# GIST : modèle pour la biologie moléculaire
# Du diagnostic à la thérapeutique

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27 avril 2023

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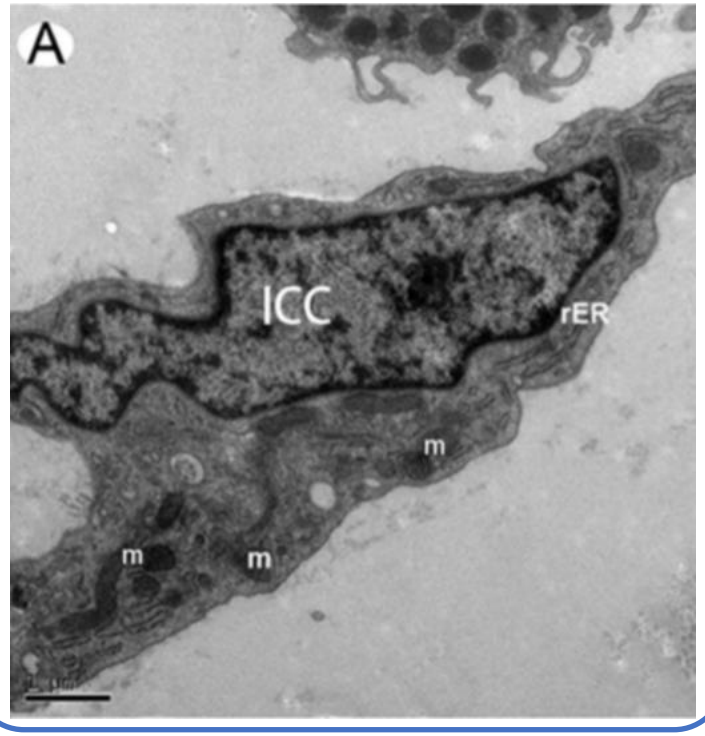
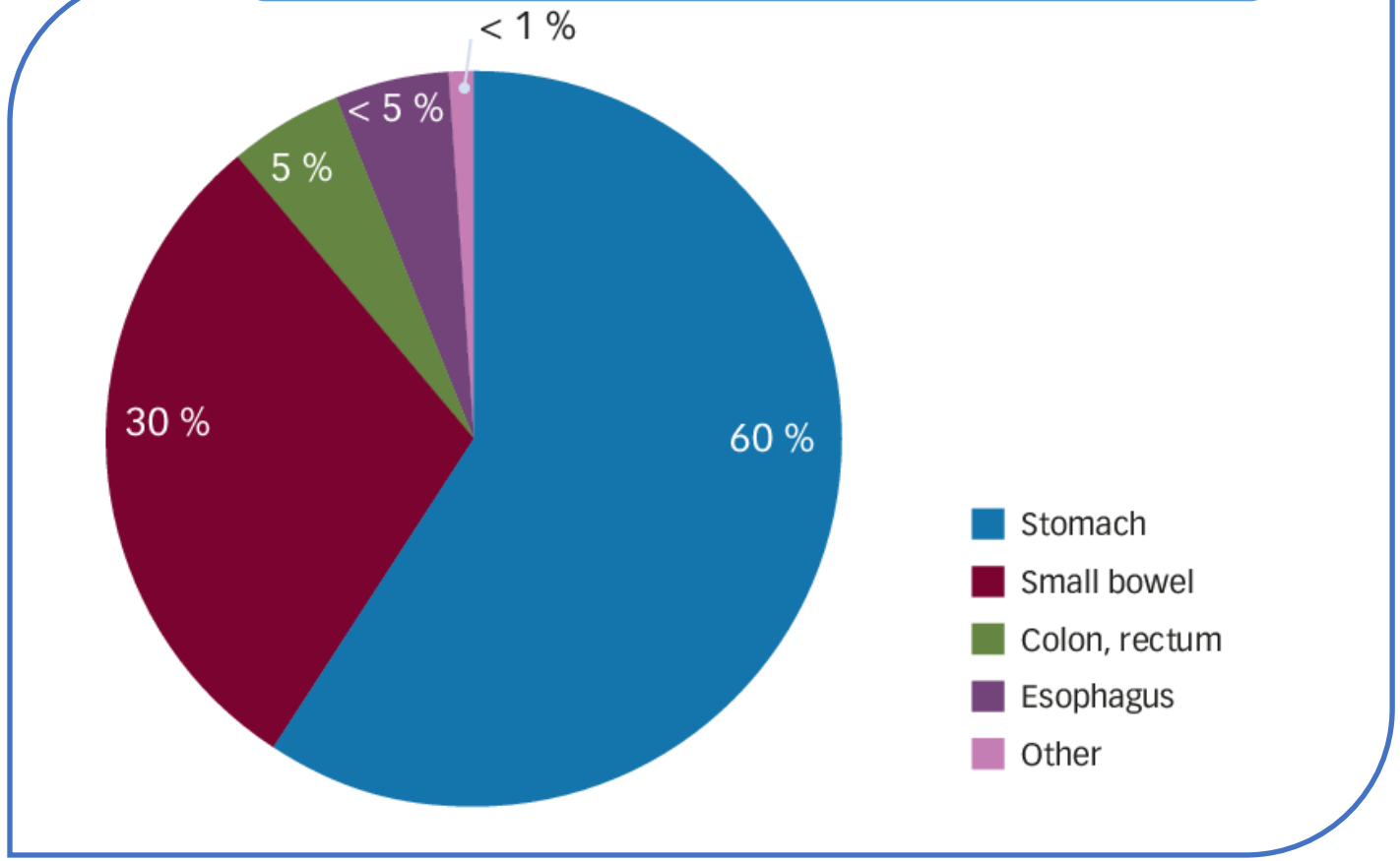
CHU Jean Minjoz - Besançon

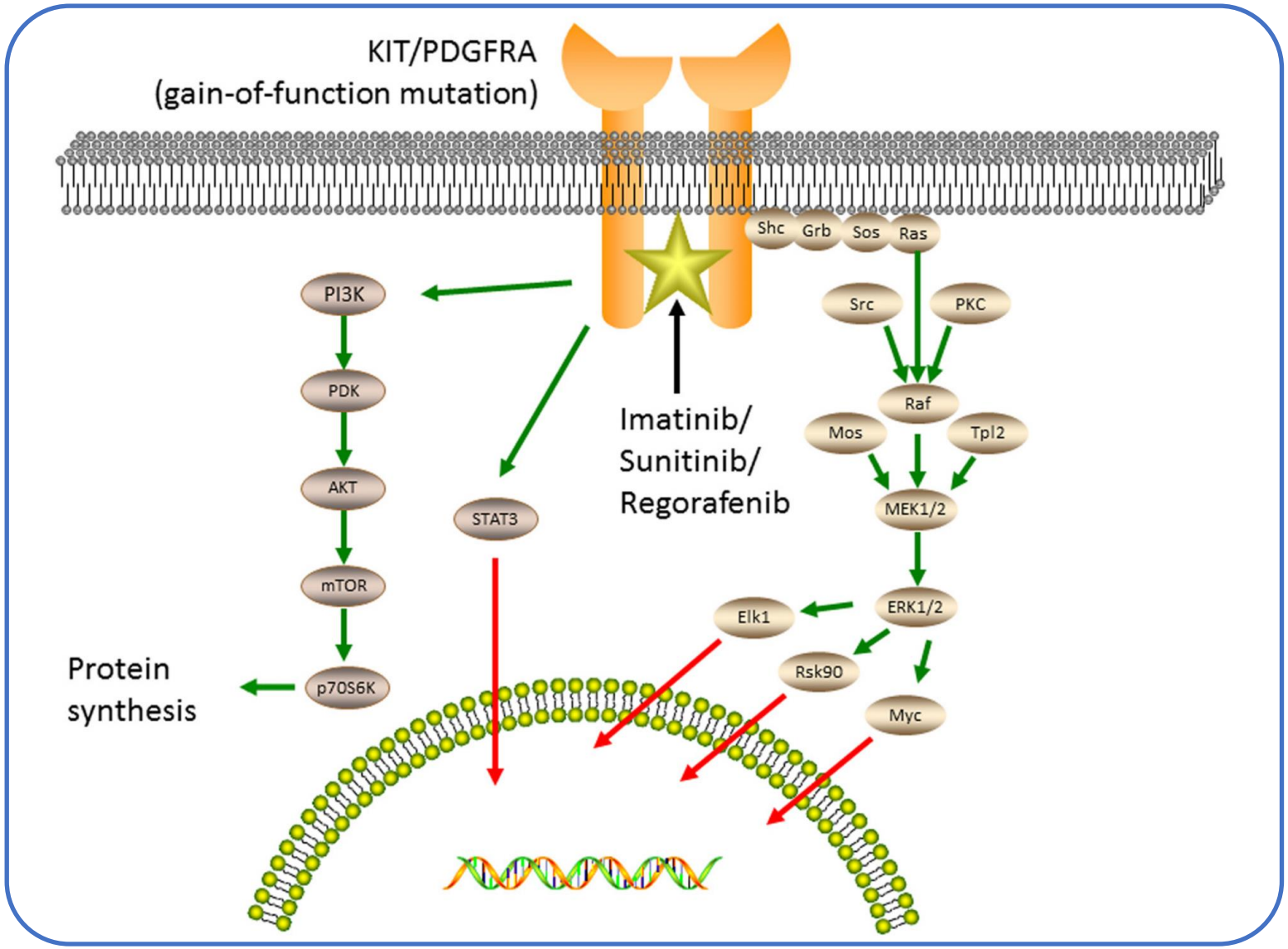
## Epidémiologie

- Rare : **15**/million d'habitants/an
- Le plus fréquent des sarcomes :
  - GIST : **600-900** cas/an (France)
  - Sarcomes : **4000** cas/an (France)




## Gastro-Intestinal Stromal Tumour (GIST)

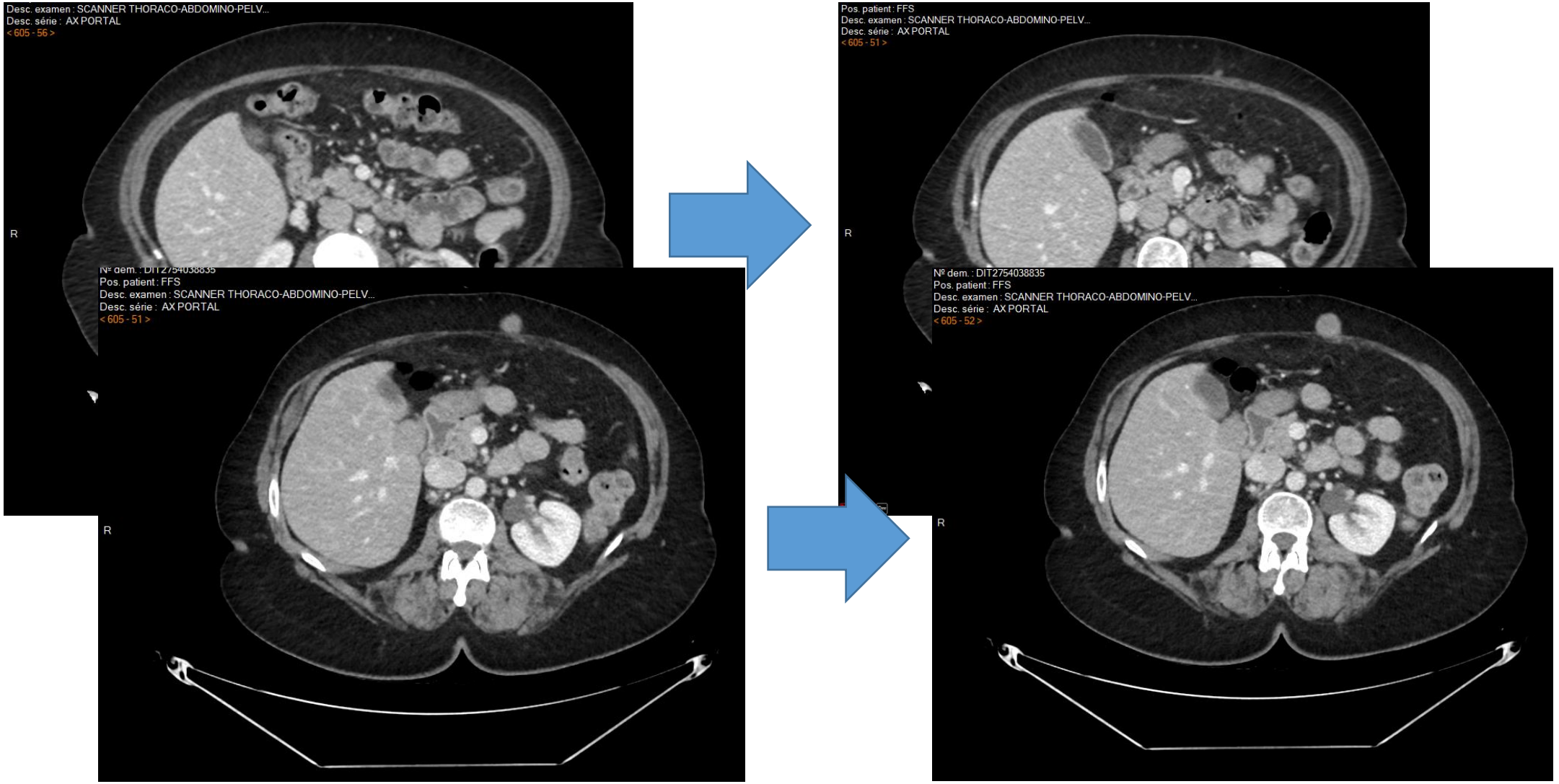





## Carcinogénèse

- Mutations activatrices de RTK
- Voies de prolifération cellulaires
  - JAK-STAT3
  - PI3K-AKT-mTOR
  - RAS-RAF-MAPK
- Régulation des fonctions cellulaires
  - Prolifération
  - Apoptose
  - Chemotaxie
  - Adhésion

