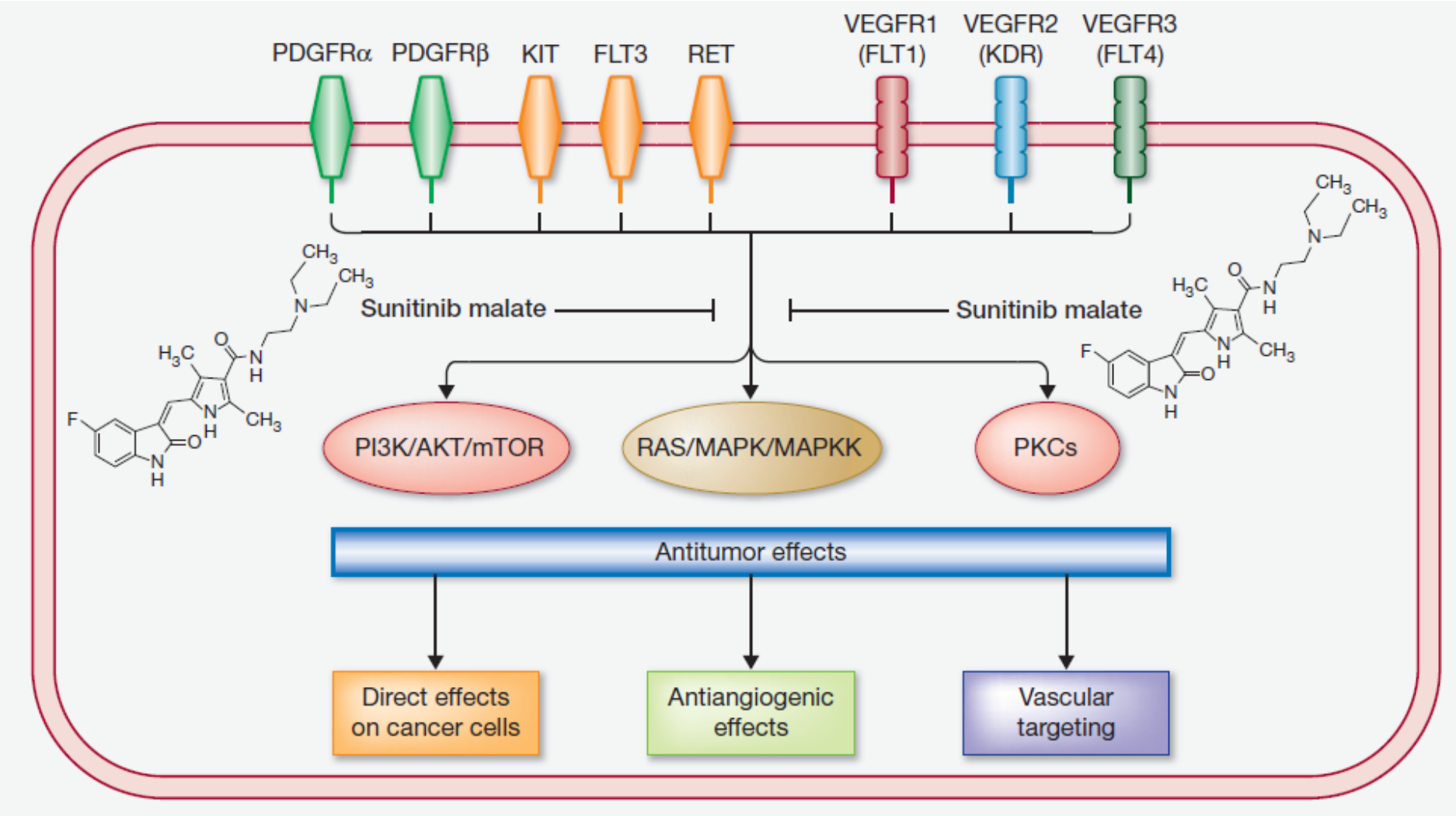
NEW INSIGHTS INTO MOLECULAR MECHANISMS OF **SUNITINIB-ASSOCIATED SIDE EFFECTS**

Sunitinibmay display collateral effects on other proteins beyond its main target receptors, eliciting undesirable and unexpected adverse events.

A better understanding of the molecular mechanisms underlying these undesirable sunitinib-associated side effects will help physicians to maximize efficacy of sunitinib and minimize adverse events.

Specific RTKs are blocked by sunitinib

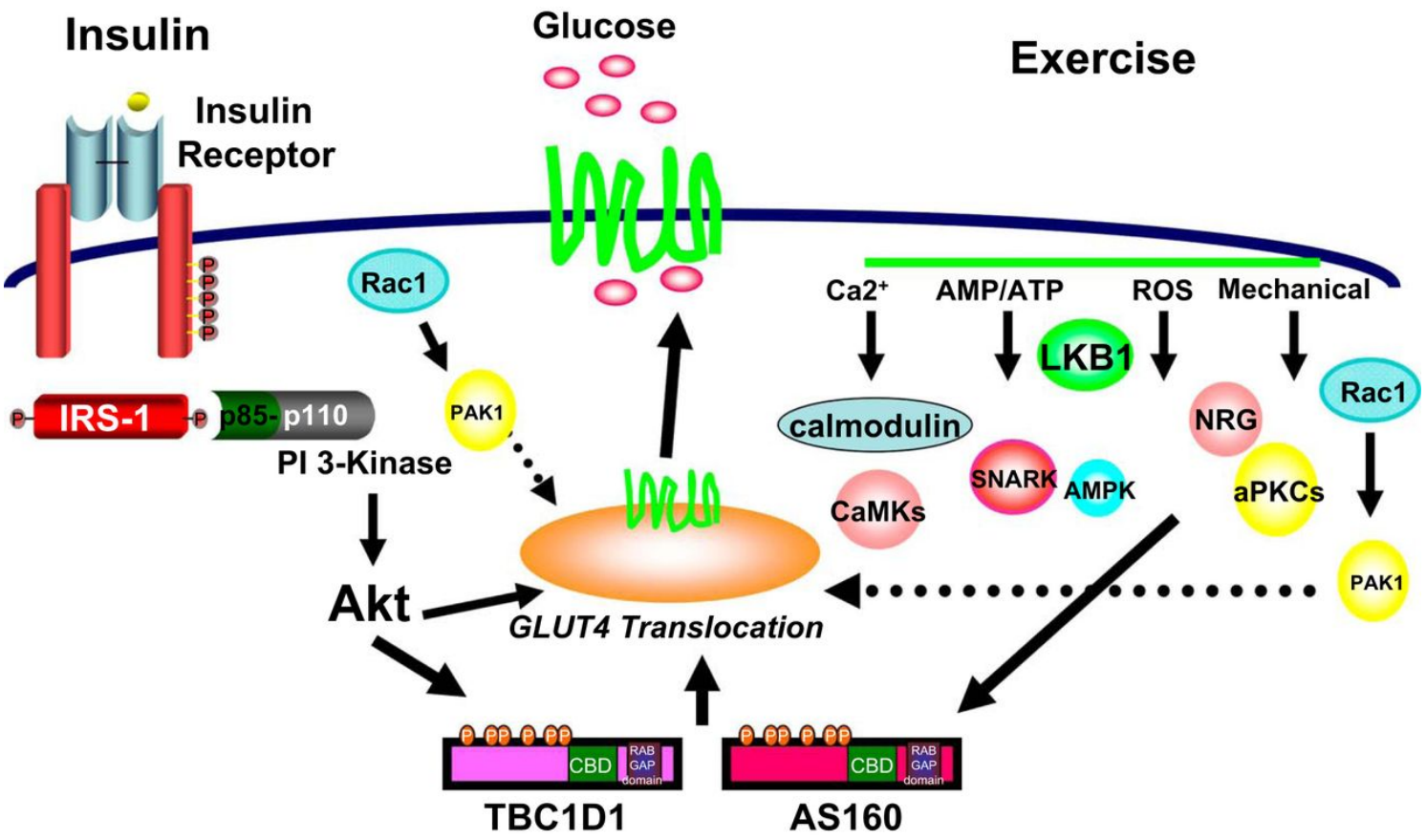


❑ Sunitinib is able to block different signaling pathways : PDGFRa and b, KIT, FLT3, RET, and VEGFRs 1, 2, and 3.

❑ Sunitinib inhibition of signaling pathways [phosphoinositide 3-kinase (PI3K)/AKT/mTOR, mitogen-activated protein kinase (MAPK), and PKC] triggers different antitumor effects

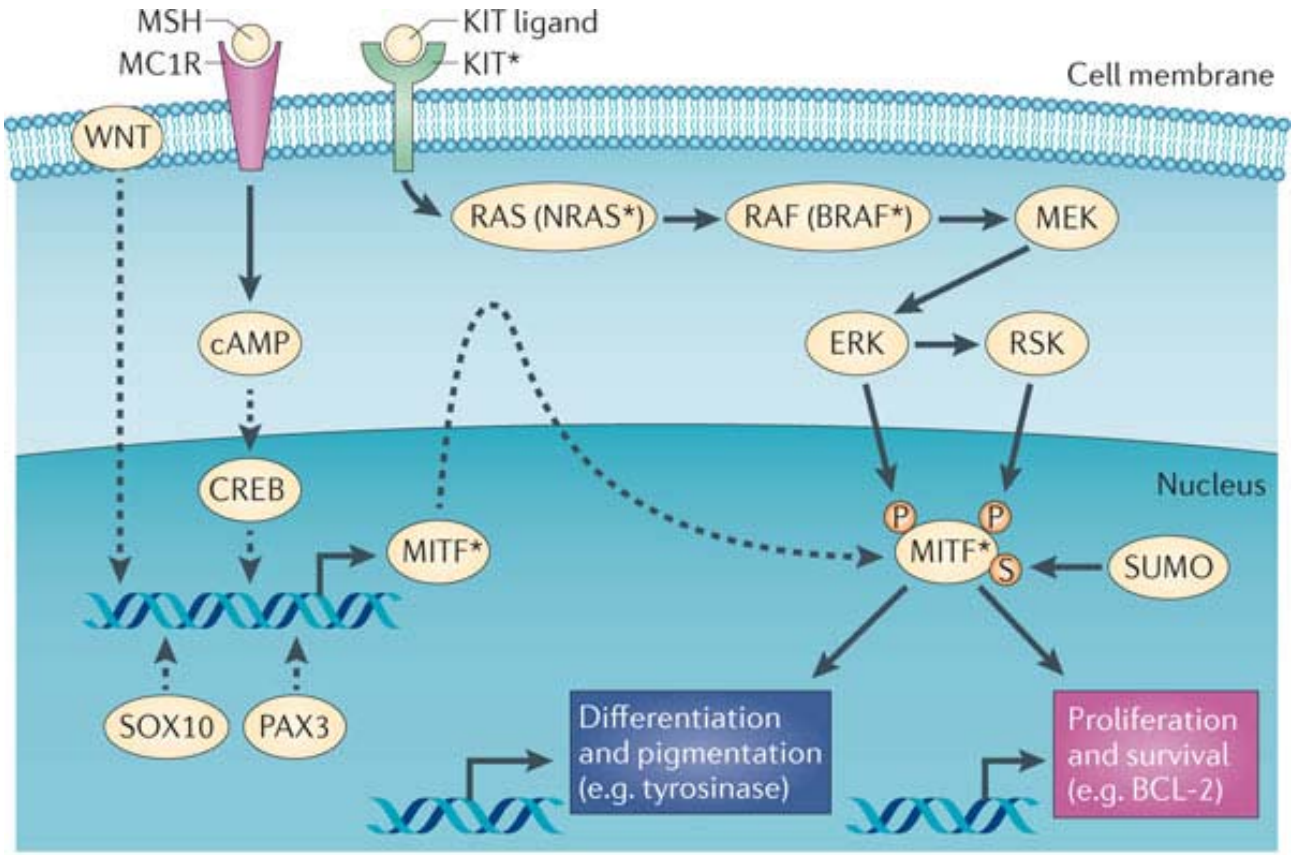
Molecular Basis of Fatigue and Asthenia

AMP-activated protein kinase
Glucose transporters (NOS)
Circadian rhythm disruption



