rectum | 84 | 32 | 15 | 6 | 1 | 0 | 0 |
| E-GIST | 61 | 13 | 3 | 2 | 1 | 0 | 0 |




| Number at risk | | | | | | | |
|---|---|---|---|---|---|---|---|
| No rupture | 1004 | 270 | 81 | 25 | 6 | 1 | 0 |
| Rupture | 57 | 6 | 0 | 0 | 0 | 0 | 0 |

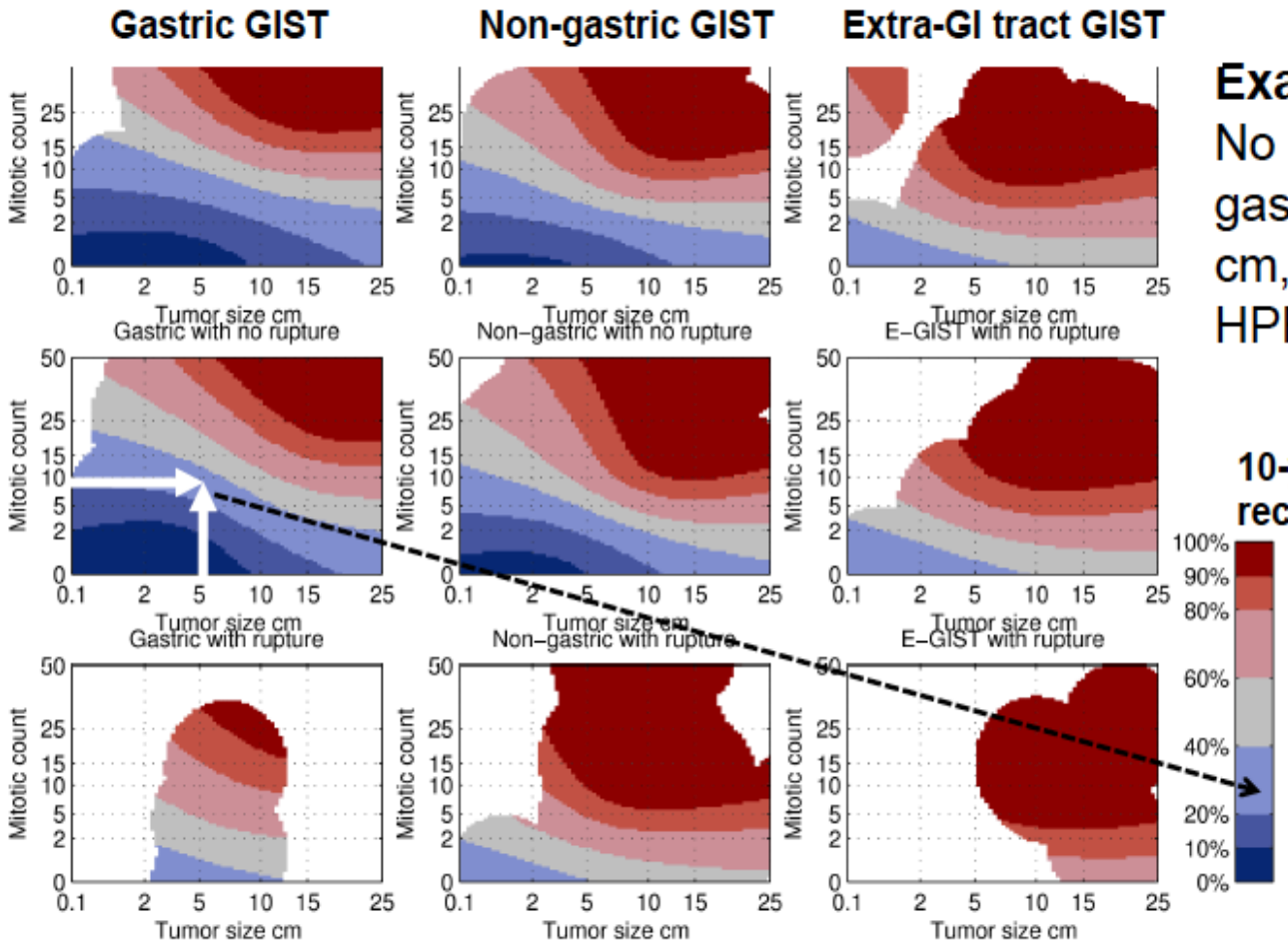
Joensuu H et al. Lancet Oncol 2012

# Risk of recurrence of gastrointestinal stromal tumour after surgery: an analysis of pooled population-based cohorts




Joensuu H et al. Lancet Oncol 2012

# Prognostic contour maps




**Example:**
No rupture, gastric GIST, 5.1 cm, 9 mitoses/50 HPFs

Joensuu H et al. Lancet Oncol 2012

# Prediction Tools MSKCC
# Survival Without Recurrence Following Surgery

## Enter Your Information

Clear Calculate

**What was the size of your tumor?**

12 cm (0 to 50)

**Where was your tumor located?**

Stomach +

**Was the mitotic index listed on your pathology report equal to or greater than 5 per 50 HPF?**

(•) Yes ( ) No

Note: Check "Yes" if the mitotic index was listed on the pathology report as greater than or equal to 5 per 50 high-powered fields (HPF) seen under the microscope.

What is mitotic index?

# Prediction Tools MSKCC
# Survival Without Recurrence Following Surgery

Memorial Sloan Kettering Cancer Center

Prediction Tools / Gastrointestinal Stromal Tumor Nomogram

## Survival Without Recurrence Following Surgery

### Your Results

PROBABILITY OF RECURRENCE-FREE SURVIVAL AFTER SURGERY FOR GASTROINTESTINAL STROMAL TUMOR

2 YR 21 5 YR 4

2 YEAR

21%

# GIST
# Μεταλλάξεις

- Γονιδιακή ανάλυση
  - Επιβεβαίωση της διάγνωσης
  - Διάγνωση CD117/DOG1-αρνητικών GIST
- Προβλεπτική και προγνωστική αξία;

# Mutations and clinicopathological features
# KIT

| Exon | Frequent mutations | Frequency | Characteristics and site | Imatinib sensitivity |
|---|---|---|---|---|
| All exons | | 80 % | All sites | |
| 8 | | Rare | Small bowel | Yes, intermediate |
| 9 | Insertion of AY 502–503 | 5–10 % | Small bowel, colon, spindle, aggressive | |
| 11 | Deletions, missense mutations, insertions | 60–70 % | All sites | Yes |
| | Deletion of codon 557 or 558 | | Aggressive, poor prognosis | |
| | Internal tandem duplication | | Benign features, clinically indolent, female, stomach | |
| 13 | K642E | 1 % | All sites | Yes |
| 17 | D820Y, N822K, Y823D | 1 % | All sites | No for D816V |

Nishida et al. Gastric Cancer 2015

# Mutations and clinicopathological features
# PDGFRA

| Exon | Frequent mutations | Frequency | Characteristics and site | Imatinib sensitivity |
|---|---|---|---|---|
| All exons | | 10 % | Epithelioid, clinically indolent | |
| 12 | Missense mutations | 1–2 % | All sites | Yes |
| 14 | N659K | <1 % | Stomach, epithelioid | Yes |
| 18 | D842V | 10–5 % | Stomach, mesentery, omentum, epithelioid | No for D842V |

Nishida et al. Gastric Cancer 2015

# Mutations and clinicopathological features
# Wild-type

| Genes | Exon | Frequent mutations | Frequency | Characteristics and site | Imatinib sensitivity |
|---|---|---|---|---|---|
| *BRAF* | | V600E | Rare | | |
| *SDHA/SDHB/SDHC/SDHD* mutations | | | ~2 % | Carney–Stratakis syndrome[a]; stomach, multiple, immunohistochemically SDHB negative | |
| | | | | Juvenile GIST; stomach, clinically indolent, multiple, immunohistochemically SDHB negative | |
| Loss of SDH expression | | | | Carney triad[b]; stomach, clinically indolent, juvenile onset, immunohistochemically SDHB negative | |
| *HRAS, NRAS* mutation | | | <1 % | | |
| *NF1* mutation | | | 1–2 % | Small bowel, clinically indolent, multiple, spindle | |

SDH succinate dehydrogenase,
SDHB succinate dehydrogenase iron–sulfur subunit (subunit B)

Nishida et al. Gastric Cancer 2015

**Table 1. Personalised medicine synopsis table**

| Biomarker | Method | Use | LoE | GoR |
|---|---|---|---|---|
| Mitotic index | Pathology | Disease classification<br>Prognostic relevance<br>Used for medical treatment decisions | IV | A |
| *KIT/PDGFRA/ BRAF* | Sanger sequencing or NGS | Disease classification<br>Prognostic relevance<br>Predictive relevance<br>Used for medical treatment decisions<br>Currently actionable/ targetable | I | A |
| SDH | IHC | Disease classification<br>Prognostic relevance<br>Predictive relevance<br>Used for medical treatment decisions | III | A |

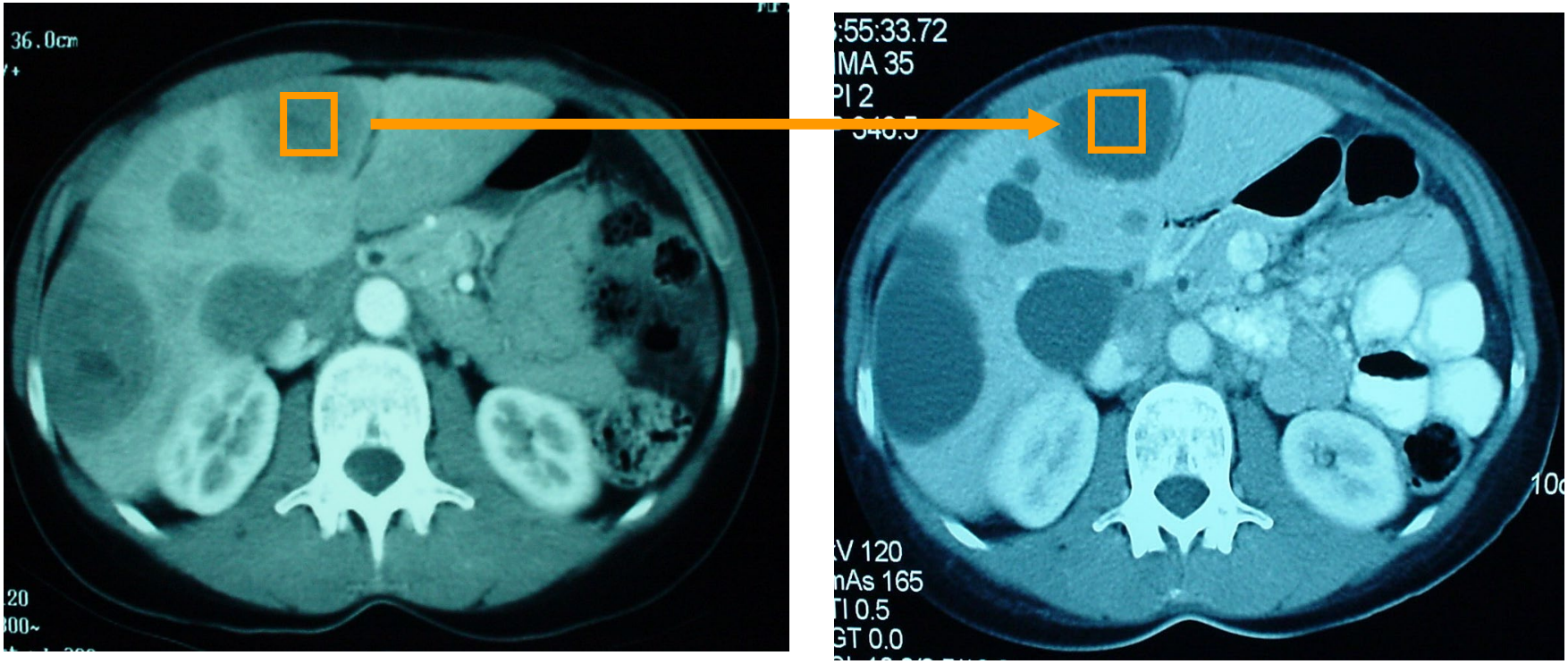
ESMO Guidelines. Ann Oncol 2018

# GIST
# Αξονική τομογραφία

- Απεικονιστική μέθοδος εκλογής
  - CT > MRI
    - MRI: ορθό, ήπαρ
- Αρχική διάγνωση
  - Εκτίμηση ενδοκοιλιακής μάζας (έκταση, μεταστάσεις)
    - Συμπαγής μάζα με ομαλά όρια, υπέρπυκνη
    - >15cm: νεκρωτικά, αιμορραγικά, εκφυλιστικά στοιχεία
  - Διερεύνηση άτυπης συμπτωματολογίας
  - Τυχαίο ενδοσκοπικό εύρημα
- Παρακολούθηση
  - Μετεγχειρητική ανά 3-6 μήνες
  - Εκτίμηση θεραπευτικού αποτελέσματος ανά 1-3 μήνες

