2015 ASCO conference, Chicago

#2595

Activity of crizotinib in relapsed MET amplified malignancies: Results of the French AcSé Program

Gilles Vassal[1], Marie-Cécile Ledeley[2], Christophe Tournigand[3], Thomas Aparicio[4], Isabelle Ray-Coquard[5], Luc Taillandier[6], Bernard Escudier[1], Benoit You[7], Anthony Goncalves[8], Catherine Lombard Bohas[9], Jean-Francois Seitz[10], Thierry André[11], Jean-Philippe Merlio[12], Laurent Arnould[13], Gilbert Ferretti[14], Yves Menu[11], Thomas Mortier[15], Etienne Lonchamp[15], Céline Mahier - Ait Oukhatar[16], Denis Moro-Sibilot[17]

[1]Gustave Roussy, Paris, France; [2]Department of Biostatistics and Epidemiology, Gustave Roussy, Cancer Campus, Grand Paris, Villejuif, France; [3]APHP, Henri-Mondor Hospital, Oncology department, Créteil, France; [4]APHP, Hospital Avicenne, Bobigny, France; [5]Centre Léon Bérard, Lyon, France; [6]Department of Neurology, Nancy, France; [7]Centre Hospitalier Lyon-Sud, Lyon, France; [8]Institut Paoli Calmettes, Marseille, France; [9]Hospital Édouard Herriot, Hospices Civils de Lyon, Lyon, France; [10]APHM Hospital La Timone, Marseille, France; [11]APHP Hospital Saint-Antoine, Paris, France; [12]Service de Biologie des Tumeurs - CHU, Bordeaux, France; [13]Centre Georges-Francois Leclerc, Dijon, France; [14]University Hospital, Grenoble, France; [15]French National Cancer Institute (INCa), Boulogne-Billancourt, France; [16]Unicancer, Paris, France; [17]Thoracic Oncology Unit CHU Grenoble, Inserm U823, Grenoble, France

AcSé Program : secured access program to innovative cancer drugs

Background

- When a marketed targeted therapy exists in a molecularly defined subgroup of patients
- When the same alteration is found in other tumour types

Risk of a wide off label use of the drug

Objective 1

Promote a secured access for all patients with an advanced refractory malignancy and no therapeutical alternative through an academic phase II clinical trial.

- One trial for each targeted treatment selected
- Withdrawal if high toxicity or no efficacy in a predefined number of patients with the same tumor type
- If efficacy coding signal: drug developpement by the pharmaceutical firm

Objective 2

Ensuring equity of access to innovation

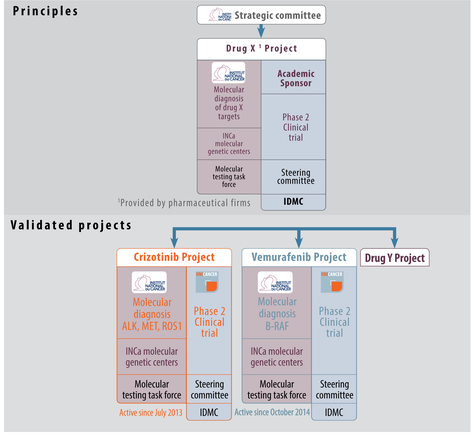
- Provide nationwide molecular tumor diagnosis for all patients through INCa molecular genetic centers
- Whatever the healthcare institution status (public hospitals, private hospitals…)
- Perform high quality tests
- Hemopathies, solid tumours

France organisation of molecular centers for personalized medicine: 28 regional centers

Partnerships between several laboratories located in University Hospitals and Cancer Centers

- Regional organization
- Cooperation between pathologists and biologists

AcSé program



Phase 2 clinical trial : secured access to crizotinib for patients with tumors harboring a genomic alteration on one of the biological targets of the drug – PI : Pr Gilles Vassal / NCT02034981

