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Biomarker-driven access to crizotinib in ALK, MET or ROS1 positive malignancies in adults and children : feasability of the French National AcSé Program

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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

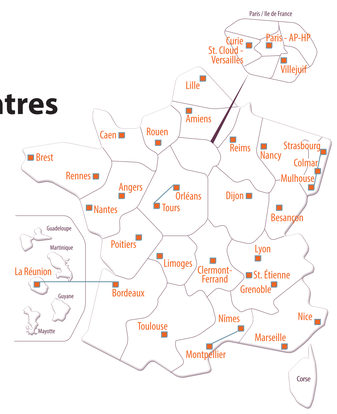
Ensuring equity of access to innovation

- 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

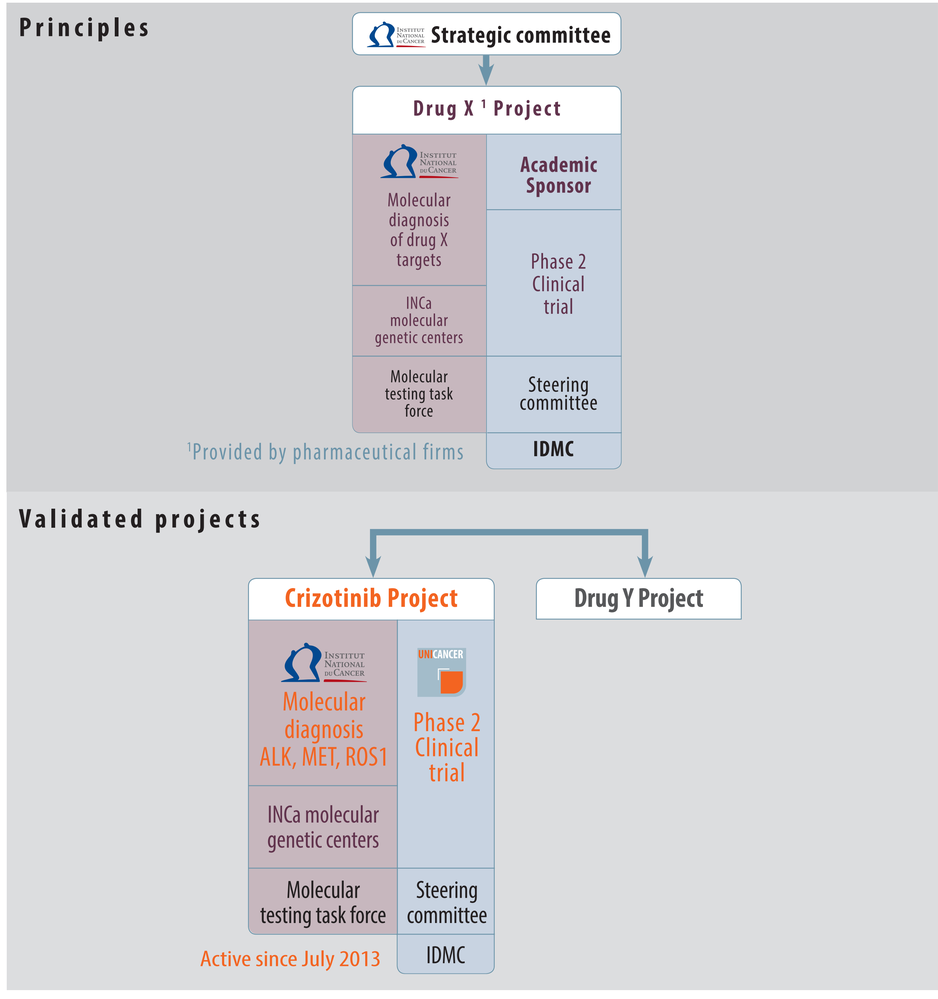
France organisation of molecular centres for personalized medicine: 28 regional centres

Partnerships between several laboratories located in University Hospitals and Cancer Centres

- 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

AcSé crizotinib

PI : Pr Gilles Vassal / NCT02034981

Background

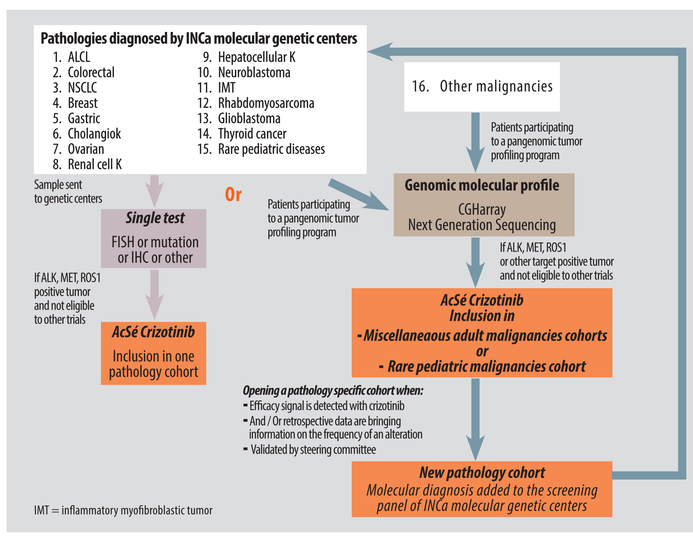
- Crizotinib is registered only for the treatment of patients with ALK+ lung cancer
- Crizotinib targets, ALK, MET and ROS1, are also altered in a wide range of malignancies in adult and children
- Pediatric dose (Mosse et al, Lancet Oncol 2013) and oral formulation available