# GIST
# Αξονική τομογραφία

Εκτίμηση αποτελεσματικότητας:
Πυκνότητα βλάβης



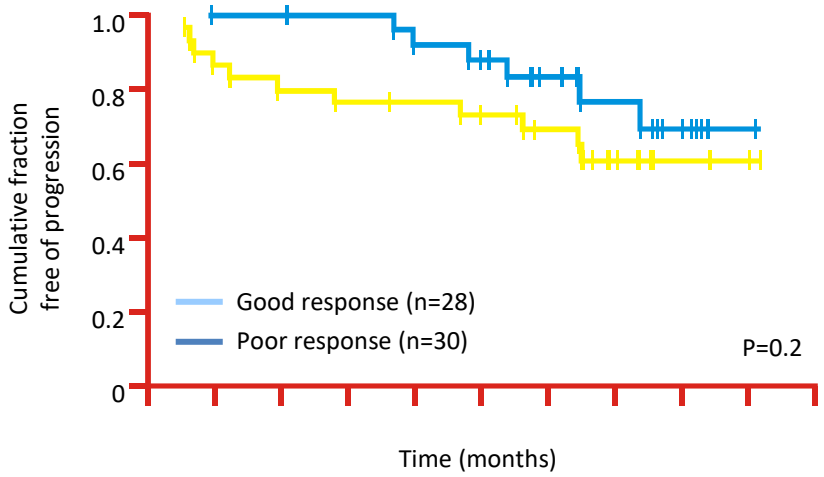

Baseline

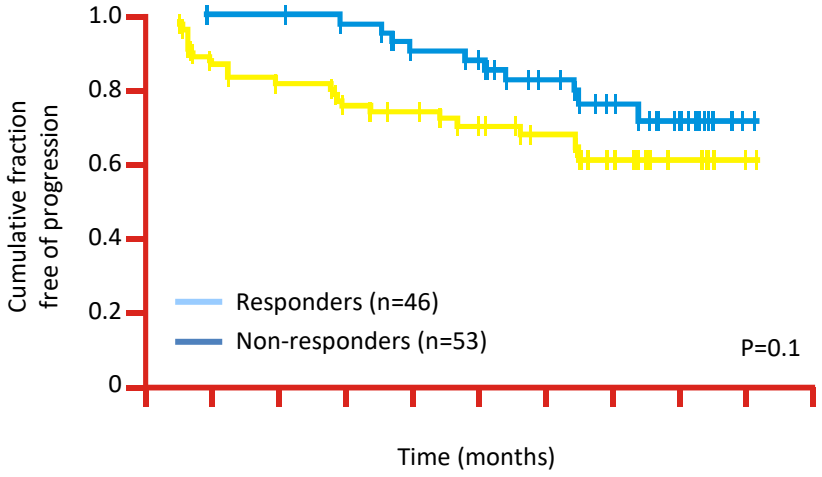
Θεραπεία με imatinib mesylate

Courtesy of Dr. G.D. Demetri

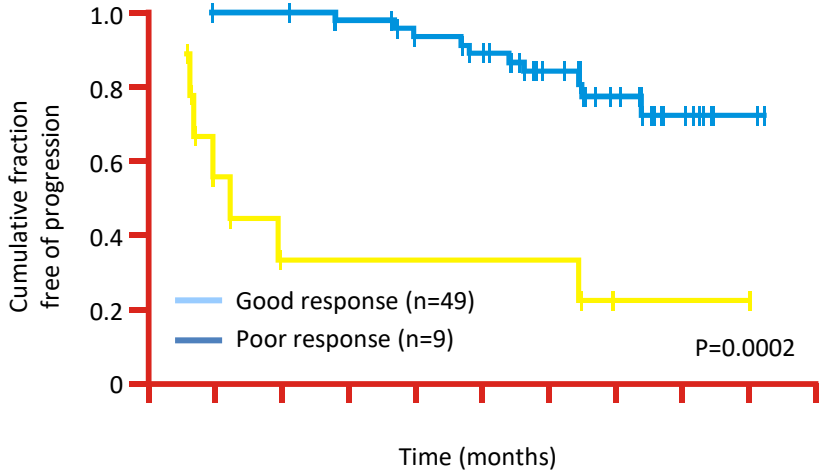
# RECIST vs. Choi Criteria: Response Assessment

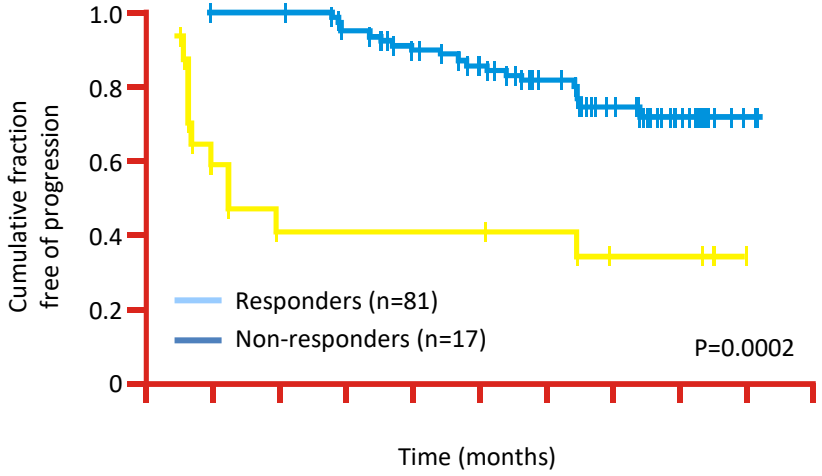
## Response by RECIST




## Response by Choi criteria




Benjamin RS et al. J Clin Oncol 2007

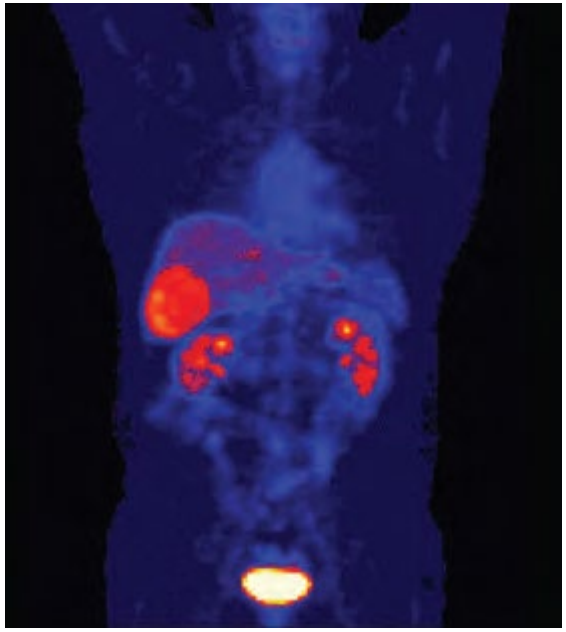
# GIST
# FDG-PET (Positron Emission Tomography)-CT

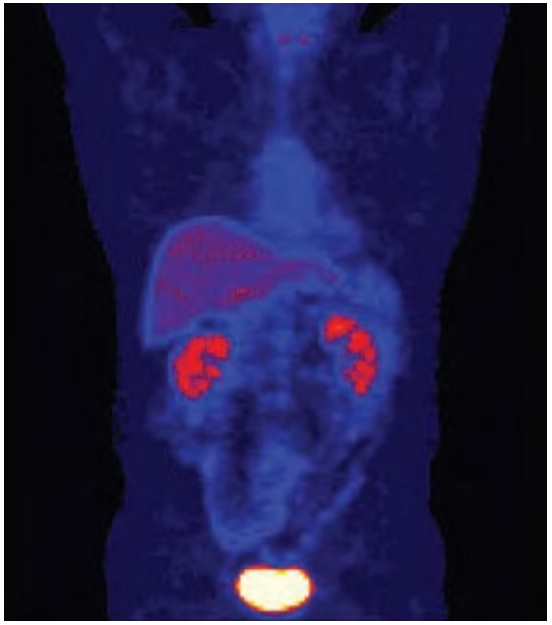
- Εκτίμηση όγκου (vs CT)
  - Αλλαγές στη μεταβολική δραστηριότητα προηγούνται των ανατομικών
  - Δ/δ: ενεργότητα όγκου vs νέκρωση
  - Μεταστάσεις που δεν είναι εμφανείς σε CT
  - Υποκαθιστά τη CT σε περιπτώσεις αλλεργίας στο σκιαστικό (περιτοναϊκή νόσος)
- Πρώιμη εκτίμηση απάντησης στη μοριακά στοχευμένη θεραπεία

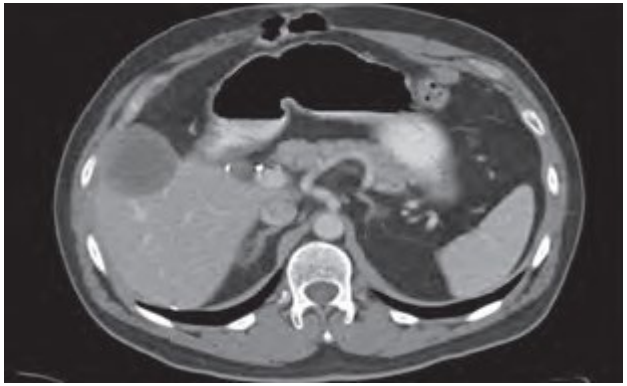
NCCN Guidelines V 2. 2018
ESMO Gudelines Ann Oncol 2014