Molecular Basis of Hair Depigmentation

Signaling pathways during hair pigmentation

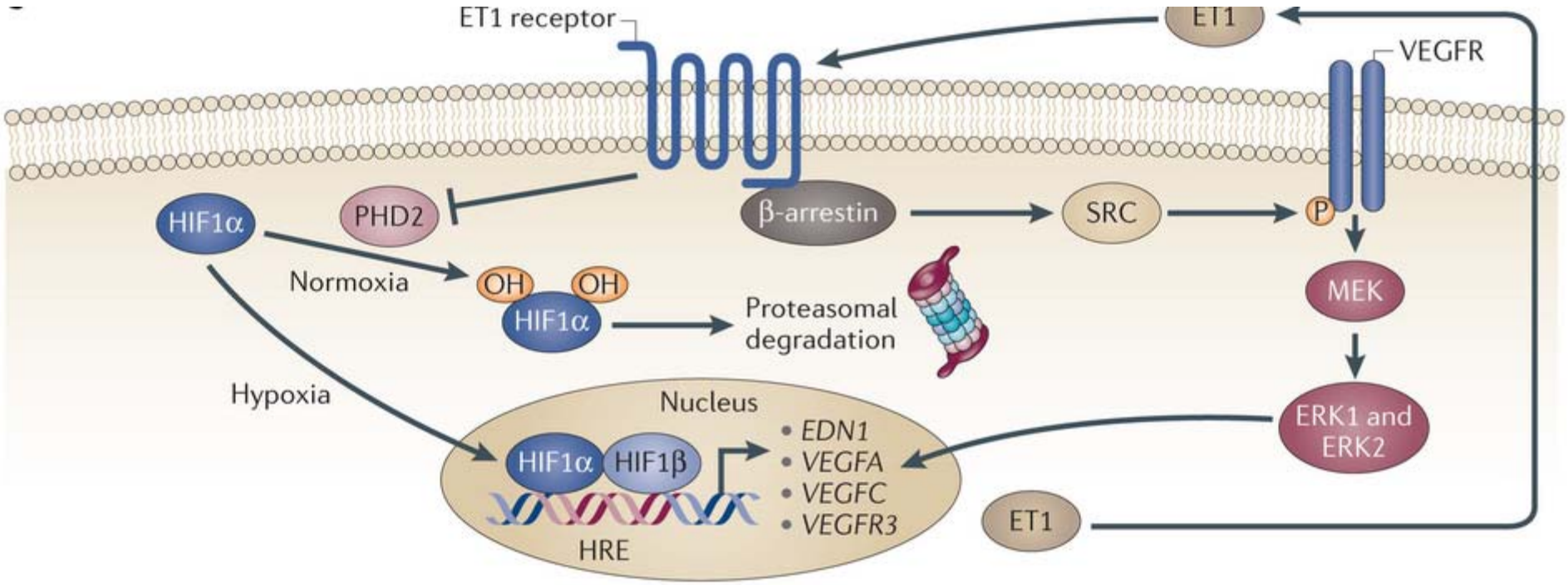


Nature Reviews | Cancer

Molecular Basis of Sunitinib Cardiotoxicity

Angiogenesis
Ribosomal protein S6 kinase and AMP-dependentkinase
Impaired mitochondrial function

Among the targets of sunitinib, only PDGFRs are expressed by cardiomyocytes
Hypoxia is a critical component of myoardial ishemia. HIF-1 is a major regulator of hypoxia



- ❑ Molecular Basis of Hypothyroidism
- ❑ Molecular Basis of Hypertension
- ❑ Molecular Basis of Dermatologic Toxicity
- ❑ Molecular Mechanisms of Rare Toxicities

CIRCULATING CYTOKINES AND MONOCYTE SUBPOPULATIONS AS **BIOMARKERS** OF OUTCOME AND BIOLOGICAL ACTIVITY **IN SUNITINIB-TREATED PATIENTS** WITH ADVANCED NEUROENDOCRINE TUMOURS

This analysis of circulating protein and cellular biomarkers in sunitinib-treated patients with pNET and carcinoid identified differences between tumour types and new candidate markers associated with outcomes, offering fresh insights into the biological activity of sunitinib and its mechanism of action.

Changes in soluble protein biomarkers during treatment and correlation with drug exposure.

Table 1. Baseline levels of soluble proteins and ratios of C1D28 to baseline levels during sunitinib treatment

Biomarker	All patients, median (range)	*N*	*P*-value	Carcinoid tumour, median (range)	*N*	pNET, median (range)	*N*	*P*-value[a]
VEGF Baseline, pg ml^{-1}	38.6 (8.2–408.5)	101		30.1 (9.2–138.9)	37	43.4 (8.2–408.5)	64	0.069
VEGF C1D28:C1D1	3.4	100	**<0.0001**	3.6	35	3.2	65	0.599
sVEGFR-2 Baseline, pg ml^{-1}	9120 (3251–15 689)	104		8722 (3251–12 776)	39	9562 (3894–15 689)	65	**0.041**
sVEGFR-2 C1D28:C1D1	0.7	102	**<0.0001**	0.8	37	0.6	65	0.105
sVEGFR-3 Baseline, pg ml^{-1}	100 850 (30 700–2 569 000)	104		96 800 (43 500–2 569 000)	39	100 800 (30 700–168 400)	65	0.817
sVEGFR-3 C1D28:C1D1	0.6	98	**<0.0001**	0.6	34	0.6	64	0.429
IL-8 Baseline, pg ml^{-1}	16.9 (3.3–763.1)	104		15.0 (3.3–763.1)	39	17.6 (6.1–130.3)	65	0.302
IL-8 C1D28:C1D1	1.8	99	**0.008**	1.4	36	1.8	66	0.528
SDF-1α Baseline, pg ml^{-1}	583.4 (209.9–2218.8)	28		414.8 (209.9–2218.8)	14	1235.7 (285.7–2049.8)	14	**0.003**
SDF-1α C1D28:C1D1	1.2	21	**0.027**	1.8	10	1.1	11	0.053

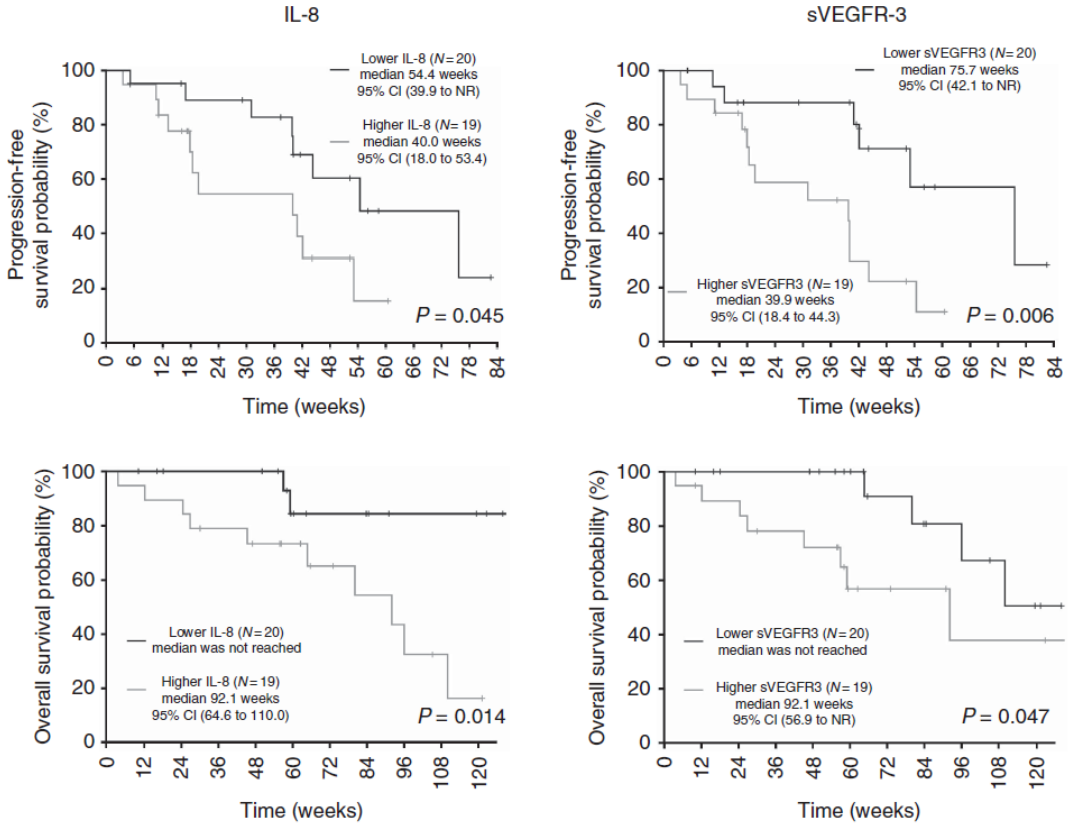
Abbreviations: C(*N*)D(*N*) = cycle number, day number; IL-8 = interleukin 8; pNET = pancreatic neuroendocrine tumour; SDF-1α = stromal cell-derived factor 1α; sVEGFR-2 = soluble VEGF receptor 2; sVEGFR-3 = soluble VEGF receptor 3; VEGF = vascular endothelial growth factor. *P*-values <0.05 are underlined and shown in bold.
[a]Wilcoxon rank-sum test comparing carcinoid with pNET.

Specimens for soluble protein assessment were collected on days 1, 14 (C1D14), and 28 (C1D28) of cycle 1, and days 1 and 28 of cycles 24 (C2D1 refers to cycle 2 day 1; online only). Vascular endothelial growth factor, IL-8, sVEGFR-2, and sVEGFR-3 concentrations were measured by enzyme-linked immunosorbent assay (ELISA).

- ❑ At C1D28, sunitinib treatment was associated with significant increases from baseline in VEGF, IL-8, and SDF-1a, and decreases in sVEGFR-2 and sVEGFR-3
- ❑ Very mild to moderate but significant correlations between plasma trough drug levels (Cmin) by C1D28 for sunitinib and changes in VEGF, sVEGFR-3, and IL-8, were found in patients with pNET,but not for sVEGFR2

- ❑ Patients with pNET high SDF-1α predicted for an increased risk of progression or death).
- ❑ Patients achieving CBR had lower SDF-1 α concentrations (median 418 (range 210–1760) vs median 1069 (range 229–2219)

Relationship between protein biomarkers and outcomes



Kaplan–Meier estimates of PFS and OS for IL-8 and sVEGFR3 in carcinoids.

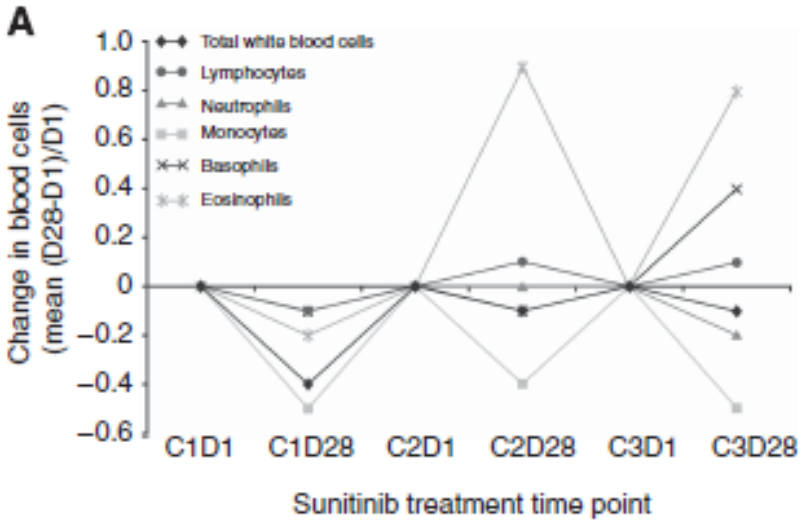
✓ Only baseline IL-8 levels were lower inpatients with.

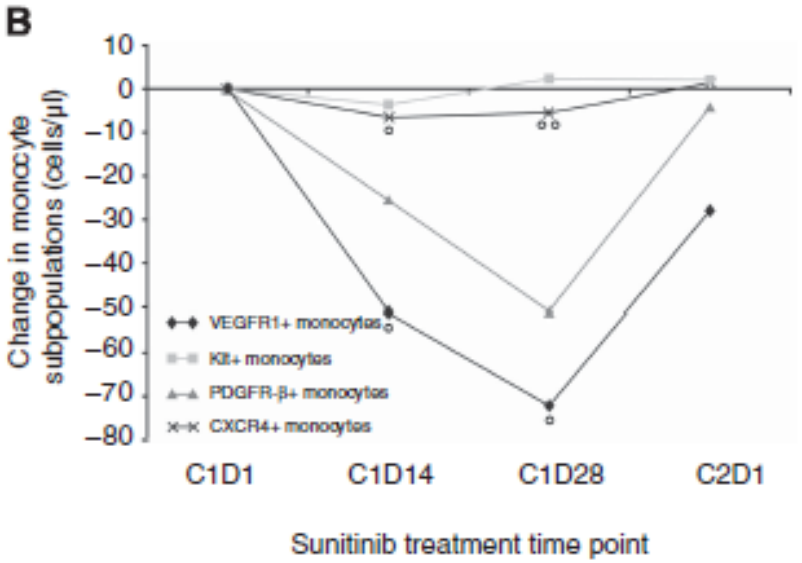
✓ High sVEGFR-3 and IL-8 levels correlated with shorter PFS and OS

❑ Patients with pNET high SDF-1α predicted for an increased risk of progression or death).

❑ Patients achieving CBR had lower SDF-1 α concentrations (median 418 (range 210–1760) vs median 1069 (range 229–2219)

Changes in WBC and monocyte subsets during sunitinib treatment.





- All WBC types, except lymphocytes and basophils, showed highly significant changes during the first three cycles of sunitinib, most notably a decrease in monocytes.

- Peripheral blood mononuclear cell specimens from 17 patients were assessed by flow cytometry at baseline, C1D14, C1D28, and C2D1. On sunitinib, CD14þ monocyte subpopulations decreased, in particular those bearing VEGFR-1 or CXCR4

Exploratory correlations between changes in cellular and plasma markers.