Li, *Oncotarget* 2017


Desc. examen : SCANNER THORACO-ABDOMINO-PELV...
Desc. série : AX PORTAL
< 605 - 56 >
R
Nº dem. : DIT2754038835
Pos. patient : FFS
Desc. examen : SCANNER THORACO-ABDOMINO-PELV...
Desc. série : AX PORTAL
< 605 - 51 >
R
Pos. patient : FFS
Desc. examen : SCANNER THORACO-ABDOMINO-PELV...
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Nº dem. : DIT2754038835
Pos. patient : FFS
Desc. examen : SCANNER THORACO-ABDOMINO-PELV...
Desc. série : AX PORTAL
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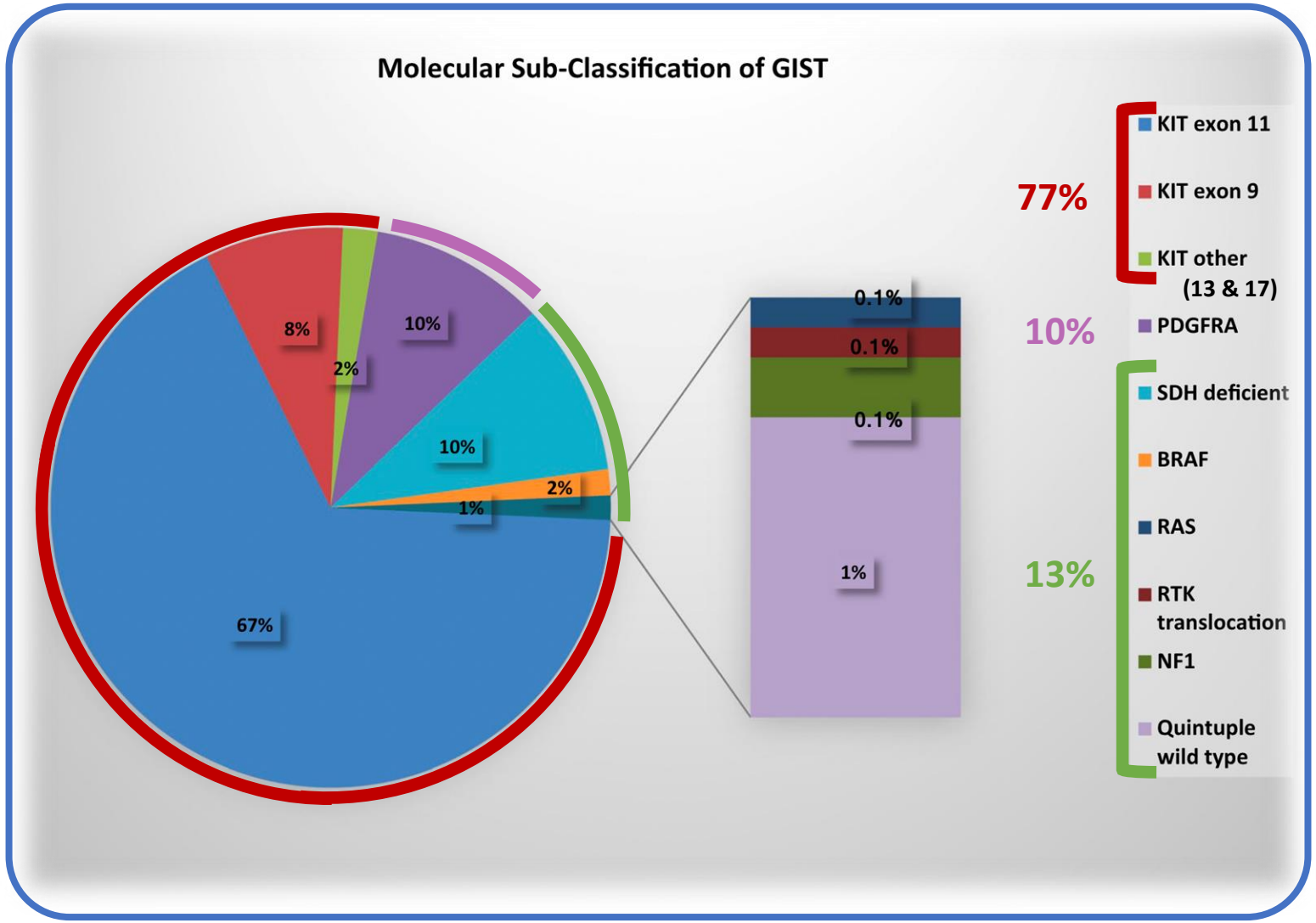
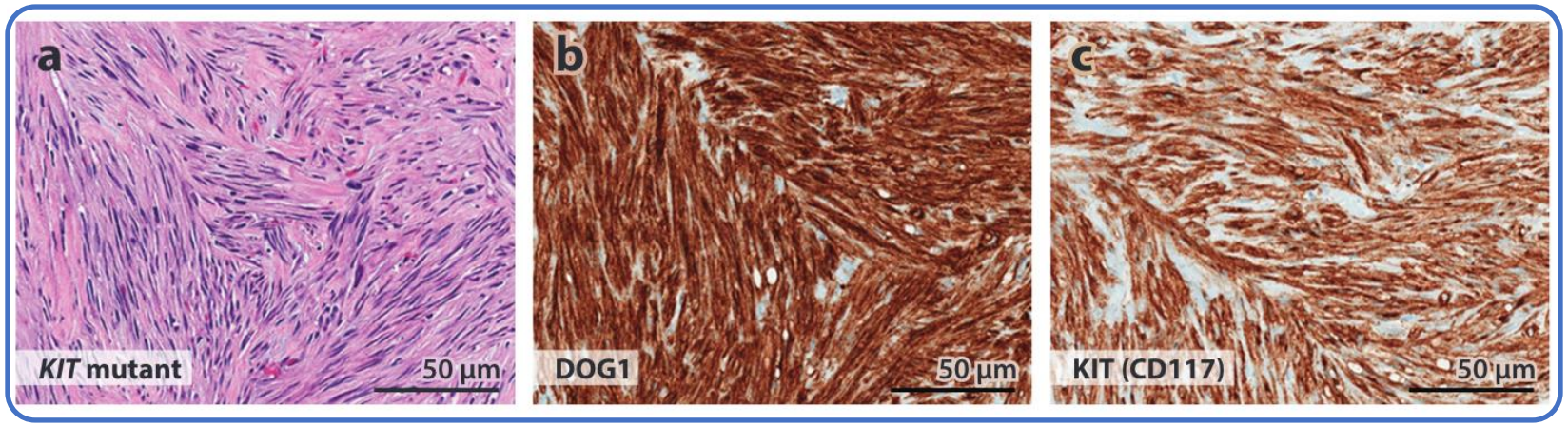



Tsvetkova, *European Oncology and Haematology* 2015

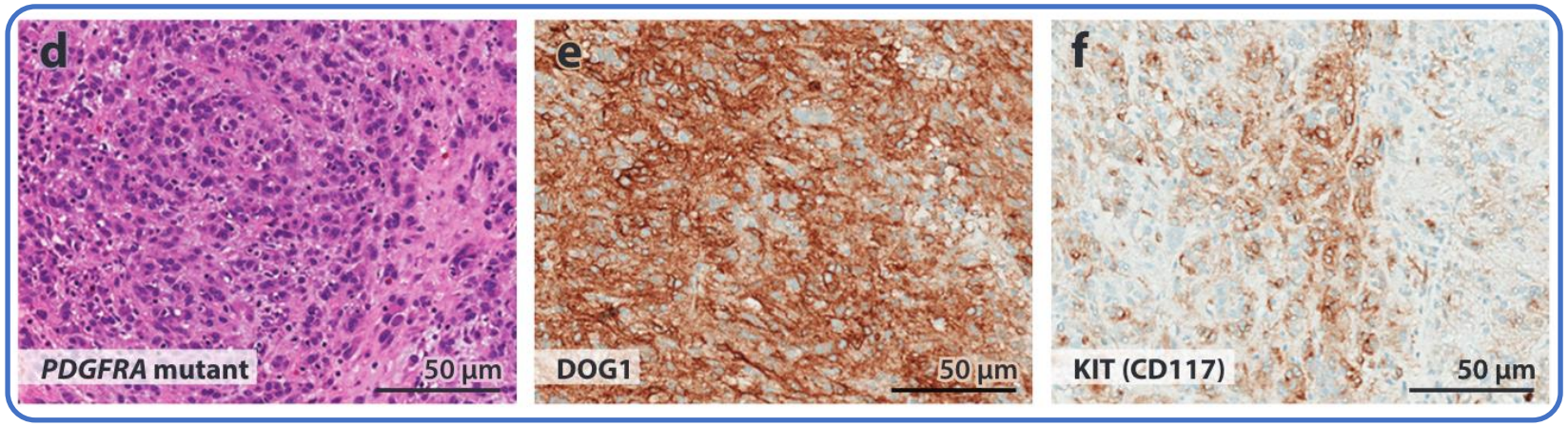
## KIT mutant GIST

- Morphologie :
  - « Spindle cell »

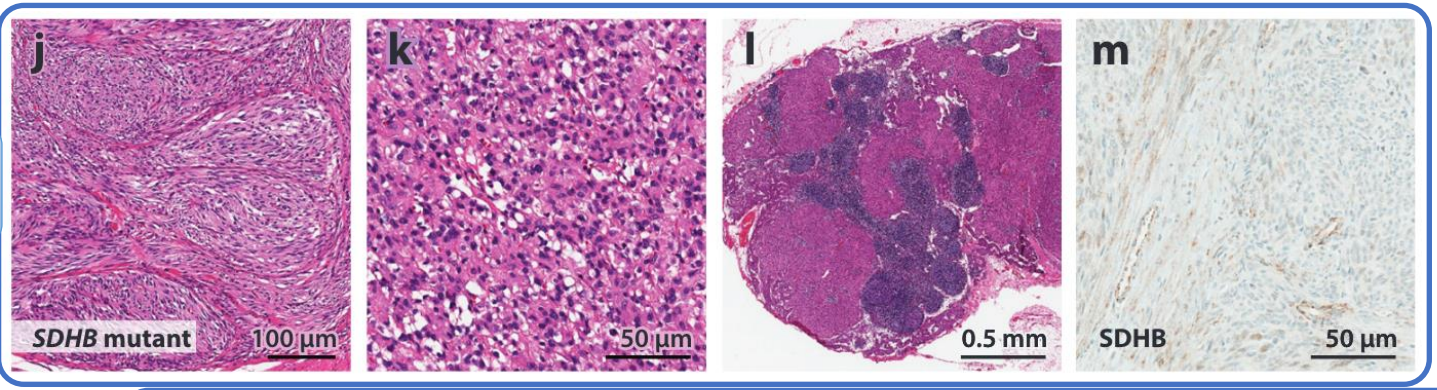



## PDGFRA mutant GIST

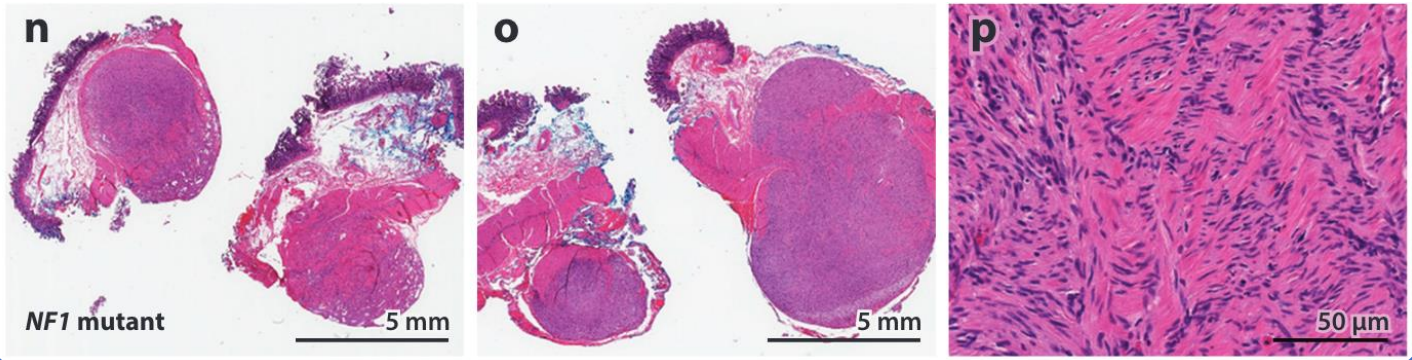
- Morphologie :
  - « Epithéloïde »