# GIST

PET-CT: Πριν και 3 εβδομάδες μετά από θεραπεία με Imatinib



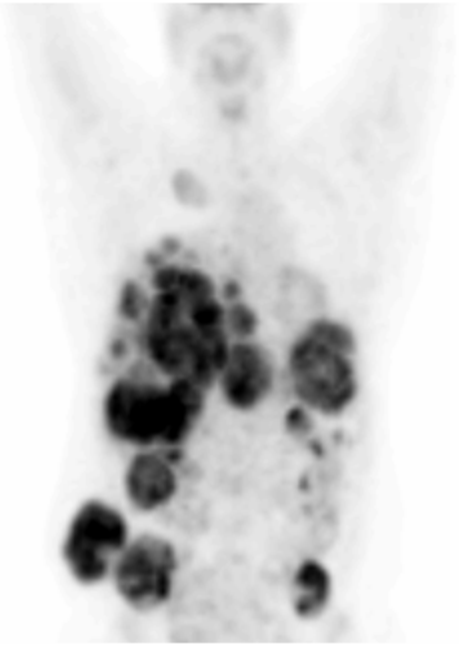




# Sunitinib Benefit in Imatinib-Resistant GIST

Baseline

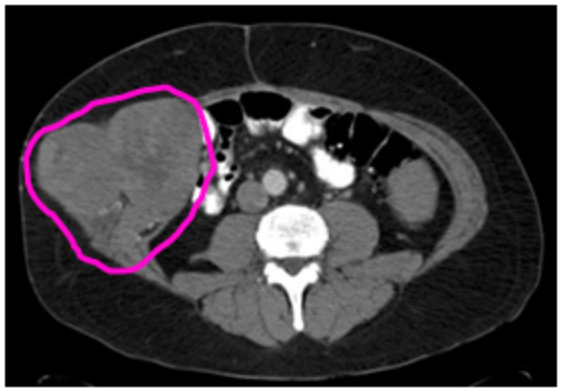
Day 7 PET



PET scan after 7 days of sunitinib

Normal heart

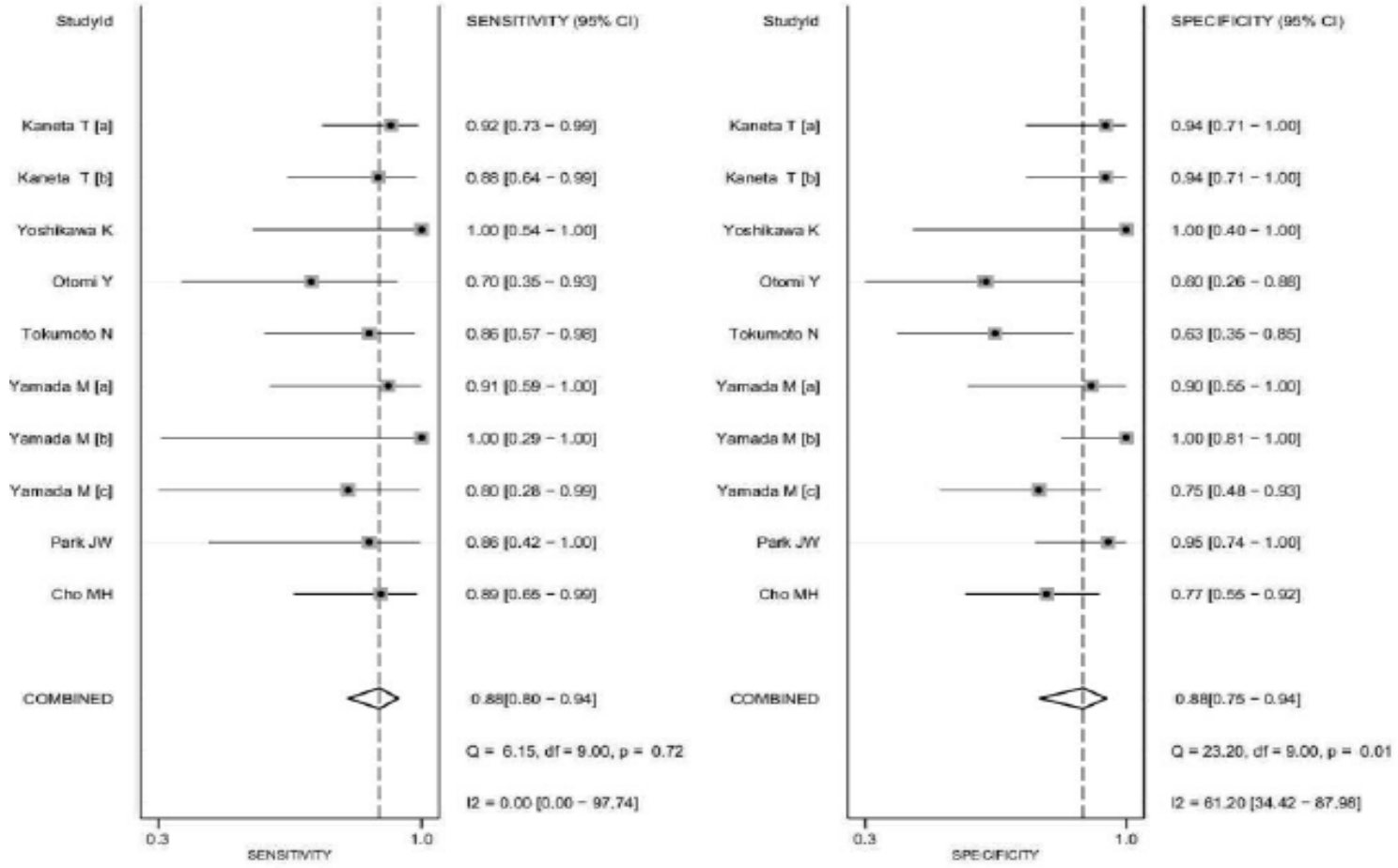
Normal kidneys



CT scan after 2 months of sunitinib

Demetri GD, et al. *Clin Cancer Res*. 2009;15:5902.

# Performance ofF-18 FDG PET/CT for Predicting Malignant Potential of Gastrointestinal Stromal Tumors: A Systematic Review and Meta-analysis




7 studies (188pts)

Pooled Sens: 0,88 Pooled Spec: 0,88

Kim SJ, Lee SW. J Gastroenterol Hepatol 2018

# GIST
# Θεραπεία

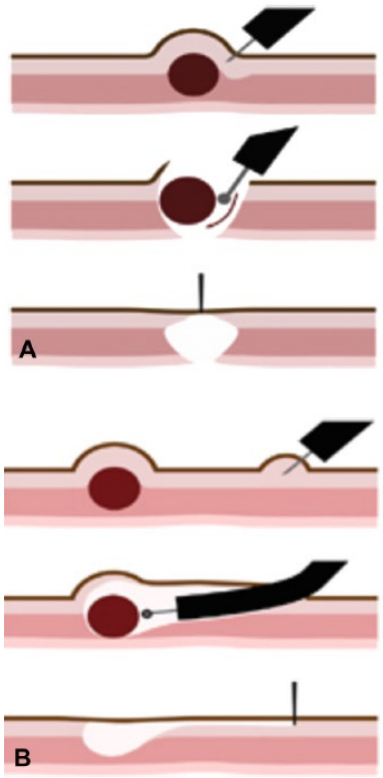
- Θεραπεία
  - Χειρουργική/ενδοσκοπική εξαίρεση
  - Φαρμακευτική
    - Προεγχειρητική
    - Επικουρική
    - Συστηματική
      - 1η γραμμή
      - 2η γραμμή

# GIST
# Χειρουργική θεραπεία

- Πλήρης εξαίρεση του όγκου με αρνητικά όρια εκτομής
  - Όγκοι > 2 cm (ESMO, NCCN)
  - Όγκοι 1-2 cm;
    - EUS ευρήματα υψηλού κινδύνου ‘κακοήθειας’
- Διερεύνηση της περιτοναϊκής κοιλότητας
- **Προσεκτική αποκόλληση από παρακείμενα όργανα ή en bloc εκτομή**
- Μη αναγκαία η ευρεία εκτομή μη προσβληθέντων τμημάτων και η αφαίρεση λεμφαδένων
- Επανεγχείρηση σε περιπτώσεις θετικών ορίων εκτομής;
- Λαπαροσκοπική αφαίρεση
  - Γαστρικοί όγκοι < 5 cm
  - Όγκοι λεπτού εντέρου;
  - **Διατήρηση της ακεραιότητας του όγκου**

# GIST
# Ενδοσκοπική εξαίρεση

- Για βλάβες <4cm
- Ενδοαυλική ανάπτυξη
- Τεχνικές




**EFTR**

**ESD**

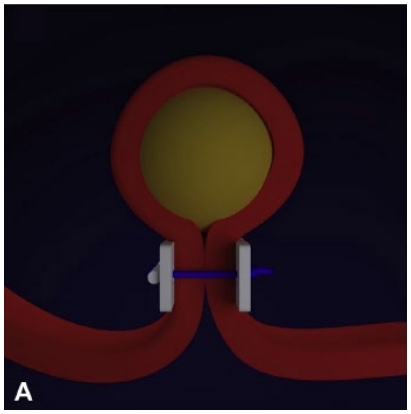
- Nontunneled exposed EFTR. [A]
- Tunneled exposed EFTR ή STER [B]

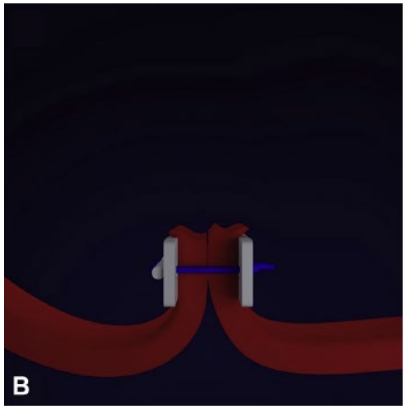
**Nonexposed EFTR**

Plicator

GERDX

Cap-mounted clips



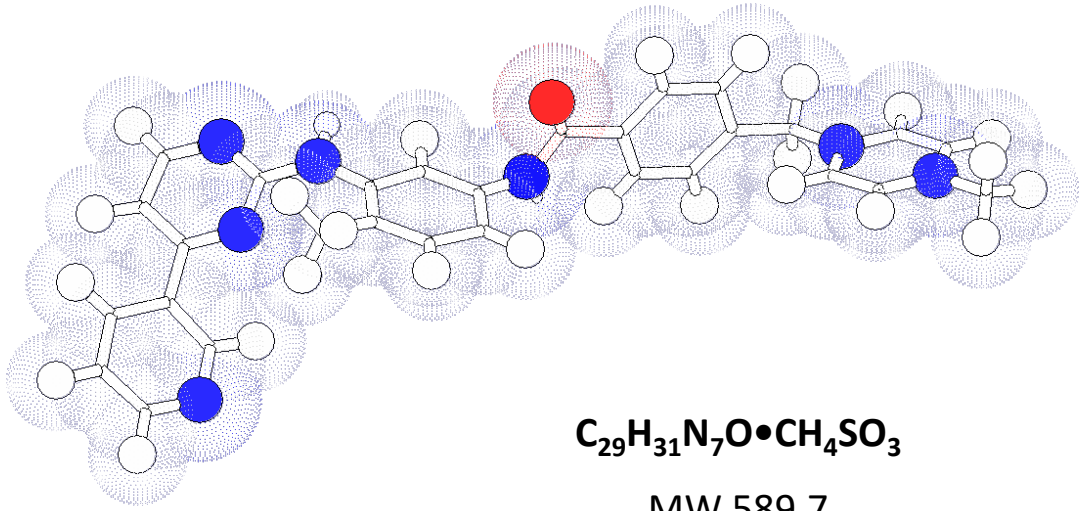



# GIST- Ενδοσκοπική εξαίρεση

| Μελέτη | Είδος | ν | Size mm | Τεχνική | SR % | En bloc | |
|---|---|---|---|---|---|---|---|
| Mönkemüller 2014 Endoscopy | Case report | 1 | 35 | Suction of omental patch through prf, closure with OTS clip [ovesco] | 100 | ναι | |
| Guo 2015 Surg Endosc | Retro | 19/23 | 12.1 ± 4.7 | Grasp the gap's sides, closure with OTS clip [ovesco] | 100 | ναι | |
| Ye 2016 AMJG | retro | 195 gastric, 3 duodenal | 17 (10–40) | traditional endoscopic resection or via submucosal tunneling (ST) clips combined with an endoloop | 97.1* | 98.6%* | 6 GIST υψηλου/ενδιάμεσου κινδύνου Χωρίς δεδομένα παρακολουθησης |
| Tan Y 2017 Surg Endosc | Retro 20 STER vs 32 EFTR | 52 gastric | 17.8 ± 7.2 vs 15.4 ± 6.6 | 20 STER vs 32 EFTR | 95 vs 96.9 | 95 vs 96.9 | mean follow-up of 10.9 and 23.8 months, respectively. |
| Lv X 2017 Surg Endosc | Metanal ysis of cs | 28 cs 1085, not only gists | NA | STER | 97.5 | 94.6 | Χωρίς δεδομένα παρακολουθησης |
| Chen T 2017 Ann Surg | retro | 28/180 | 26 (20–50) | STER | | 90.6 | 36m |
| Schmidt A, 2015 Endoscopy | retro | 18/31 | 19.0 (9 – 42) | Nonexposed endoscopic full-thickness resection | 100 | 90.3 | 7.1m |