Table 3. Correlation between change from baseline to C1D28 in monocyte count and plasma markers

	Correlation with change in monocytes, expressed as Spearman correlation coefficient (ρ)/*P*-value		
	Carcinoid tumour ($n = 37$)	pNET ($n = 62$)	All patients ($N = 99$)
Change in VEGF	−0.25/0.16	−0.13/0.33	−0.17/0.10
Change in sVEGFR-2	0.130/0.46	**0.31/0.01**	0.19/0.07
Change in sVEGFR-3	**0.37/0.04**	0.22/0.10	**0.32/0.002**
Change in IL-8	−0.06/0.75	−0.10/0.45	−0.07/0.53

Abbreviations: IL-8 = interleukin 8; pNET, pancreatic neuroendocrine tumour; sVEGFR-2 = soluble VEGF receptor 2; sVEGFR-3 = soluble VEGF receptor 3; VEGF = vascular endothelial growth factor. Correlation coefficients with *P*-values ≤0.05 are shown in bold.

✓ Change from baseline to C1D28 in monocyte count showed moderately positive correlations with sVEGFR-3 change in all patients, particularly in those with carcinoid, and with sVEGFR-2 changes inpatients with pNET.

❑ Positive correlations were observed between changes in IL-8 and

❑ CXCR4-expressing monocytes and CEP, suggesting that IL-8 may contribute to mobilization and/or tumour recruitment of these cells.

❑ Negative correlations were found between changes in sVEGFR-2 and sVEGFR-3, and mature CEC

Conclusion

❑ Changes in VEGF, sVEGFR-2, sVEGFR-3, SDF-1a, and IL-8 during the first cycle of sunitinib treatment were independent of tumour type and were similar in range to those in patients with renal cell and hepatocellular carcinomas and GIST. Most of these changes are related to the effects of the drug on host rather than tumour cells.

❑ **Sunitinib exerts antitumour and antiangiogenic effects via tyrosine kinase inhibition on signalling cascades that regulate tumour growth, survival, and angiogenesis. high pre-treatment sVEGFR-2 levels were associated with longer OS in patients with pNET, the first such report.**

❑ SDF-1a/CXCR4 pathway and the relative value of IL-8, sVEGFR-2, and sVEGFR-3 should be further investigated in well-differentiated NET in comparison with other emerging markers of prognosis such as chromogranin A and neuron-specific enolase

❑ the specific targeting of VEGFR-1 and CXCR4 monocytes may be a novel and important contributor to the effectiveness of sunitinib and perhaps other VEGFR-targeted agents in NET and other cancer types.

However these findings regarding IL-8 and sVEGFR-3 in carcinoid tumours, sVEGFR-2 in NETs, and SDF-1a in both should therefore be viewed as exploratory, and will require further evaluation and confirmation

SU11248 induces growth arrest a of GIST-T1 cells

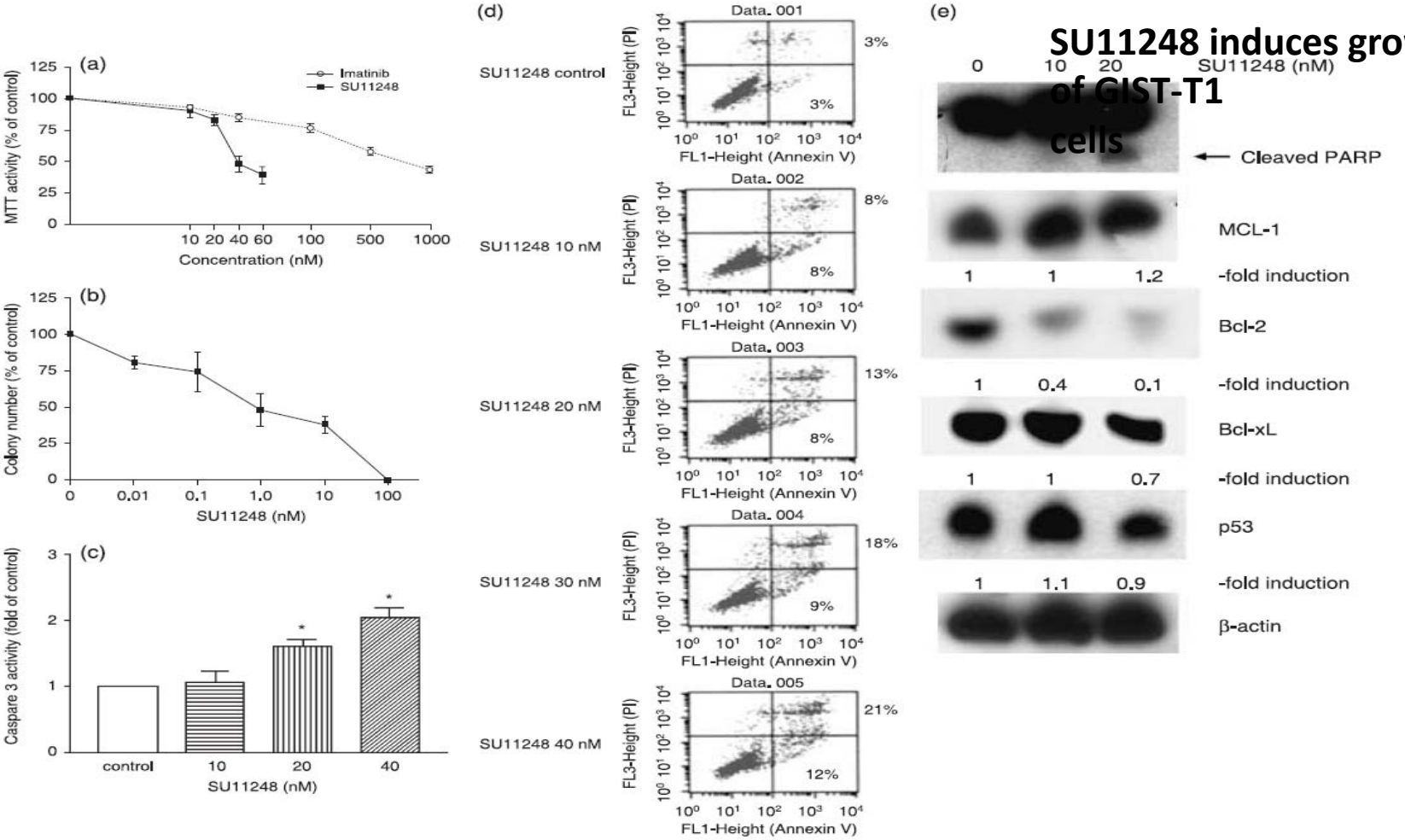


Fig. 1. SU11248 induces growth arrest and apoptosis of gastrointestinal stromal tumor (GIST)-T1 cells. (a) MTT assay. GIST-T1 (2×10^5/mL) cells were plated in 96-well plates and cultured with various concentrations of SU11248 (10–60 nM) or imatinib (10–1000 nM). After 4 days, the cells were treated with MTT for 4 h and absorbance was measured. Results represent the mean ± SD of three experiments carried out in triplicate. (b) Colony forming assay. GIST-T1 cells (500 cells/plate) were cultured with various concentrations of SU11248 (0.01–100 nM). Colonies (>40) were enumerated after 14 days of incubation. Results are expressed as a mean percentage of control plates containing 0.001% dimethylsulfoxide (control diluent). Each point represents the mean of three independent experiments on triplicate plates. Bars represent the SD. (C) Caspase-3 assay. GIST-T1 cells were cultured with various concentrations of SU11248 (10–40 nM). After 48 h, cells were harvested and proteins were extracted. Caspase-3 activity was measured using DEVE (Asp-Glu-Val-Asp) as a substrate. Results represent the mean ± SD of three experiments carried out in duplicate. Statistical significance was determined by the paired *t*-test. $^*P < 0.05$. (D) Annexin V binding. Annexin binding and propidium iodide staining were analyzed by FACscan. Lower left quadrants, viable cells. Lower right quadrants, early apoptotic cells. Upper right quadrants, non-viable late apoptotic/necrotic cells. These results represent the mean of triplicate plates. (E) Western blot analyses. GIST-T1 cells were cultured in the presence of SU11248 (10 or 20 nM). After 48 h, cells were harvested and proteins were extracted and subjected to western blotting. The polyvinylidene fluoride membrane was probed sequentially with anti-poly (ADP-ribose) polymerase (PARP), Mcl-1, Bcl-2, Bcl-xL, p53 and β-actin antibodies, and band intensities were measured using densitometry. Two repeated experiments yielded similar results.

Développement clinique du Sunitinib de la phase I à la phase III

Thomas Filleron

Institut Claudius Regaud, IUCT-O ,Toulouse

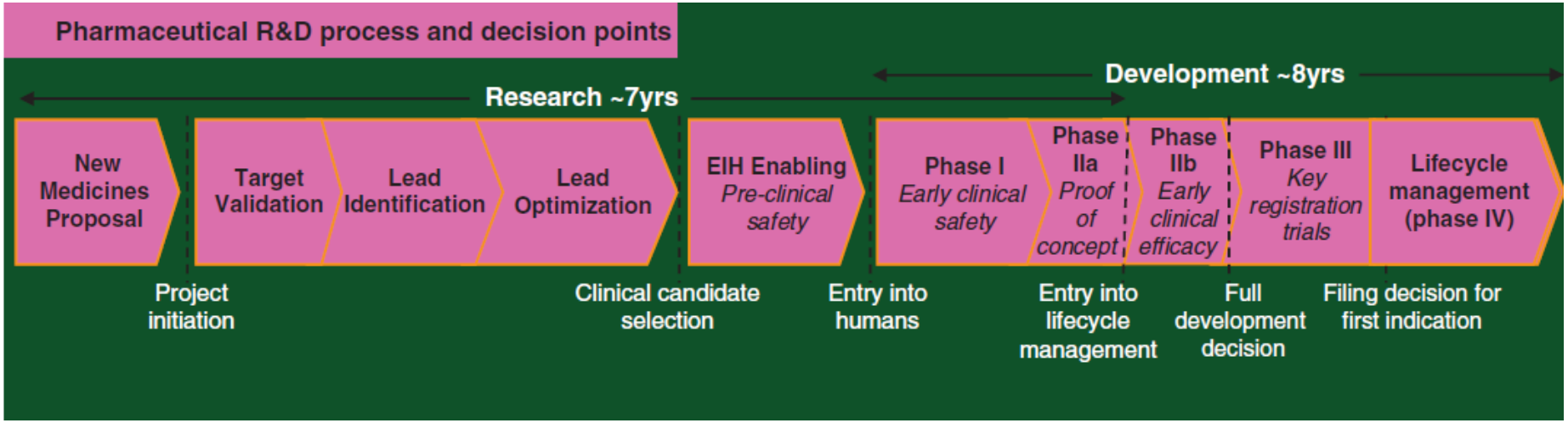
La grande Motte, Octobre 2015

Développement d'un médicament en cancérologie

Le développement d'une molécule

industry corner - clinical trials

(Dhingra, Annals of Oncology 2015)



Le développement d'une molécule

industry corner - clinical trials

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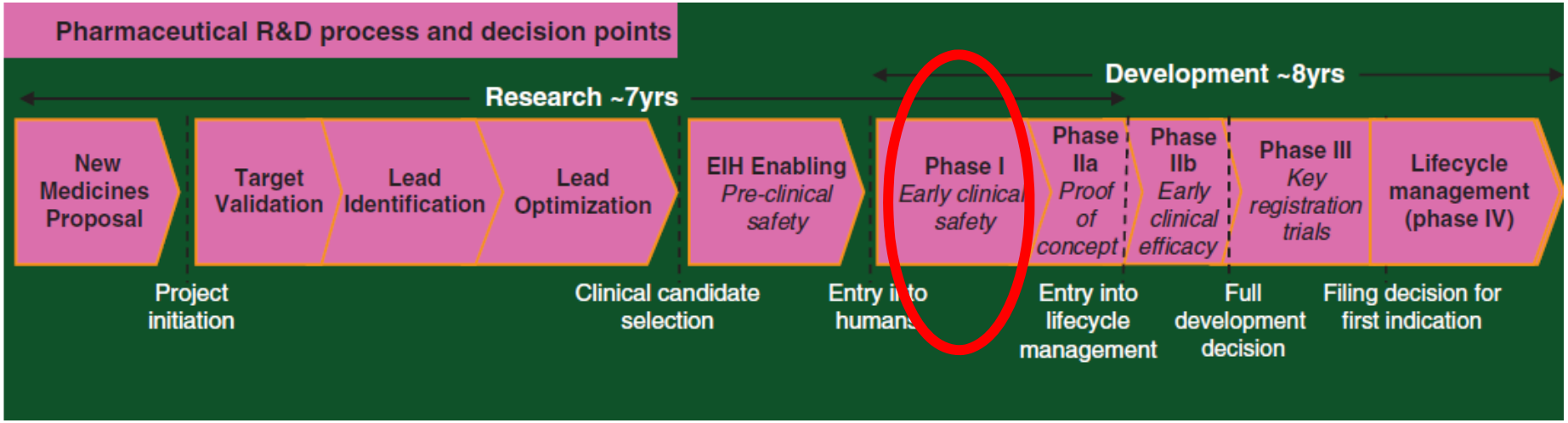

Phase I en hématologie

An Innovative Phase I Clinical Study Demonstrates Inhibition of FLT3 Phosphorylation by SU11248 in Acute Myeloid Leukemia Patients

Clinical Cancer Research 5465 O'Farrell

Vol. 9, 5465–5476, November 15, 2003

A phase 1 study of SU11248 in the treatment of patients with refractory or resistant acute myeloid leukemia (AML) or not amenable to conventional therapy for the disease

Fiedler BLOOD, 1 FEBRUARY 2005 • VOLUME 105, NUMBER 3

Safety, Pharmacokinetic, and Antitumor Activity of SU11248, a Novel Oral Multitarget Tyrosine Kinase Inhibitor, in Patients With Cancer

Faivre S

JOURNAL OF CLINICAL ONCOLOGY

VOLUME 24 · NUMBER 1 · JANUARY 1 2006

- Objectifs:
  - Evaluer la tolérance du SU11248 chez les patients traités pour tumeur solide

- Patients et méthode
  - Essai de Phase I d'escalade de doses
  - DLT évaluée pendant le cycle 1
  - Paliers de dose 15 (30 q2d), 30daily, 42daily, 59 daily

mg/m^2), and 100 to 150 mg/d (59 mg/m^2). Hematologic dose-limiting toxicity (DLT) was defined as at least a grade 4 hematologic toxicity or grade 3 thrombocytopenia accompanied by a grade 3 or greater hemorrhage. Nonhematologic DLTs were defined as any grade 3 or greater adverse event that was considered related to the study drug except nausea and vomiting that responded to antiemetic therapy.

