Université Paris Cité

Groupement d'hôpitaux Paris Centre
COCHIN
BROCA
HÔTEL-DIEU

SERVICE DE GASTROENTÉROLOGIE
D'ENDOSCOPIE ET D'ONCOLOGIE DIGESTIVE

AP-HP.Centre-Université Paris Cité
Hôpital Cochin

gastrocochin.com

12h00-13h00 Symposium DECIPHERA – Actualités dans les GIST

12h20-12h40 Quoi de neuf dans le traitement des GIST ?

Pr Romain Coriat

Romain Coriat

Service de gastroentérologie, d'endoscopie et d'oncologie digestive

CHU Cochin

romain.coriat@aphp.fr

Samedi 4 mai 2024

20 ème JOURNEE DE GASTRO-ENTEROLOGIE

DE l'HOPITAL COCHIN

(APHP.Centre Université Paris Cité)

Lieu : Ecole du Val-de grâce - 1 place Alphonse Laveran 75 230 Paris Cedex 05

Liens d'intérêt

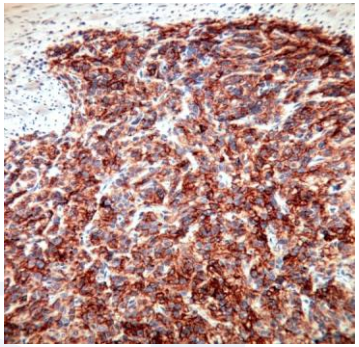
- AAA
- IPSEN
- AMGEN
- BAYER
- Pierre Fabre
- BMS
- Merck
- Sanofi
- Deciphera (En lien avec la présentation)
- Oseus

- Le Cancer.fr
- Cancerodigest

GIST : Tumeur de la cellule de CAJAL

Cellule de Cajal 1906

- Cellules motrices pacemaker de l'intestin



GIST

- Tumeur Stromale : Mutations activatrices de KIT

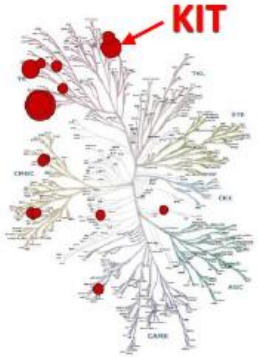
Hirota et al, Science 1998

Imatinib mesylate

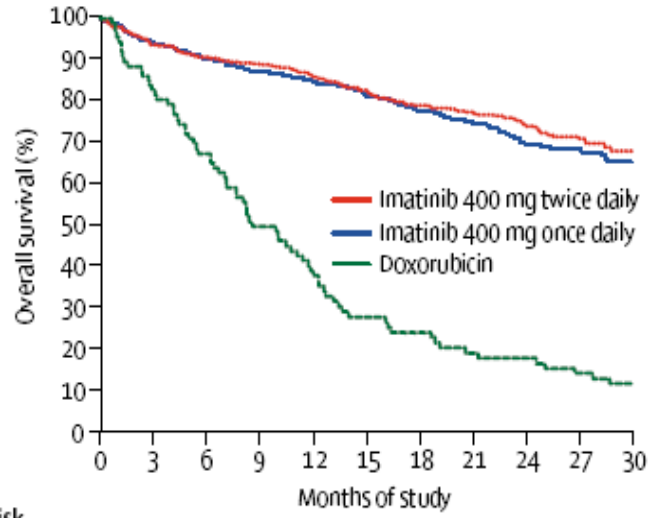
- Inhibiteur de tyrosine kinases (inhibiteur de KIT) et de BCR-ABL
- Métabolisme : CYP3A4, CYP1A2
- 1/2 vie : 18 heures
- **Posologie 400 mg/jour à distance des repas**

Druker et al, Nature Med 1996

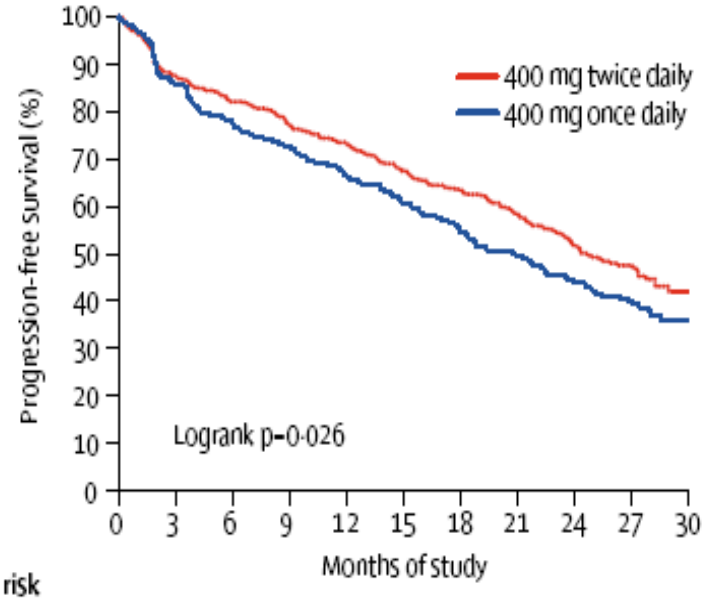
GIST avancées: Imatinib Mesylate



Survie globale



Number at risk						
Imatinib 400 mg once daily	473	423	387	315	192	49
Imatinib 400 mg twice daily	473	427	399	323	201	51
Doxorubicin	86	57	31	19	14	8



Number at risk											
400 mg once daily	473	404	366	338	307	270	228	184	127	71	25
400 mg twice daily	473	414	388	365	343	300	266	218	147	96	39