# GIST
# Φαρμακευτική θεραπεία

- Imatinib Mesylate
  - Εκλεκτικός αναστολέας της τυροσινικής κινάσης
  - Κατηγορία: Phenylaminopyrimidines
  - 1996: STI-571, αναστολέας κινάσης ABL στη ΧΜΛ



$C_{29}H_{31}N_7O \bullet CH_4SO_3$

MW 589.7

# GIST
## Επικουρική θεραπεία

- **ESMO**: Adjuvant imatinib for 3 years is the standard when the risk of GIST relapse is **significant**. It should not be considered when the risk is low. There is room for shared decision-making when the risk is intermediate.[1]
- **NCCN**: Postoperative imatinib for 36 months should be considered for **high-risk** GISTs.[2]

1 ESMO Guidelines Ann Oncol2014
2 NCCN guidelines v. 6.2019

# GIST
# Adjuvant trials

| ClinicalTrials.gov Identifier | Phase | Design | Key Eligibility Criteria | Primary End Point | Main Results |
|---|---|---|---|---|---|
| ACOSOG Z9001[35] (NCT00041197) | III | Randomized; imatinib 400 mg/d for 1 year *v* placebo for 1 year | Size ≥ 3 cm | RFS | HR, 0.6; 95% CI, 0.43 to 0.75 ($P < .001$). No difference in OS ($P < .19$) |
| EORTC 62024[36] (NCT00103168) | III | Randomized; imatinib 400 mg/d for 2 years *v* observation | Intermediate or high risk according to NIH consensus classification[29] | IFFS | 5-year IFFS, 87% *v* 84%; HR, 0.79; 98.5% CI, 0.50 to 1.25 ($P = .21$). No difference in OS |
| SSG XVIII/German[37] (NCT00116935) | III | Randomized; imatinib 400 mg/d 1 *v* 3 years | High risk using modified NIH criteria[30] (size ≥ 10 cm, rupture, mitotic count > 10 per 50 HPFs, or size > 5 cm and mitotic rate > 5 per 50 HPFs) | RFS | 5-year RFS, 71% *v* 52%; HR, 0.60; 95% CI, 0.44 to 0.81 ($P < .001$). 5-year OS, 92% *v* 85%; HR, 0.60; 95% CI, 0.37 to 0.97 ($P = .036$). |
| SSG XXII (NCT02413736) | III | Randomized; imatinib 400 mg/d for 3 *v* 5 years | Gastric GIST with > 10 mitoses per 50 HPFs, nongastric with > 5 mitoses per 50 HPFs, or rupture | RFS | Accrual ongoing |
| ImadGist (NCT02260505) | III | Randomized; imatinib 400 mg/d for 3 *v* 6 years | Estimated risk of recurrence ≥ 35% | DFS | Accrual ongoing |
| ACOSOG Z9000[38] (NCT00025246) | II | Single cohort; imatinib 400 mg/d for 1 year | Size > 10 cm, rupture, up to 4 peritoneal implants | OS | 5-year OS, 83% |
| Japanese study[39] (NCT00171977) | II | Single cohort; imatinib 400 mg/d for 1 year | High risk according to NIH consensus classification[29] | RFS | 3-year RFS, 43% |
| Korean study[40] (NCT00278876) | II | Single cohort; imatinib 400 mg/d for 2 years | Size ≥ 10 cm, mitotic count ≥ 10 per 50 HPFs, or size 5-10 cm and mitotic count 5-10 per 50 HPFs | RFS | 5-year RFS, 46% |
| PERSIST-5[41] (NCT00867113) | II | Single cohort; imatinib 400 mg/d for 5 years | Size ≥ 2 cm and mitotic count ≥ 5 per 50 HPFs, or nongastric GIST ≥ 5 cm | RFS | 5-year RFS, 90% |

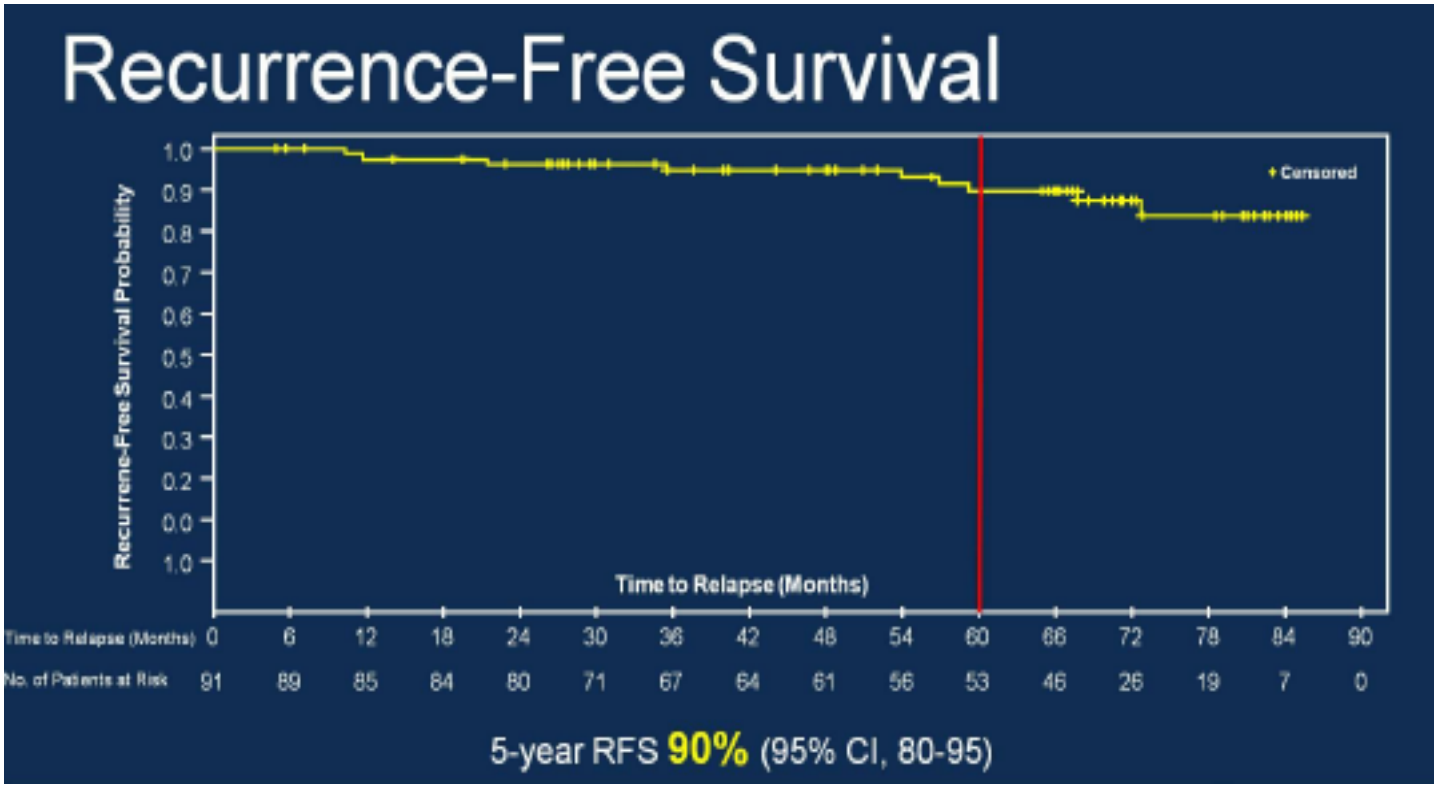
Von Mehren et al. J Clin Oncol 2018

# GIST
# Επικουρική θεραπεία με Imatinib

- Το διάστημα χορήγησης των 36 μηνών είναι αρκετό;

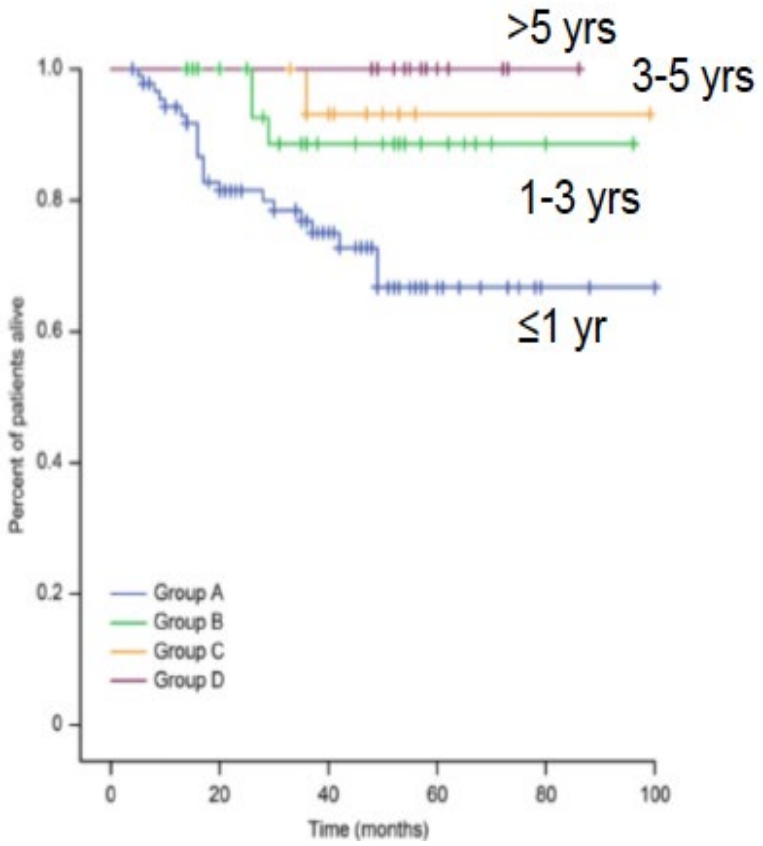
# PERSIST-5: Five years of adjuvant imatinib