AcSéCrizotinib

Background

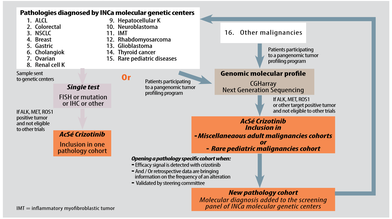
- Crizotinib is registered only for the treatment of patients with ALK+ lung cancer
- Crizotinib targets, ALK, MET and ROS1, are also altered in a wide range of malignancies in adult and children
- Pediatric dose (Mosse et al, Lancet Oncol 2013) and oral formulation available

Main objective: Identification of subsets of patients that may benefit from treatment

Population

- Patients ≥1 year
- Advanced disease harboring a genomic alteration in a crizotinib target
- Patients not eligible for any other active academic or industry trial targeting the same alteration

Molecular diagnosis process



Cohorts

A/ Pathology cohorts « one pathology, one target alteration » diagnosed by INCa molecular genetic centers

1. ALCL, children and adults, ALK translocated
2. Colorectal cancer, adults, ALK translocated
3. Colorectal cancer, adults, MET amplified
4. Colorectal cancer, adults, MET mutated
5. NSCLC, adults, MET amplified
6. NSCLC, adults, ROS1translocated
7. Breast cancer, adults, ALK translocated
8. Gastric and gastroesophageal junction cancer, adults, MET amplified
9. Cholangiocarcinoma, adults, ROS1 translocated
10. Ovarian cancer, adults, MET amplified
11. Clear renal cell carcinoma, adults, ALK translocated
12. Clear renal cell carcinoma, adults, ALK amplified
13. Papillary renal cell carcinoma, adults, MET mutated or MET amplified
14. Hepatocellular carcinoma, adults, MET amplified
15. Neuroblastoma, children and adults, ALK amplified or ALK mutated
16. Inflammatory Myofibroblastic Tumor (IMT), children and adults, ALK translocated
17. Rhabdomyosarcoma (RMS) (alveolar and embryonal), children and adults, ALK amplified
18. Glioblastoma, adults, MET amplified
19. Anaplastic thyroid cancer, adults, ALK mutated or ALK translocated
20. Thyroid cancer (follicular + medullary + papillary), adults, MET mutated

B/ Rare pediatric malignancies cohort

- Diagnosed by INCa molecular genetic centers: hepatoblastoma MET amplified or mutated, renal medullary carcinoma ALK translocated, anaplastic medulloblastoma MET amplified or mutated, HGG or DIPG MET amplified
- Any other pathology with an altered crizotinib target evidenced through genomic profiling

C/ Miscellaneous adult malignancies

- Any other pathology with an altered crizotinib target evidenced through genomic profiling

Treatment scheme

- Cycles are defined in 28-day periods
- Disease response assessed every 8 weeks
- Safety assessed continuously
- Adult: 250 mg x 2/day; child: 280 mg/m² x 2/day
- Treatment pursed until disease progression, unacceptable toxicity, intercurrent conditions that preclude continuation of treatment, or patient refusal

Statistical design

- Main endpoint: objective response (CR, PR) after 2 cycles. May be changed to the best response for cohorts that are displaying delayed responses
- Three statistical 2-stage designs are considered for cohorts to anticipate 3 situations in terms of expected response rate and incidence. Accrual stops if 0 response / N1 pts; else additional pts are recruited up to N
  - General case: most of the cohorts
  - Optimistic design: NSCLC with ROS1 translocation and ALCL
  - Rare diseases: IMT, neuroblastoma, glioblastoma, RMS, cohorts identified from the pangenomic programs

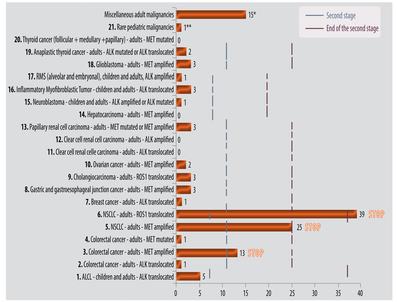
Situation	Design parameters				Decision rule			
	P0	P1	Alpha	Beta	N1	k1	N	k
General case	10%	30%	10%	10%	11	0	25	4
Optimistic case	20%	40%	10%	10%	7	0	37	7
Very rare disease	10%	30%	15%	15%	8	0	20	3