Safety, Pharmacokinetic, and Antitumor Activity of SU11248, a Novel Oral Multitarget Tyrosine Kinase Inhibitor, in Patients With Cancer

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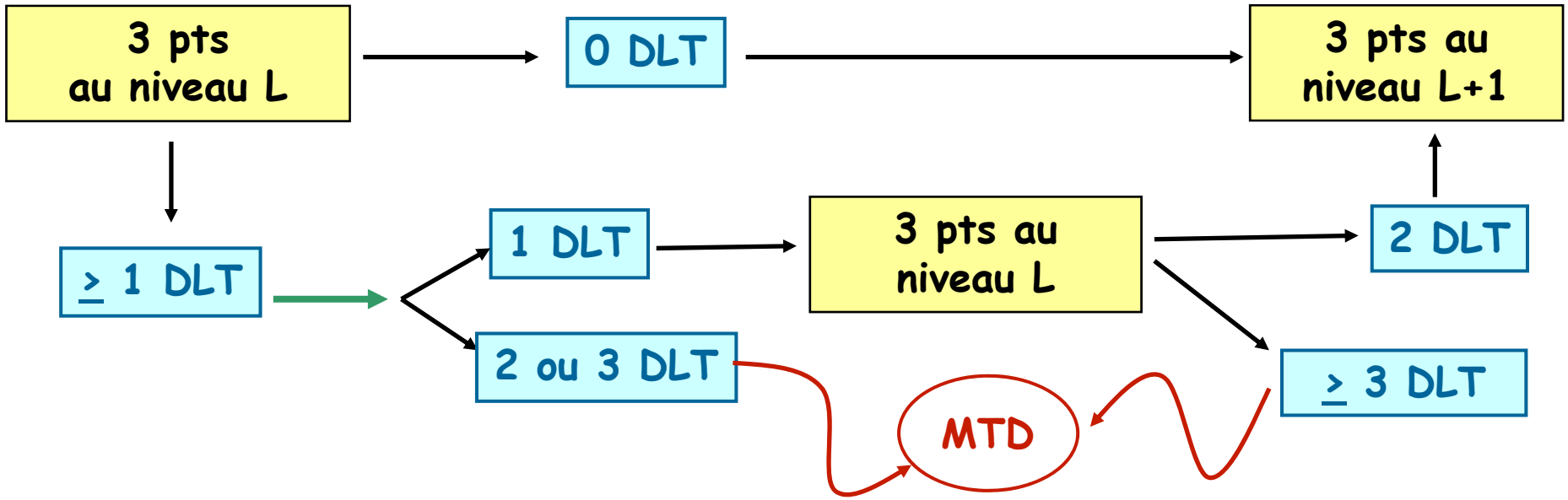
JOURNAL OF CLINICAL ONCOLOGY
VOLUME 24 · NUMBER 1 · JANUARY 1 2006



Au moins 9 pts doivent être inclus à la MTD

La MTD est définie par le niveau de dose où moins de 33% des patients présentent une DLT

Safety, Pharmacokinetic, and Antitumor Activity of SU11248, a Novel Oral Multitarget Tyrosine Kinase Inhibitor, in Patients With Cancer

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VOLUME 24 · NUMBER 1 · JANUARY 1 2006

28 pts inclus entre juin 2001 et septembre 2003

Table 1. Patient Characteristics

		No. of Patients
No. of patients		
Total included		28
Assessable		27
Sex		
Male		15
Female		13
Age, years		
Median	55	
Range	33-78	
Performance status*		
0		22
1		3
2		3
Previous treatment regimens for advanced disease		
Median	2	
Range	0-9	
Tumor types		
Renal cell carcinoma		4
Neuroendocrine tumors		4
Colorectal cancer		3
Non–small-cell lung cancer		2
Mesotheliomas		2
Uterine carcinoma		2
Breast cancer		2
Pancreas adenocarcinoma		2
Angiosarcoma		2
Esophagus carcinoma		1
Undifferentiated carcinoma of nasopharynx		1
Parotid adenocarcinoma		1
Melanoma		1
Gastrointestinal stromal tumor		1

*Eastern Cooperative Oncology Group.

Safety, Pharmacokinetic, and Antitumor Activity of SU11248, a Novel Oral Multitarget Tyrosine Kinase Inhibitor, in Patients With Cancer

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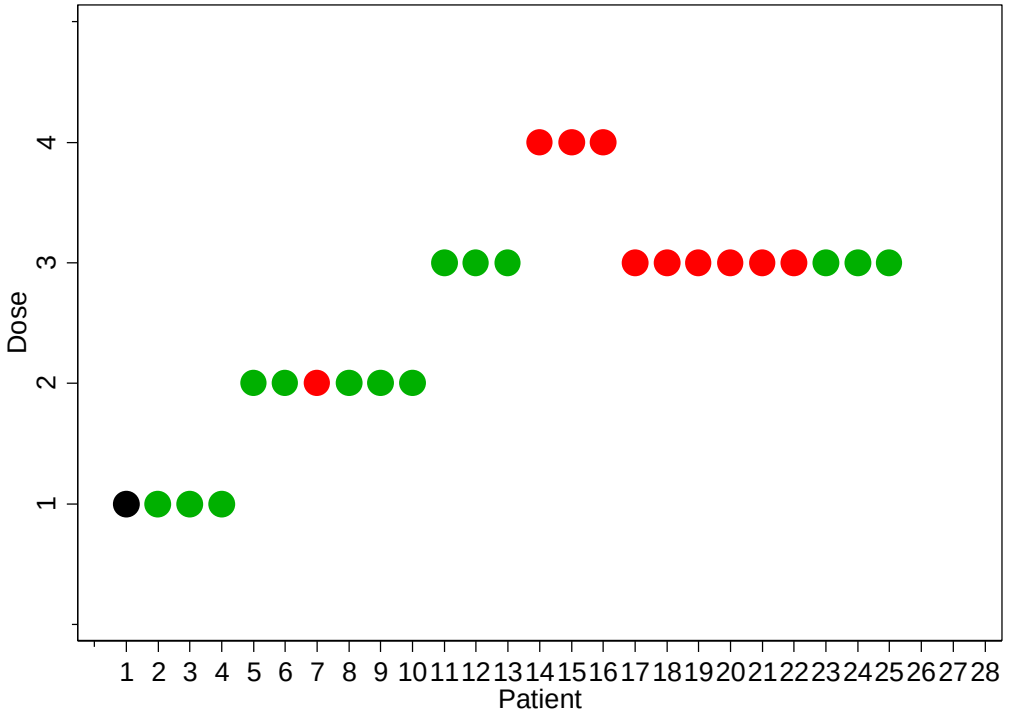
Escalade de dose



+ de 33% des pts présentent une DLT

Safety, Pharmacokinetic, and Antitumor Activity of SU11248, a Novel Oral Multitarget Tyrosine Kinase Inhibitor, in Patients With Cancer

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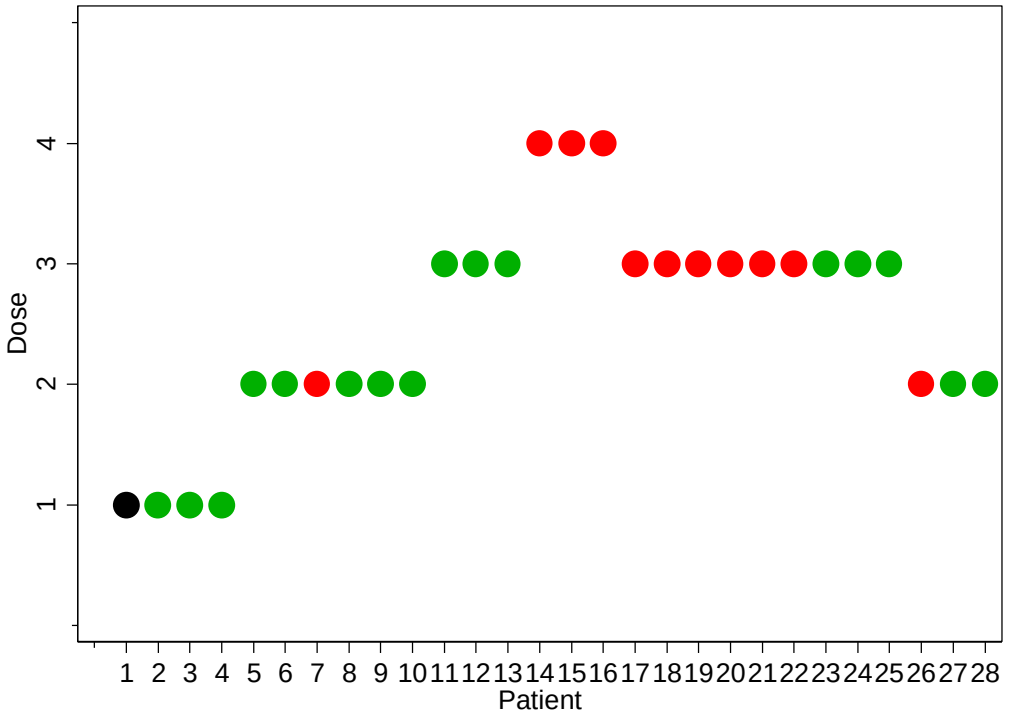
Escalade de dose



Safety, Pharmacokinetic, and Antitumor Activity of SU11248, a Novel Oral Multitarget Tyrosine Kinase Inhibitor, in Patients With Cancer

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Table 3. Sunitinib Grade 3 to 4 Toxicity per Patient and Cycle

Flat Dose (mg/m^2)	50 mg/d (30 mg/m^2)	75-100 mg/d (42 mg/m^2)	100-150 mg/d (59 mg/m^2)
No. of patients	9	12	3
No. of cycles	25	27	7
General toxicity			
Asthenia			
Per patient	2	6	2
Per cycle	2	9	2
Nausea/vomiting			
Per patient	—	1	—
Per cycle	—	3	—
Hypertension			
Per patient	—	1	1
Per cycle	—	1	1
Phlebitis			
Per patient	—	1	—
Per cycle	—	1	—
Pulmonary embolism			
Per patient	—	—	1
Per cycle	—	—	1
Neutropenia			
Per patient	3	2	—
Per cycle	10	4	—
Thrombocytopenia			
Per patient	2	2	1
Per cycle	3	2	1
Skin/mucous toxicity			
Palmar-plantar erythrodys-esthesia syndrome			
Per patient	—	1	—
Per cycle	—	1	—
Edema peripheral			
Per patient	1	1	—
Per cycle	1	1	—
Esophagitis			
Per patient	—	1	—
Per cycle	—	1	—

Safety, Pharmacokinetic, and Antitumor Activity of SU11248, a Novel Oral Multitarget Tyrosine Kinase Inhibitor, in Patients With Cancer

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Table 6. Antitumor Effects of Sunitinib