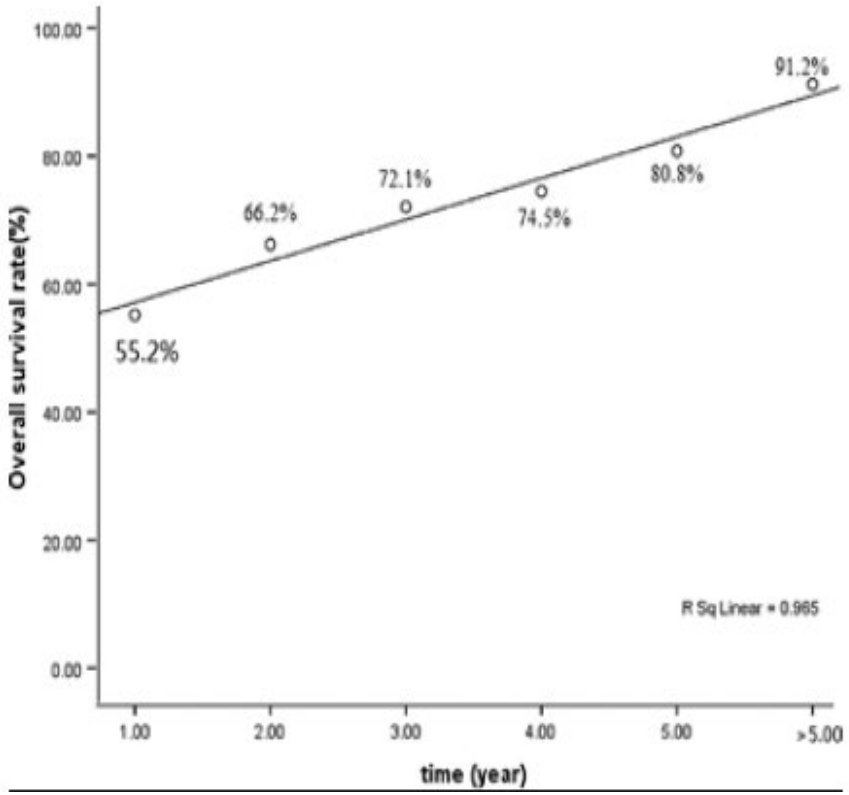
- 67 (74%) pts: high risk, 24 (26%): intermediate risk
- 45 (49%)/ 91 patients discontinued adjuvant imatinib




Chandrajit R et al. ASCO Annual Meeting 2017

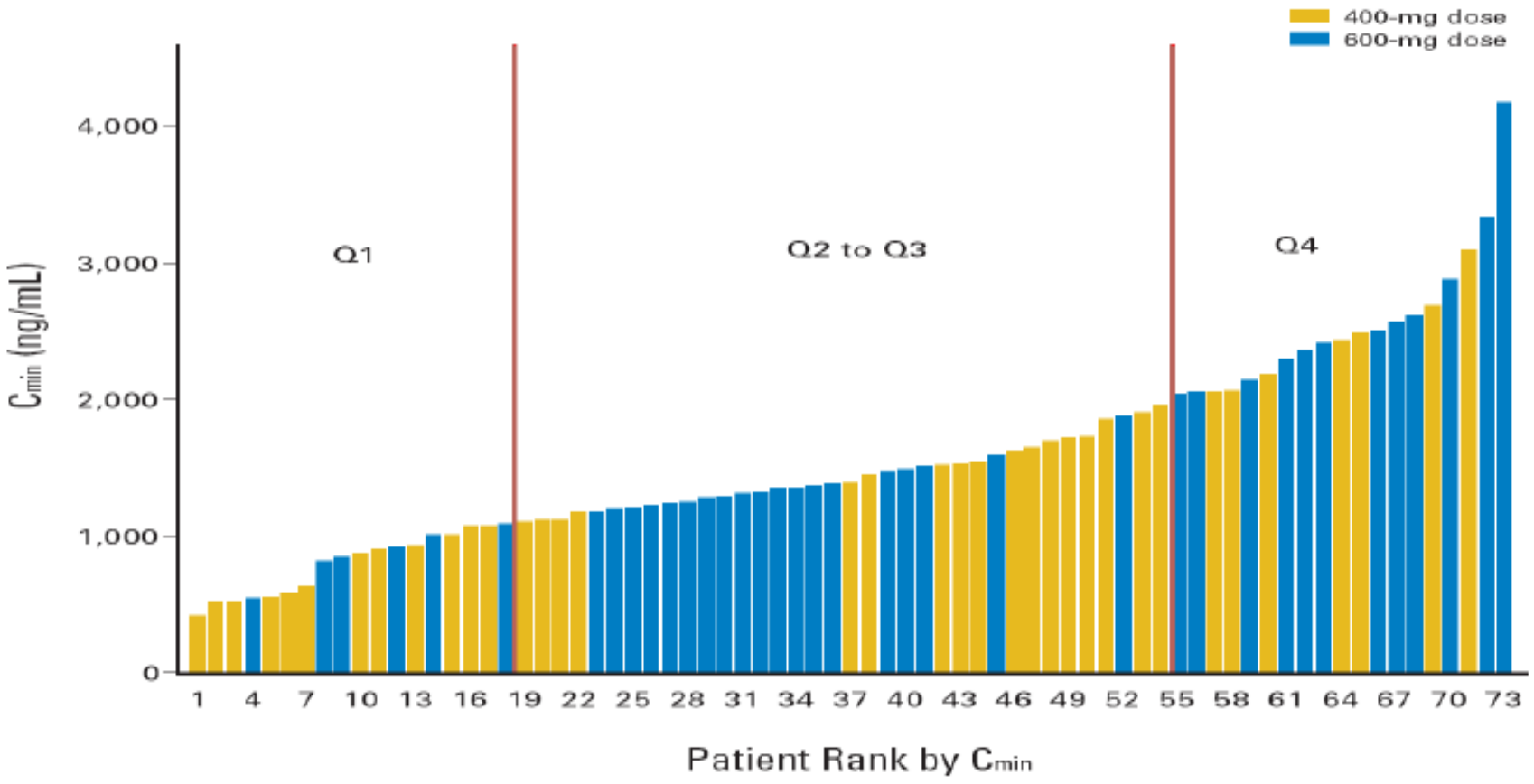
# Effect on overall survival: A retrospective analysis



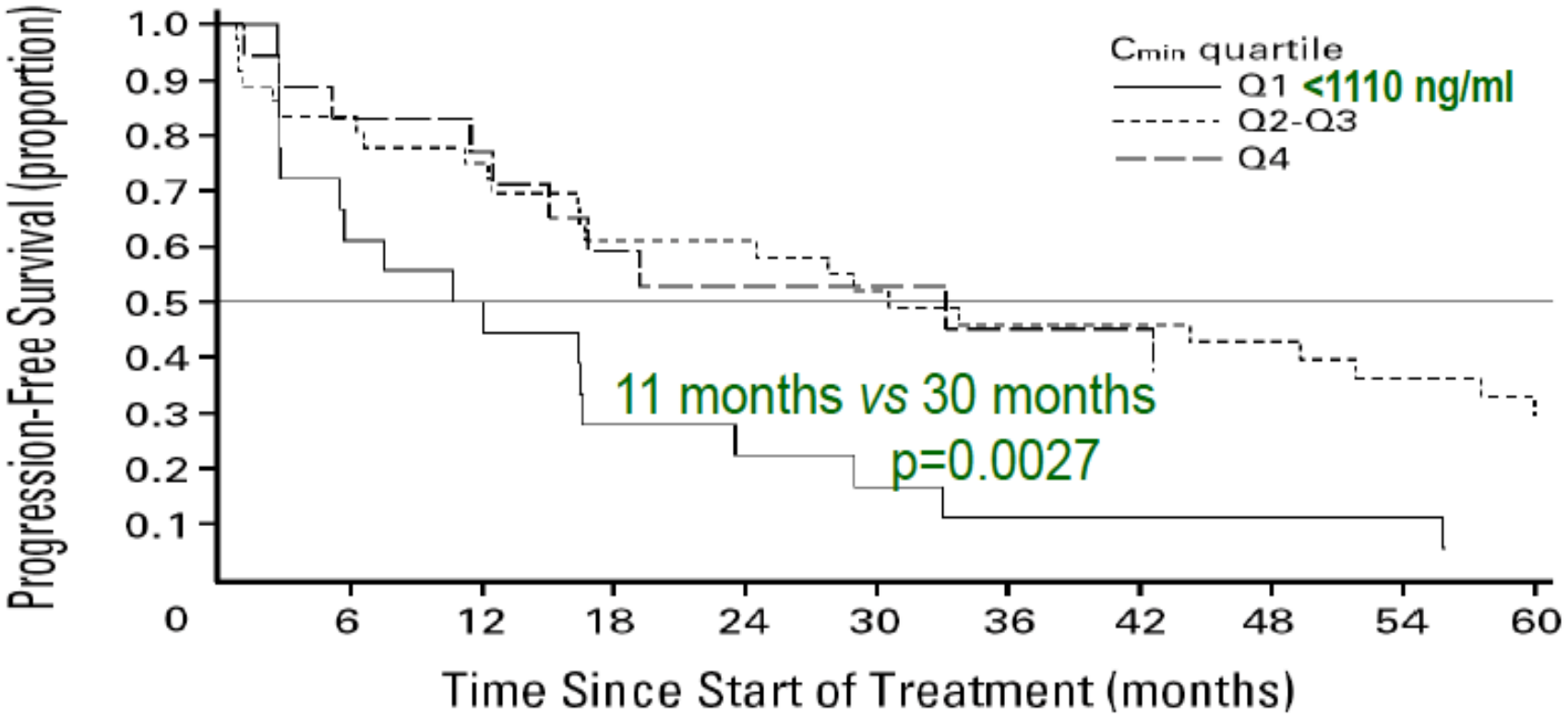

Lin et al. J Cancer Res Clin Oncol 2017

# Wide distribution of Imatinib exposure without reliable correlation with dose




Demetri et al. J Clin Oncol. 2009

# GIST patients with lowest imatinib blood levels had higher risk for rapid disease progression




Demetri et al. J Clin Oncol. 2009

# Plasma levels of imatinib (trough)

400 mg/day: trough levels exceeded 1,000 ng/mL in all cases
300 mg/day: although the trough levels tended to be low compared to 400 mg/day cases, they exceeded 800 ng/mL

| Case | Gender | Body weight, kg | Imatinib dose, mg/day | Plasma level (trough), ng/mL | Overall response |
|---|---|---|---|---|---|
| 1 | M | 52 | 400 | 2,077 | PR |
| 2 | M | 66 | 400 | 1,313 | PR |
| 3 | M | 40.5 | 300 | 1,039 | PR |
| 4 | M | 56 | 400 | 1,026 | PR |
| 5 | F | 45 | 300 | 955 | SD |
| 6 | F | 59 | 300 | 807 | PR |
| 7 | M | 59 | 400 | 1,303 | NE |

PR: partial response, SD: stable disease,
NE: not evaluated

Ogata et al. Digestion 2018

# Προσδιορισμός επιπέδων φαρμάκου στο αίμα: πότε και σε ποιους;

- Ασυνήθιστες παρενέργειες
- Υποψία αλληλεπιδράσεων με άλλα λαμβανόμενα σκευάσματα
- Έλεγχος συμμόρφωσης
- Μη ανταπόκριση
- Ερευνητικοί λόγοι

# Initial Treatment of Metastatic GIST

- Important to do molecular testing before selecting therapy

*KIT* or *PDGFRA* mutation* (~85% of pts) → Imatinib

- Remaining 15% of patients:
  - Molecular testing may reveal another appropriate targeted therapy based on result (eg, *BRAF* mutation, *NTRK* fusion)
  - ~10% of patients have inactivation of SDH complex; no standard therapy

**PDGFRA* D842V mutation is not responsive to imatinib.

NCCN. Soft Tissue Sarcoma. V2.2019.

# First-Line GIST Treatment: Imatinib

- Inhibits several kinases, including KIT, PDGFRA
- Dosing suggestions[a]:
  - *KIT* exon 11 mutation: standard 400-mg dose
  - *KIT* exon 9 mutation: start with 400 mg, increase up to 800 mg
- Most *PDGFRA* mutations are responsive; D842V is an exception
- Common toxicities[b]:
  - Edema; GI (nausea, vomiting, diarrhea); muscle cramps; fatigue

a. NCCN. Soft Tissue Sarcoma. V2.2019; b. Gleevec® PI 2018.