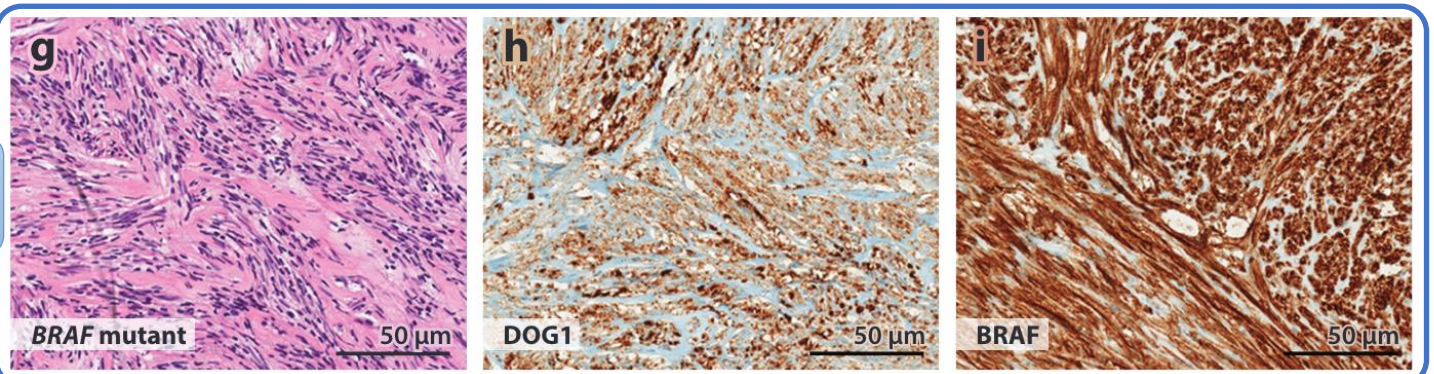
**SDHB mutant GIST**



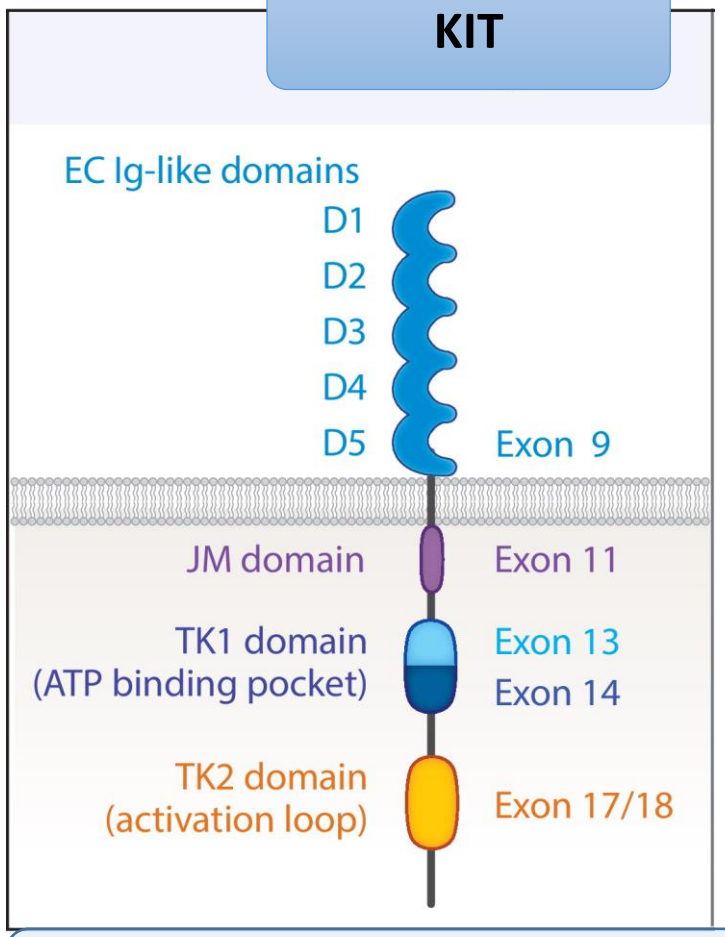

**NF1 mutant GIST**




**BRAF mutant GIST**

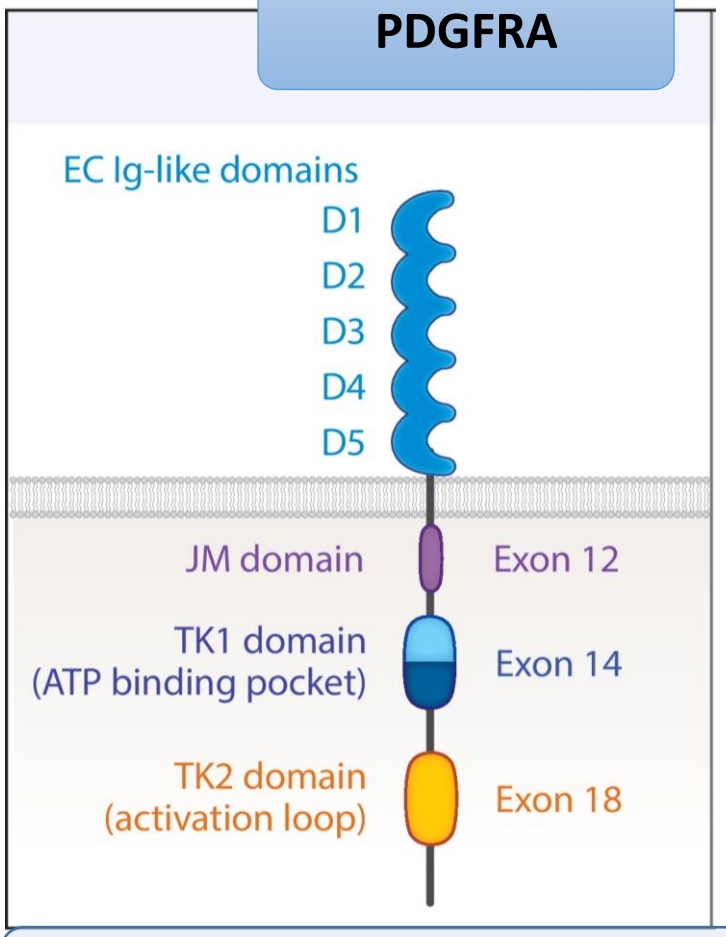


## KIT

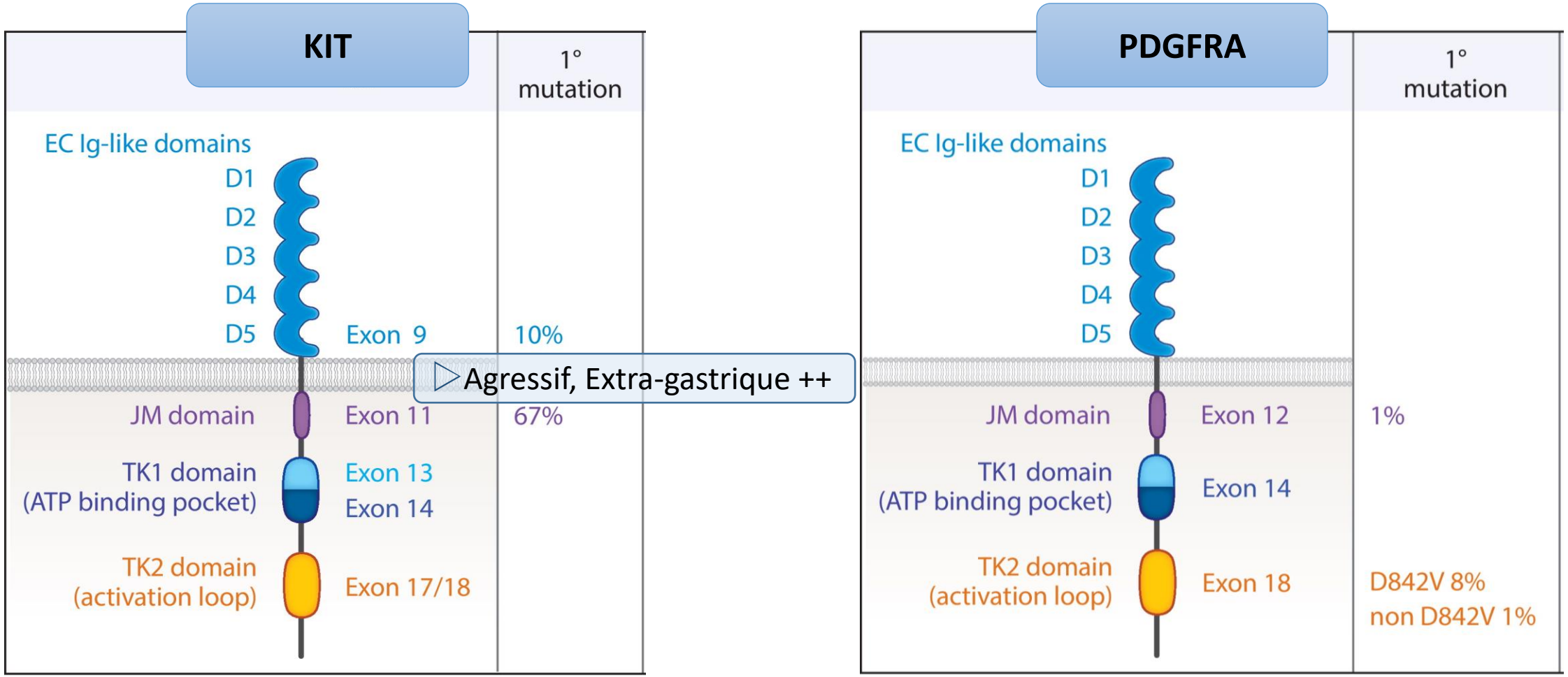



▷Physiologiquement : **Maintien des pop cellulaires**
▷Hématopoïèse, Gamétogénèse, Mélanogénèse

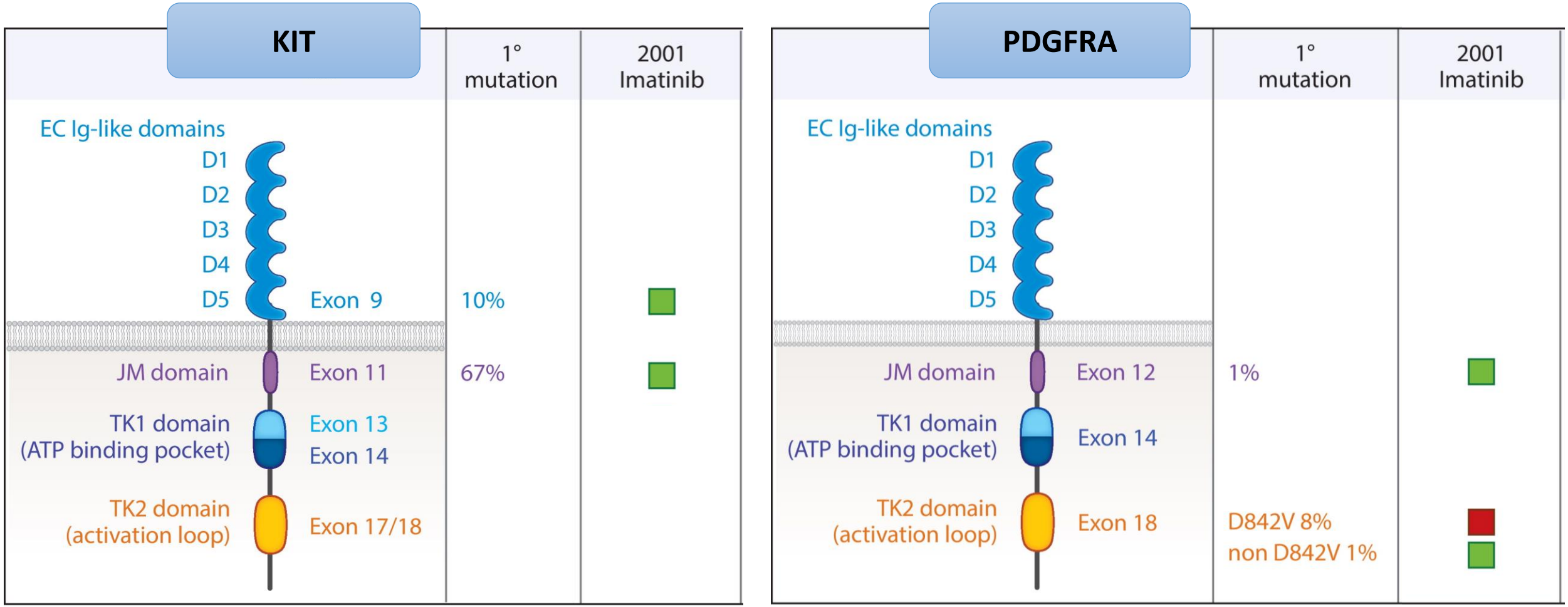
## PDGFRA




▷Physiologiquement : **Neurotransmission**
▷Motilité digestive


KIT
1° mutation
EC Ig-like domains
D1
D2
D3
D4
D5
Exon 9
10%
Agressif, Extra-gastrique ++
JM domain
Exon 11
67%
TK1 domain
(ATP binding pocket)
Exon 13
Exon 14
TK2 domain
(activation loop)
Exon 17/18
PDGFRA
1° mutation
EC Ig-like domains
D1
D2
D3
D4
D5
JM domain
Exon 12
1%
TK1 domain
(ATP binding pocket)
Exon 14
TK2 domain
(activation loop)
Exon 18
D842V 8%
non D842V 1%

▷KIT, BCR-ABL, PGDFR alpha/beta



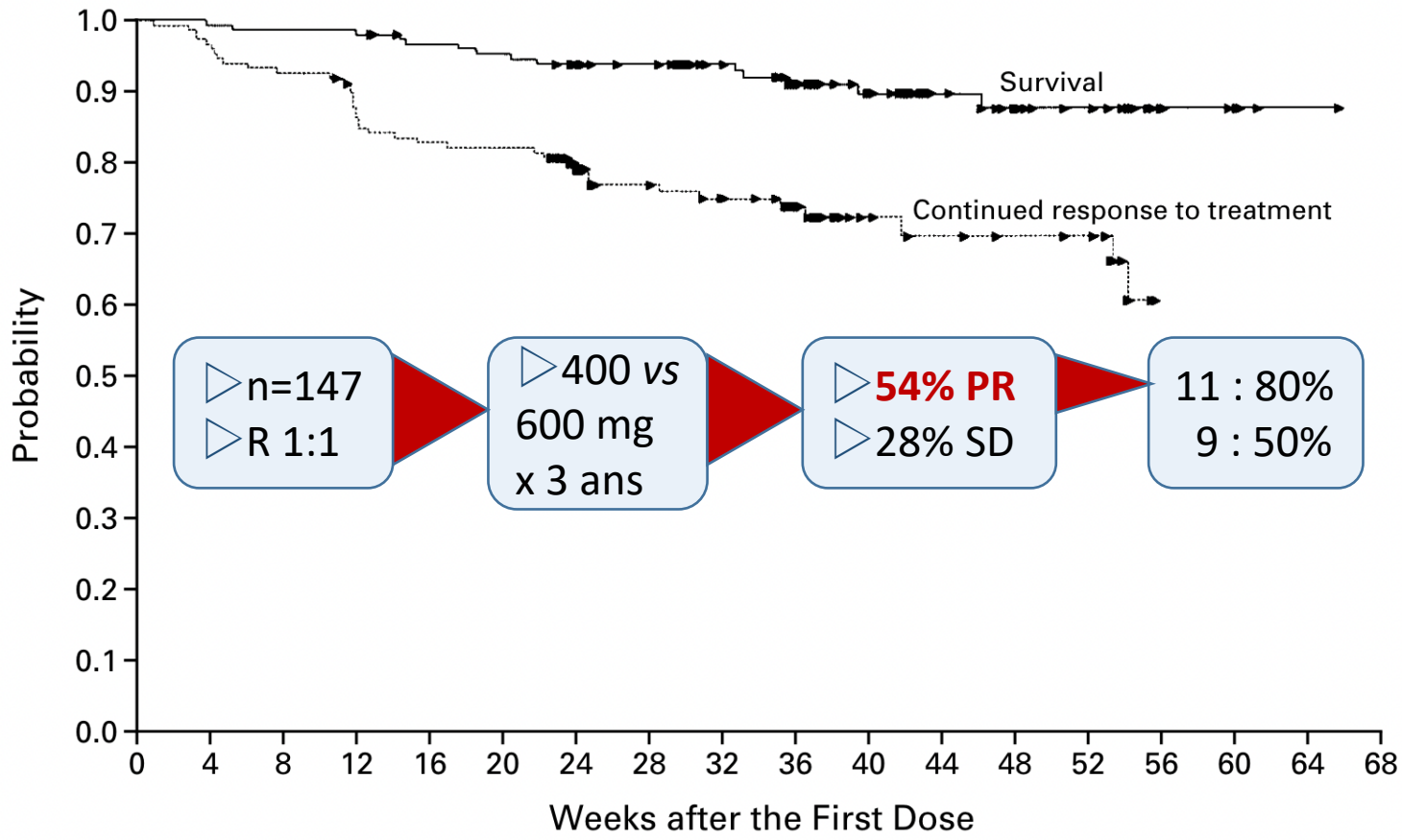
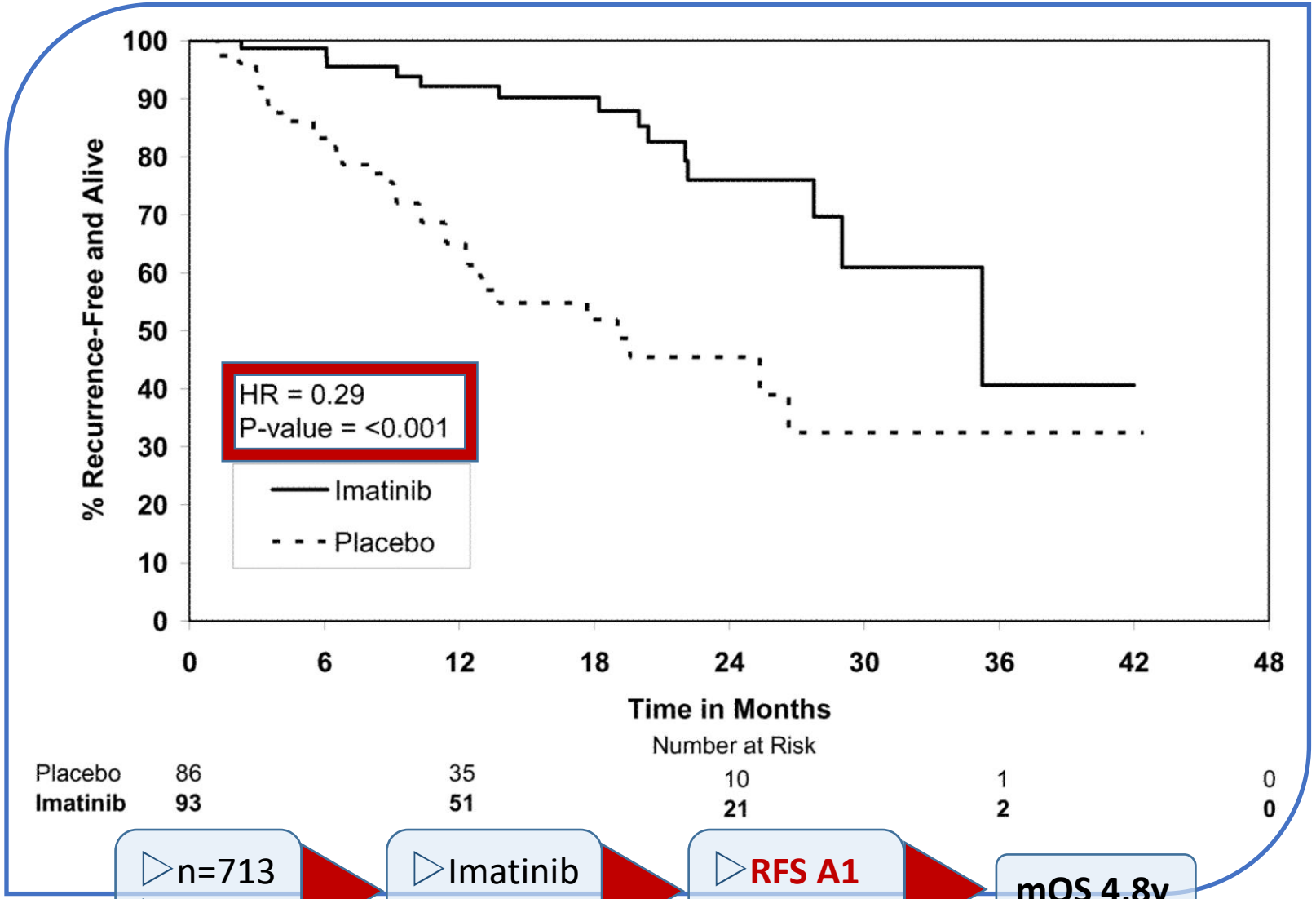



