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Biomarker-driven access to crizotinib in ALK, MET or ROS1 positive (+) malignancies in adults and children: the French national AcSé Program.

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Abstract #5138

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 tumor types

Risk of a wide off label use of the drug

Objectives

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
- Efficacy signal force to inform pharmaceutical firms for drug development decision making

2/ Ensuring equity of access to innovation

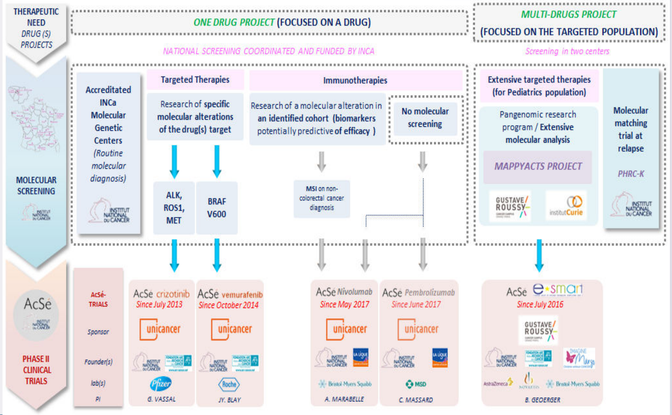
- Provide nationwide molecular tumor diagnosis for all patients through INCa molecular genetic centers
- Whatever the healthcare institution status (public hospitals, private hospitals…)
- Perform high quality tests
- Hemopathies, solid tumors

France organization of the 28 molecular centers for personalized medicine

Partnerships between laboratories located in University Hospitals and Cancer Centers

- Regional organization
- Cooperation between pathologists and biologists AcSé program

AcSé program



AcSé crizotinib

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 : Gilles VASSAL / NCT02034981

Background

- Crizotinib is registered for treating ALK and ROS1-translocated lung cancer.
- Crizotinib is also a MET inhibitor.
- Crizotinib activity in MET-amplified (+) tumors was explored within the French National Cancer Institute (INCa) AcSé program.
- This included access to tumor molecular diagnoses and an exploratory multi-tumor 2-stage design phase II trial.

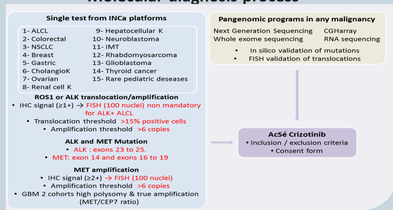
Main objective

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



Biomarker testing

Whole screening activity (at March, 2018)	Number of positive cases	Patients included
19 764 tests (=13 179 screened patients)	611	246 (from 08/2013 to 03/2018)

Treatment plan

- Treatment pursed until progression, unacceptable toxicity, undercurrent conditions, physician decision or patient refusal
- Safety assessed continuously
- Disease response assessed every 8 weeks with CT and/or PET-CT. All imaging and response evaluation were centrally reviewed and response was evaluated according to Lugano criteria taking into account metabolic response when available or to RECIST 1.1 criteria in patients with only CT-based evaluation.

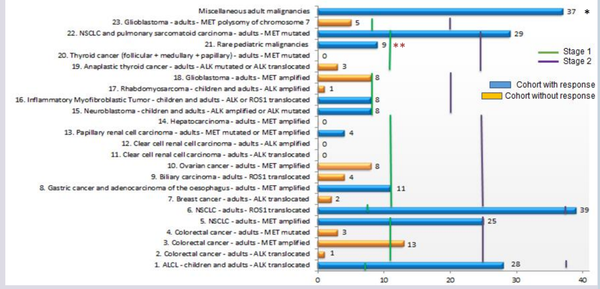
Statistical design

- Main endpoint: objective response (CR, PR) after 2 cycles. May be changed to the best response for cohorts that are displaying delayed responses
- 3 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: ALCL and NSCLC with ROS1 translocation
- 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.
- Centers: declared 198 - open 186 - recruiting 85.
- Population: 246 pts inclued (including 27 children). Median age : 58 years old [1-92].