# Investigational Approaches: Avapritinib

- Selective KIT and PDGFRA inhibitor
- Active against *PDGFRA* D842V and KIT exon 17[a]
- Phase 1 NAVIGATOR study[b]
  - Efficacy
    - *PDGFRA* exon 18 (n = 43): CBR 95%; ORR 86%; mDOR NR
    - ≥ 4th-line (n = 111): CBR 41%; ORR 22%; mDOR 10.2 mo
  - Safety
    - Grade 3/4 TRAEs: anemia (16.2%), fatigue (6.4%), bilirubin (3.9%), cognitive effects (3.9%), diarrhea (2.9%)

a. Gebreyohannes YK, et al. *Clin Cancer Res.* 2019;25:609-618; b. Heinrich MC, et al. ASCO® 2019. Abstract 11022.

# GIST Νεοεισαγωγική θεραπεία

National Comprehensive Cancer Network®

## NCCN Guidelines Version 6.2019
## Gastrointestinal Stromal Tumors (GIST)

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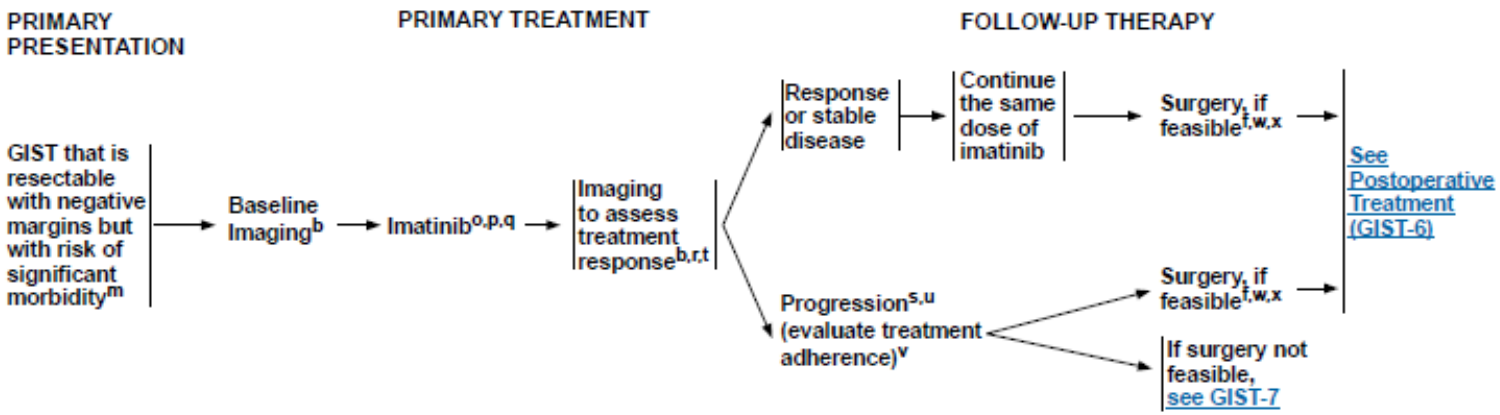


[b] See Principles of Imaging (SARC-A).
[f] See Principles of Surgery for GIST (GIST-C).
[m] Some patients may rapidly become unresectable; close monitoring is essential.
[o] If life-threatening side effects occur with imatinib not managed by maximum supportive treatment, then consider sunitinib.
[p] Medical therapy is the usual course of treatment. However, patient may proceed to surgery if bleeding or symptomatic.
[q] Because patients with advanced GISTs have different responses to imatinib, mutational testing should be performed. Approximately 90% of patients have disease that responds to imatinib when their tumors have a *KIT* exon 11 mutation; approximately 50% of patients have disease that responds when their tumors harbor a *KIT* exon 9 mutation, and the likelihood of response improves with the use of 800 mg imatinib rather than the standard 400 mg dose. Most mutations in the *PDGFRA* gene are associated with a response to imatinib, with the notable exception of D842V. In the absence of *KIT* and *PDGFRA* mutations, advanced GISTs have a 0%–45% likelihood of responding to imatinib, although tumors known to be SDH deficient or having alternative drivers (eg, *NF1*, *BRAF*) are unlikely to benefit. Metastatic disease with acquired drug resistance is usually the result of secondary, imatinib-resistant mutations in *KIT* or *PDGFRA*. SDH-deficient GIST may have a higher probability of response to sunitinib.
[r] PET may give indication of imatinib activity after 2–4 weeks of therapy when rapid readout of activity is necessary. Diagnostic abdominal/pelvic CT or MRI with contrast is indicated every 8–12 weeks; routine long-term PET follow-up is rarely indicated. Frequency of response assessment imaging may be decreased if patient is responding to treatment.
[s] Rarely, increase in tumor size may not indicate lack of drug efficacy; all clinical and radiographic data should be taken into account, including lesion density on CT.
[t] Progression may be determined by abdominal/pelvic CT or MRI with contrast with clinical interpretation; PET scan may be used to clarify if CT or MRI are ambiguous.
[u] Suggest referral to a sarcoma specialty center.
[v] Assess medication adherence before determining that therapy was ineffective.
[w] Collaboration between medical oncologist and surgeon is necessary to determine the appropriateness of surgery, following major response or sustained stable disease. Maximal response may require treatment for 6 months or more to achieve.
[x] Imatinib can be stopped right before surgery and restarted as soon as the patient is able to tolerate oral medications. If other TKIs, such as sunitinib or regorafenib, are being used, therapy should be stopped at least one week prior to surgery and can be restarted based on clinical judgment or recovery from surgery.

**Note: All recommendations are category 2A unless otherwise indicated.**
**Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.**

# GIST Συστηματική θεραπεία-1η γραμμή

National Comprehensive Cancer Network®

## NCCN Guidelines Version 6.2019
## Gastrointestinal Stromal Tumors (GIST)

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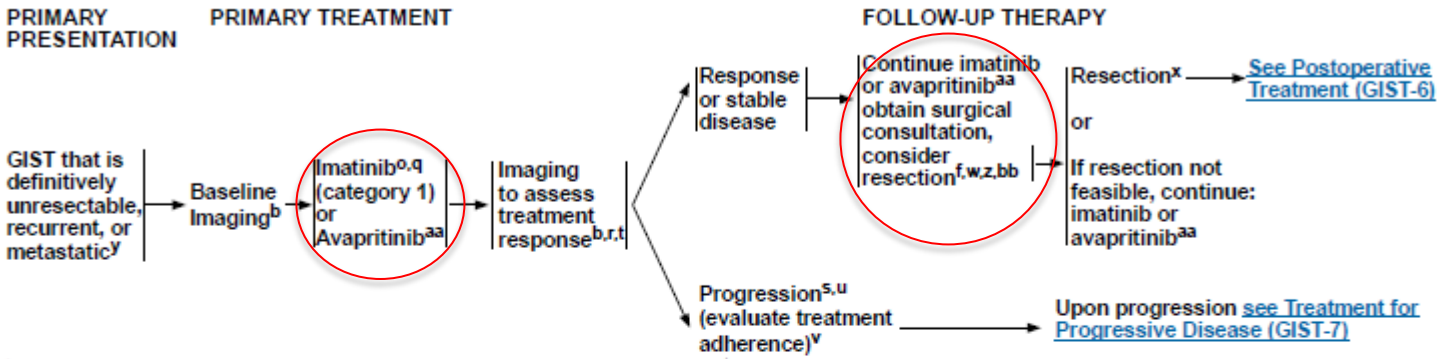


[b] See Principles of Imaging (SARC-A).
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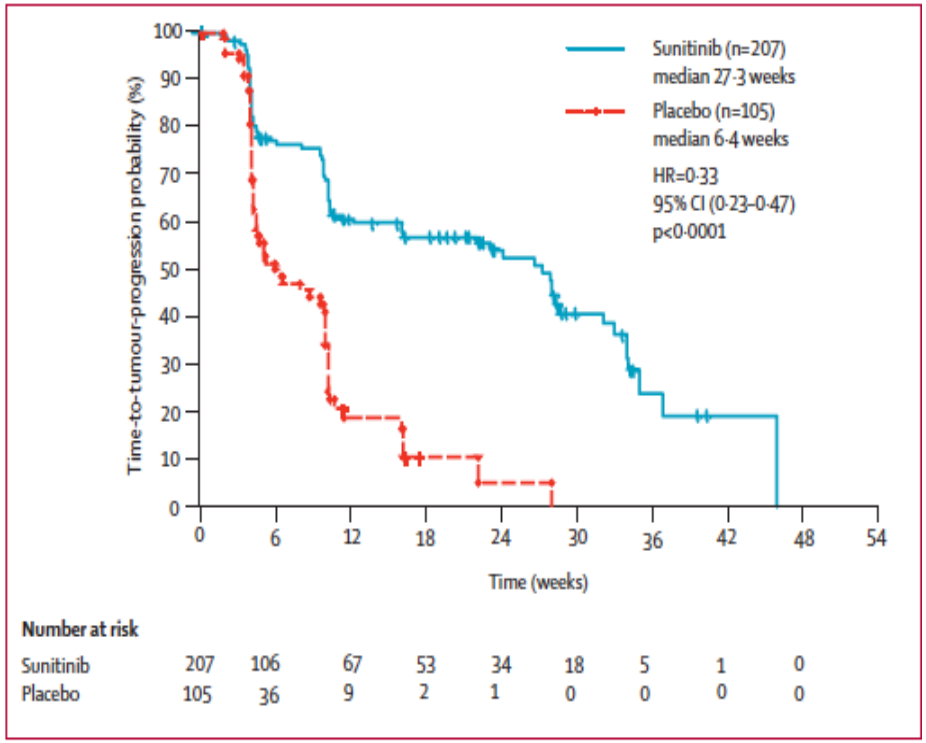
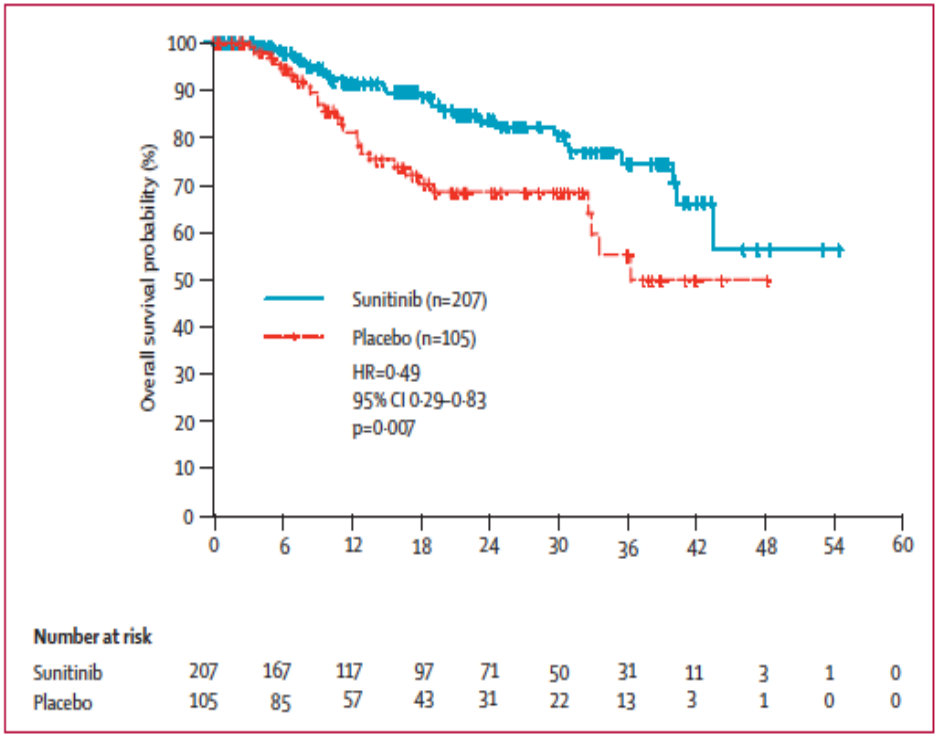
[t] Progression may be determined by abdominal/pelvic CT or MRI with contrast with clinical interpretation; PET scan may be used to clarify if CT or MRI are ambiguous.
[u] Suggest referral to a sarcoma specialty center.
[v] Assess medication adherence before determining that therapy was ineffective.
[w] Collaboration between medical oncologist and surgeon is necessary to determine the appropriateness of surgery, following major response or sustained stable disease. Maximal response may require treatment for 6 months or more to achieve.
[x] Imatinib can be stopped right before surgery and restarted as soon as the patient is able to tolerate oral medications. If other TKIs, such as sunitinib or regorafenib, or avapritinib are being used, therapy should be stopped at least one week prior to surgery and can be restarted based on clinical judgment or recovery from surgery.
[y] Consider baseline PET, if using PET during follow-up. PET is not a substitute for CT.
[z] No definitive data exist to prove whether surgical resection improves clinical outcomes in addition to TKI therapy alone in metastatic GIST. Prospective randomized trials are underway to assess whether or not resection changes outcomes in patients with metastatic GIST responding to TKI therapy.
[aa] Indicated for GIST with *PDGFRA* exon 18 mutation, including *PDGFRA* D842V mutations.
[bb] Consider resection if complete resection can be obtained in primary metastatic disease.