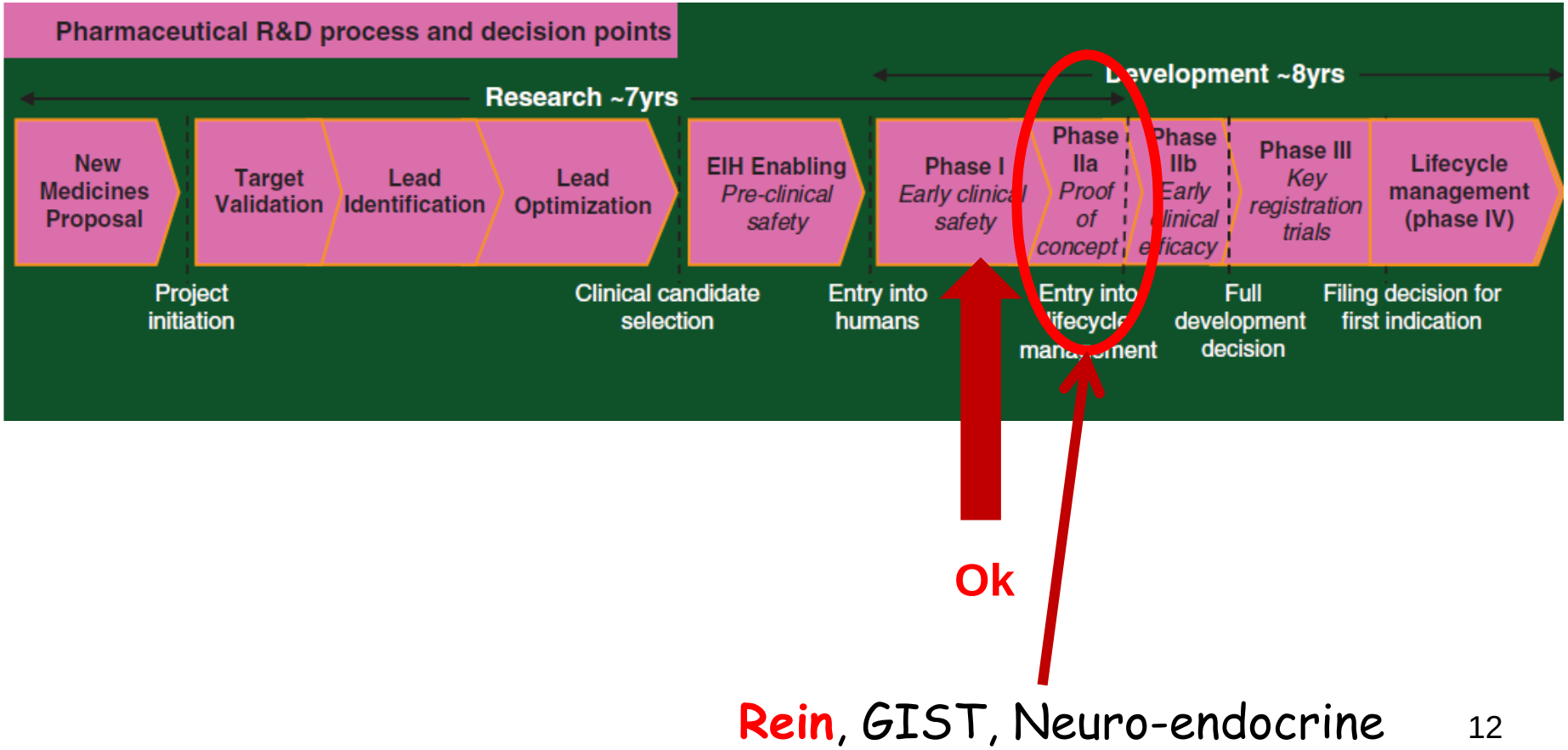
Sunitinib Dose	No. of Patients Entered	Objective Response/ Patients Assessable for Response and Responding Tumor Types	Tumor Stabilization		Tumor Progression	Tumor Necrosis	Tumors With Necrosis	Type of Complications
			No. of Patients	Duration (months)				
50 mg q2d	3	0/3	—		3	—	—	—
100 mg q2d	1	1/1 Renal cell carcinoma	—		—	1/1	Renal (local recurrence)	None
50 mg daily	9	0/6	1	12	5	1/9	Cervix (irradiated area)	Rectal fistula
75 mg daily	11	3/9 Neuroendocrine tumor Renal cell carcinoma GIST*	2	4 and 5	—	3/11	Rectum (irradiated area) UCNT (lung metastasis) GIST (peritoneal metastasis)	Bladder and rectal fistula Infection in necrotic area Peritonitis with toxic death
100 mg daily	3	2/3 Renal cell carcinoma* ACUP	1	6	—	1/3	Renal (local recurrence)	None (preventive surgery)
150 mg daily	1	0/1	1	3	—	—	—	—
Total	28	6/22	5/22		8/22	6/28	—	—

Abbreviations: q2d, every 2 days; ACUP, adenocarcinoma of unknown primary; GIST, gastrointestinal stromal tumor; UCNT, undifferentiated carcinoma of nasopharynx type.
*Patients with > 90% necrosis on postoperative pathologic specimen.

4 Réponses et 2 SD avec nécrose
Rein, GIST, NEuroendocrine

Le développement d'une molécule

MTD identifiée suite à la phase I
Dose Recommandée (30 daily mg/m2) => 50mg daily



Rein, GIST, Neuro-endocrine

Activity of SU11248, a Multitargeted Inhibitor of Vascular Endothelial Growth Factor Receptor and Platelet-Derived Growth Factor Receptor, in Patients With Metastatic Renal Cell Carcinoma

(Motzer)

VOLUME 24 · NUMBER 1 · JANUARY 1 2006

JOURNAL OF CLINICAL ONCOLOGY

- Objectifs: Evaluer l'activité et la toxicité du SU11248 chez les patients traités pour un mRCC réfractaire

- Critères de jugement:
  - Principal: taux de réponse objective (i.e CR and PR) selon les critères RECIST
  - Secondaires: Toxicités (NCI CTC AE), QoL (EQ-5D+FACIT,-Fatigue), TTP, OS, Biomarker

- Nombre de Sujets Nécessaires:
  - Schéma de Simon Minimax en deux étapes
  - P>= 15%, alpha=5%, power=85%

} => 63 pts

Non précisé dans l'article: Nb de patients à l'étape 1. Bornes d'arrêt à chaque étape. 1 seule hypothèse

Activity of SU11248, a Multitargeted Inhibitor of Vascular Endothelial Growth Factor Receptor and Platelet-Derived Growth Factor Receptor, in Patients With Metastatic Renal Cell Carcinoma

(Motzer)

VOLUME 24 · NUMBER 1 · JANUARY 1 2006

JOURNAL OF CLINICAL ONCOLOGY

- Janvier à Juillet 2003

Table 1. Patient Characteristics and Best Responses to SU11248 Treatment

Characteristic	No.	%
Total	63	100
Sex		
Male	43	68
Female	20	32
Age, years		
Median	60	—
Range	24-87	—
ECOG performance status		
0	34	54
1	29	46
Prior nephrectomy		
Yes	58	92
No	5	8
Prior systemic treatment		
Interferon-alpha*	35	56
IL-2*	19	30
Interferon-alpha + IL-2*	9	14
Radiation therapy	25	40
Histology		
Clear cell	55	87
Papillary	4	6
Sarcomatoid variant (not otherwise specified)	1	2
Unspecified	3	5
Site of metastatic disease		
Lung	52	81
Liver	10	16
Bone	32	51
No. of metastatic sites		
1	8	13
≥ 2	55	87
MSKCC risk factors for second-line therapy[6]		
0	34	54
≥ 1	29	46
Best response to SU11248 treatment		
Partial response	25	40
Stable disease for ≥ 3 months	17	27
Progressive disease, stable disease for < 3 months or not assessable	21	33

Activity of SU11248, a Multitargeted Inhibitor of Vascular Endothelial Growth Factor Receptor and Platelet-Derived Growth Factor Receptor, in Patients With Metastatic Renal Cell Carcinoma

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	N	%
Réponse Complete	0	0
Réponse Partielle	25	40
SD>=3 mois	17	27
PD ou SD<3mois	21	33

95%CI=[28%;53%]

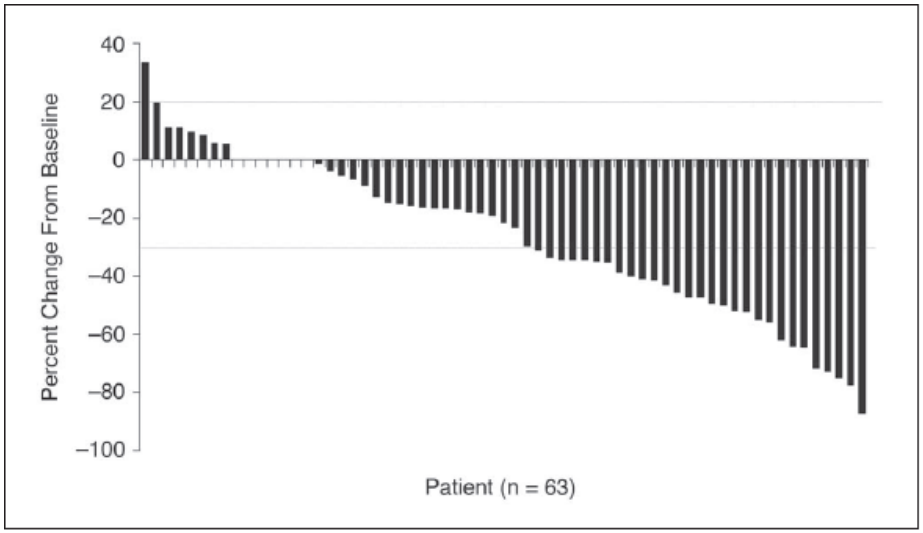
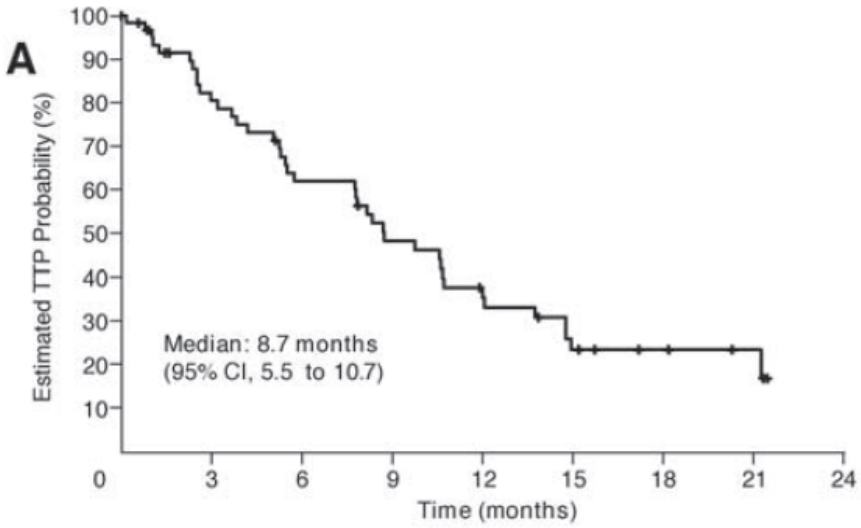


Fig 1. Maximal percentage of tumor reduction for target lesions by Response Evaluation Criteria in Solid Tumors (RECIST).



Activity of SU11248, a Multitargeted Inhibitor of Vascular Endothelial Growth Factor Receptor and Platelet-Derived Growth Factor Receptor, in Patients With Metastatic Renal Cell Carcinoma

(Motzer)

VOLUME 24 · NUMBER 1 · JANUARY 1 2006

JOURNAL OF CLINICAL ONCOLOGY

Durée du traitement 9 ms [<1 ; 24+]

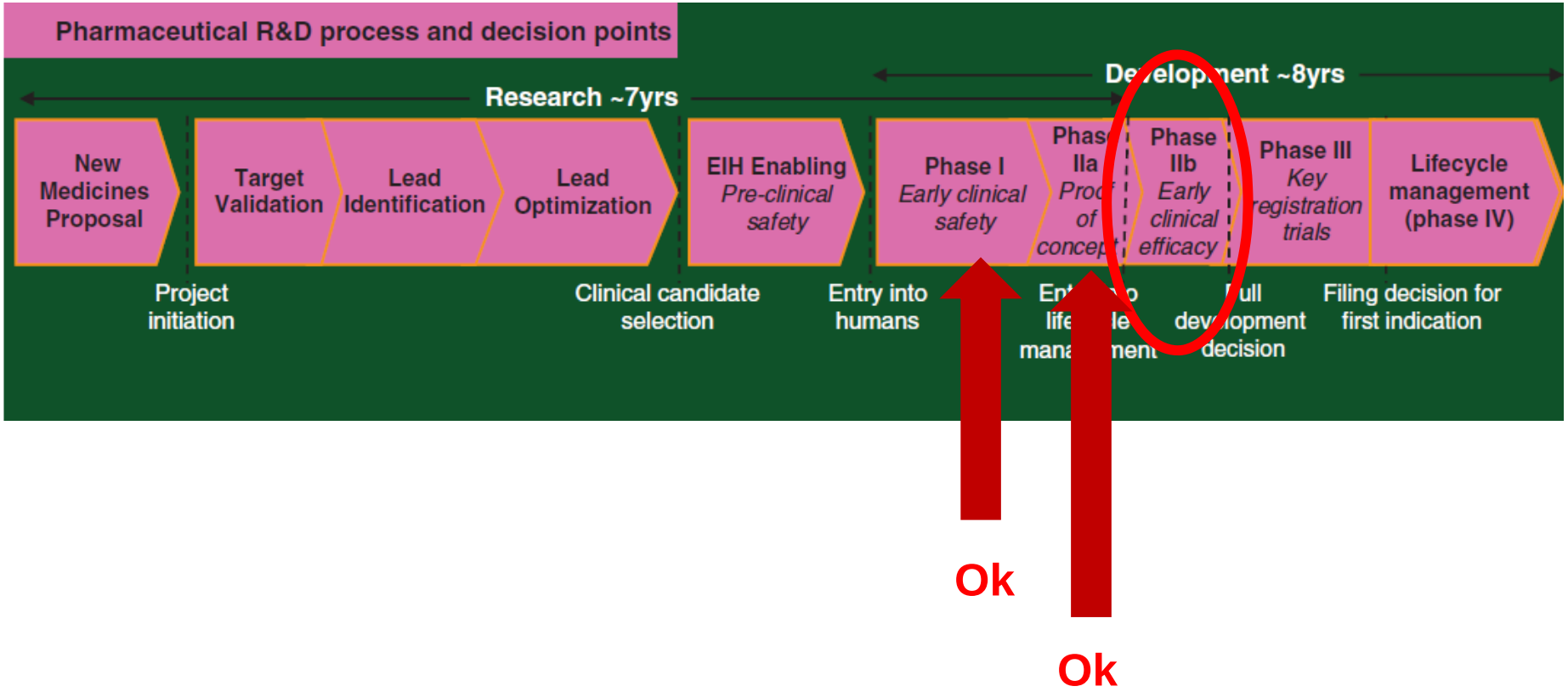
Table 2. Selected Treatment-Related Adverse Events of Interest and Laboratory Abnormalities by Grade Occurring in at Least 5% of Patients (n = 63)