L'Imatinib ne guérit pas les GIST

…. Les patients finissent par progresser

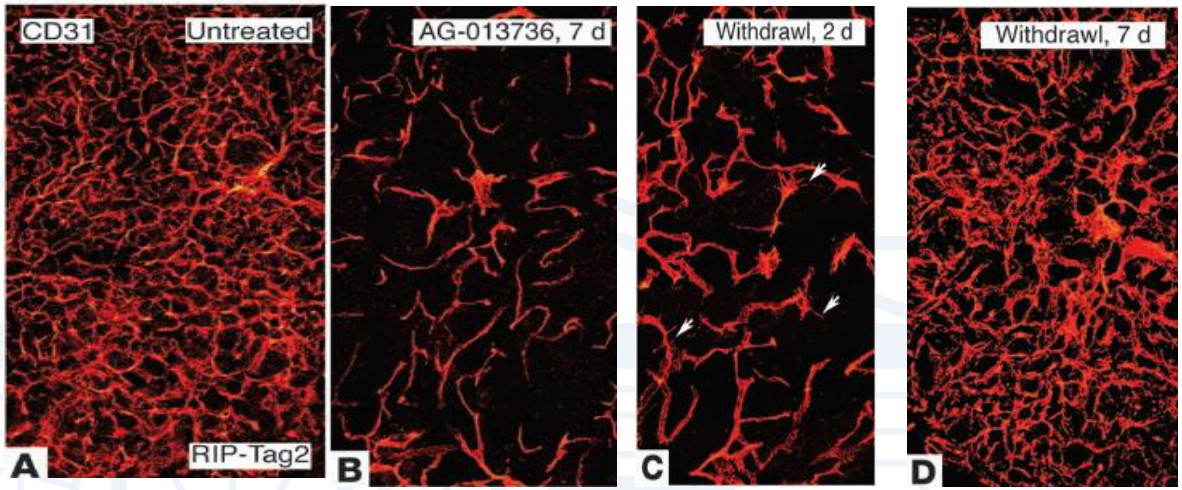
Verweij, Lancet 2006

Attention avec les ITK – Pseudo progression

Effets des ITK sur angiogénese

Réversibilité de l'action des anti angiogéniques

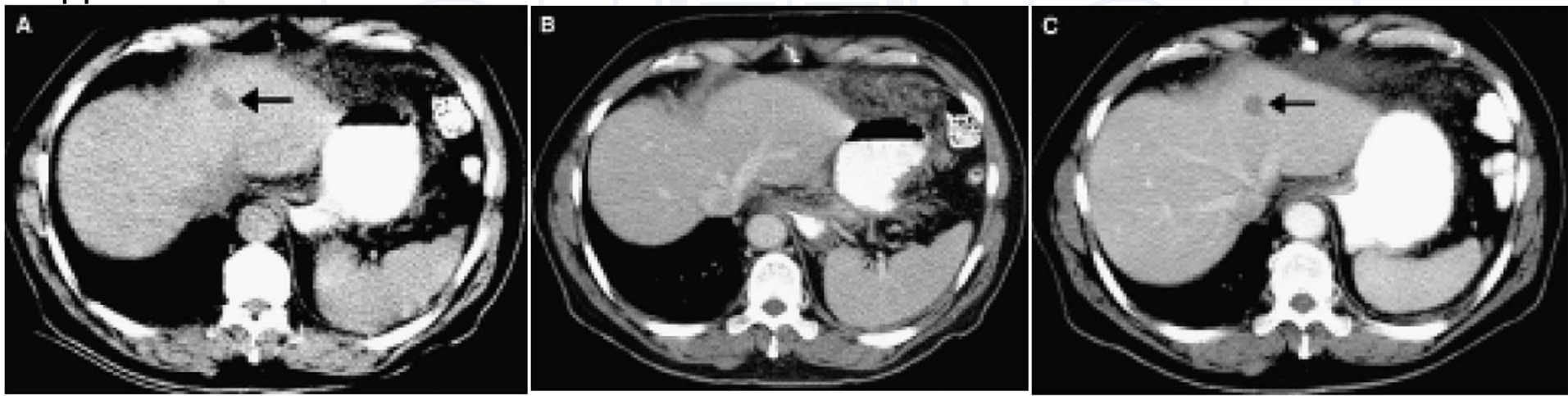
Nécrose tumorale
Diminution de la vascularisation
Persistance de péricytes



Mancuso et al, J of Clinical Invest, 2006

Apparition d'une « fausse » nouvelle lésion sous ITK

Patel et al, Cancer Treat Rev, 2012



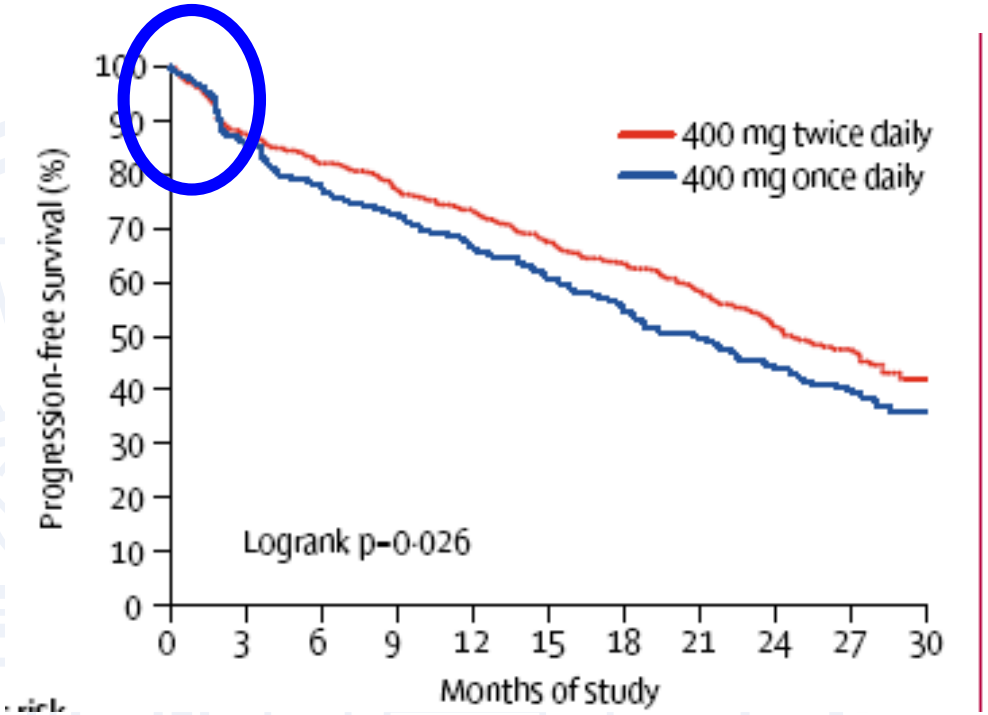
Imatinib dans les GIST avancées : 2 types de progression

1. Progression précoce:

- juste après l'initiation
- Résistance primaire ou intrinsèque

2. Progression tardive:

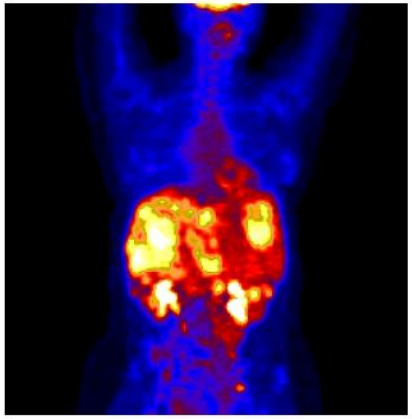
- > 3mois
- Résistance secondaire (acquise ou augmentée) sous la pression de l'imatinib



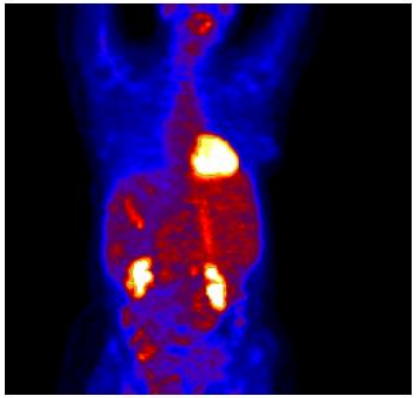
Verweij, Lancet 2006

Imatinib dans les GIST avancées: Progression précoce

Intérêt du 18-FDG PET Scanner

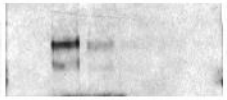


Avant traitement

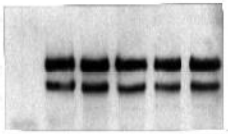


< 24 heures
après la 1ère dose

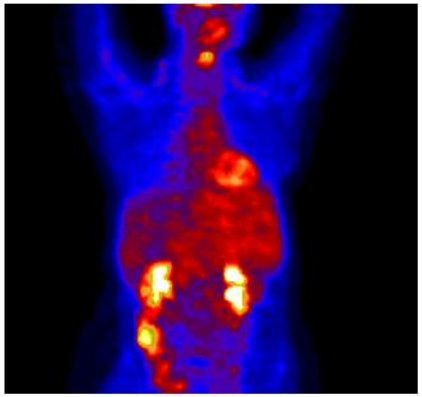
0 1 9 24 48h



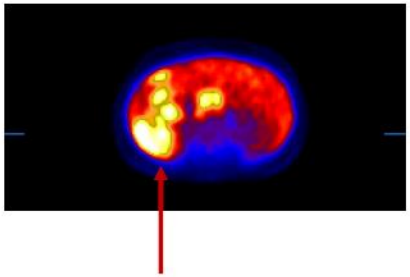
Kit active
rapidement inactivé



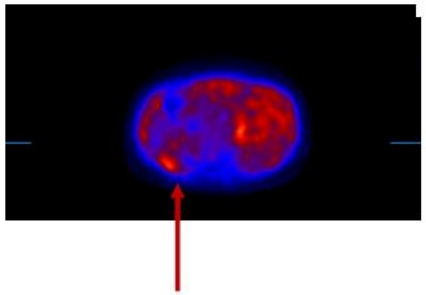
protéine Kit non affectée



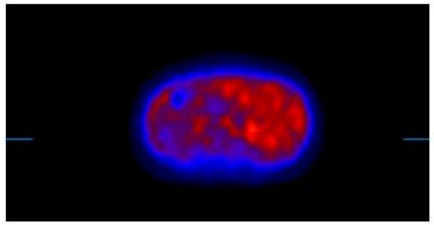
20 ans après, patient sous imatinib



Tumeur active



Tumeur inactive

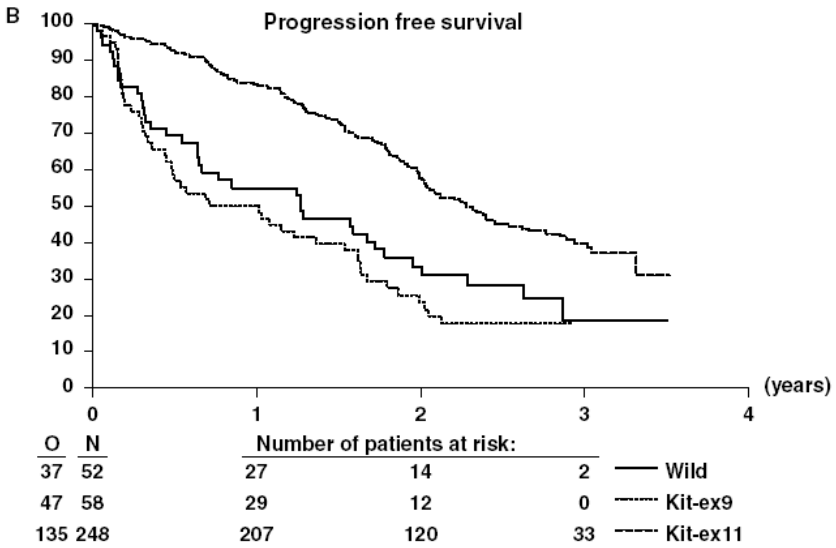


Diapo : Dr Le Cesne (IGR)