**Figure 1.** Kaplan–Meier Estimates of Overall Survival and Time to Treatment Failure for All Patients. Each arrowhead represents the point at which a patient's data were censored.

## **Imatinib** (GLIVEC®)

- AMM 2002 :
  - GIST Kit (CD117) +
  - **non résécables**
  - et/ou **métastatiques**
  - x6-12m +/- résection secondaire

Demetri, *NEJM* 2002




- n=713
- R 1:1

→ Imatinib *vs* placebo

→ **RFS A1 98 vs 83%**

→ **mOS 4,8y**

## **Imatinib** (GLIVEC®)

- AMM 2002 :
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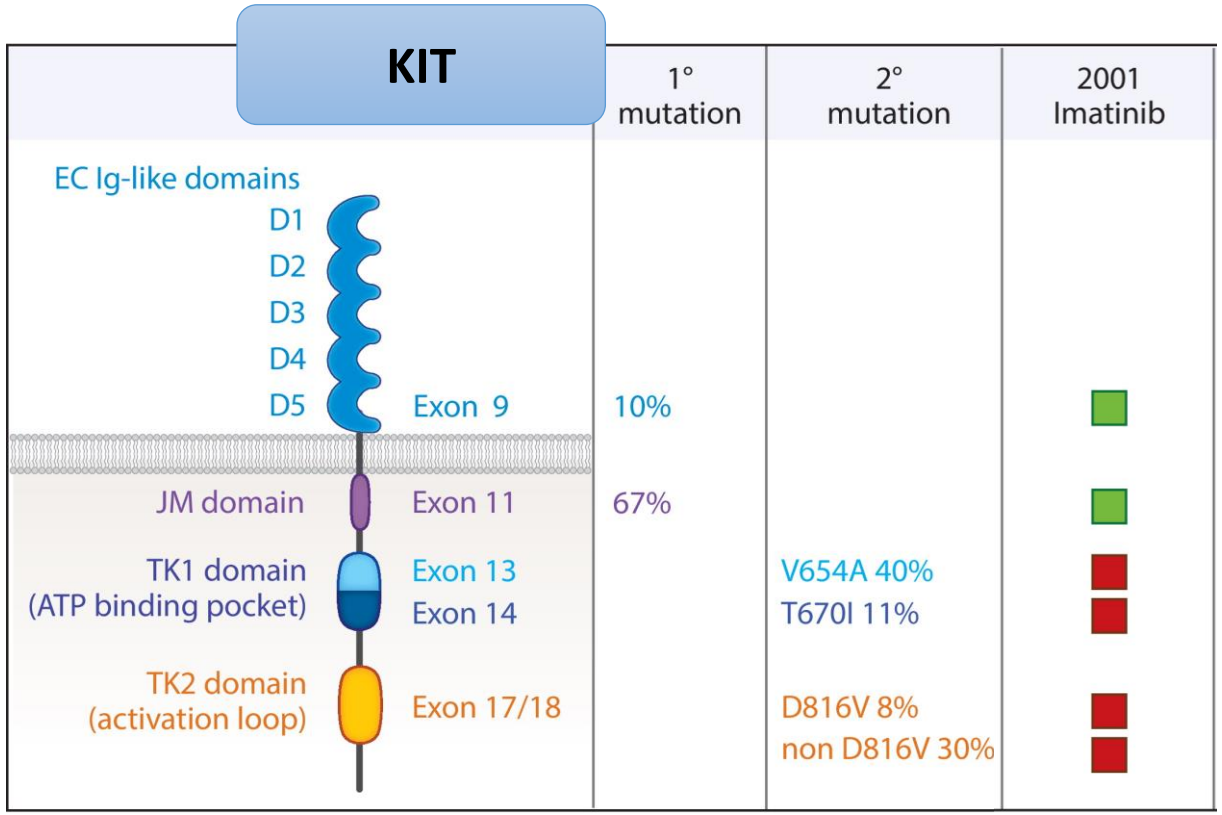
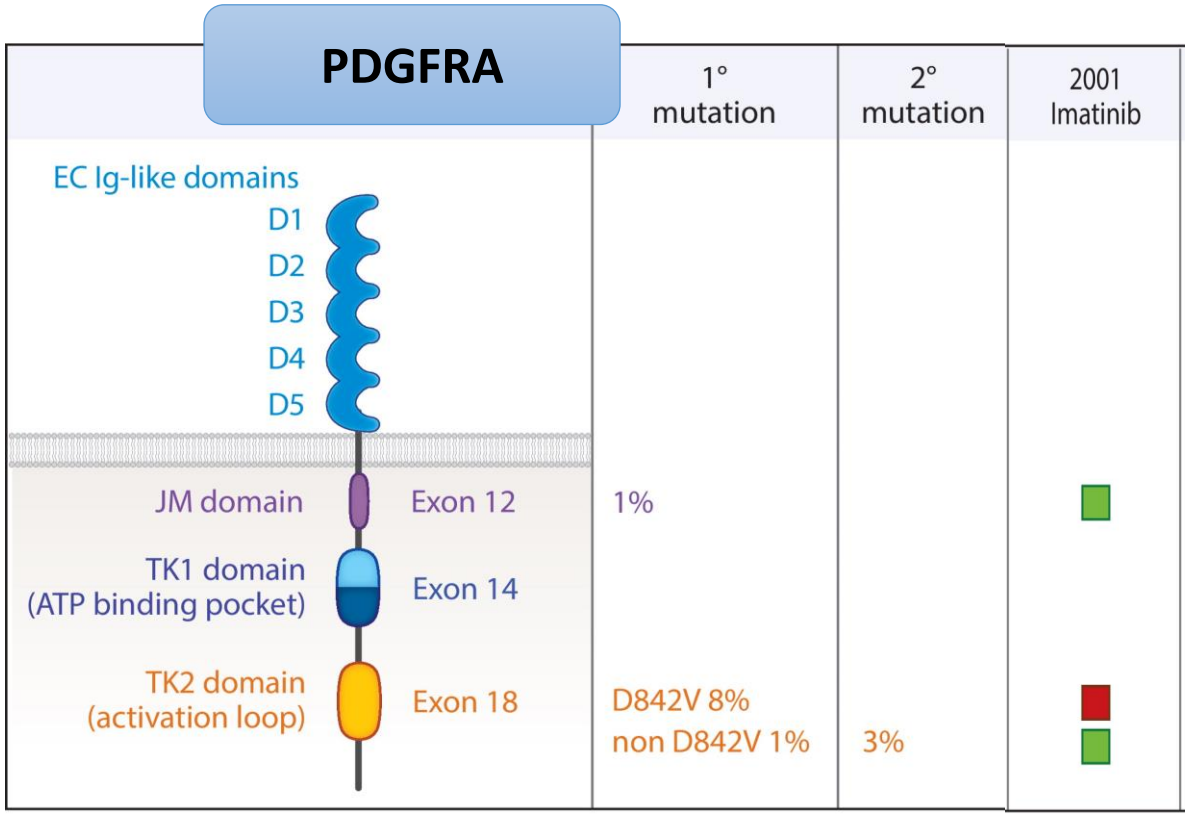
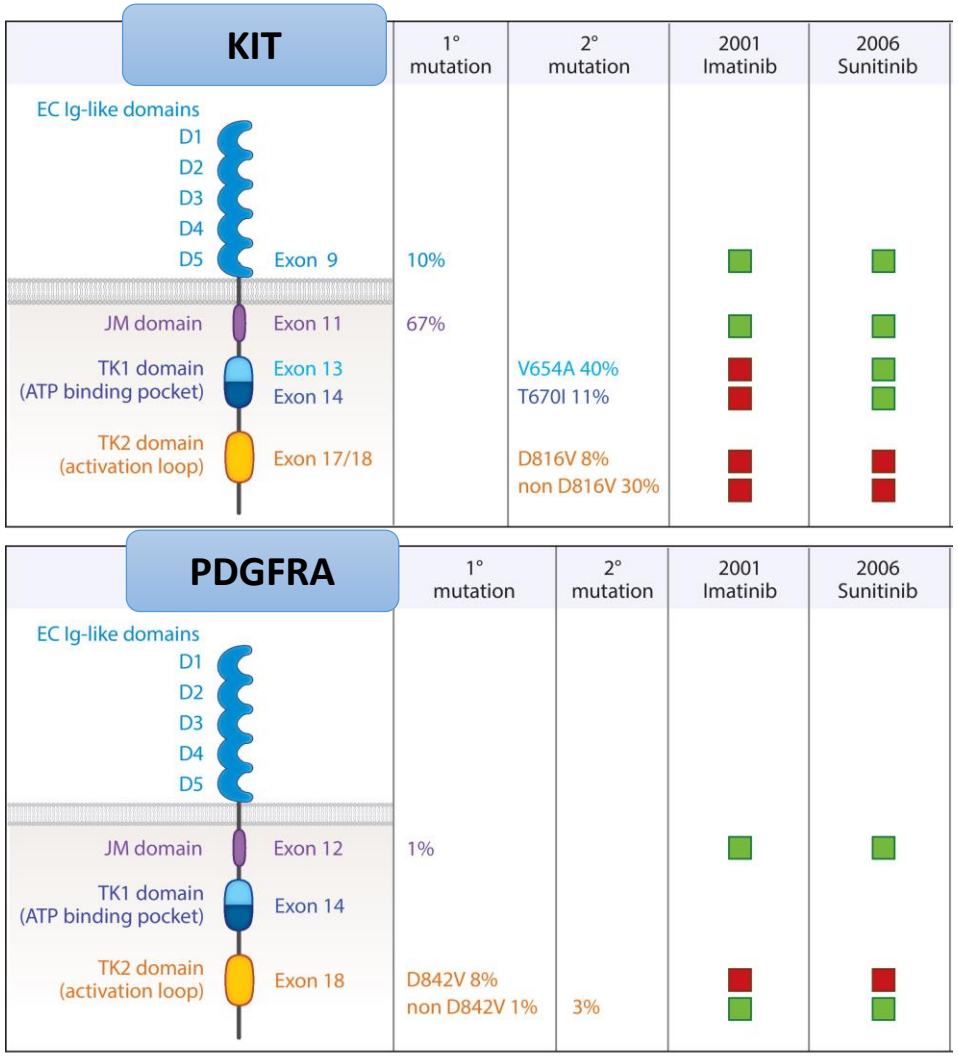
  - **non résécables**
  - et/ou **métastatiques**
  - x6-12m +/- résection secondaire
- AMM 2009 :
  - GIST Kit (CD117) +
  - **Adjuvant**
  - Risque significatif de rechute
  - **x3 ans**
- AMM ? :
  - **Néo-adjuvant** ?
  - **GIST Wild Type** ?