**Note: All recommendations are category 2A unless otherwise indicated.**
**Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.**

# Sunitinib in advanced GIST after Imatinib failure
# Phase III trial



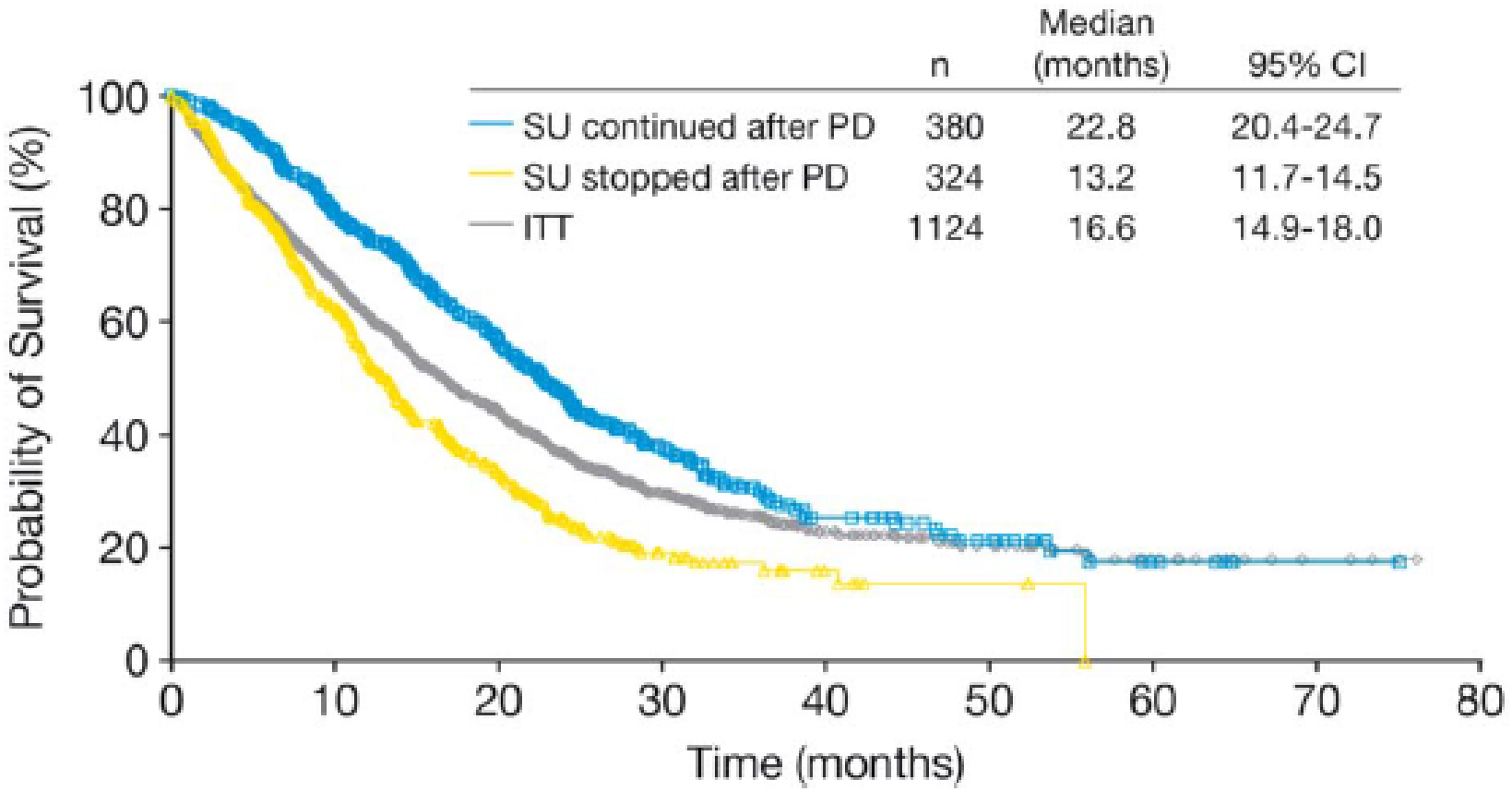




TTP (w)
Sunitinib: 27,3  Placebo: 6,4  p< 0,0001

Dmetri G et al. Lancet 2006

# Clinical Outcomes of Patients With Advanced Gastrointestinal Stromal Tumors: Safety and Efficacy in a Worldwide Treatment-Use Trial of Sunitinib

1124 pts



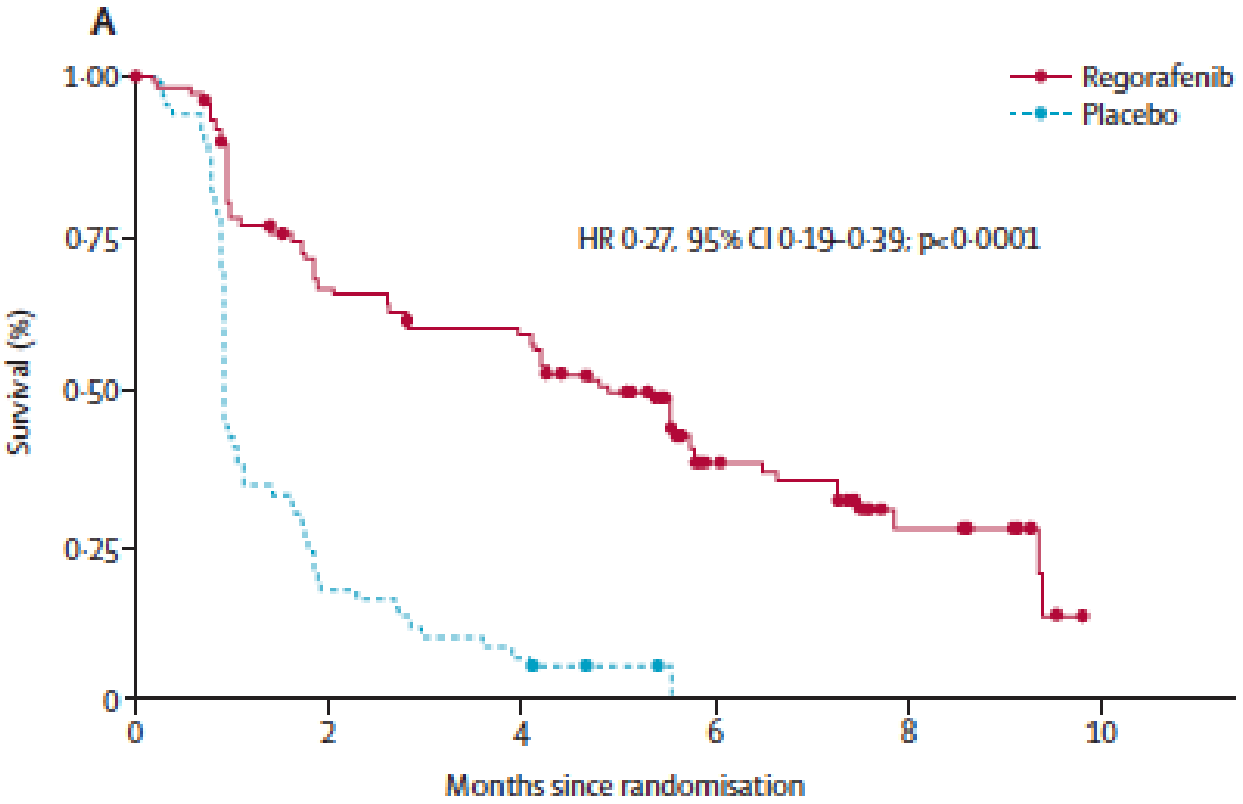

Reichardt P et al. Cancer 2015

# Θεραπεία GIST
# Sunitinib (Sutent, Pfizer)

- Έγκριση FDA: 1/2006
- Αναστολέας KIT, PDGFRA, VEGFR
- 2ης γραμμής θεραπεία
  - Αντίσταση στη θεραπεία με Imatinib (α'-γενής β'-γενής)
  - Δυσανεξία στη θεραπεία με Imatinib
- Χορήγηση από του στόματος
  - 50mg x1, 4 εβδ., 2 εβδ. διακοπή
  - 37,5 mg x1 (συνεχής χορήγηση)

# Efficacy and safety of regorafenib for advanced GISTs after failure of imatinib and sunitinib (GRID): an international, multicentre, randomised, placebo-controlled, phase 3 trial

240 pts

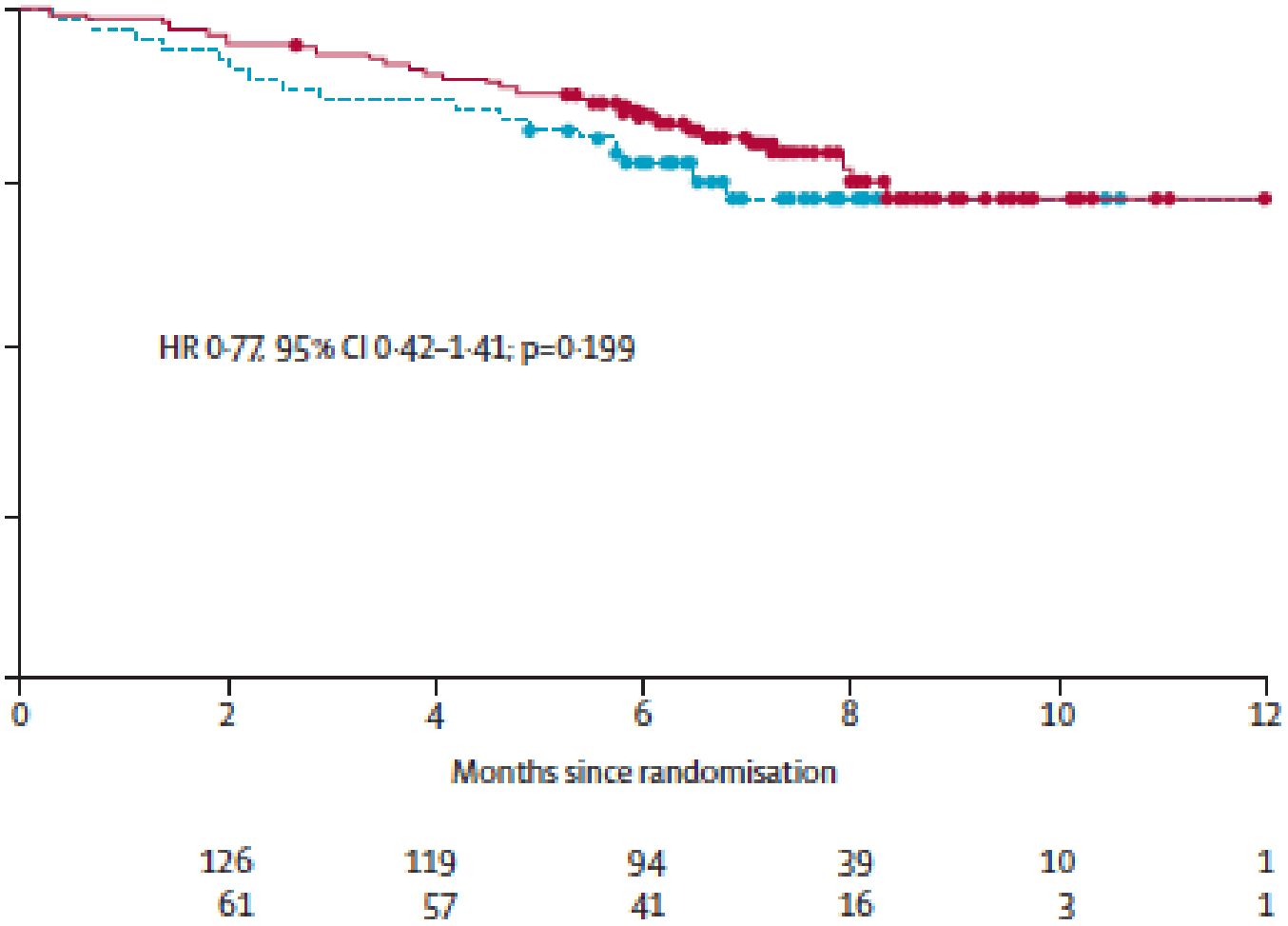



PFS (primary endpoint)