Adverse Event	Grade 2		Grade 3		Grade 4		Total	
	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%
Treatment-related adverse events								
Fatigue	17	27	7	11	0	0	24	38
Diarrhea	13	21	2	3	0	0	15	24
Nausea	10	16	2	3	0	0	12	19
Dyspepsia	10	16	0	0	0	0	10	16
Stomatitis	11	17	1	2	0	0	12	19
Vomiting	6	10	2	3	0	0	8	13
Constipation	8	13	0	0	0	0	8	13
Ejection fraction decline*	6	9	1	2	0	0	7	11
Anorexia	4	6	0	0	0	0	4	6
Dermatitis	4	6	1	2	0	0	5	8
Hypertension	2	3	1	2	0	0	3	5
Laboratory abnormalities								
Lymphopenia	25	40	20	32	0	0	45	72
Neutropenia	20	32	7	11	1	2	28	45
Anemia	17	27	5	8	1	2	23	37
Hyperlipasemia	2	3	12	19	1	2	15	24
Thrombocytopenia	11	18	0	0	0	0	11	18
Creatinine	9	14	0	0	0	0	9	14
Creatine kinase	7	11	1	2	1	2	9	15
Hyperamylasemia	1	2	5	8	0	0	6	10
Hepatic transaminase	3	5	2	3	0	0	5	8
Total bilirubin	3	5	0	0	0	0	3	5

*On two or more assessments of cardiac function.

Le développement d'une molécule

En conclusion: Activité du sunitib chez les patients mRCC en deuxième ligne



Sunitinib in Patients With Metastatic Renal Cell Carcinoma

(Motzer, JAMA 2006)

- Objectif: confirmer l'activité du sunitib en 2ième ligne chez les patients traités pour un mRCC

- Patients et Méthodes

  - Critère de jugement

    + Principal: taux de réponse objective confirmé (i.e CR and PR) selon les critères RECIST (Relecture)

    + Secondaires: Durée de la réponse, PFS (Progression ou décès), OS, Toxicités (NCI CTC AE)

  - Nombre de Sujets nécessaires:

    Montrer que le taux de réponse objective est>= 5%. L'inclusion de 100 pts permet d'avoir une puissance de 80% si le taux observé est de 15. (méthode exacte). Rejet de HO si >=11 Réponse objective

Sunitinib in Patients With Metastatic Renal Cell Carcinoma

(Motzer, JAMA 2006)

- Entre Février et novembre 2004

Table 2. Patient Baseline Characteristics

Characteristics	No. (%)
Total intent-to-treat population	106 (100)
Sex	
Men	67 (63)
Women	39 (37)
Age, median (range), y	56 (32-79)
ECOG performance status	
0	58 (55)
1	48 (45)
Prior systemic treatment	
Interferon-alfa	47 (44)
IL-2	50 (47)
Interferon-alfa plus IL-2	9 (9)
Prior radiation therapy	20 (19)
Main sites of metastatic disease	
Lung	86 (81)
Liver	29 (27)
Bone	27 (26)
Lymph nodes	62 (59)
No. of disease sites	
1	13 (12)
2	38 (36)
≥3	55 (52)
No. of MSKCC risk factors for second-line therapy*	
0	61 (58)
≥1	45 (42)

Table 3. Best Response to Sunitinib Treatment

Response	Patients Assessed, No. (%)*	
	Independent Third Party†	Investigator‡
Complete response	0	1 (1)
Partial response	36 (34)	45 (43)
Stable disease for ≥3 mo	30 (29)	23 (22)
Progressive disease, stable disease for <3 mo, or not evaluable	39 (37)	36 (34)

Taux de RO	34%	44 %
95% CI,	[25-44]	[34; 53]

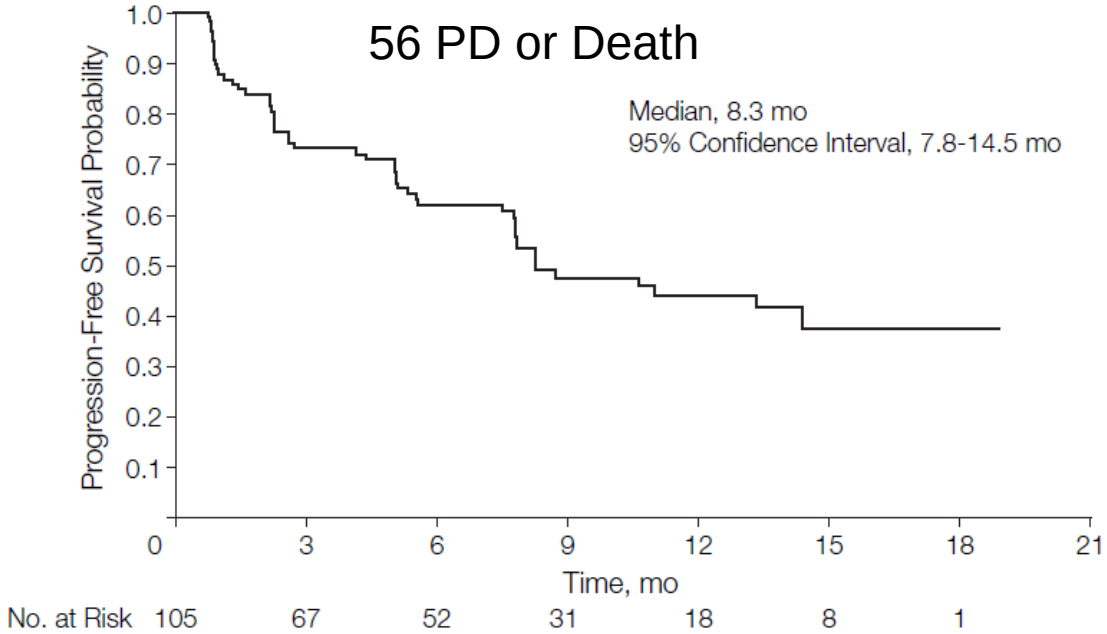
1 pt exclu des analyses d'efficacité
(autre type de cancer)

Durée de la réponse:
-10 PD or death chez les RO
- median 10m (95%Ci: 8 ; NC)

Sunitinib in Patients With Metastatic Renal Cell Carcinoma

(Motzer, JAMA 2006)

Figure 3. Progression-Free Survival by Independent Third-Party Core Imaging Laboratory Assessment (N = 105)



- Survie Globale
  - 31 pts décédés
  - Median OS : Not Reached
  - 6 months OS: 79% (95% CI, 70%-86%).

Sunitinib in Patients With Metastatic Renal Cell Carcinoma

(Motzer, JAMA 2006)

- Tolérance
  - Nb de cycle de traitement: med 5 [0; 11] (~7 mois)

Table 4. Most Commonly Reported Treatment-Related Adverse Events and Selected Laboratory Abnormalities by Grade*

Adverse Event	Patients (N = 106)			
	Grade 2	Grade 3	Grade 4†	Total‡
Treatment-related adverse events, No. (%)				
Fatigue	18 (17)	12 (11)	0	30 (28)
Diarrhea	18 (17)	3 (3)	0	21 (20)
Dyspepsia	16 (15)	1 (1)	0	17 (16)
Hypertension	11 (10)	6 (6)	0	17 (16)
Hand-foot syndrome	9 (8)	7 (7)	0	16 (15)
Nausea	14 (13)	0	0	14 (13)
Stomatitis	9 (8)	5 (5)	0	14 (13)
Anorexia	12 (11)	1 (1)	0	13 (12)
Mucosal inflammation	12 (11)	1 (1)	0	13 (12)
Vomiting	11 (10)	0	0	11 (10)
Dysgeusia	10 (9)	0	0	10 (9)
Extremity pain	6 (6)	1 (1)	0	7 (7)
Rash	3 (3)	0	0	3 (3)
Laboratory abnormalities, No. (%)				
Neutropenia§	28 (26)	15 (14)	2 (2)	45 (42)
Lipase increased	12 (11)	15 (14)	3 (3)	30 (28)
Anemia‖	21 (20)	4 (4)	2 (2)	27 (26)
Thrombocytopenia¶	16 (15)	6 (6)	0	22 (21)

Sunitinib in Patients With Metastatic Renal Cell Carcinoma

(Motzer, JAMA 2006)

- Analyse poolée

Table 6. Pretreatment Predictors of Progression-Free Survival for Patients Treated With Sunitinib (N = 168)

	No. of Patients (N = 168)*	No. Progression-Free or Alive	Progression-Free Survival, mo: Median	Progression-Free Survival, mo: 95% Confidence Interval	*P* Value
Hemoglobin					
≥Lower limit of normal	97	52	10.9	8.7-14.8	<.00
<Lower limit of normal	71	18	4.2	2.6-5.5	
Corrected calcium					
≤10 mg/dL	162	69	8.2	7.8-10.4	.23
>10 mg/dL	6	1	3.6	1.5-12.0	
Eastern Cooperative Oncology Group performance status					
0	91	42	10.4	8.2-12.1	.002
1	77	28	5.1	2.8-8.1	
Liver metastases					
Yes	38	11	5.5	4.1-8.4	.03
No	130	59	8.8	7.9-12.0	
Lung metastases					
Yes	137	56	7.9	5.8-9.8	.65
No	31	14	8.8	5.4-13.8	
No. of disease sites					
0 or 1	21	12	13.8	7.9-21.2	.04
2 or ≥3	147	58	7.9	5.5-8.7	
Alkaline phosphatase					
≤120 U/L	123	57	8.3	7.9-10.6	.06
>120 U/L	45	13	5.5	2.3-10.7	

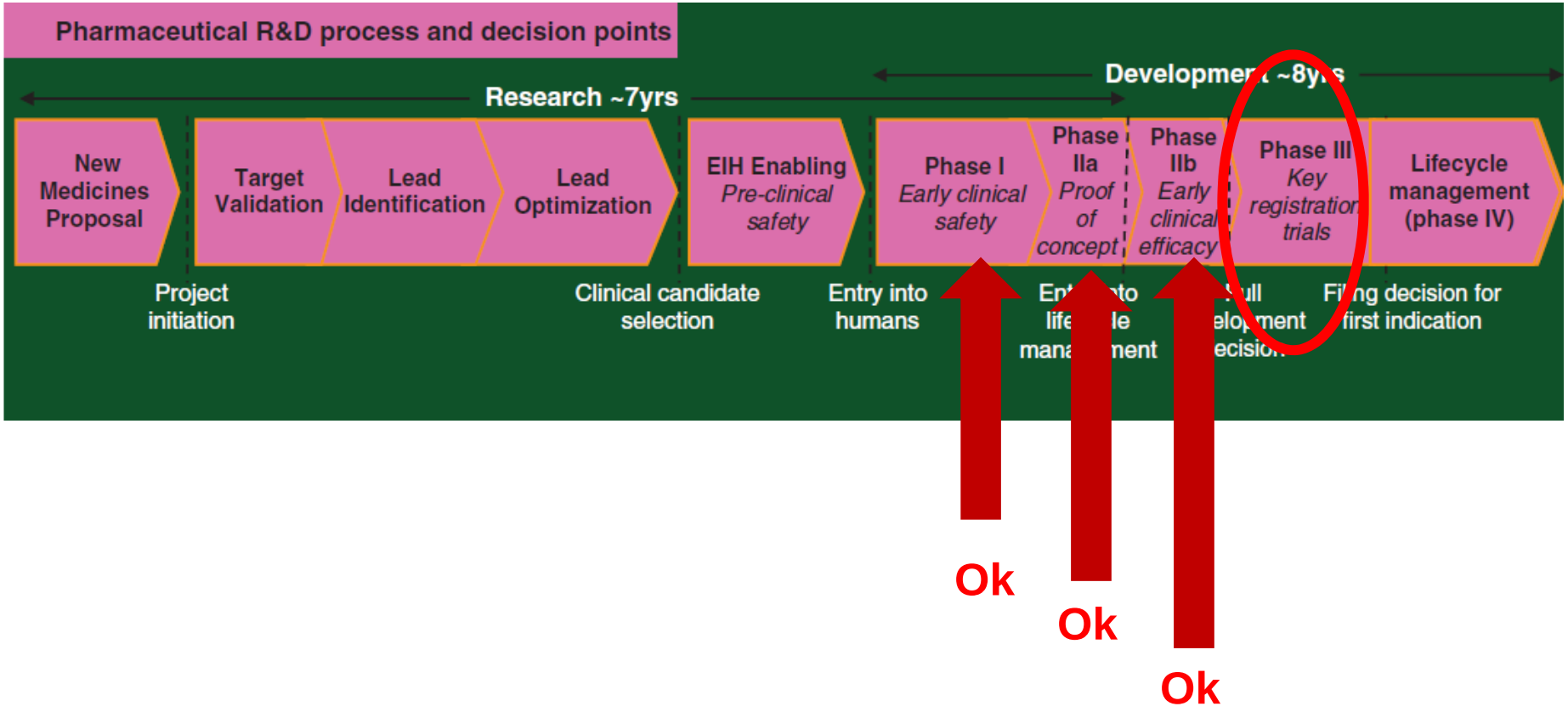
*Pooled analysis population.