De Matteo, *Lancet* 2009

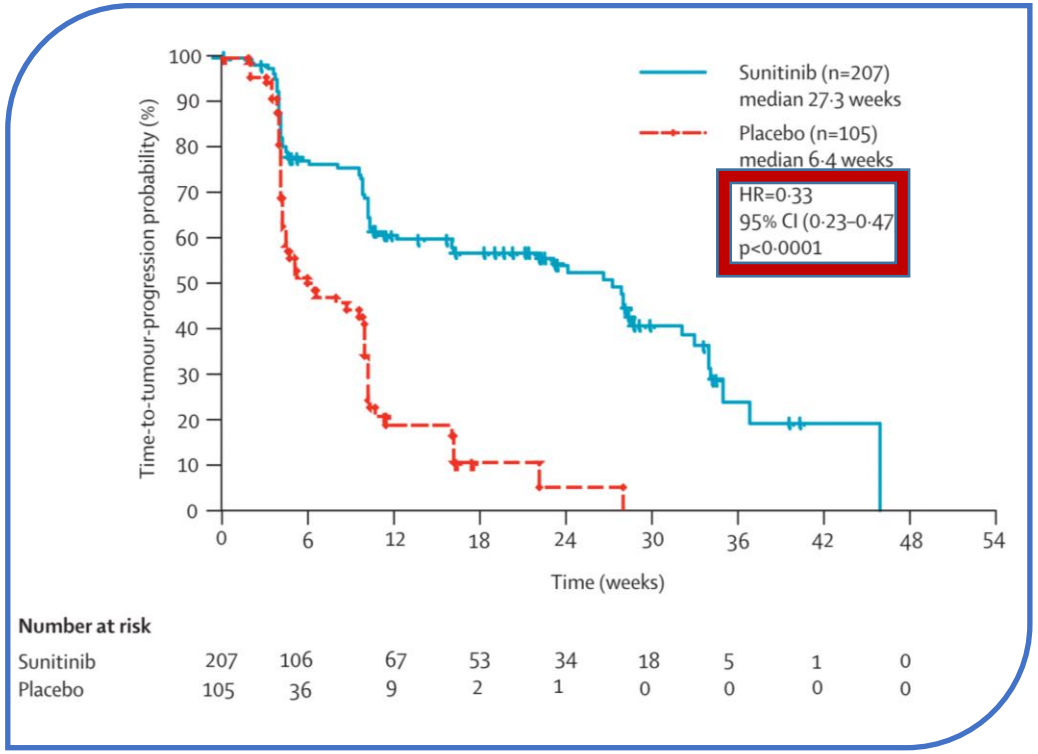

KIT
1° mutation
2° mutation
2001 Imatinib
EC Ig-like domains
D1
D2
D3
D4
D5
Exon 9
10%
JM domain
Exon 11
67%
TK1 domain
(ATP binding pocket)
Exon 13
Exon 14
V654A 40%
T670I 11%
TK2 domain
(activation loop)
Exon 17/18
D816V 8%
non D816V 30%


PDGFRA
1° mutation
2° mutation
2001 Imatinib
EC Ig-like domains
D1
D2
D3
D4
D5
JM domain
Exon 12
1%
TK1 domain
(ATP binding pocket)
Exon 14
TK2 domain
(activation loop)
Exon 18
D842V 8%
non D842V 1%
3%



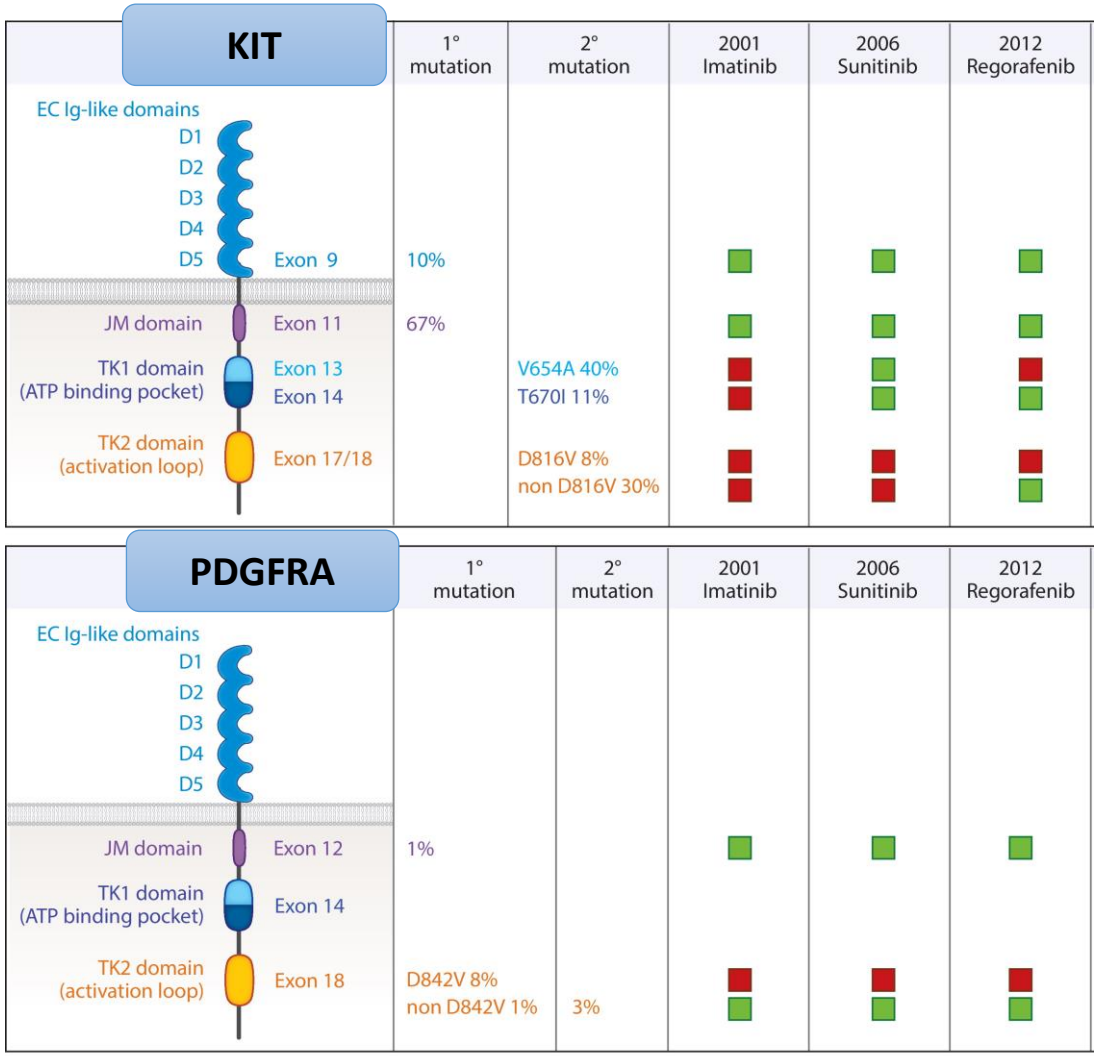

## Sunitinib (SUTENT®)

- AMM 2006 :
  - **L2 non résécables / métastatique**
  - **Si toxicité / résistance L1 Imatinib**



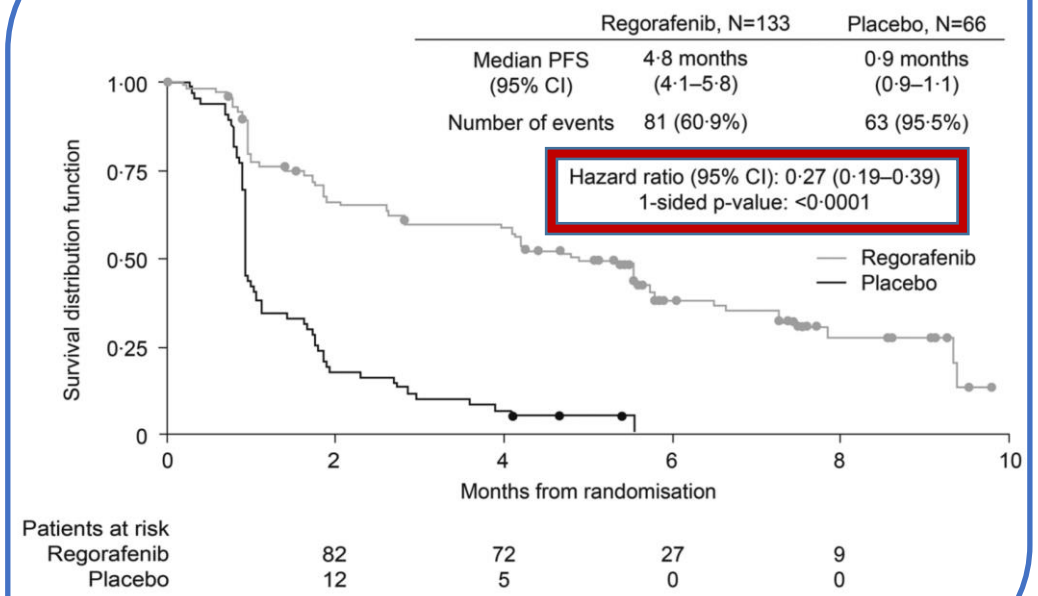

Dermawan, *Annual Review of Pathology* 2022

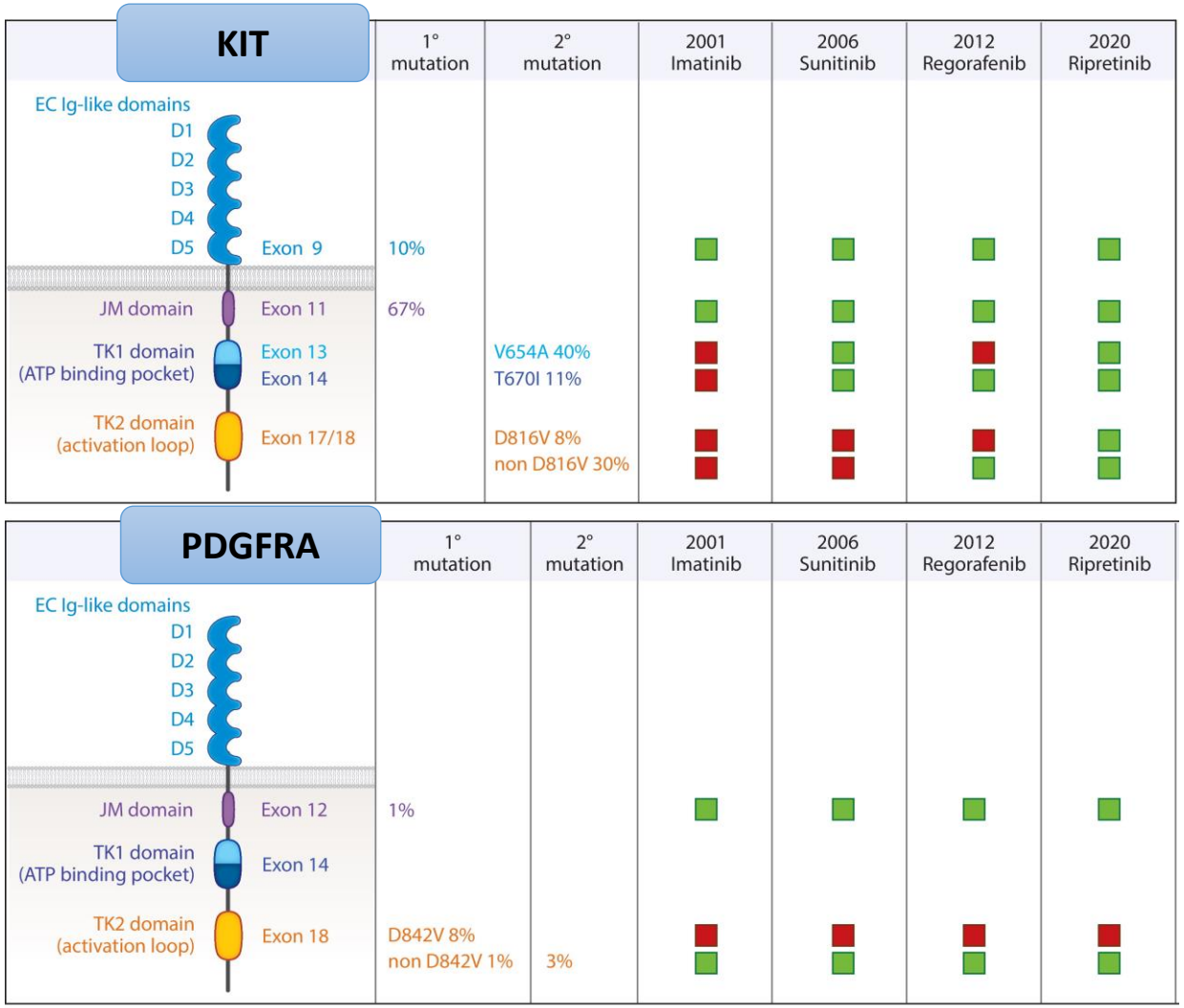
Demetri, *Lancet* 2006




## Regorafenib (NEXAVAR®)

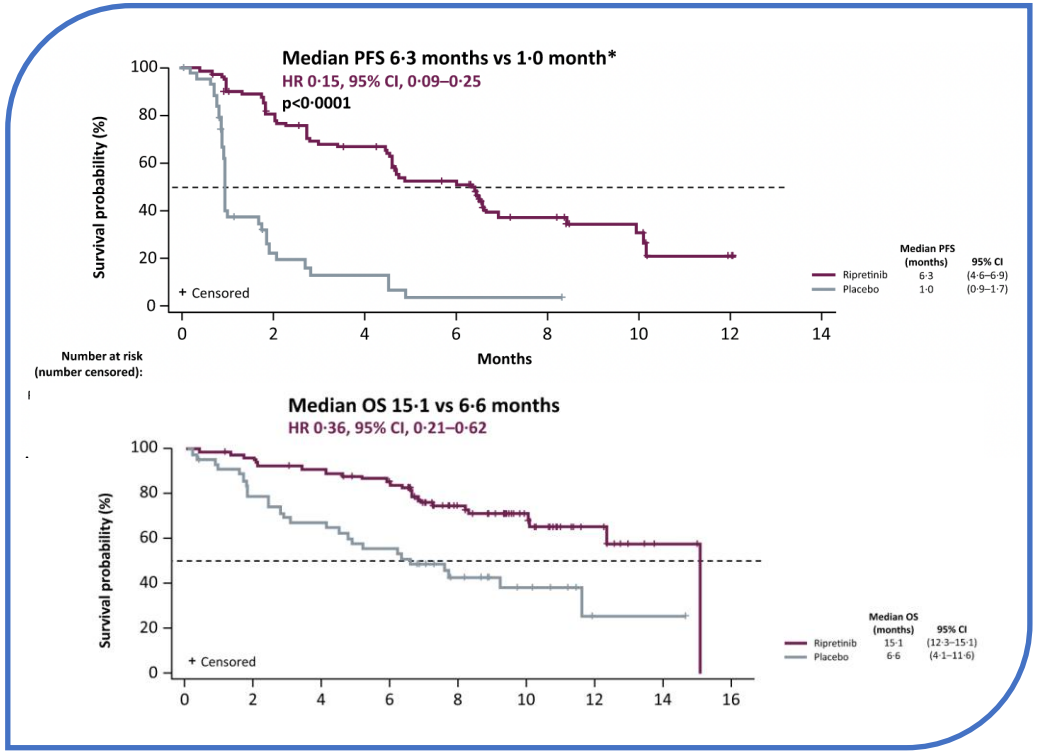
- AMM 2016 :
  - **L3 non résécables / métastatique**
  - **Si toxicité / résistance L1-2**