- Sample size estimation: 500 pts
- Investigating centers: up to 250

Accrual

Whole screening activity (at March 15, 2015)	Number of positive cases	Patients included
11 496 tests (=4 771 screened patients)	297	125 From August 5, 2013 to May 7, 2015

Inclusions per cohort



** one uterine leiomyosarcoma – ALK translocated; one pancreatic cancer – ROS1 mutated; one neuroblastoma – ROS1 mutated ; one renal cancer – ROS1 amplified; two NSCLC – MET mutated; one NSCLC – ALK mutated; one NSCLC – ALK amplified ; one adenocarcinoma of the urachus – MET amplified; one cholangiocarcinoma – MET amplified; one gallbladder cancer – MET amplified; one B large cell lymphoma – ALK translocated; one carcinoma of the esophagus – MET amplified; one sarcomatoid carcinoma of the small intestine – ALK translocated and one unknown primary carcinoma – ALK translocated.*

*** one mesothelioma - ALK translocated.*

Cohorts – MET amplified

Accrual

Pathology	MET screening activity (MET amplified at March 15, 2015)	Number of positive cases	Patients included (From November 5, 2013 to May 7, 2015)	Statistical 2-stage design
NSCLC	1 550	113	25	General case
Colorectal	699	21	13	General case
Gastric	209	12	3	General case
Ovary	320	5	2	General case
Kidney	54	1	1	General case
Hepatocarcinoma	68	1	0	General case
Glioblastoma	260	13	4	Very rare disease
	3 160	166	48	

Cohort	Frequency N=52
03. Colorectal - Ampli. MET	13 (25%)
05. NSCLC - Ampli. MET	25 (48%)
08. Gastric - Ampli. MET	3 (6%)
10. Ovary - Ampli. MET	2 (4%)
13. Kidney - Mut. or Ampli. MET	1* (2%)
18. Glioblastoma - Ampli. MET	4 (8%)
24. Miscellaneous rare adults - from pangenomic program**	4 (8%)

** Two additional patients were recruited in this cohort with a MET-mutation; they are not included in the current analysis focused on patients with MET-amplification*

*** One adenocarcinoma of the urachus; one cholangiocarcinoma; one gallbladder cancer; one carcinoma of the esophagus*

Patients characteristics

Disease characteristic	Frequency N=52
SEX	
Male	33 (63%)
AGE (Years)	
Median (range)	59 (30 ; 92)
Time between histological diagnosis and inclusion (months) (3 Missing Data (MD))	
Median	21 (-1* ; 81)
Time between last recurrence and inclusion (months) (3 MD)	
Median	1 (0 ; 44)
Metastatic disease at inclusion (1 MD)	46 (90%)
Prior chemotherapy (1 MD)	50 (98%)
1 line	4 (8%)
2 lines	14 (28%)
3 lines or more	32 (64%)
Material for molecular analysis	
Primary tumor	35 (67%)
Metastasis	17 (33%)

Patients on treatment

To May 7, 2015:

- 12 are still on treatment
- 42 stopped their treatment

Reasons for treatment discontinuation	Frequency N=42
Progression	32
Toxicity	5
ALAT and ASAT increase	2
Fatigue + ASAT increase	1
Ascites (with hospitalization)	1
No detail yet	1
Death	2
Pulmonary embolism	1
Respiratory distress	1
Other	2
Patient choice*	1
Doctor choice**	1
Unknown	1