Imatinib dans les GIST avancées : Progression précoce

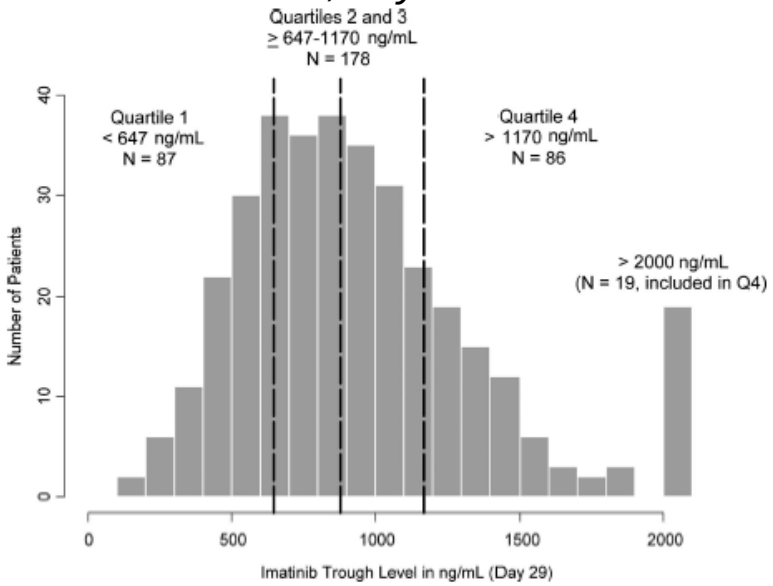
Principalement liée au statut mutationnel: Large differences at steady state

Exon-9 mut/wt tumors fare worse compared to exon-11 mut tumors



Debiec-Rychter, EJC 2006

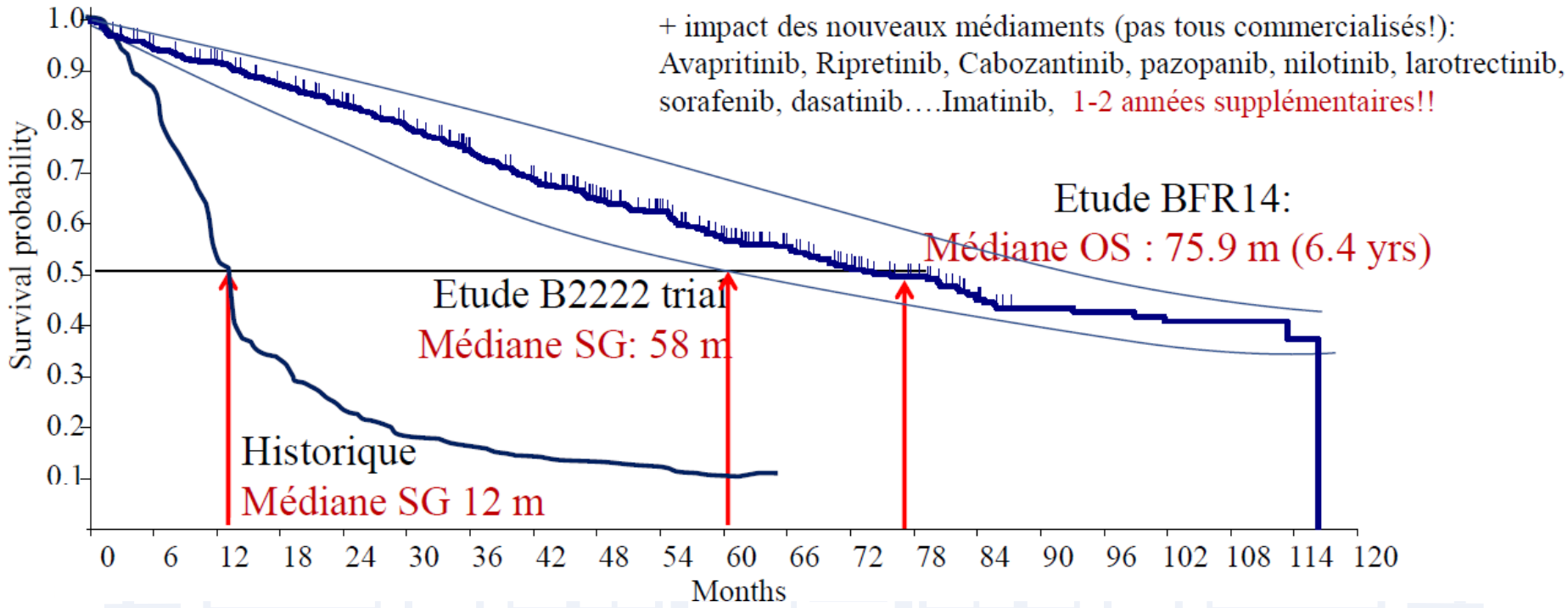
351 CML patients treated with 400 mg imatinib, day 29



Larson, Blood 2008

Imatinib: Progression précoce

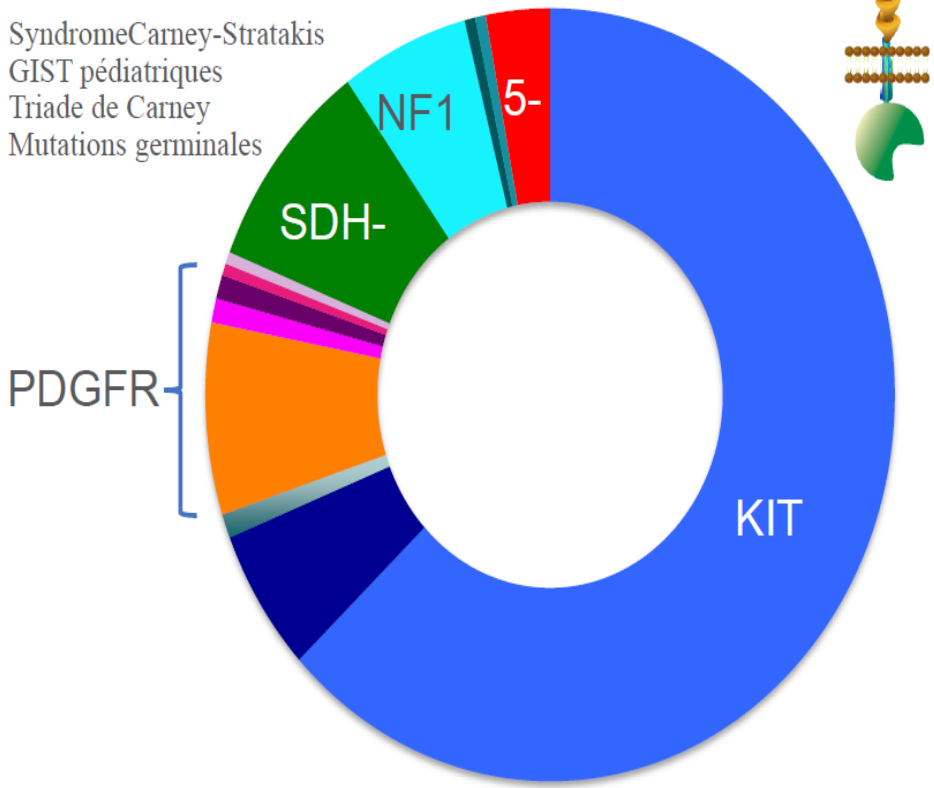
GIST avancés - Survie globale

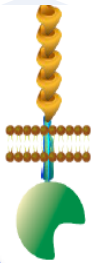


Blanke et al, JCO 2008
Le Cesne et al, Lancet Oncol 2010
Patrikou et al, EJC 2015

Mieux comprendre les GISTs

Classification moléculaire des GIST (NGS)





- KIT ex 11 (63%)
- KIT ex 9 (6%)
- KIT ex 13 (1%)
- PDGFRA ex 18 D842V (8%)
- PDGFRA ex 12 (1%)
- PDGFRA ex 14 (1%)
- PDGFRA ex 18 other (0.5%)
- PDGFRA ex 12 & 14 (0.5%)
- SDH Deficient (9%)
- NF1 related (6%)
- BRAF (0.5%)
- BRAF & NF1 (0.5%)
- Quintuple WT (3%)