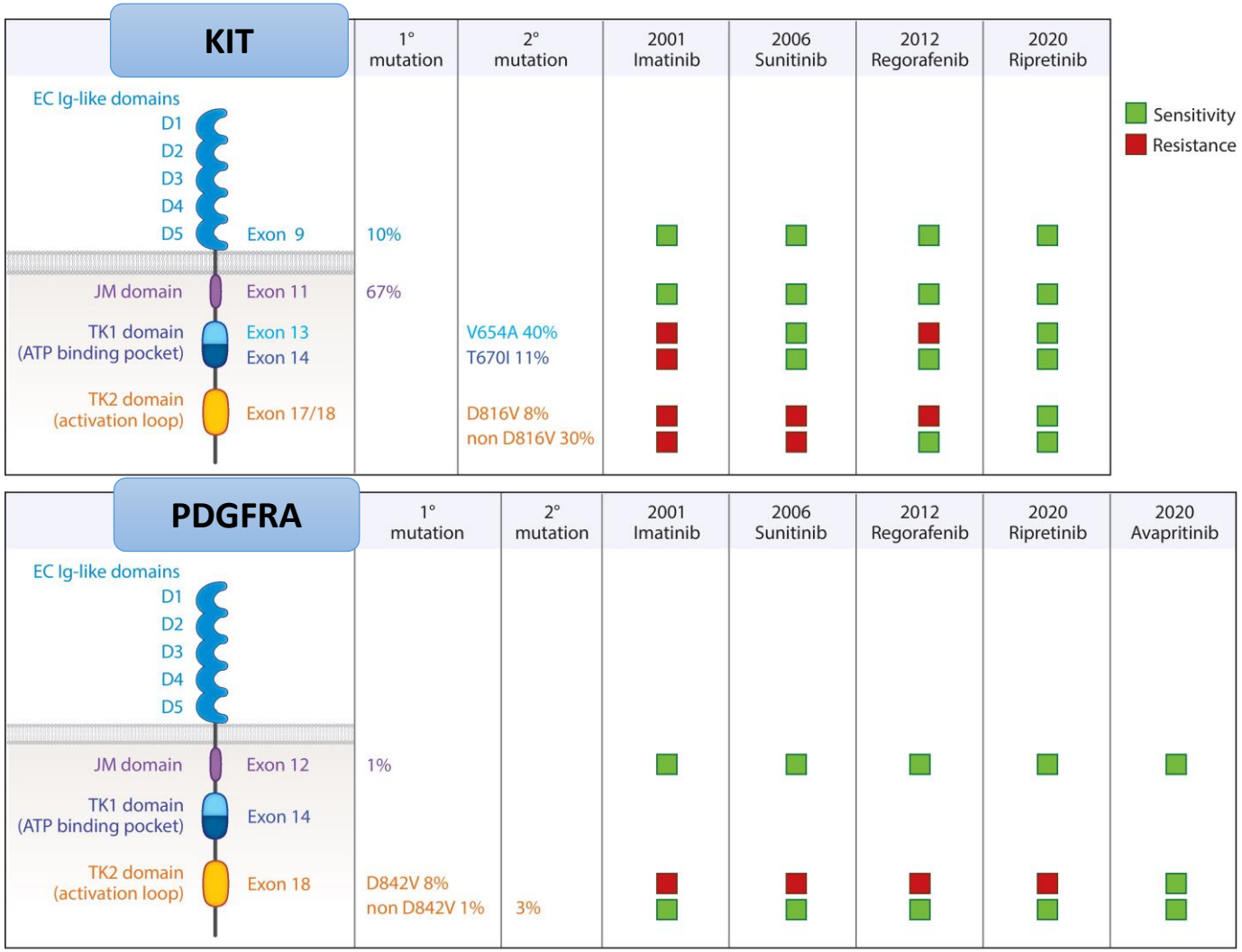

## Ripretinib (QINLOCK®)

- AMM 2022 :
  - **L4 non résécables / métastatique**
  - **Si toxicité / résistance L1-2-3**




Dermawan, *Annual Review of Pathology* 2022

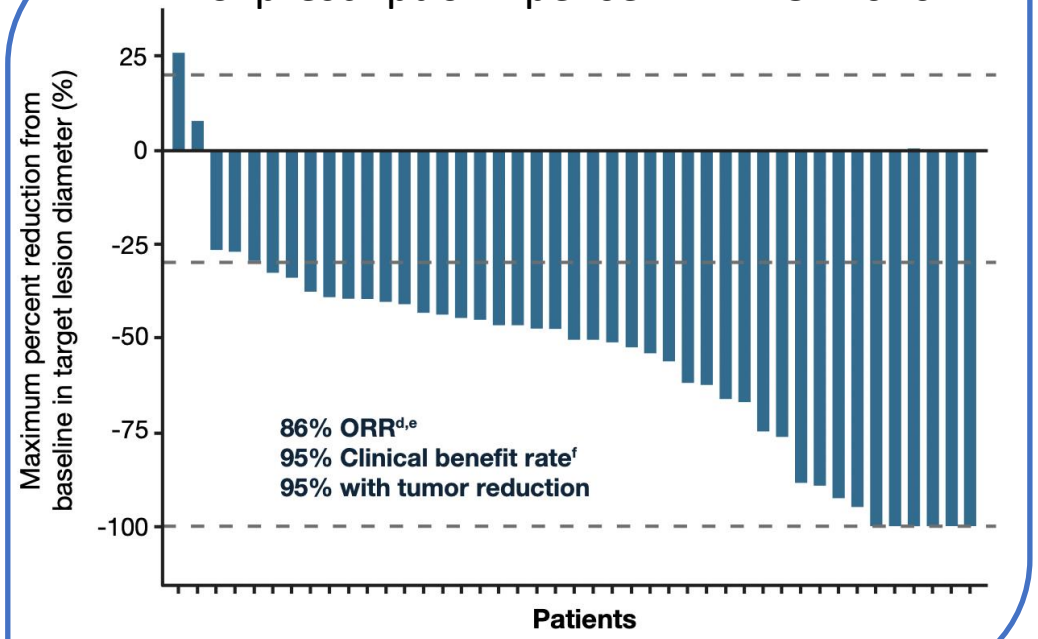
« INVICTUS » Blay, *Lancet Oncol* 2020




## Avapritinib (AYVAKIT®)

- Accès Précoce 2021 :
  - **L1 non résécables / métastatique**
  - **Si mutation D842V de PDGFRA**

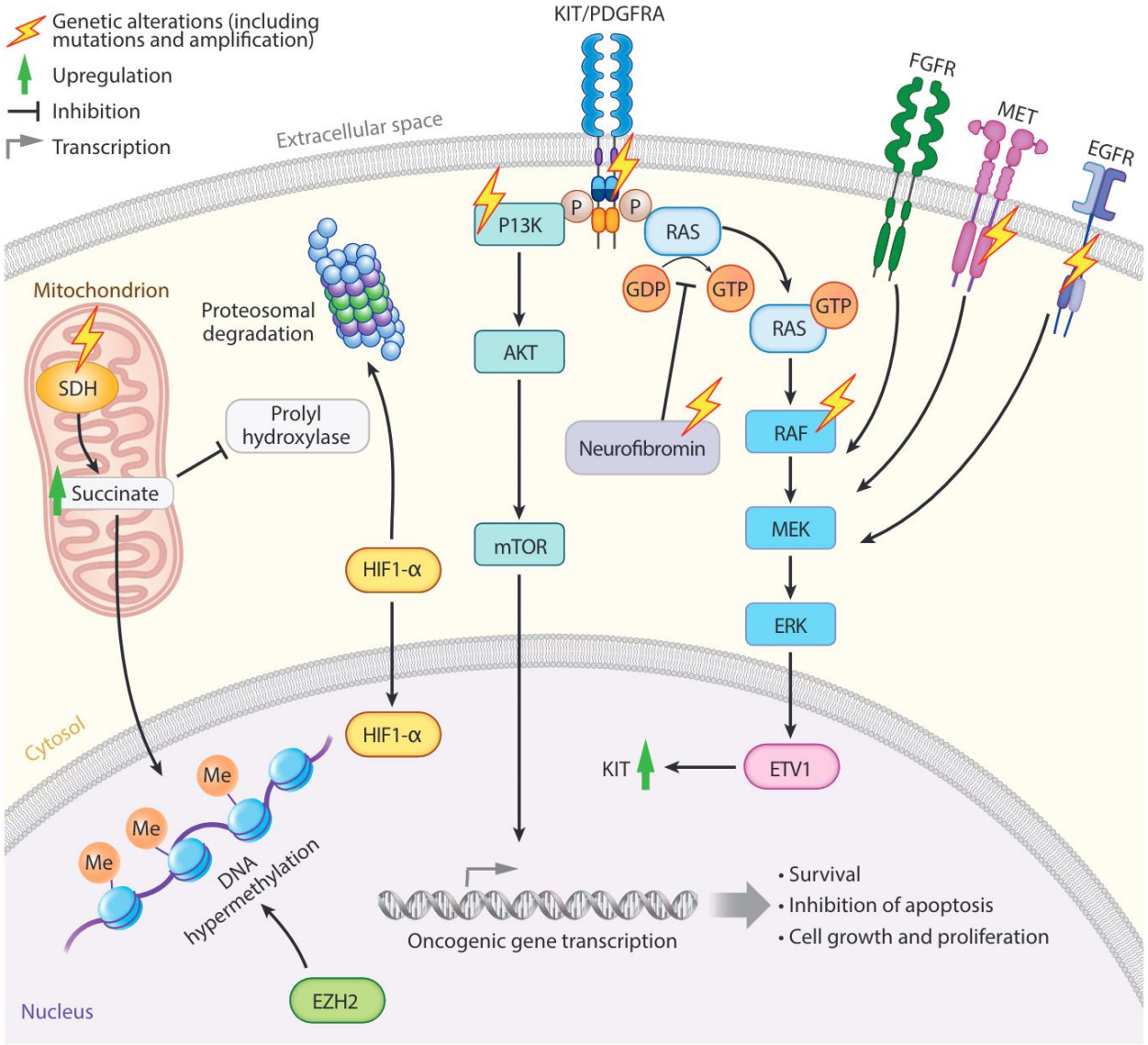
Si prescription : penser AVIATOR2020




=> VOYAGER : Ph3 L3-4 *vs* regorafenib

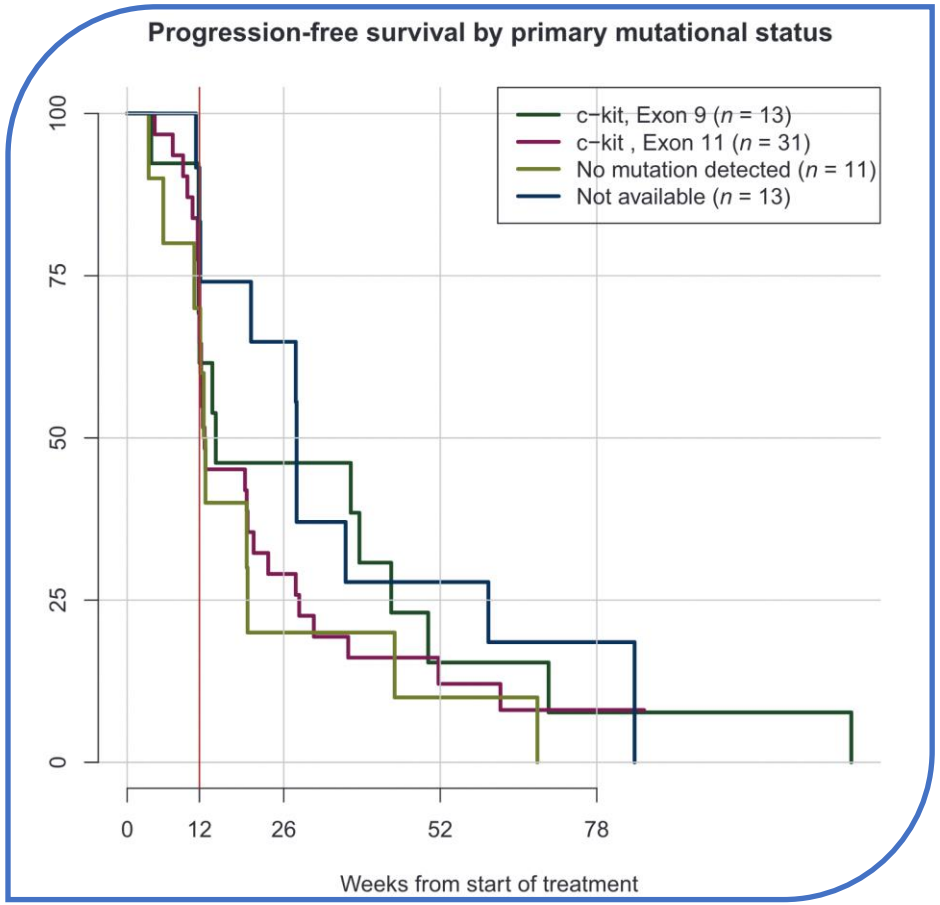
Dermawan, *Annual Review of Pathology* 2022