Inclusions per cohorts



** 3 NSCLC – ALK amplified*
1 NSCLC – ALK mutated
1 SCLC – MET mutated + ROS1 mutated
1 urachal adenocarcinoma – MET amplified
4 cholangiocarcinoma – MET amplified
2 cholangiocarcinoma – ALK translocated
1 cholangiocarcinoma – ALK mutated
1 cholangiocarcinoma – MET mutated

*** 1 mesothelioma – ALK translocated*
1 atypical meningioma – ROS1 translocated
1 sarcoma – MET translocated

1 gallbladder – MET amplified
1 pancreas cancer – ROS1 mutated
1 pancreas cancer – ALK mutated
1 kidney cancer – ROS1 amplified
1 kidney cancer – ALK translocated
1 bladder cancer – MET translocated
1 prostate cancer – ALK translocated
1 olorectal cancer – ALK mutated

1 glioma – MET translocated
1 glioma – MET amplified
1 infiltrating glioma – MET amplified

2 leiomyosarcoma – ALK translocated
1 small intestine sarcomatoid cancer – ALK translocated
1 larynx carcinoma– MET amplified
1 neuroblastoma – ROS1 mutated
1 B large cell lymphoma – ALK translocated
1 papillary thyroid carcinoma – ALK translocated
1 ethmoid adenocarcinoma – MET amplified

1 liposarcoma – ETV6 NTRK alteration
1 medullary glioma – MET amplified and MET translocated

1 breast cancer – ROS1 translocated
1 ovarian cancer – MET mutated
1 ovarian cancer – ALK mutated
1 melanoma – ALK translocated
1 melanoma – ROS1 translocated
1 face epidermoid carcinoma – MET amplified
1 unknown primary carcinoma – ALK translocated.
1 anoplastic pleomorphic xanthoastrocytoma – MET amplified

RESULTS

Biomarkers testing

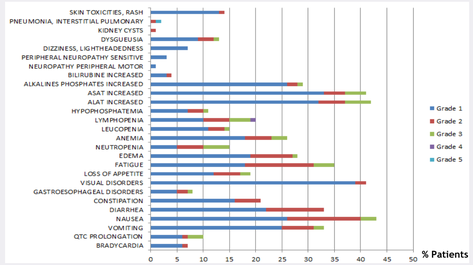
	ALK Amp	ALK Mut	ALK trans	MET Amp	MET Mut	ROS1 trans
Colorectal	2/788 (0,3%)		2/874 (0,2%)	28/939 (3%)	15/1388 (1%)	
NSCLC				251/4171 (6%)	76/1007 (7,5%)	77/4050 (1,9%)
Breast	5/521 (1%)		2/544 (0,4%)			
Esogastric				35/570 (6%)		
K biliary carcinoma		0/75 (0%)	1/29 (3,4%)	6/107 (5,6%)		4/692 (0,6%)
Ovarian cancer				7/640 (1%)		
Renal carcinoma	0/260 (0%)		0/280 (0%)	3 /83 (3,6%)	9/256 (3,5%)	
Hepatocarcinoma				5/190 (2,6%)		
Neuroblastoma	2/56 (3,6%)	7/65 (11,0%)	1/44 (2,3%)			
IMT			4/12 (33%)			1/4 (25%)
Rhabomyosarcoma	1/44 (2,3%)		2/42 (4,8%)			
Glioblastoma				60/1232 (4,9%)		
Thyroid	0/189 (0%)	1/173 (0,6%)	2/236 (0,8%)		2/185 (1,1%)	
Spitzoid melanoma			0/9 (0%)			0/9 (0%)
	10/1858 (0,5%)	8/313 (2,5%)	14/2070 (0,7%)	395/7932 (5%)	102/2836 (3,6%)	82/4755 (1,7%)