Lostes-Bardajiet al
TherAdvMed Oncol 2021, Vol. 13: 1–12

Mutations sensible à l'IM
Mutations résistantes à l'IM

Stratégie dans les GIST

GIST

90%

GIST Non Métastatique

Biopsie obligatoire si ≥ 2 cm
Résection si ≥ de 2 cm
Surveillance si < 2 cm
Surveillance cas particulier

10%

GIST Métastatique

L1 : Imatinib mesylate
Dose : 400 mg par jour ; 800 mg si Ex9
Si D842V : Avapritinib

Si chirurgie en fonction de l'analyse
Discuter traitement adjuvant (3 ans)
Sauf : Mutation D842V de PDGFR, NF1 et SDH

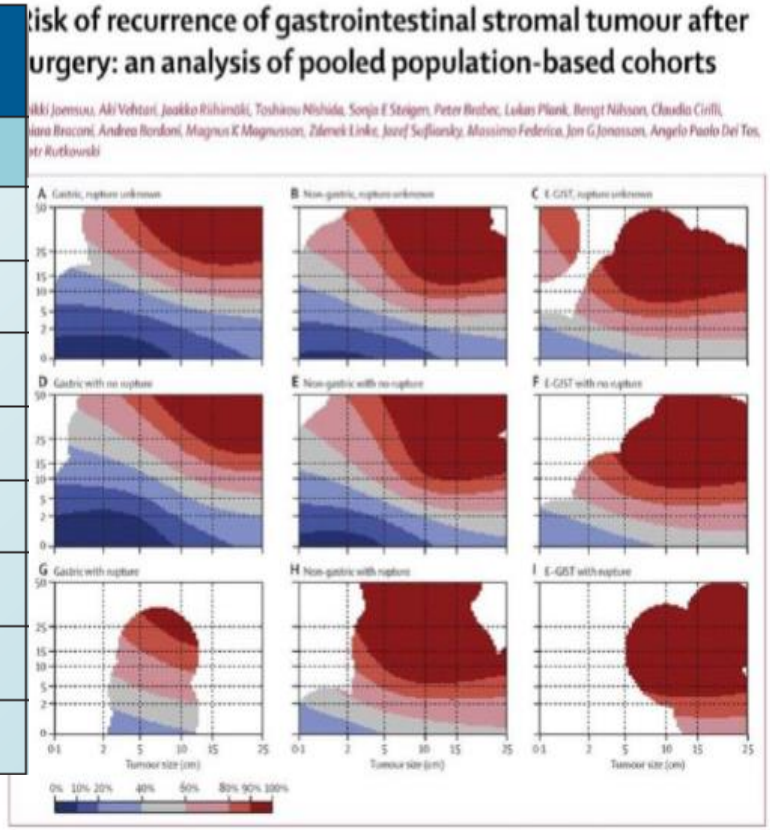
Si chirurgie complexe Imatinib 6-12 mois puis Chirurgie et Imatinib adjuvant (3 ans au total)

Estimation du risque de récidive dans les GIST localisées réséquées

Classifications pronostiques

Groupe	Paramètres de la tumeur		Caractérisation du risque de métastases en fonction de la localisation des GIST (% de patients avec progression tumorale durant le suivi)			
	Taille	Index mitotique	Estomac	Jejunum et Ileum	Duodénum	Rectum
1	≤ 2 cm	≤ 5/50CFG	aucun (0%)	aucun (0%)	aucun (0%)	aucun (0%)
2	> 2 ≤ 5 cm	≤ 5/50CFG	très bas (1,9%)	bas (4,3%)	bas (8,3%)	bas (8,5%)
3a	> 5 ≤ 10 cm	≤ 5/50CFG	bas (3,6%)	modéré (24%)		
3b	> 10 cm	≤ 5/50CFG	modéré (12%)	élevé (52%)	élevé** (34%)	élevé** (57%)*
4	≤ 2 cm	> 5/50CFG	(0%)*	(50%)*		élevé (54%)*
5	> 2 ≤ 5 cm	> 5/50CFG	modéré (16%)	élevé (73%)	élevé (50%)	élevé (52%)
6a	> 5 ≤ 10 cm	> 5/50CFG	élevé (55%)	élevé (85%)		
6b	> 10 cm	> 5/50CFG	élevé (86%)	élevé (90%)	élevé** (86%)	élevé** (71%)

Miettinen M, Lasota J. GIST: Pathology and prognosis at different sites. Seminars in diagnosis pathology 2006,23,70-83



Joensuu H, et al. Lancet Oncol 2012

Evolution de la prise en charge thérapeutique dans les GIST avancées

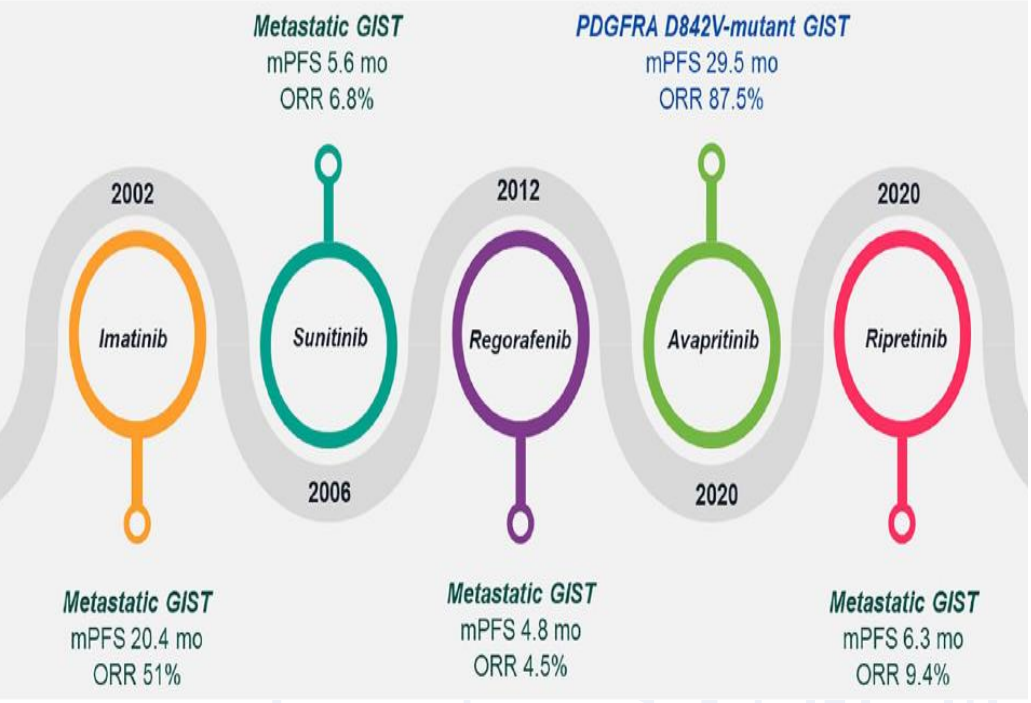
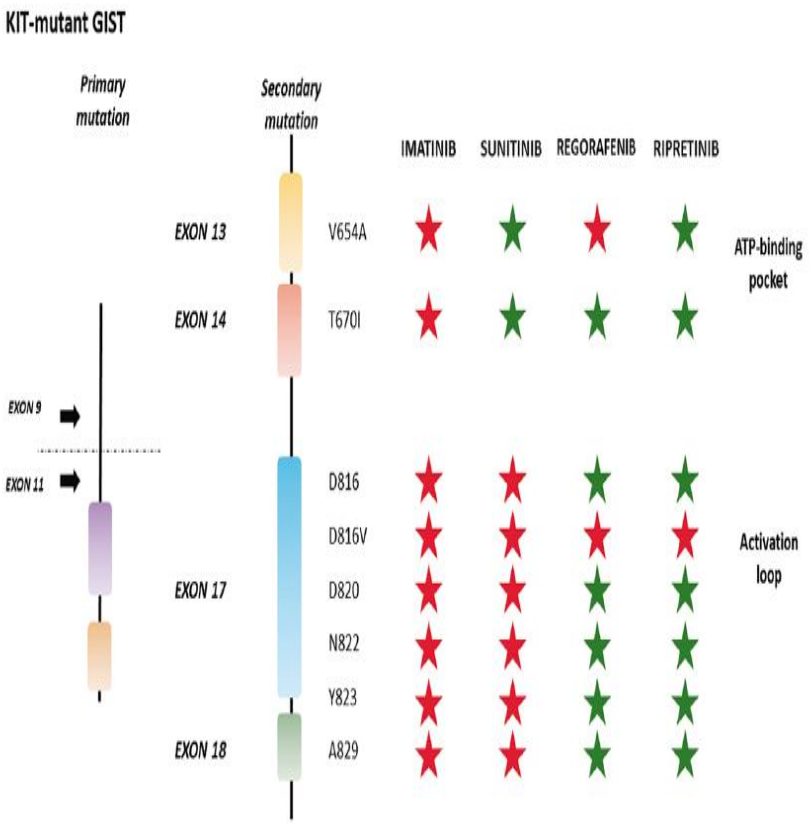


Figure 1. Timeline of approved TKIs for the treatment of advanced or metastatic GIST. mo, months; mPFS, median progression-free survival; ORR, overall response rate.