« NAVIGATOR » Heinrich, *Lancet Oncol* 2020



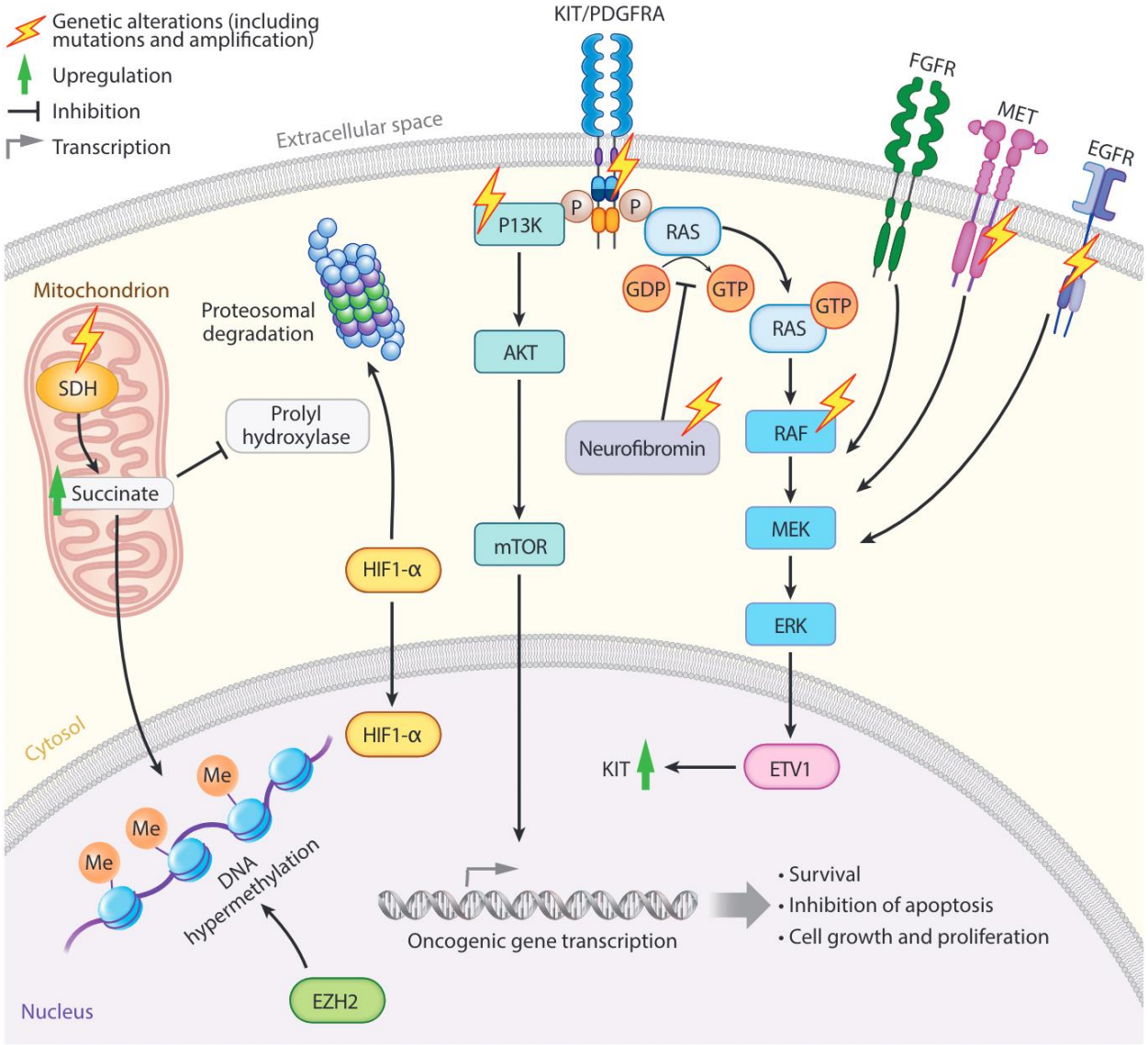

**Pazopanib** (VOTRIENT®) (FGFR)

▷PAS D'AMM




Dermawan, *Annual Review of Pathology* 2022

PAZOGIST Mir, *Lancet Oncol* 2016 ; Eriksson, *ESMO Open* 2021




**Pazopanib** (VOTRIENT®) (FGFR)

- PAS D'AMM

**Masitinib** (MASIVET®) (FGFR)

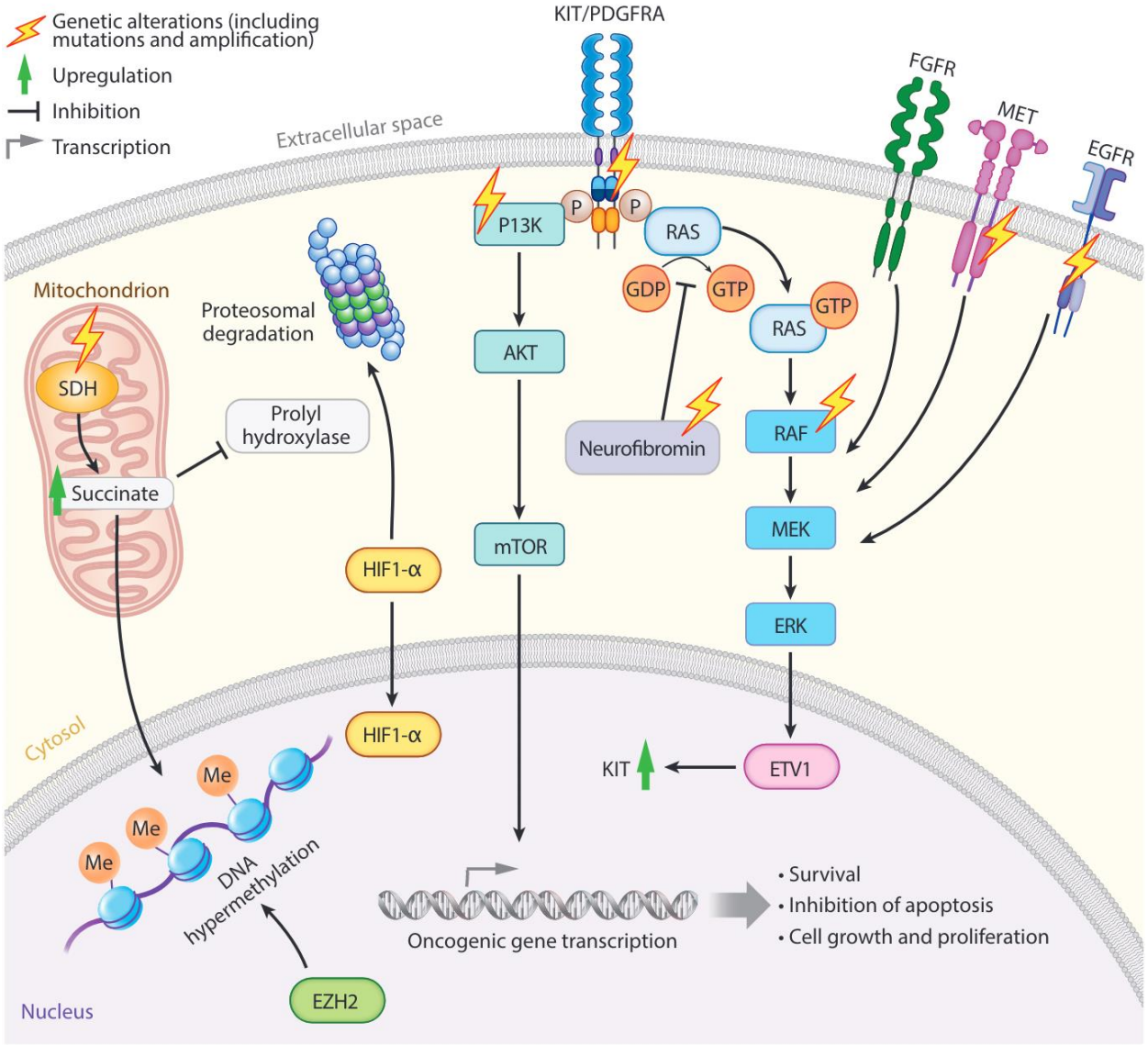
- // SEP, Asthme, Alz..

**Dasatinib** (SPRYCEL®)

- + IMATINIB
- + IPILIMUMAB

**Lenvatinib**

- **LENVAGIST** (Ph2 L3+)




**TKI anti MET**

- Crizotinib
- Cabozantinib

**TKI anti MEK**

- Brinimetinib + imatinib

**TKI anti PI3K & CDK4-6**

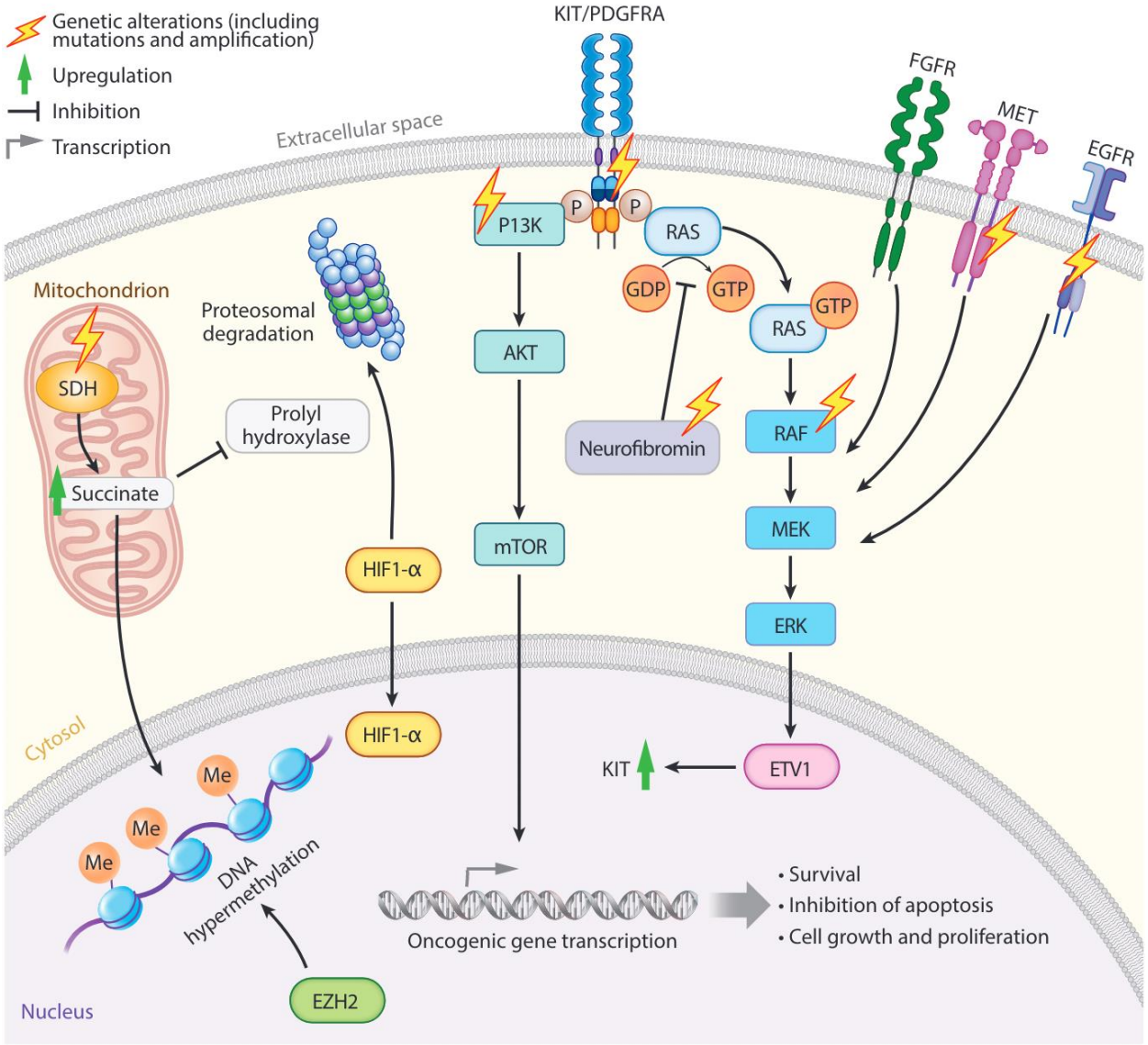
- Alpelisib
- Palbociclib

**TKI anti HSP90**

- L2 après imatinib ?

...

Cohen, *Cancer Res* 2015 ; Ran, *Cancer Discov* 2015 ; Bauer, *Cancer Res* 2006 ; Wagner, *EJC* 2016




**mAB conjugué anti KIT**

▷LOP628 (+ Maytansine)

**mAB anti CTLA + anti KIT**

▷Ipilimumab + Imatinib

**mAB anti PDL1 + anti VEGF**

▷Avelumab + Axitinib

**Bloquer la transcription KIT**

▷Flavopiridol ALVOCIDIB

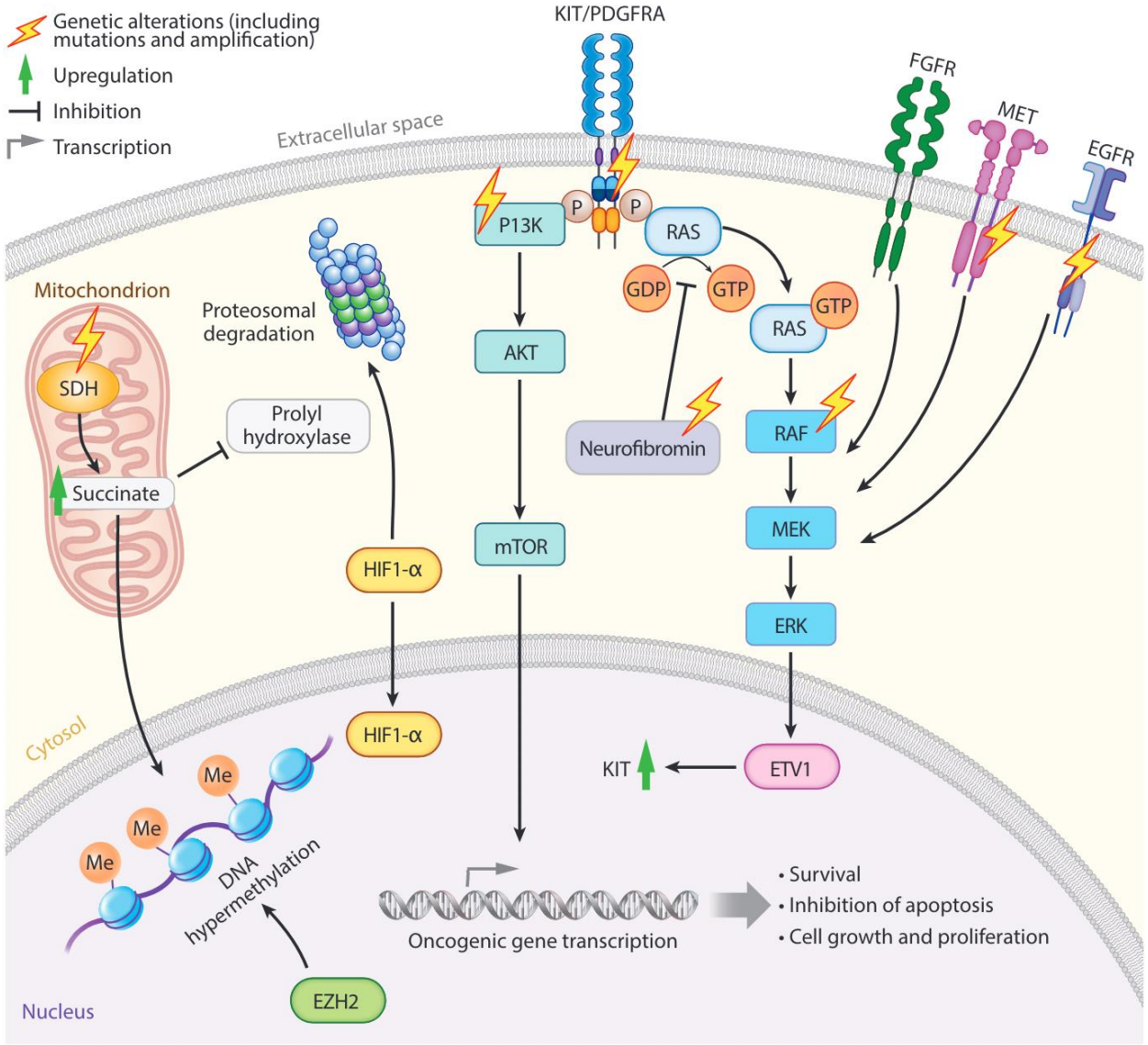
...