Regorafenib: 4,8 m Placebo: 0,9 m p< 0,0001

Demetri G et al. Lancet 2013

# Efficacy and safety of regorafenib for advanced GISTs after failure of imatinib and sunitinib (GRID): an international, multicentre, randomised, placebo-controlled, phase 3 trial




OS: ns

Demetri G et al. Lancet 2013

# Third-Line GIST Treatment: Regorafenib

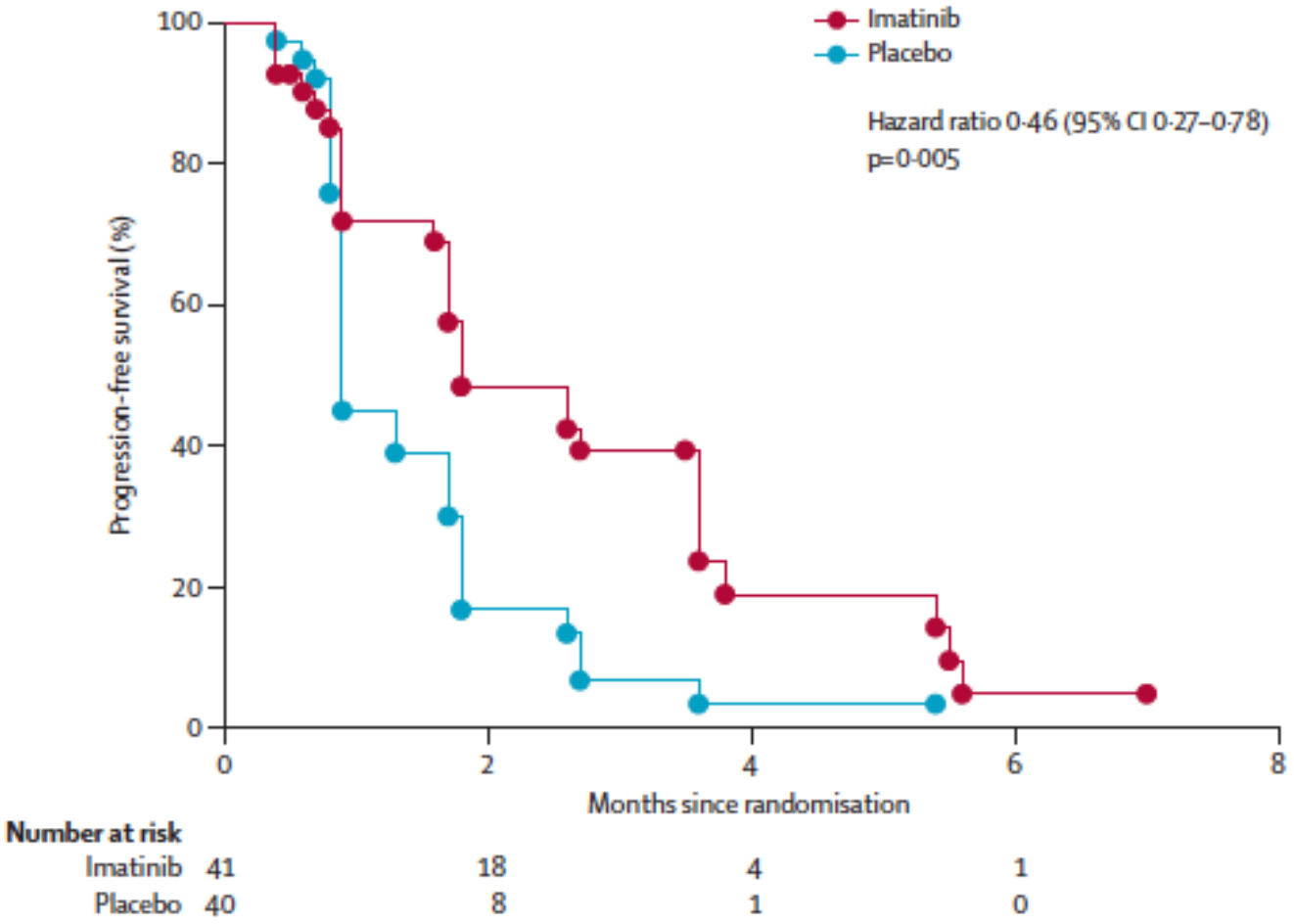
- Inhibits KIT, PDGFRA, RET, RAF1, BRAF, VEGFR, FGFR[a]
- FDA-approved for use after imatinib and sunitinib[b]
  - Dosed at 160 mg daily 21 of 28 days
- Efficacy
  - mPFS 4.8 mo; ORR 4.5%[c]
- Common toxicities[b]:
  - Hand-foot skin reaction; fatigue; diarrhea; hypertension; dysphonia; mucositis; rash; nausea

a. Bauer S, et al. *Drugs*. 2015;75:1323-1334; b. Stivarga® PI 2018;
c. Demetri GD, et al. *Lancet*. 2013;381:295-302.

# Resumption of imatinib to control metastatic or unresectable GISTs after failure of imatinib and sunitinib (RIGHT): a randomised, placebo-controlled, phase 3 trial

Imatinib: 41 pts
Placebo: 40 pts

PFS (m)
Imatinib: 1,8
Placebo: 0,9
P< 0,005



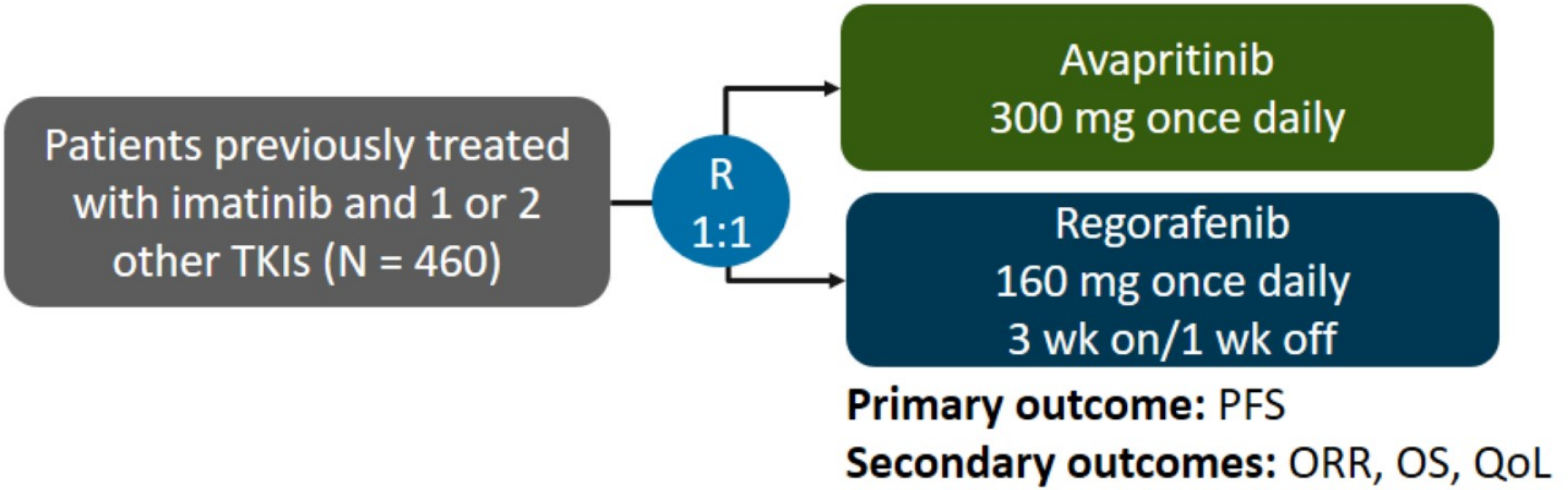

Kang YK et al. Lancet )ncol 2013

# Investigational Approaches: Crenolanib

- Inhibits FLT3, PDGFR, KIT
- Active against *PDGFRA* D842V[a]
- Dose-escalation phase 1/2 study (N = 20)[b]
  - Efficacy
    - 31% CBR (5/16) in patients with D842V
    - 2/16 PRs
  - Safety
    - Grade 3/4 AEs: LFT elevations (n = 3), anemia (n = 3)

a. Heinrich MC, et al. *Clin Cancer Res.* 2012;18:4375-4384; b. von Mehren M, et al. ASCO® 2016. Abstract 11010.

# VOYAGER: Phase 3 Trial of Avapritinib in Third- and Fourth-Line GIST




**Primary outcome:** PFS

**Secondary outcomes:** ORR, OS, QoL

- Additional clinical trials are planned, including second-line trial that includes genotype testing

ClinicalTrials.gov. NCT03465722.

# Key Takeaways

- Select best available therapy based on molecular profile
  - For *KIT* exon 11, frontline imatinib is standard
  - For *KIT* exon 9, try to dose-escalate imatinib
  - If *BRAF* mutation, consider off-label BRAF inhibitor
  - If *NTRK* fusion, use on-label larotrectinib
  - If SDH-deficient, refer to GIST center
  - If D842V, enroll in clinical trial or obtain active agent through expanded access

**If no suitable therapy is available, find a clinical trial**

# **GIST**
## Multidisciplinary Team

- Molecular Biolo**GIST**
- Patholo**GIST**
- Gastroenterolo**GIST**
- Medical Oncolo**GIST**
- Surgical Oncolo**GIST**
- Radiolo**GIST**

15η Πανελλήνια Εκπαιδευτική Συνάντηση ΕΛΙΓΑΣΤ

Ελληνικό Ίδρυμα Γαστρεντερολογίας και Διατροφής

# "Εξελίξεις στη Γαστρεντερολογία και Ηπατολογία"

6-8 Μαρτίου 2020

Αθήνα, Ξενοδοχείο Divani Caravel
Αίθουσα MACEDONIA

Θα χορηγηθούν μόρια Συνεχιζόμενης Ιατρικής Εκπαίδευσης (CME-CPD credits) από τον Πανελλήνιο Ιατρικό Σύλλογο.

Ευχαριστώ για την προσοχή σας