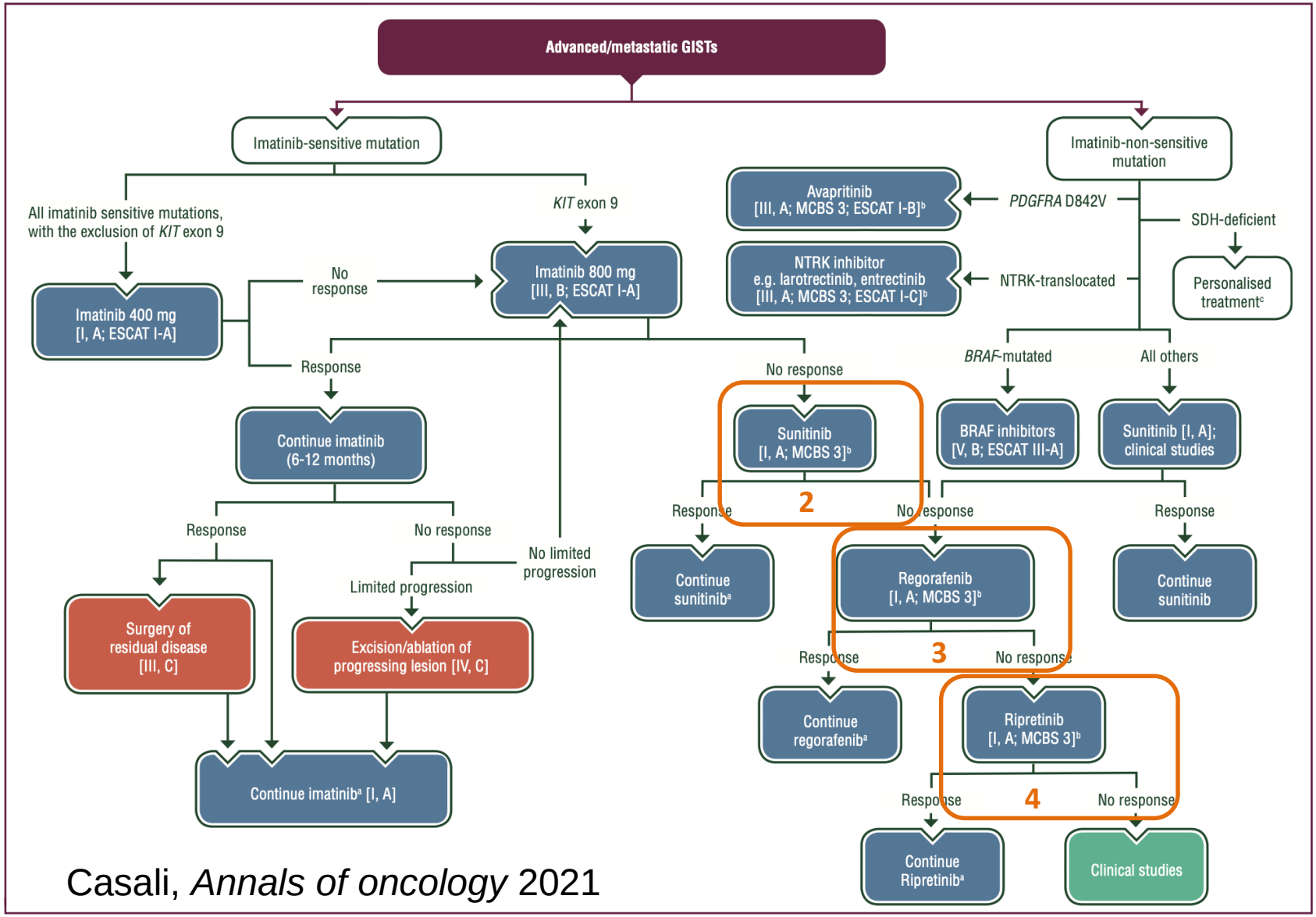


Julia Lostes-Bardajà et al, Ther Adv in Med Oncol, 2021

R. Coriat

Groupement Hospitalier Paris Centre
COCHIN BROCA HÔTEL-DIEU

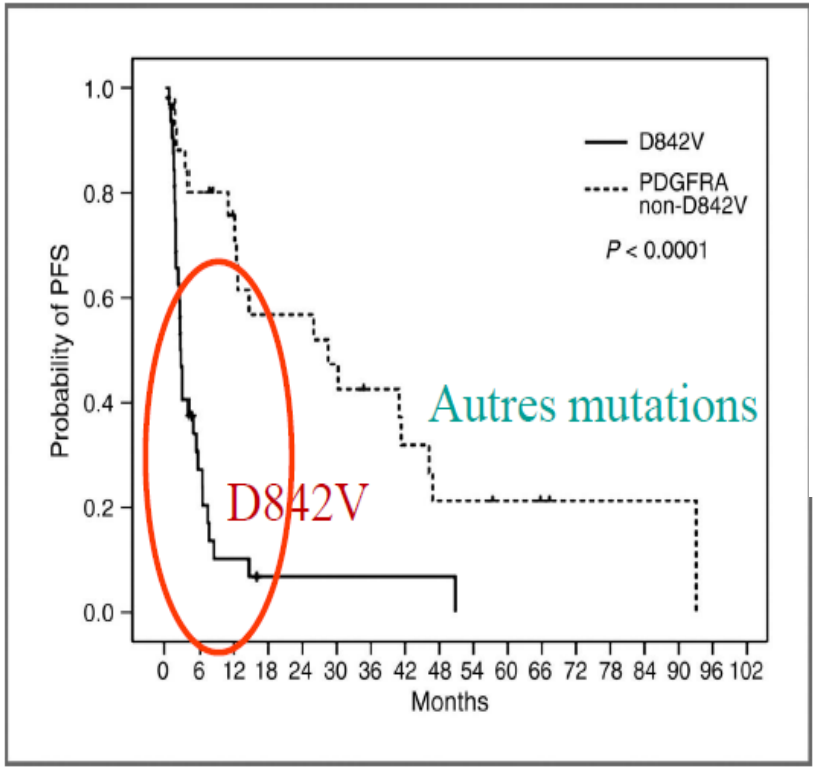
ESMO Guidelines

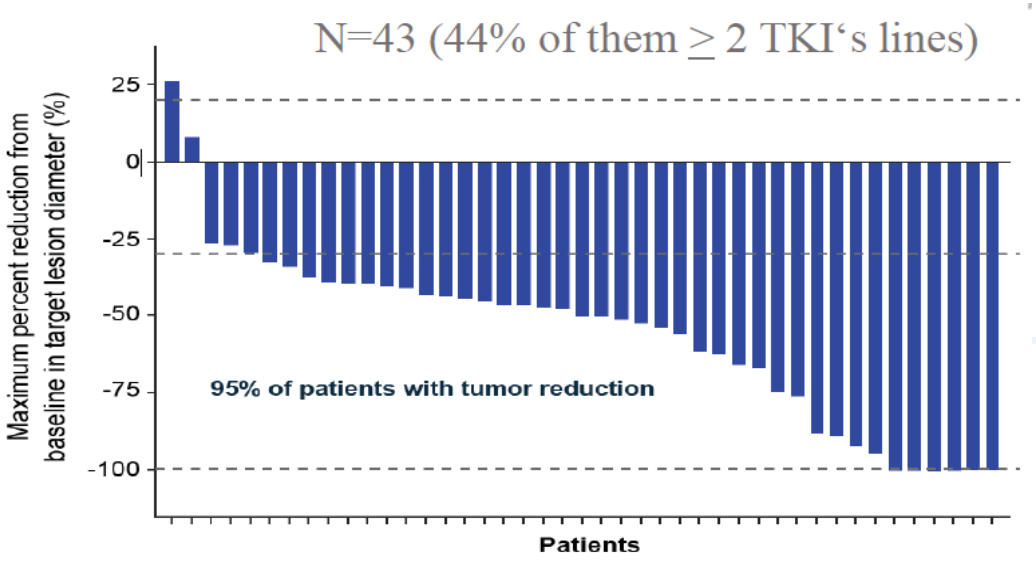


Casali, *Annals of oncology* 2021

Stratégie thérapeutique dans les GIST avancées

ITK dans les GIST muté D842V PDGFR (Exon 18 et autres)