Analyse Multivariée

	HR	95CI	p
Hemoglobin			
>=Low Lim	1		
<= Low Lim	0.35	0.25-0.56	.001

Le développement d'une molécule

En conclusion: Confirmation de l'activité du sunitib chez les patients mRCC en deuxième ligne



Sunitinib versus Interferon Alfa in Metastatic Renal-Cell Carcinoma

(Motzer)

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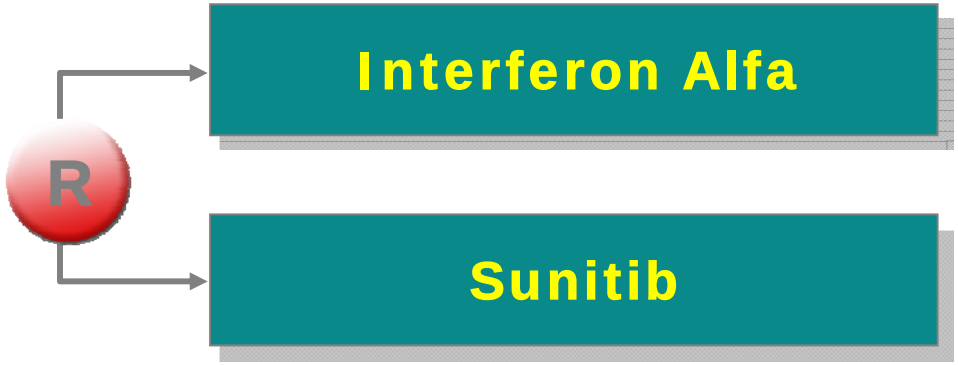
- Traitement std en 1iere ligne
  - Taux de réponse: 5 à 20%
  - Médiane survie globale ~12 mois
- Sunitib en 2ième ligne
  - Taux de réponse 42% (analyse poolée)

- Phase III en 1ière ligne



Sunitinib versus Interferon Alfa in Metastatic Renal-Cell Carcinoma

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- Patients et Méthodes
  - Critère de jugement
    + Principal: survie sans progression (progression ou décès) revue centralisé
    + Secondaires: Taux de réponse, OS, Toxicités (NCI CTC AE), QoL
  - Nombre de Sujets nécessaires:
    Amélioration de la médiane de PFS 4.7 m vs 6.1 mois
    => 471 evts à observer pour alpha à 5% bilat. Puissance de 90%
    Inclusion de 490 pts
    3 analyses planifiées. Méthode o'brien Fleming
    Résultats présentés dans l'article 2ième analyse.

Sunitinib versus Interferon Alfa in Metastatic Renal-Cell Carcinoma

(Motzer)

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- Inclusion: Aout 2004 à Octobre 2005

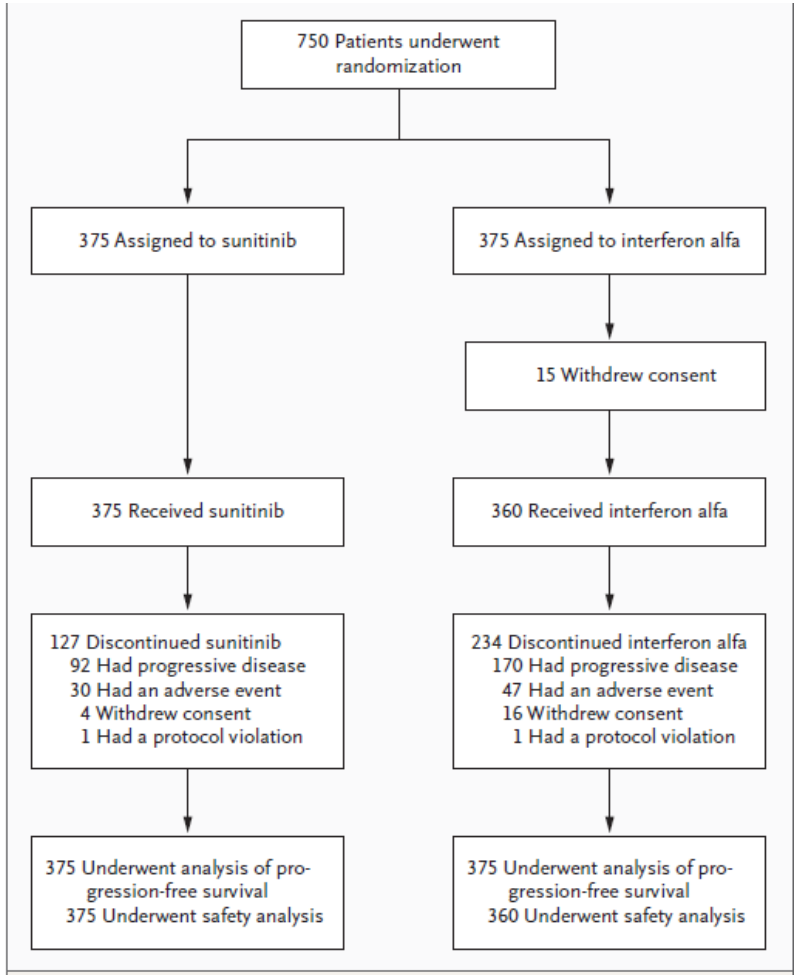

Figure 1. Patient Enrollment and Outcomes.

Caractéristiques Initiales (pas de différence entre les bras

	SU	INF
Durée trt (m) med Range	6 [1; 15]	4 [1; 13]

Sunitinib versus Interferon Alfa in Metastatic Renal-Cell Carcinoma

(Motzer)

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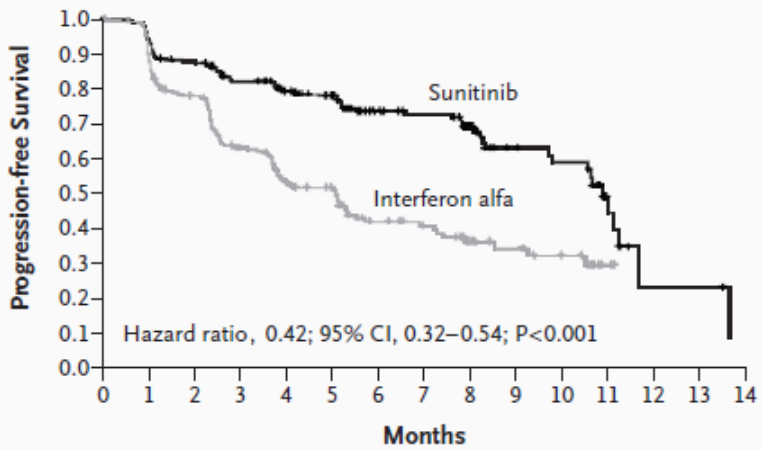
Table 3. Best Tumor Response.*

Response	Independent Central Review†		Investigator Assessment	
	Sunitinib (N=335)	Interferon Alfa (N=327)	Sunitinib (N=374)	Interferon Alfa (N=373)
	no. of patients (%)			
Objective response‡	103 (31)	20 (6)	137 (37)	33 (9)
Complete response	0	0	1 (<1)	0
Partial response	103 (31)	20 (6)	136 (36)	33 (9)
Stable disease	160 (48)	160 (49)	176 (47)	213 (57)
Progressive disease or disease could not be evaluated	72 (21)	147 (45)	61 (16)	127 (34)



No. at Risk

Sunitinib	375	235	90	32	2
Interferon alfa	375	152	42	18	0

Figure 2. Kaplan–Meier Estimates of Progression-free Survival (Independent Central Review).

	SU	INF
PFS Relecture	11 [10; 12]	5 [4;6]
PFS Invest	11 [8; 14]	4 [4;5]

Données de survie globale non mature

Sunitinib versus Interferon Alfa in Metastatic Renal-Cell Carcinoma

(Motzer)

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Table 2. Adverse Events and Selected Laboratory Abnormalities.*

Variable	Sunitinib (N=375)			Interferon Alfa (N=360)		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
	percent					
Adverse event						
Diarrhea†	53	5	0	12	0	0
Fatigue†	51	7	0	51	11	1
Nausea	44	3	0	33	1	0
Stomatitis	25	1	0	2	1	0
Vomiting†	24	4	0	10	1	0
Hypertension†	24	8	0	1	1	0
Hand–foot syndrome†	20	5	0	1	0	0
Mucosal inflammation	20	2	0	1	1	0
Rash	19	1	1	6	1	0
Asthenia	17	4	0	20	4	0
Dry skin	16	1	0	5	0	0
Skin discoloration	16	0	0	0	0	0
Changes in hair color	14	0	0	1	0	0
Epistaxis	12	1	0	1	0	0
Pain in a limb	11	1	0	3	0	0
Headache	11	1	0	14	0	0
Dry mouth	11	0	0	6	1	0
Decline in ejection fraction	10	2	0	3	1	0
Pyrexia	7	1	0	34	0	0
Chills	6	1	0	29	0	0
Myalgia	5	1	0	16	1	0
Influenza-like illness	1	0	0	7	1	0

Sunitinib versus Interferon Alfa in Metastatic Renal-Cell Carcinoma

(Motzer)

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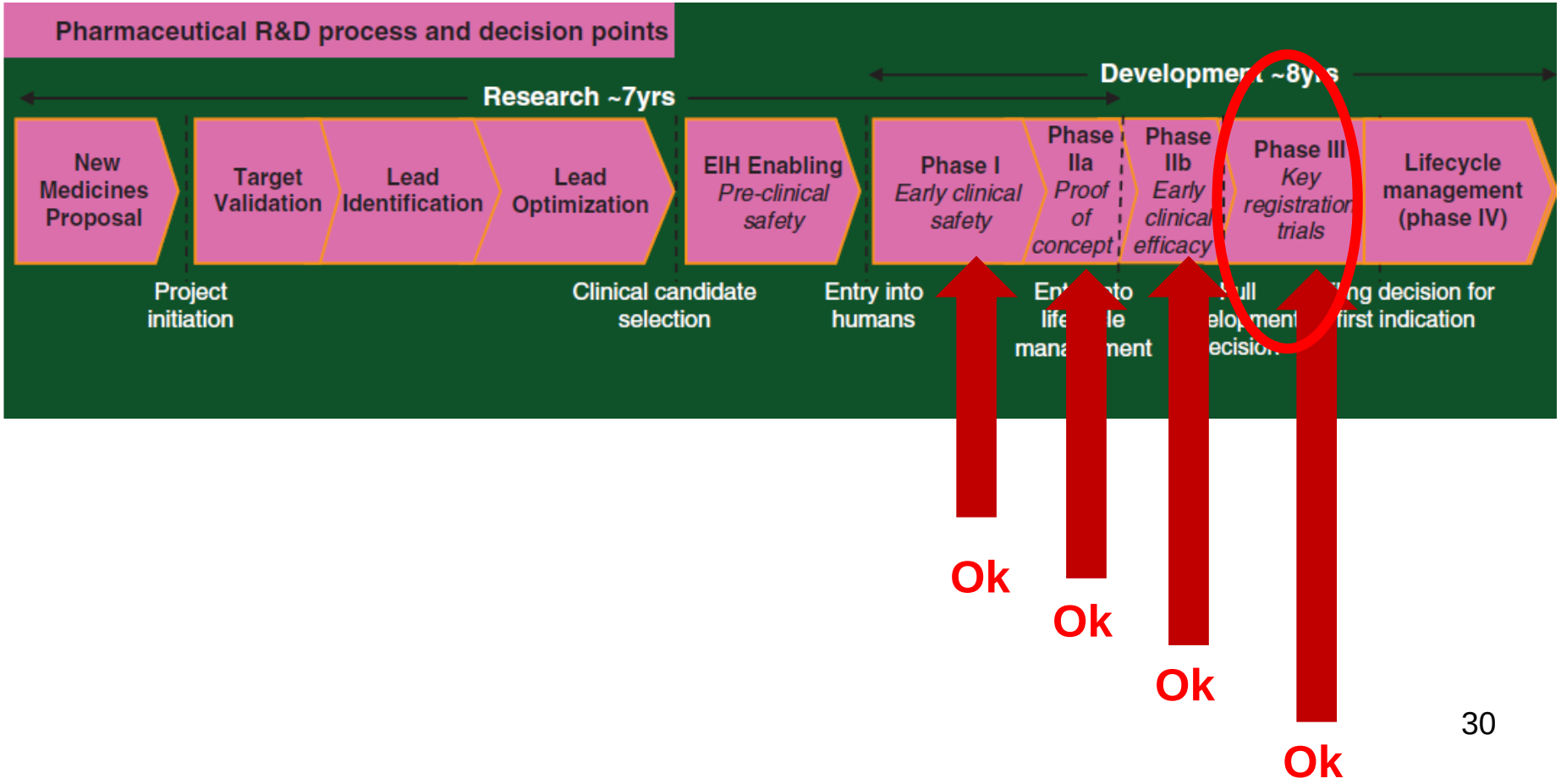
Laboratory abnormality						
Leukopenia†	78	5	0	56	2	0
Neutropenia†	72	11	1	46	7	0
Anemia	71	3	1	64	4	1
Increased creatinine	66	1	0	49	1	0
Thrombocytopenia†	65	8	0	21	0	0
Lymphopenia†	60	12	0	63	22	0
Increased lipase†	52	13	3	42	5	1
Increased aspartate aminotransferase	52	2	0	34	2	0
Increased alanine aminotransferase	46	2	1	39	2	0
Increased alkaline phosphatase	42	2	0	35	2	0
Increased uric acid	41	0	12	31	0	8
Hypophosphatemia	36	4	1	32	6	0
Increased amylase†	32	4	1	28	2	1
Increased total bilirubin	19	1	0	2	0	0

Le développement d'une molécule

En conclusion: cet essai de phase III a montré qu'en première ligne pour mRCC le sunitib améliorait la pfs par rapport à INF-alfa



Et maintenant, que vais-je-faire ?

