Real-world effectiveness and safety of sotorasib in patients with KRAS G12C mutated metastatic non-small cell lung cancer (NSCLC): results of the IFCT-2102 Lung KG12Ci study

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Background

Sotorasib has demonstrated robust activity in phase 3 trial in pretreated NSCLC patients (pts) with *KRAS G12C* mutation. However, its effectiveness and safety in a real-world setting, particularly when administered after treatment with immune checkpoint inhibitors remains to be confirmed.

Methods

Multicenter retrospective study including NSCLC pts who received at least 1 dose of sotorasib as part of the French expanded access (ATU) program.

The primary objective was to evaluate real-world progression-free survival (rwPFS), and the secondary objectives included overall survival (OS) and reporting of sotorasib-related hepatic toxicity. Pts who received sotorasib until 08.08.2021 were included in the nominative ATU (ATUn) and pts who received sotorasib from 09.08.2021 were included in the cohort ATU (ATUc). Inclusions were exhaustive per participating centers (76).

Study flowchart

Follow up:
All (n=458): 16.4 months (IC95%: [15.5; 17.3])
ATUn (n=255): 13.6 months (IC95%: [13.2; 14.5])
ATUc (n=203): 20.9 months (IC95%: [19.1; 21.3])

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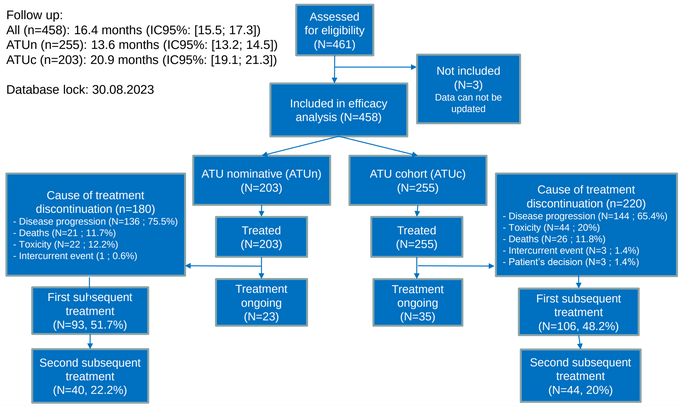


Best response under sotorasib

	ATUn (N=203)	ATUc (N=255)	All (N=458)
Complete response	1 (0.6%) [0.0% - 1.7%]	1 (0.5%) [0.0% - 1.4%]	2 (0.5%) [0.0% - 1.2%]
Partial response	62 (35%) [28.0% - 42.1%]	63 (30.6%) [24.3% - 36.9%]	125 (32.6%) [27.9% - 37.3%]
Objective Response	63 (35.6%) [28.5% - 42.6%]	64 (31.1%) [24.7% - 37.4%]	127 (33.2%) [28.4% - 37.9%]
Stable disease	55 (31.1%) [24.3% - 37.9%]	60 (29.1%) [22.9% - 35.3%]	115 (30%) [25.4% - 34.6%]
Disease Control	118 (66.7%) [59.7% - 73.6%]	124 (60.2%) [53.5% - 66.9%]	242 (63.2%) [58.4% - 68.0%]
Progression disease	59 (33.3%) [26.4% - 40.3%]	79 (38.3%) [31.7% - 45.0%]	138 (36%) [31.2% - 40.8%]
Not evaluable	0	3 (1.5%) [0.0% - 3.1%]	3 (0.8%) [0.0% - 1.7%]
Not done/Missing	26	49	75

Baseline characteristics

			ATUn (N=203)	ATUc (N=255)	All (N=458)
Sex	Female	N (%)	95 (46.8)	104 (40.8)	199 (43.4)
Age		Median	65.8	65.9	65.8
		Min-Max	[38.7-85.1]	[35.9-89.7]	[35.9-89.7]
Smoking status	Smoker	N (%)	194 (96.5)	240 (94.5)	434 (95.4)
	Never	N (%)	7 (3.5)	14 (5.5)	21 (4.6)
Pack year		Median	35.0	35.0	35.0
		Min-Max	[1-120]	[5-120]	[1-120]
Histology	Adenocarcinoma	N (%)	192 (94.6)	239 (93.7)	431 (94.1)
	Squamous	N (%)	4 (2.0)	4 (1.6)	8 (1.7)
	Others	N (%)	7 (3.4)	12 (4.7)	19 (4.2)
PS at sotorasib initiation	0-1	N (%)	98 (74.2)	122 (69.7)	220 (71.7)
	≥2	N (%)	34 (25.8)	53 (30.3)	87 (28.3)
Stage at diagnostic	I-IIIA	N (%)	29 (14.4)	52 (20.6)	81 (17.8)
	IIIB-IVB	N (%)	173 (85.6)	201 (79.4)	374 (82.2)
Brain metastasis at sotorasib initiation	Yes	N (%)	77 (37.9)	97 (38.0)	174 (38.0)
	No	N (%)	126 (62.1)	158 (62.0)	284 (62)
Number of previous line of systemic treatments	1	N (%)	57 (28.1)	114 (44.7)	171 (37.3)
	2	N (%)	63 (31)	60 (23.5)	123 (26.9)
	3	N (%)	26 (12.8)	40 (15.7)	66 (14.4)
	≥4	N (%)	55 (27.1)	40 (15.7)	95 (20.7)
PDL1 expression (IHC) *	Negative	N (%)	72 (35.5)	89 (34.9)	161 (35.2)
	1-49 %	N (%)	62 (30.5)	94 (36.9)	156 (34.1)
	≥ 50 %	N (%)	48 (23.6)	59 (23.1)	107 (23.4)
Description of other tumoral alterations**	EGFR	N (%)	1 (0.5)	1 (0.4)	2 (0.4)
	HER2	N (%)	1 (0.5)	0 (0)	1 (0.2)
	ALK	N (%)	0 (0)	0 (0)	0 (0)
	ROS1	N (%)	0 (0)	3 (1.2)	3 (0.7)
	BRAF	N (%)	3 (1.5)	3 (1.2)	6 (1.3)
	TP53	N (%)	32 (15.8)	30 (11.8)	62 (13.5)
	STK11	N (%)	21 (10.3)	30 (11.8)	51 (11.1)
	KEAP1	N (%)	4 (2)	4 (1.6)	8 (1.7)
	MET	N (%)	0 (0)	3 (1.2)	3 (0.7)
	Other biomarkers	N (%)	4 (2)	7 (2.7)	11 (2.4)

