2015 ASCO conference, Chicago

#8065

Crizotinib in patients with advanced ROS 1 rearranged non-small cell lung cancer (NSCLC)
Preliminary results of the AcSé phase II trial

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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

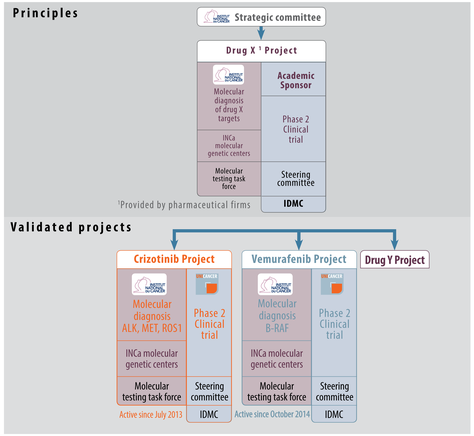
- Provide nationwide molecular tumor diagnosis for all patients through INCa molecular genetic centers
- Whatever the healthcare institution status (public hospitals, private hospitals…)
- Perform high quality tests
- Hemopathies, solid tumours

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

AcSé Crizotinib

Background

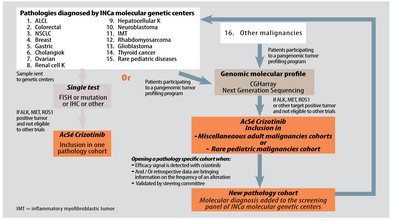
- Crizotinib is registered only for the treatment of patients with ALK+ lung cancer
- Crizotinib targets, ALK, MET and ROS1, are also altered in a wide range of malignancies in adult and children
- Pediatric dose (Mosse et al, Lancet Oncol 2013) and oral formulation available

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, ROS1 translocated
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

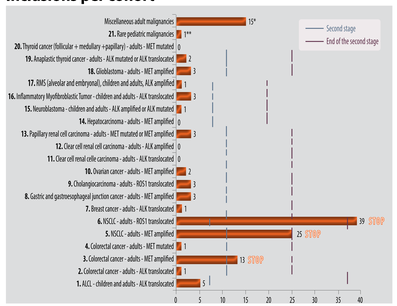
Situation	Design parameters				Decision rule			
	P0	P1	Alpha	Beta	N1	k1	N	k
General case	10%	30%	10%	10%	11	0	25	4
Optimistic case	20%	40%	10%	10%	7	0	37	7
Very rare disease	10%	30%	15%	15%	8	0	20	3

- 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.*

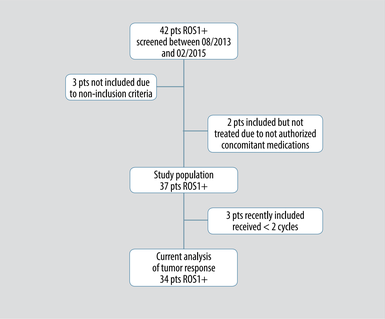
*** one mesothelioma - ALK translocated.*

Cohort NSCLC – ROS1 translocated

Accrual

ROS1 screening activity (NSCLC, ROS1 translocated at March 15, 2015)	Number of positive cases	Patients included
1 504	39	39 From August 5, 2103 to February 23, 2015

Consort diagram



Patients characteristics

Disease characteristic	Frequency N=37 (%)
SEX	
Female	26 (70)
AGE (Years)	
Median (range)	62 (33 ; 81)
TOBACCO	
NO Smoker	26 (70)
Smoker	11 (30)
PA – Median (Range)	15 (2 – 40)
Time between histological diagnosis and inclusion (2 Missing Data (MD))	
Median (Range)	15 months (1 ; 123)
Time between last recurrence and inclusion (2 MD)	
Median (Range)	1 month (0 ; 36)
Metastatic disease at inclusion (2 MD)	33 pts (89)
Prior chemotherapy (2 MD)	35 pts (95%)
1 line	10 pts (27)
2 lines	10 pts (27)
3 lines or more	15 pts (41)
Material for molecular analysis	
Primary tumor	26 pts (70)
Metastasis	11 pts (30)

Patients on treatment

To May 7, 2015:

- 24 still on treatment
- 13 stopped their treatment

Reasons for treatment discontinuation	Frequency N=13
Progression	7
Toxicity	2
Grade 3 Edema and dysphagia	1
Grade 3 ALAT and ASAT inscrease	1
Death not related to disease progression or toxicity	2
Pulmonary embolism	1
Accidental death	1
Miscellaneous	2
Intercurrent disease	1
Physician decision	1

The current median treatment duration : 14,7 months

Efficacy
Tumor evaluations were performed every 2 Cycles

Reponse at two cycles

Cohort	Physician / Central review				Early death	Awaited	Total
	CR	PR	SD	PD			
06.NSLC - Trans. ROS1	0	18*	10	4	2	3	37

** Including 9 PR confirmed by the reviewer and 9 not yet reviewed*

ORR at two cycles was 18/34=53% [95%CI, 35% ; 70%]
DCR was 28/34=82% [65% ; 93%]

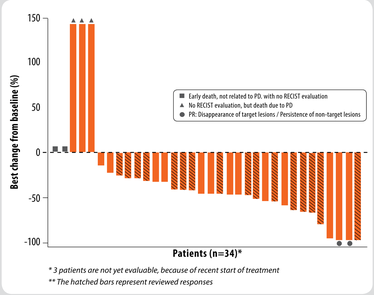
Best response

Cohort	Physician / Central review				Early death	Awaited	Total
	CR	PR	SD	PD			
06.NSLC - Trans. ROS1	1*	23*	5	3	2	3	37

** Including 1 CR and 13 PR confirmed by the reviewer and 10 PR not yet reviewed*

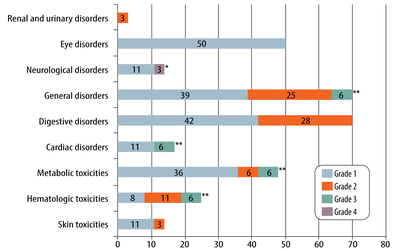
ORR at best response was 24/34=71% [53% ; 85%]
DCR was 29/34=85% [69% ; 95%]

Waterfall plot



** 3 patients are not yet evaluable, because of recent start of treatment*
*** The hatched bars represent reviewed responses*

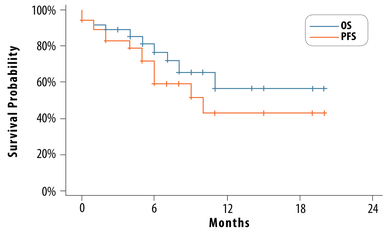
Overall toxicity (cohort 6) (% of pts)



** Grade 4: one dysgueusia*
*** Grade 3: 1 œdema + 1 asthenia, 1 bradycardia + 1 QTc prolongation, 2 transaminases increased, 1 neutropenia + 1 lymphopenia*

Survival Data

PFS: PFS median : 10 months [6 – NA*] ; 14 progressions or deaths
OS: OS median: NA*; 10 deaths
*NA = Not Achieved



OS	37	18	4	2	0
PFS	37	17	3	2	0

Conclusion

Crizotinib was well tolerated and achieved a robust treatment response rate in ROS1+ NSCLC. These results underline the interest of integrating ROS1 in biomarkers routine screening

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 MET amplified malignancies (#2595) presented at session « Developmental Therapeutics – Clinical Pharmacology and Experimental Therapeutics" (May 30, 8:00 AM – 11:30 AM McCormick Place: S Hall A, poster board #311).