Avapritinib: Approbation (FDA) en Janvier 2020 dans les GIST PDGFRA exon 18 incluant D842V
Utilisé aussi en néoadjuvant et 1ère ligne

Résistance de l'imatinib dans les GIST muté D842V

95% des patients ont une réduction tumorale sous Avapritinib

Cassier P et al, CCR 2012

Heinrich et al, CTOS 2019

Tolérance avapritinib

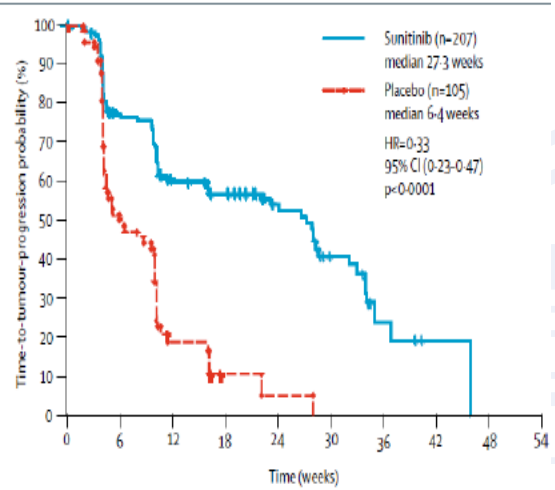
Preferred term, n (%)	*PDGFRA* D842V population (n = 56)	Safety population (N = 250)
Nausea	38 (68)	161 (64)
Fatigue	35 (63)	157 (63)
Anaemia	37 (66)	136 (54)
Diarrhoea	37 (66)	112 (45)
Periorbital oedema	27 (48)	110 (44)
Vomiting	21 (38)	106 (42)
Decreased appetite	23 (41)	101 (40)
Increased lacrimation	21 (38)	88 (35)
Memory impairment	23 (41)	81 (32)
Peripheral oedema	21 (38)	80 (32)
Abdominal pain	19 (34)	64 (26)
Constipation	12 (21)	64 (26)
Hair colour changes	16 (29)	62 (25)
Dizziness	16 (29)	59 (24)
Face oedema	13 (23)	57 (23)
Increased blood bilirubin	16 (29)	54 (22)
Hypokalaemia	14 (25)	48 (19)
Headache	13 (23)	48 (19)
Dysgeusia	13 (23)	47 (19)
Decreased weight	15 (27)	46 (18)
Dyspepsia	13 (23)	44 (18)
Cough	15 (27)	39 (16)
Neutropenia	14 (25)	29 (12)
Upper respiratory tract infection	12 (21)	27 (11)

- Toxicité neuro-cognitive
  - 46% patients
  - 3% hémorragie
- Mécanimes ?

Jones et al., EJC 2021

Stratégie thérapeutique dans les GIST avancées

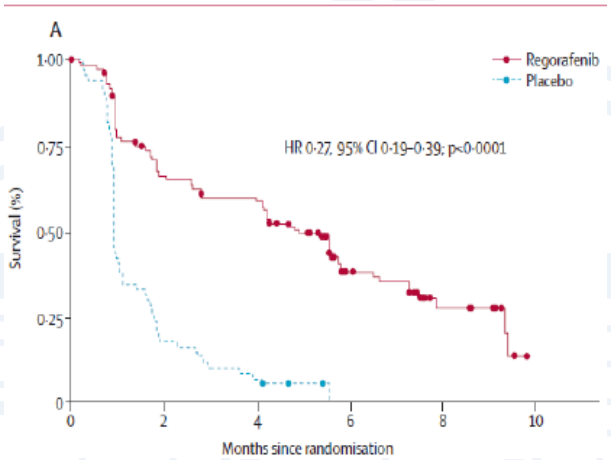
Sunitinib
L2



HR 0,33
mPFS **5,6 mois** vs 1,47
Réponse Objective: 5,1%

AMM : 2006

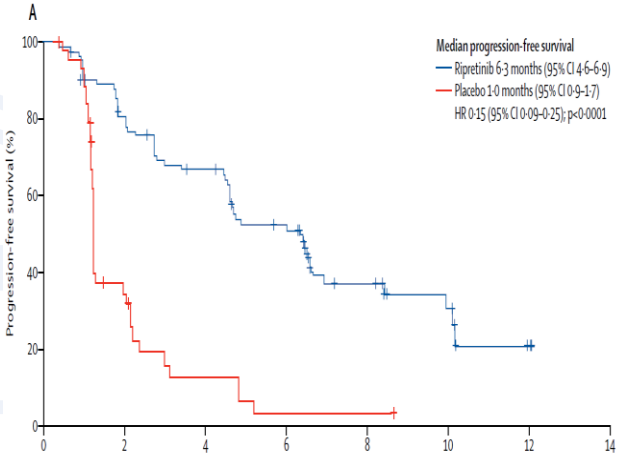
Régorafenib
L3



HR 0,27
mPFS **4,8 mois** vs 0,9
Réponse Objective: 4,5%

2014

Ripretinib
L4



HR 0,15
mPFS **6,3 mois** vs 1,0
Réponse Objective: 9,4%

2020

Demetri et al Lancet Oncol 2006; Lancet Oncol 2013
Blay et al, Lancet Oncol 2020

Les profils de tolérance après l'imatinib

Sunitinib

	Sunitinib (n=202)			Placebo (n=102)		
	Grade 1/2	Grade 3	Grade 4	Grade 1/2	Grade 3	Grade 4
Non-haematological*						
Fatigue	58 (29%)	10 (5%)	0 (0%)	20 (20%)	2 (2%)	0 (0%)
Diarrhoea	52 (26%)	7 (3%)	0 (0%)	8 (8%)	0 (0%)	0 (0%)
Skin discolouration	50 (25%)	0 (0%)	0 (0%)	6 (6%)	0 (0%)	0 (0%)
Nausea	47 (23%)	1 (1%)	0 (0%)	10 (10%)	1 (1%)	0 (0%)
Anorexia	38 (19%)	0 (0%)	0 (0%)	5 (5%)	1 (1%)	0 (0%)
Dysgeusia	36 (18%)	0 (0%)	0 (0%)	2 (2%)	0 (0%)	0 (0%)
Stomatitis	30 (15%)	1 (1%)	0 (0%)	2 (2%)	0 (0%)	0 (0%)
Vomiting	30 (15%)	1 (1%)	0 (0%)	5 (5%)	1 (1%)	0 (0%)
Hand-foot syndrome	19 (9%)	9 (4%)	0 (0%)	2 (2%)	0 (0%)	0 (0%)
Rash	24 (12%)	2 (1%)	0 (0%)	5 (5%)	0 (0%)	0 (0%)
Asthenia	18 (9%)	6 (3%)	0 (0%)	2 (2%)	2 (2%)	0 (0%)
Mucosal inflammation	24 (12%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Dyspepsia	22 (11%)	1 (1%)	0 (0%)	1 (1%)	0 (0%)	0 (0%)
Hypertension	15 (8%)	6 (3%)	0 (0%)	4 (4%)	0 (0%)	0 (0%)
Epistaxis	14 (7%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Hair-colour changes	14 (7%)	0 (0%)	0 (0%)	2 (2%)	0 (0%)	0 (0%)
Dry mouth	13 (6%)	0 (0%)	0 (0%)	1 (1%)	0 (0%)	0 (0%)
Glossodynia	11 (6%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Haematological						
Anaemia†	117 (58%)	7 (4%)	0 (0%)	59 (58%)	2 (2%)	0 (0%)
Leucopenia	104 (52%)	7 (4%)	0 (0%)	5 (5%)	0 (0%)	0 (0%)
Neutropenia	86 (43%)	17 (8%)	3 (2%)	4 (4%)	0 (0%)	0 (0%)
Lymphopenia	80 (40%)	18 (9%)	1 (1%)	31 (30%)	2 (2%)	1 (1%)
Thrombocytopenia	72 (36%)	8 (4%)	1 (1%)	4 (4%)	0 (0%)	0 (0%)

Data are number (%). *Treatment-related. †Anaemia was included in the table, despite a difference of less than 5% between the treatment groups, because of its frequency and clinical relevance in GIST.