Etude SUP-R

IP: Dr C Chevreau, PK: Pr E Chatelut

Promoteur Institut Claudius Regaud

Financement PHRC-I 2015

L'étude SUP-R

- Background
  - Cancer du Rein 1ière Ligne Méta: Standard de trt Pazopanib ou Sutent

(Motzer, 2013)	Pazopanib	Sunitinib
% Arrêt du traitement lié a un AE	24%	20%
Médiane de PFS	8.4m	10m

- Objectif Principal
  - Partie 1: Modéliser les relations entre le pk du sutent ou du pazo et les toxicités
  - Partie 2: Evaluer l'intérêt du suivi thérapeutique (TDM) par PK sur la faisabilité du traitement (arrêt du traitement lié aux AE) et l'efficacité (non progression à 1 an)

- Objectifs Secondaires (Partie 2)
  - Evaluer l'efficacité (OR, PFS, OS)
  - Evaluer la toxicité
  - Evaluer le syndrome main pied
  - Evaluer la Qualité de vie

Etude Ancillaire: Corrélation polymorphisme Tox et Efficacité

Schéma de l'étude – Nombre de Sujets Nécessaires

- Partie 1: Phase Pilote (2 strates: Pazo et Sutent)
  - Inclusion de 40 patients / Strates (pas d'hypothèse stat)

- Partie 2: Phase II non randomisée avec 2 strates (Pazo et Sutent)

  - Pazopanib (Motzer, NEJM 2013)

    Taux d'arrêt du traitement lié à un AE: 24%

    Médiane PFS 8.4 mois (95%CI=[8.3; 10.9])

    => Extrapolation PFS à 1 ans : 35%

  - Sunitib (Motzer, NEJM 2013)

    Taux d'arrêt du traitement lié à un AE: 20%

    Médiane PFS 10 mois (95%CI=[8.3; 10.9]

    => Extrapolation PFS à 1 ans : 44%

Nombre de Sujets Nécessaires – Strate Sunitib

- Revue de la littérature
  - Taux d'arrêt du traitement lié à un AE: 20%
  - Médiane PFS 10 mois (95%CI=[8.3; 10.9]
    => Extrapolation PFS à 1 ans : 44%

  (Motzer, NEJM 2013

- Nombre de Sujets Nécessaires:
  - Co-critères principaux– Schéma proposé par chang (chang, Stat Med)

- Hypothèses

  - H0: Proportion d'arrêt lié à un AE ≥20%(=Ptox0) ou Taux de Non progression à 1 an≤45%(=Peff0)

  - H1: Proportion d'arrêt lié à un AE≤10%(=Ptox1) et Taux de Non progression à 1 an≥60%(=Peff1)

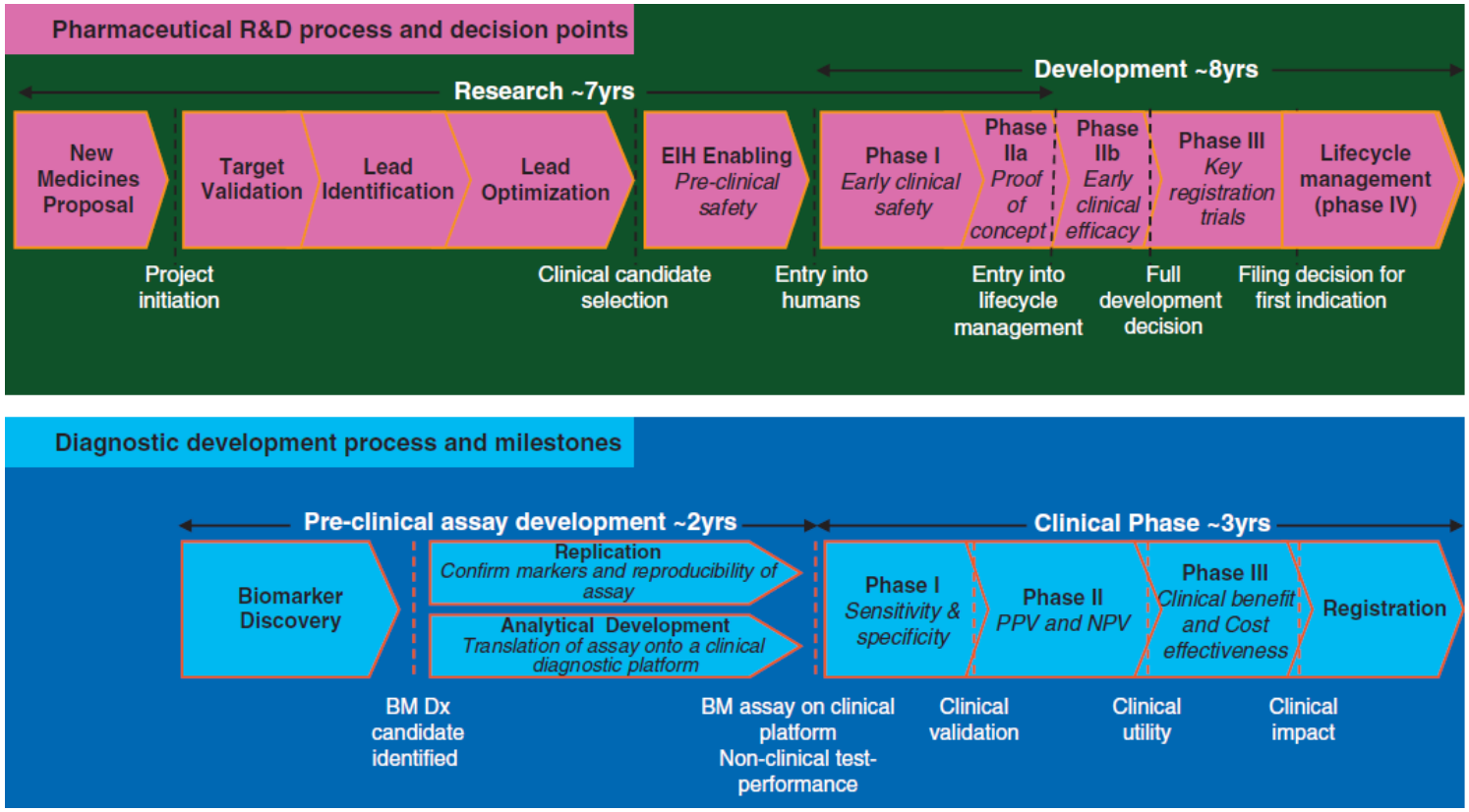
alpha=0.10, 1-beta=0.80 =>75patients
Zone de rejet de H0

Nb patients sans arrêt du trt lié à un ae	≤20
Nb de Patient sans progression à 1 an	≥40

Nombre de Sujets Nécessaires

	Pazopanib	Sunitinib
pEff0	35%	45%
PEff1	50%	60%
PTox0	25%	20%
PTox1	10%	10%
Alpha, 1-Beta	0.10, 0.80	0.10, 0.80
Nombre de Patients	59	75
Rejet de H0 - Nb patients sans arrêt du trt lié à AE ET - Nb de Patient sans progression à 1 an	 ≤10 ≥26	 ≤20 ≥40
Alpha Exact Beta Exact	0.097 0.803	0.093 0.808

Le développement d'une molécule

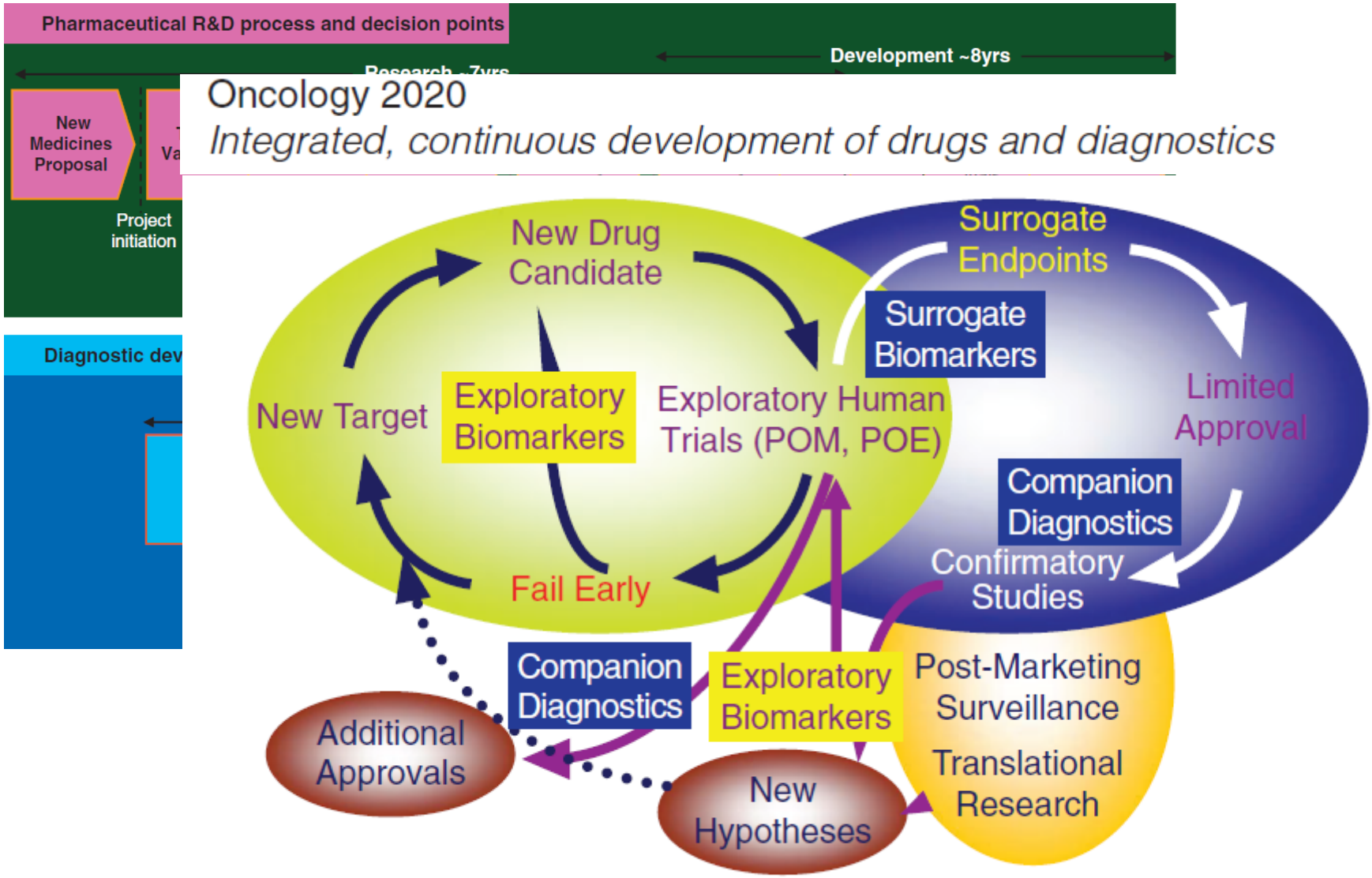


Traditional drug development paradigm

Linear, sequential, slow process for drugs and companion diagnostic development

(Dhingra, Ann Oncol. 2015)

Le développement d'une molécule



POM = Proof of mechanism; POE = Proof of efficacy

(Dhingra, Ann Oncol. 2015)