Efficacy

Positive cohorts		Pts analysed	CR/PR at 2 months	ORR% [CI 95%] at 2 months	Best response (CR/PR)	ORR% [CI 95%] best response
ALCL	ALK trans	24	12	54 [29-71]	12	54 [29-71]
NSCLC	MET amp	25	4	16 [4.5-36.1]	8	32 [15-54]
	ROS1 trans	37	17	47.2 [30-64]	25	67.6 [50-82]
	MET mut	28	3	11 [2-28]	10	40 [21-61]
Esogastric	MET amp	9	3	33 [7-70]	5	56 [21-86]
IMT	ALK trans / ROS1 trans	8	3	38 [9-76]	6	75 [35-97]
Neuroblastoma	ALK amp or mut	8	-	-	1	13 [0.3-53]
Kidney	MET amp or mut	4	-	-	1	25 [1-81]
Miscellaneous	pediatrics	9	0	-	3*	
	adults	37	1**	-	1**	

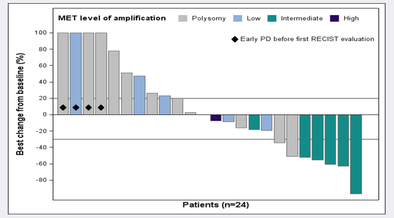
**Sarcoma ETV6NTRK , Mesothelioma ALK trans, Meningioma ROS1 trans*
***Kidney ALK trans.*

Related toxicities



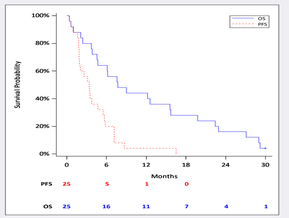
Focus on Non-Small Cell Lung Cancers

MET amplification NSCLC



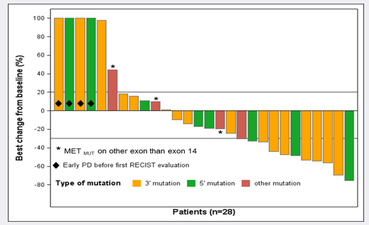
MET amplification classification	MET/Centromere ratio
Polysomy	≤1.8
Low	≥1.8–≤2.2
Intermediate	>2.2–<5.0
High	≥5.0

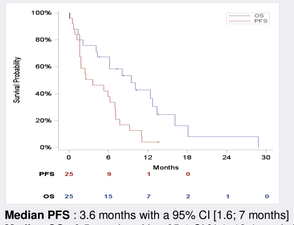
Level of *MET* amplification:
- not predictive of response at 2 cycles (CR or PR) p=0.3
- But predictive of best response p=0.04.



Median PFS : 3.4 months 95% CI [1.9; 5.5 months]
Median OS : 7.7 months 95% CI [4.6; 15.7 months]

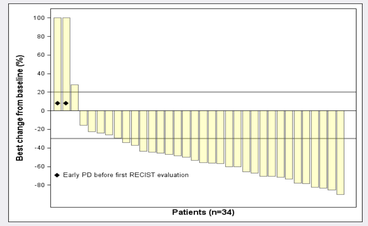
MET exon 14 mutation NSCLC

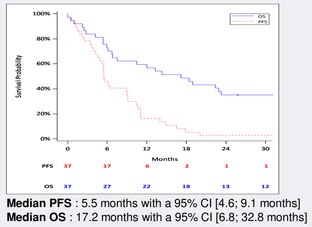




Median PFS : 3.6 months with a 95% CI [1.6; 7 months]
Median OS : 9.5 months with a 95% CI [4.1; 13.4months]

ROS1 translocation NSCLC





Median PFS : 5.5 months with a 95% CI [4.6; 9.1 months]
Median OS : 17.2 months with a 95% CI [6.8; 32.8 months]

Since start study, crizotinib was registered for ROS1+ stage IV NSCLC (08/2016).

Conclusion

Crizotinib showed activity in pediatric and adults malignancies with ALK, ROS1 and MET alterations.

The AcSé program provided a secured national access to both biomarker testing and treatment for children and adolescents with life threatening malignancies.

Acknowledgements

Patients & families
AcSé crizotinib investigators teams
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Collaborative groups

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

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