Table 2: **Adverse events that occurred with a frequency of at least 5% greater on sunitinib than on placebo in per-protocol population**

Régorafenib

	Regorafenib (N=132*)			Placebo (N=66)		
	Any grade	Grade 3	Grade 4	Any grade	Grade 3	Grade 4
Any event	130 (98%)	77 (58%)	2 (2%)	45 (68%)	5 (8%)	1 (2%)
Hand-foot skin reaction	74 (56%)	26 (20%)	0	9 (14%)	0	0
Hypertension	64 (49%)	30 (23%)	1 (1%)	11 (17%)	2 (3%)	0
Diarrhoea	53 (40%)	7 (5%)	0	3 (5%)	0	0
Fatigue	51 (39%)	3 (2%)	0	18 (27%)	0	0
Oral mucositis	50 (38%)	2 (2%)	0	5 (8%)	1 (2%)	0
Alopecia	31 (24%)	2 (2%)	0	1 (2%)	0	0
Hoarseness	29 (22%)	0	0	3 (5%)	0	0
Anorexia	27 (21%)	0	0	5 (8%)	0	0
Rash, maculopapular	24 (18%)	3 (2%)	0	2 (3%)	0	0
Nausea	21 (16%)	1 (1%)	0	6 (9%)	1 (2%)	0
Constipation	20 (15%)	1 (1%)	0	4 (6%)	0	0
Myalgia	18 (14%)	1 (1%)	0	6 (9%)	0	0
Voice alteration	14 (11%)	0	0	2 (3%)	0	0

Data are n (%). *Excluding one patient who did not receive study treatment.

Table 2: **Drug-related adverse events in ≥10% of patients during double-blind treatment period**

Demetri et al. The Lancet 2006; Demetri et al. The Lancet 2013

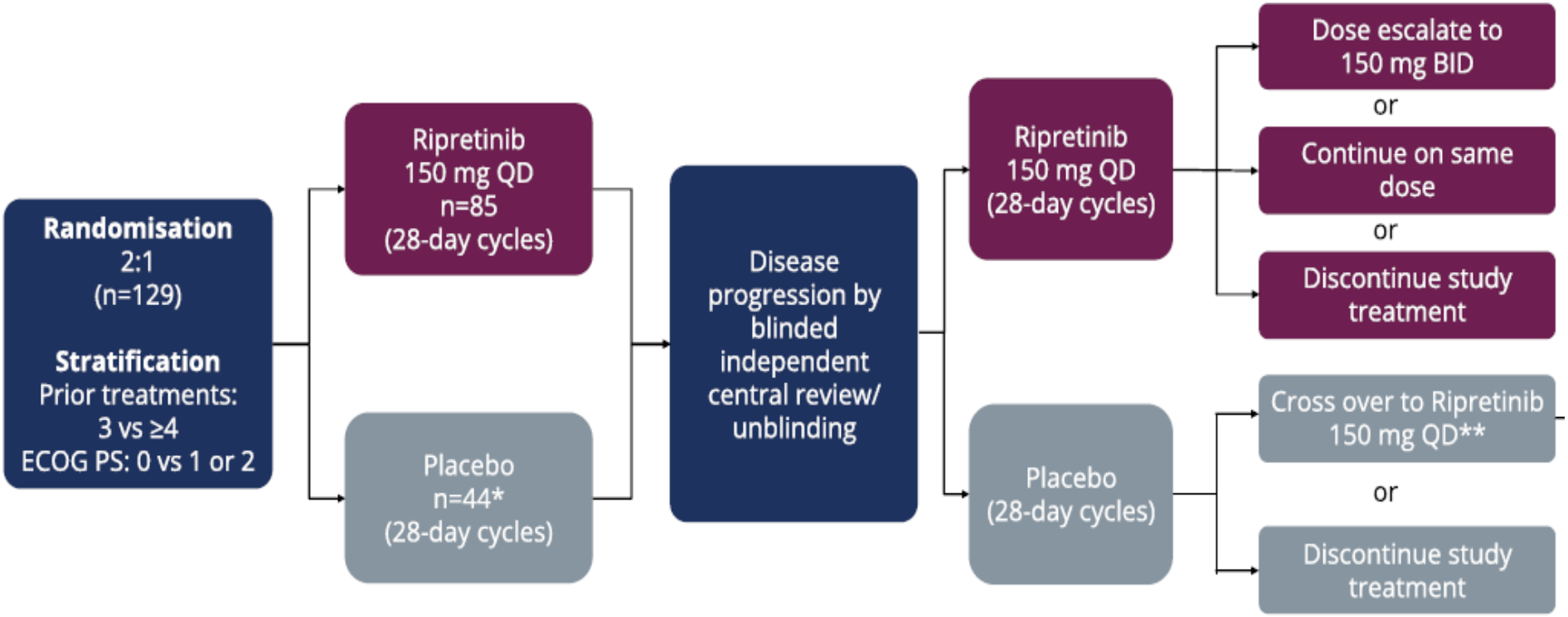
INVICTUS : ripretinib vs placebo dans les GIST avancées (4e ligne)

Etude INVICTUS

Phase 3 randomisée

GIST métastatique après Imatinib Sunitinib Regorafenib

Objectif Principal : Survie sans progression



Blay et al, Lancet Oncol 2020

INVICTUS : ripretinib vs placebo dans les GIST avancées (4e ligne)

Caractéristiques des patients

Characteristics	Ripretinib (n=85)	Placebo (n=44)
Age (years) Median (min, max)	59 (29, 82)	65 (33, 83)
18–64 years	57 (67%)	22 (50%)
65–74 years	20 (24%)	12 (27%)
≥ 75 years	8 (9%)	10 (23%)
Gender		
Male (%)	47 (55%)	26 (59%)
Race		
White (%)	64 (75%)	33 (75%)
Region		
US (%)	40 (47%)	20 (46%)
ECOG PS (%)		
ECOG PS 0	37 (44%)	17 (39%)
ECOG PS 1/2	48 (56%)	27 (61%)
Number of prior therapies (%)		
3	54 (64%)	27 (61%)
≥4 (range, 4-7)	31 (36%)	17 (39%)

Characteristics	Ripretinib (n=85)	Placebo (n=44)
Primary mutation (central testing of tumour tissue) n (%)		
KIT exon 9	14 (17%)	6 (14%)
KIT exon 11	47 (55%)	28 (64%)
Other KIT	2 (2%)	2 (5%)
PDGFRA	3 (4%)	0
KIT/PDGFRA wild type	7 (8%)	3 (7%)
Not available / not done*	12 (14%)	5 (11%)
Primary tumour site, n (%)		
Gastric	40 (47)	18 (41)
Jejunum or ileum	20 (24)	8 (18)
Mesenteric or omental	6 (7)	6 (14)
Other	7 (8)	4 (9)
Duodenum	2 (2)	8 (18)
Colon or rectum	9 (11)	0
Unknown	1 (1)	0
Median sum of longest diameters of target lesions (mm), range**	123 (28-495)	142 (17-412)