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 cancer, adults, MET amplified
9. Cholangiocarcinoma, adults, ROS1-translocated
10. Ovarian cancer, adults, MET amplified
11. Clear cell renal cell carcinoma, adults, ALK-translocated
12. Clear cell renal cell carcinoma, adults, ALK-amplified
13. Papillary renal cell carcinoma, adults, MET mutated (+ MET amplified)
14. Hepatocellular carcinoma, adults, MET amplified
15. Neuroblastoma, children and adults, ALK-amplified + ALK mutated
16. IMT, children and adults, ALK-translocated
17. Rhabdomyosarcoma (alveolar and embryonal), children and adults, ALK-amplified
18. Glioblastoma, adults, MET amplified. This cohort will only be open after amendment
19. Anaplastic thyroid cancer, adults, ALK mutated
20. Thyroid cancer (follicular + medullary + papillary), adults, MET mutated

B/ Rare pediatric malignancies cohort

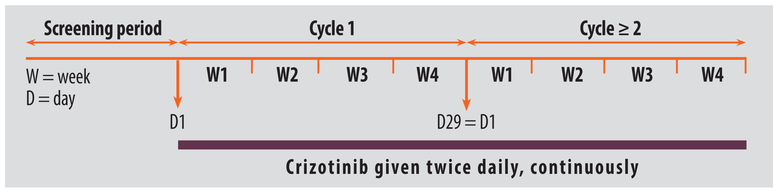
- Diagnosed by INCa molecular genetic centers : hepatoblastoma MET amplified or mutated, renal medullary carcinoma ALK translocated, anaplastic medulloblastoma MET amplified or mutated, HGG or DIPG MET amplified
- Any other pathology with an altered crizotinib target evidenced through genomic profiling

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
- Treatment pursed until disease progression, unacceptable toxicity, intercurent conditions that preclude continuation of treatment, or patient refusal
- Adult: 250 mg x 2; child: 280 mg/m² x 2



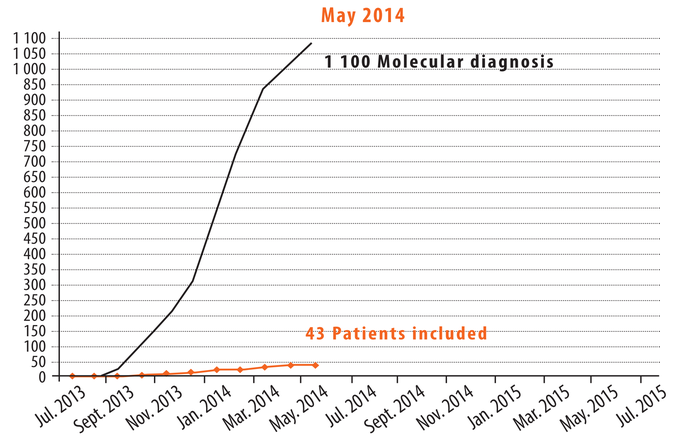
Statistical design

- 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

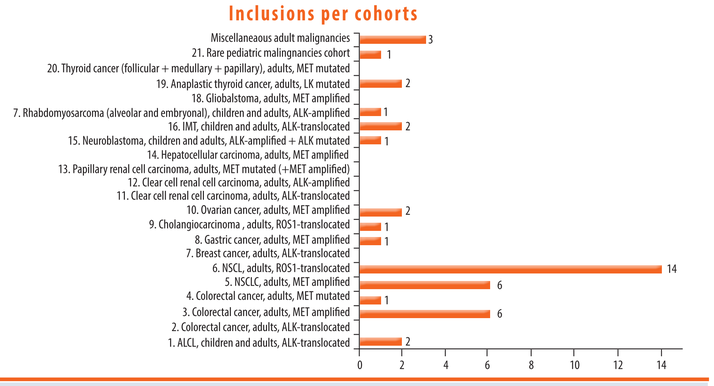
Situation	Design parameters				Decision rule			
	P0	P1	Alpha	Beta	N1	k1	Nk	k
General case	10%	30%	10%	10%	11	0	25	4
Optimistic case	20%	40%	10%	10%	7	0	37	7
Very rare disease	10%	30%	15%	10%	8	0	20	3

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

Accrual



Inclusions per cohorts



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)
- Franchophone 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)