** Anxiety and abdominal pain*

*** Disorders swallowing, followed by death*

The current median treatment duration: 2.1 months

Efficacy

Best response

Cohort	Physician / Central review				Early death	Awaited	Total
	CR	PR	SD	PD			
03. Colorectal - Ampli. MET	0	0	2	11			13
05. NSCLC Ampli. MET	0	8	7	8	2		25
08. Gastric - Ampli. MET	0	0	1	2			3
10. Ovarian - Ampli. MET	0	0	1	1			2
13. Kidney - Mut. ou Ampli. MET	0	1	0	0			1
18. Glioblastoma - Ampli. MET	0	0	0	2		2	4
24. Various uncommon adults - Pangenomic	0	0	1	1		2	4
Total	**0**	**9***	**12**	**25****	**2**	**4**	**52**

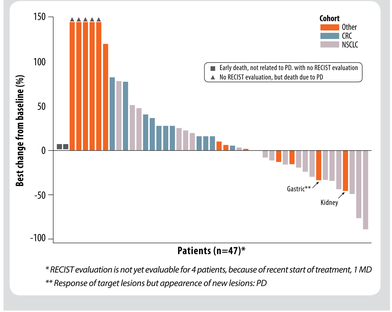
** Including 3 patients with PR confirmed by the reviewer, 6 not yet reviewed*

*** Including 6 patients with no RECIST evaluation but early death related to disease progression*

ORR was 9/48=19%[9% ; 33%]

DCR was 21/48=43% [29% ; 59%]

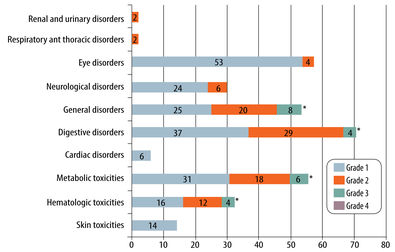
Waterfall plot



** RECIST evaluation is not yet evaluable for 4 patients, because of recent start of treatment, 1 MD*

*** Response of target lesions but appearence of new lesions: PD*

Overall toxicity (All ampli MET) (% of pts)

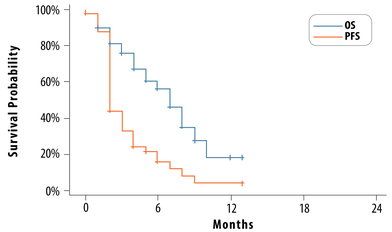


** Grade 3: 2 œdema + 2 asthenia, 1 gastroesophageal disorder, 2 transaminases increased + 1 alcaline phosphates increased with bilirubine increased, 2 neutropenia*

Survival Data

PFS: PFS median: 2 months [2 - 3] ; 42 progressions or deaths

OS: OS median: 7 months [5 - 9] ; 23 deaths



OS	52	15	2	0
PFS	62	8	1	0

Conclusion

Nationwide biomarker-driven access to crz for pts with MET+ malignancy is feasible. Crizotinib showed responses in MET+ lung. No response was observed in MET+ colon cancer.

Study support

Study receives :

- Financial support from INCa
- Financial support from the ARC Foundation, the UNICANCER's partner for Personalized Medicine research
- The institutional support from Pfizer

Collaborative groups

- French Pediatric Society (SFCE)
- Intergroupe Francophone de Cancerologie Thoracique (IFCT)
- Francophone Neuro-Oncologist Association (ANOCEF)
- French Cooperative Gynecological Cancer Research Group (ARCAGY-GINECO)
- French Genito-Unirary Cancer Cooperative Groups (GETUG / AFU)
- French Breast Cancer Intergroup - UNICANCER (UCBG)
- Lymphoma Study Association (LYSA)
- French Sarcoma Group - Bone Tumor Group (GSF-GETO)
- French Digestive Cancers Groups (UCGI / FFCD) / GERCOR)
- French Thyroid Cancer Network (TUTHYREF)

Results of ROS1 arranged NSCLC presented at session « Lung Cancer – Non Small Cell Metastatic (June 1, 8:00 AM – 11:30 AM McCormick Place : 5 Hall A, poster board #388)