Blay et al, Lancet Oncol 2020

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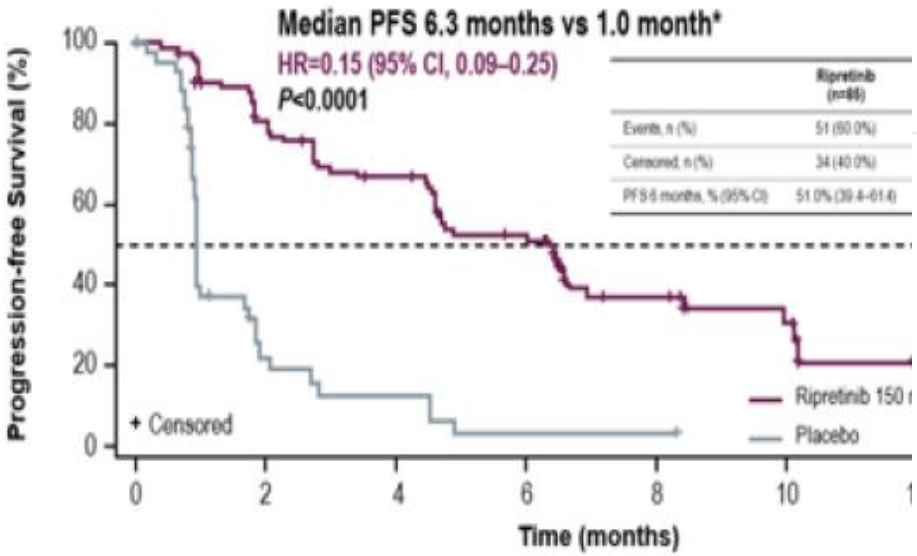
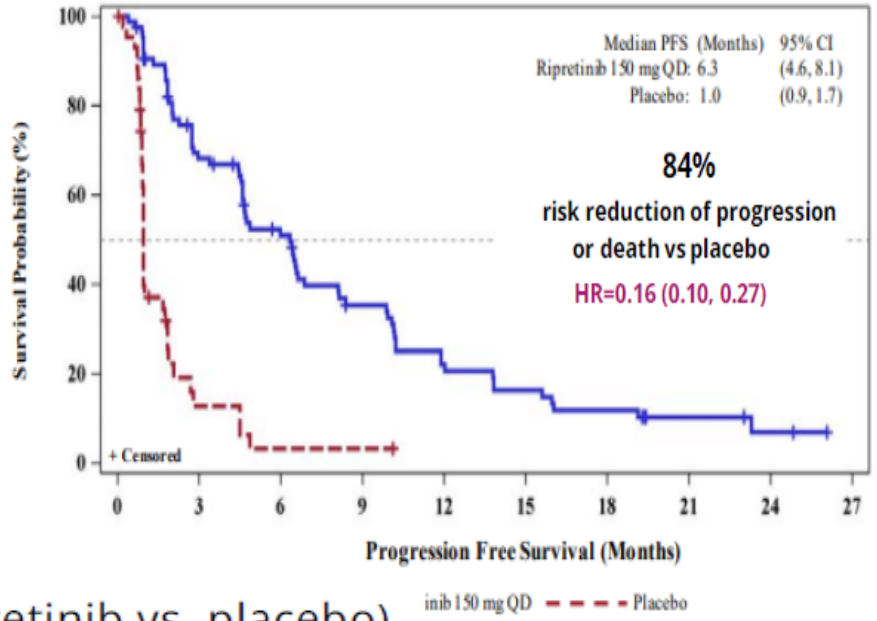
INVICTUS : ripretinib vs placebo dans les GIST avancées (4e ligne)

Objectif principal : Survie sans progression

Primary Analysis (May 31, 2019)



Additional 14-months follow-up (August 10, 2020)



Baisse du risque de progression ou de décès de 85%

- **Stable disease at 6 weeks**: 66% vs. 20% (ripretinib vs. placebo)
- **Stable disease at 12 weeks**: 47% vs. 5 % (ripretinib vs. placebo)

Blay et al, Lancet Oncol 2020

R. Coriat

Groupement d'hôpitaux Paris Centre
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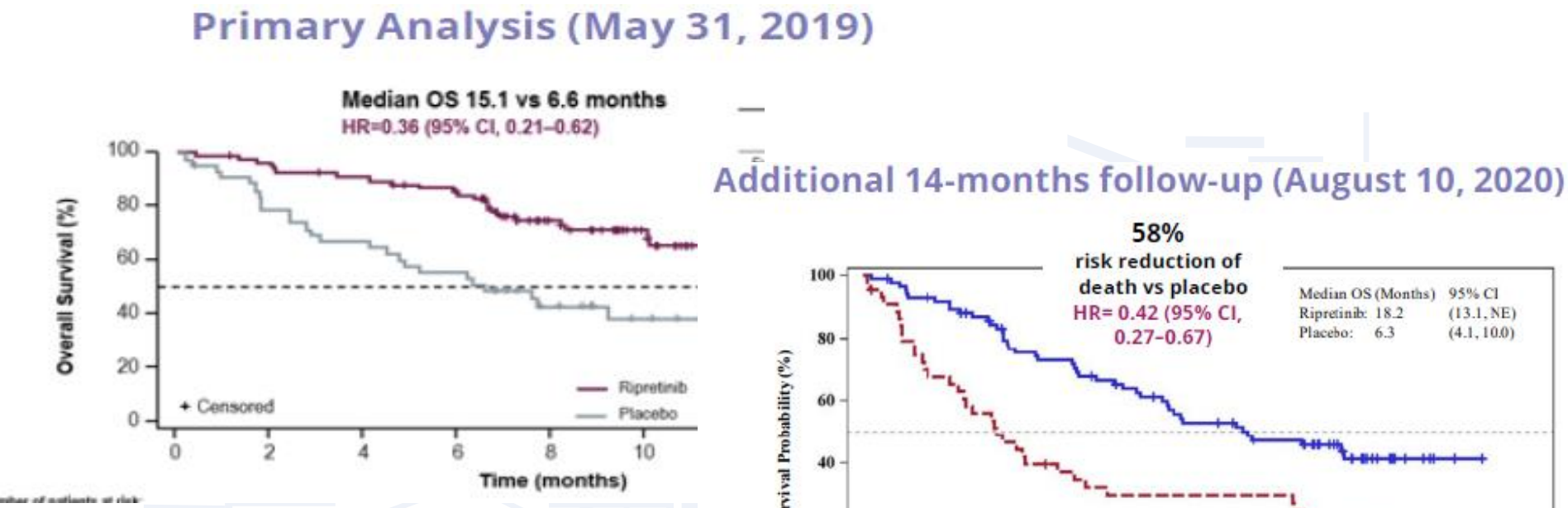
INVICTUS : ripretinib vs placebo dans les GIST avancées (4e ligne)

Survie globale



Ripretinib SGm (2020): 18,2 mois vs 6,3 mois
Baisse du risque de décès de 58%
HR 0,42

Blay et al, Lancet Oncol 2020

INVICTUS : ripretinib vs placebo dans les GIST avancées (4e ligne)

Effets indésirables

	Ripretinib group (n=85)				Placebo group (n=43)*			
	Grade 1-2	Grade 3	Grade 4	Grade 5	Grade 1-2	Grade 3	Grade 4	Grade 5
Alopecia	42 (49%)†	-	-	-	1 (2%)		-	-
Myalgia	23 (27%)	1 (1%)	-	-	4 (9%)	0	-	-
Nausea	21 (25%)	1 (1%)	-	-	1 (2%)	0	-	-
Fatigue	20 (24%)	2 (2%)	-	-	6 (14%)	1 (2%)	-	-
Palmar–plantar erythrodysesthesia syndrome	18 (21%)	0	-	-	0	0	-	-
Diarrhoea	17 (20%)	1 (1%)	0	0	2 (5%)	1 (2%)	0	0
Constipation	13 (15%)	0	0	0	3 (7%)	0	0	0
Decreased appetite	12 (14%)	1 (1%)	0	0	2 (5%)	1 (2%)	0	0
Weight loss	23 (27%)	0	-	-	3 (7%)	0	-	-
Blood bilirubin increased	23 (27%)	0	0	-	0	0	0	-
Arthralgia	10 (12%)	0	-	-	0	0	-	-
Muscle spasms	10 (12%)	0	-	-	2 (5%)	0	-	-
Hypertension	4 (5%)	3 (4%)	0	0	1 (2%)	0	0	0
Lipase increase	4 (5%)	4 (5%)	0	-	0	0	0	-
Pain in extremity	5 (6%)	1 (1%)	-	-	1 (2%)	0	-	-
Hypophosphataemia	3 (4%)	2 (2%)	0	0	0	0	0	0
Anaemia	2 (2%)	0	1 (1%)	0	1 (2%)	2 (5%)	1 (2%)	0

Blay et al, Lancet Oncol 2020

Stratégie thérapeutique dans les GIST

GIST

NB : Confirmation Histologique seulement si CI chirurgicale ou doute diagnostique

Absence de métastase

Chirurgie
Options si GIST gastrique < 2 cm : chirurgie ou surveillance

Traitement Adjuvant si lésion de haut risque ou perforée: Imatinib 3 ans.

Pas de traitement si mutation D842V de PDGFRA

NB : pour les lésions intermédiaires, indication à discuter au cas par cas

Tumeur métastatique :
Recherche mutation de KIT sur Exon 9, 11 et 13 et mutations de PDGFRA

1ère ligne :
IMATINIB (Glivec®) 400mg/jour

Si mutation de KIT exon 9 : **Imatinib 800mg/jour**

Si mutation D842V de PDGFRA : **avapritinib 300 mg/jour**

2eme ligne :
Si dose initiale d'**Imatinib** de 400mg/j, augmentation à **800 mg/j**
Sinon : **SUNITINIB** 37.5 mg/jour

3eme ligne :
Régorafenib 160 mg/jour

4eme ligne :
Ripretinib 150 mg/j

Ne pas oublier de discuter le dossier en RCP NETSARC

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