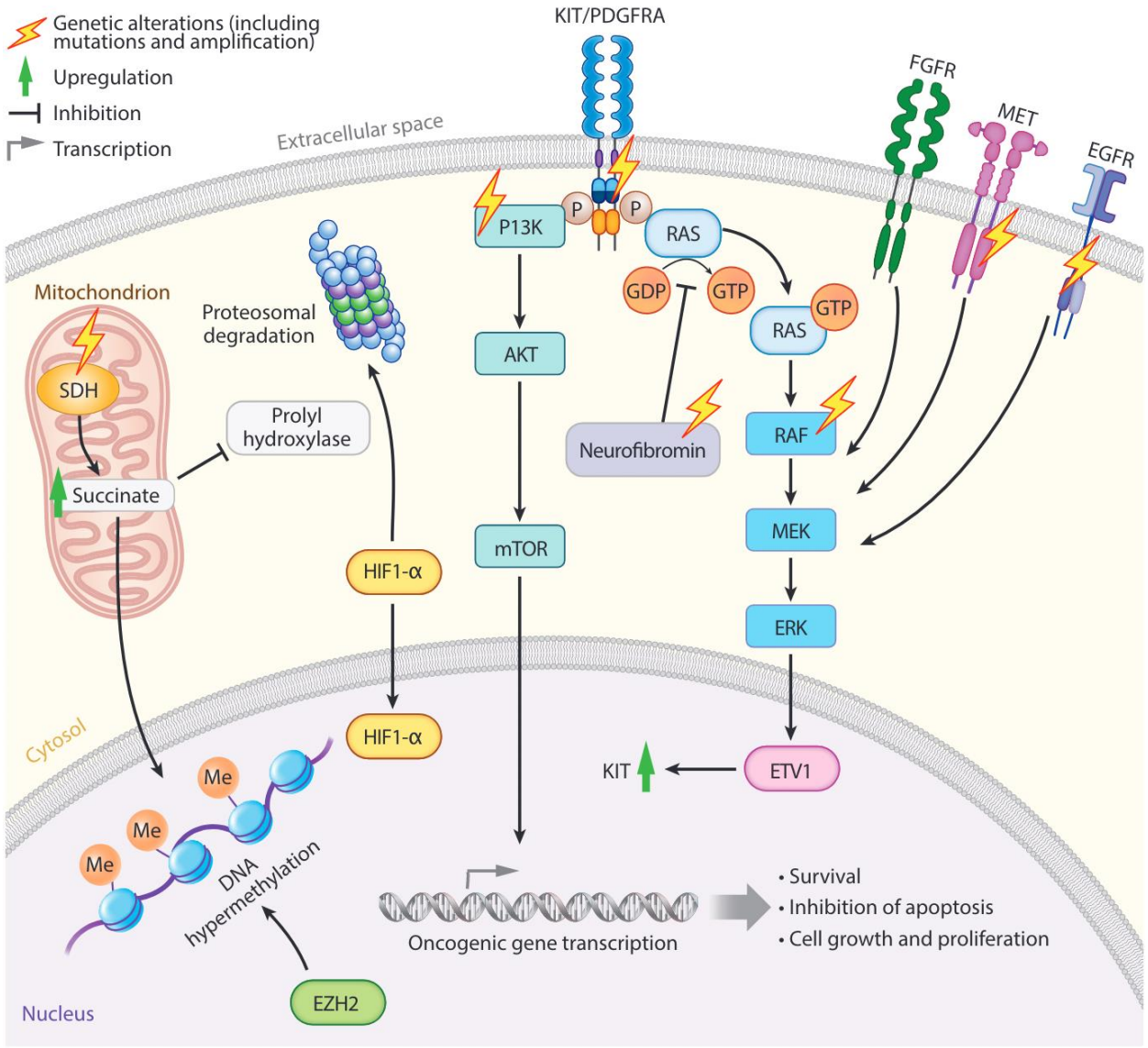
Dermawan, *Annual Review of Pathology* 2022

Balachandran, *Nat Med* 2011 ; D'Angelo, *Clin Cancer Res 2017 ;* Reilley, *Cancer* 2017

## GIST associées à la SDH

- Carence en Succinate Dehydrogenase (SDH)
  - Majorité des **GIST pédiatriques**, 8% totales
  - **Enfant** & jeunes adultes, prédominance **F**>M
  - Quasi exclusivement **Gastriques**
- Triade de Carney (1977) :
  - **GIST**, **Paragangliome**, **Chondrome pulmonaire**
  - Quasi exclusivement féminin
  - Inactivation **épigénétique** par hyper-méthylation du promoteur SDHC
- Diade de Carney = Sd de Carney-Stratakis :
  - **GIST** (gastrique+++), **Paragangliome**
  - Transmission autosomale dominante
  - Mutation **germinale** inactivatrice d'un gène codant pour une sous unité du complexe SDH






## GIST associées à la voie RAS/MAPK

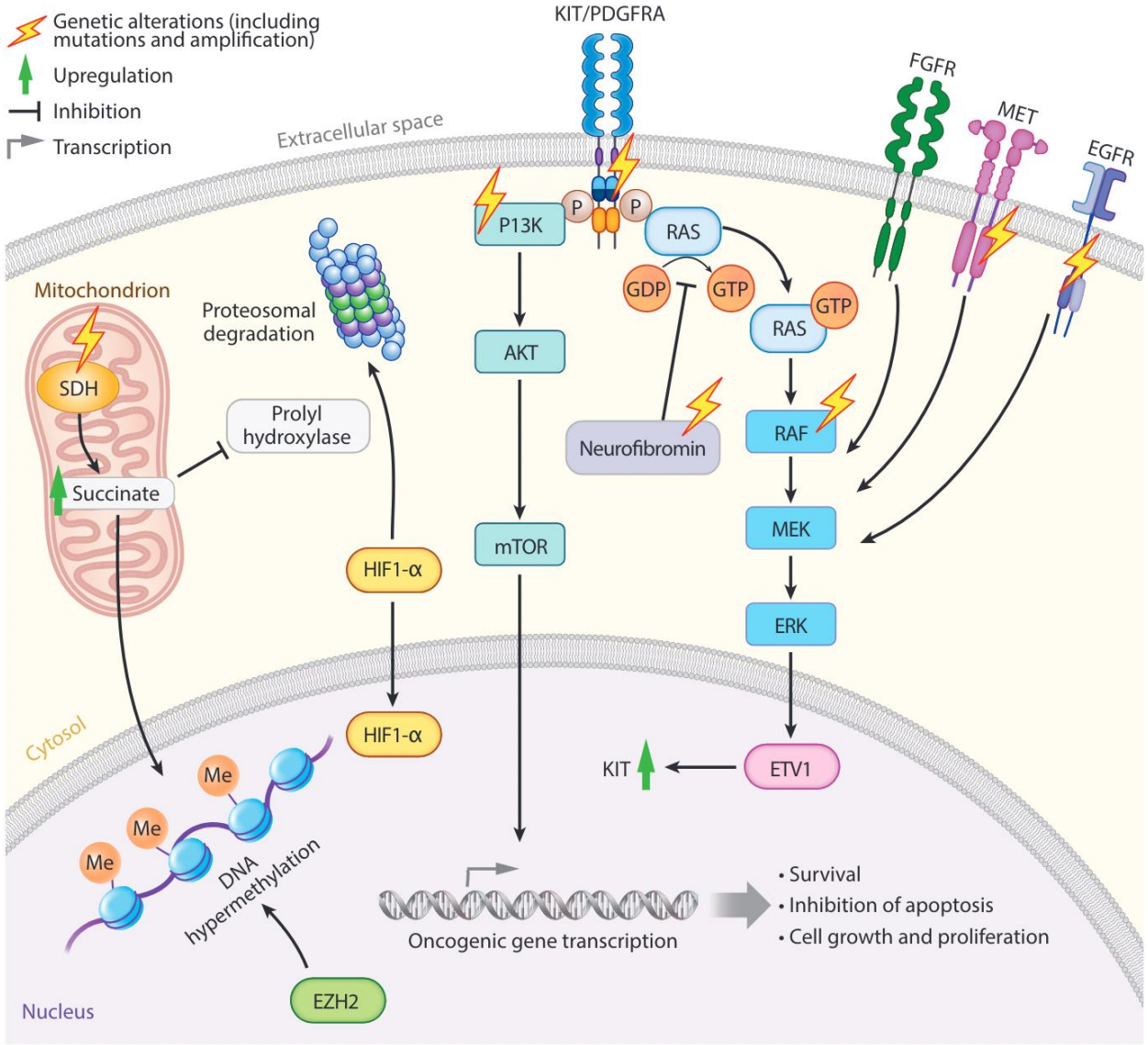
- Neurofibromatose de type 1 :
  - Risque : 7% / vie
  - Autosomique dominante (>> somatique)
  - Dysfonction **Neurofibromine**
    - Inhibe voie RAS/MAPK
  - GIST **multiples**, **Intestin grêle** ++

- Multiples et rares
  - **BRAF** V600E (driver // mélanome, CCR, CB)
  - **RAS** (collaborative)

Dermawan, *Annual Review of Pathology* 2022

## GIST quadruples négatives

- Multiples et rares
  - Mutations activatrices drivers
    - **PIK3CA**
  - Surexpression / Activation
    - **EGFR**
    - **IGF1**
  - Fusions
    - **FGFR1**-HOOK3 & FGFR1-TACC
    - **NTRK3**-ETV6 & LMNANTRK1
      - Larotrectinib & Entrectinib
  - Hyperméthylation
    - **EZH2**
      - Tazemetostat



# GIST & biologie moléculaire

| | |
|---|---|
| **Valeur diagnostique** | KIT+, DOG1, SDHB, NF1, BRAF (**IHC**) |
| **Valeur pronostique** | Mutation KIT Exon 9 (**Génotypage**) |
| **Valeur prédictive** | KIT Exon 9 *vs* 11, PDGFRA Exon 18 D842V |
| **Valeur théranostique** | Nouvelles cibles (selon **Séquençage**) |

GIST AWARENESS DAY 13/07

**Merci pour votre attention**

# GIST : modèle pour la biologie moléculaire
# Du diagnostic à la thérapeutique

Dr Clément BOLOGNINI

27 avril 2023

Chef de Clinique Oncologie Médicale
CHU Jean Minjoz - Besançon

## Le mystère des micro-GIST

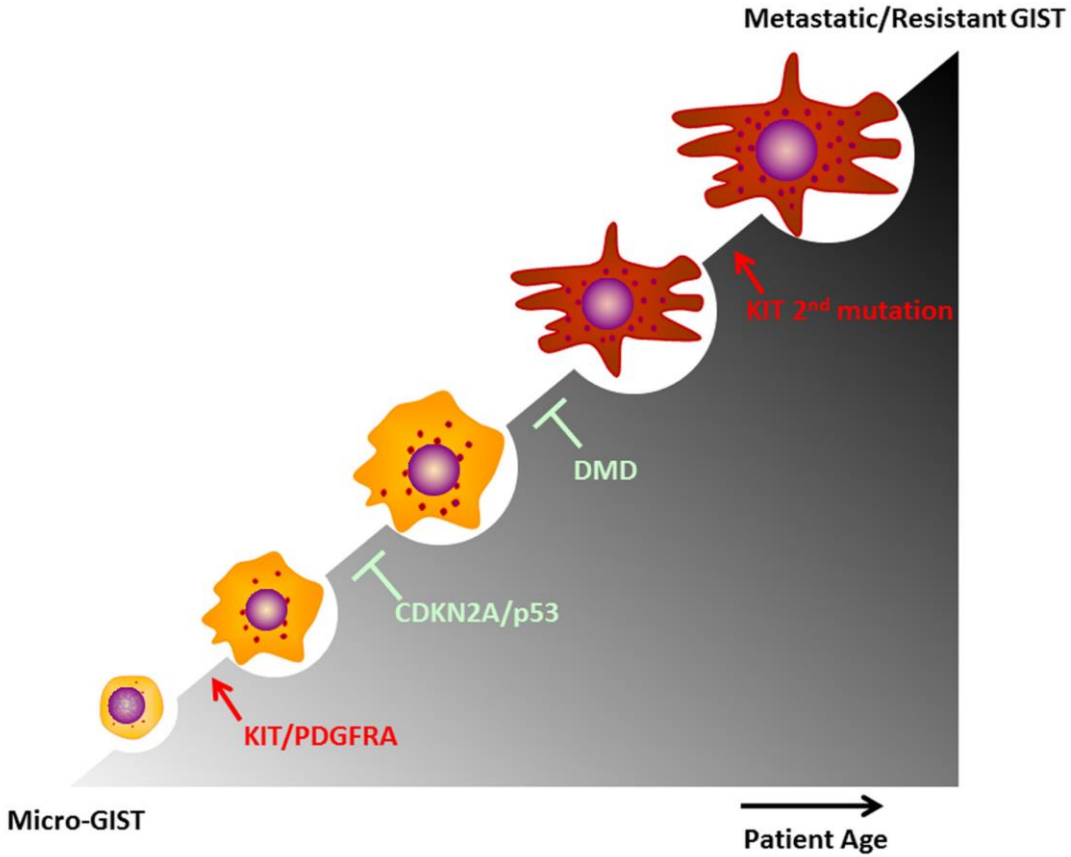
- 20 à 30% des adultes porteurs
- Mutations KIT & PDGFRA sans prolifération !
- Mutations supplémentaires nécessaires ?

## CDKN2A, RB1, TP53 & MDM2 ?

- Cycle cellulaire & Anti-CDK4-6 ?

## Dystrophine

- Rôle de liaison CML & MEC (vs migration/invasion)
- Valeur pronostique ? Thérapeutique ?




Li, *Oncotarget* 2017