* Not done and undetermined are not presented
** When the test was performed (not done EGFR: 22 (4.8%); HER2: 74 (16.2%); ALK: 42 (9.2%); ROS1: 100 (21.8%); BRAF: 51 (11.1%); others: 328 (71.6%))

Patients were heavily pretreated: over 60% of patients received ≥ 2 lines of treatment before sotorasib.

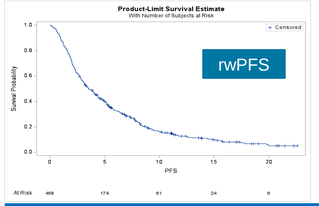
Best central nervous system response under sotorasib

	ATUn (N=77)	ATUc (N=97)	All (N=174)
Complete response	2 (3.2%) [0.0% - 7.5%]	2 (2.6%) [0.0% - 6.2%]	4 (2.9%) [0.1% - 5.7%]
Partial response	14 (22.2%) [12.0% - 32.5%]	10 (13.2%) [5.6% - 20.8%]	24 (17.3%) [11.0% - 23.5%]
Objective Response	16 (25.4%) [14.6% - 36.1%]	12 (15.8%) [7.6% - 24.0%]	28 (20.1%) [13.5% - 26.8%]
Stable disease	34 (54%) [41.7% - 66.3%]	31 (40.8%) [29.7% - 51.8%]	65 (46.8%) [38.5% - 55.1%]
Disease Control	50 (79.4%) [69.4% - 89.4%]	43 (56.6%) [45.4% - 67.7%]	93 (66.9%) [59.1% - 74.7%]
Progression disease	13 (20.6%) [10.6% - 30.6%]	31 (40.8%) [29.7% - 51.8%]	44 (31.7%) [23.9% - 39.4%]
Not evaluable	0	2 (2.6%) [0.0% - 6.2%]	2 (1.4%) [0.0% - 3.4%]
Not done/Missing	14	21	35

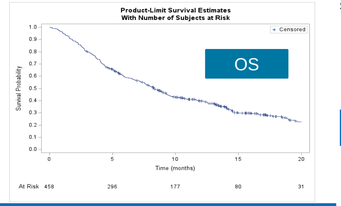
Best central nervous system (CNS) response was defined as the best response on CNS metastases recorded from the start of treatment with sotorasib until disease progression or start of further anti-cancer treatment.

Efficacy: rwPFS and OS

	All (N=458)
Event: N (%)	399 (87.1)
Median rwPFS: months [95% CI]	3.5 [3.1-4.2]
6-m PFS: % [95% CI]	32.8 [28.5-37.2]
12-m PFS: % [95% CI]	12.5 [9.4-16]



	All (N=458)
Event: N (%)	318 (69.4)
Median OS: months [95% CI]	8.3 [7.5-9.3]
6-m OS: % [95% CI]	59.2 [54.5-63.5]
12-m OS: % [95% CI]	39.6 [35-44.2]



Multivariate analysis for OS

Factors		N	Univariate model HR	95% CI	P	Multivariate model (stepwise selection*) HR	95% CI	p
Sex	Female	199	1.00		.	1.00	-	-
	Male	259	1.21	[0.96 - 1.51]	0.099	1.21	[0.91-1.61]	0.19
Age	<70 years	312	1.00		.			
	≥70 years	146	0.94	[0.74 - 1.18]	0.59			
PS	<2	220	1.00		.	1.00	-	-
	≥2	87	2.13	[1.59 - 2.86]	<0.0001	2.12	[1.58-2.84]	< 0.0001
Brain metastasis	No	284	1.00		.			
	Yes	174	1.19	[0.95 - 1.49]	0.14			

For multivariate analysis, the input p-value for stepwise selection is 0.2

Most frequent sites of progression

		ATUn (N=176)	ATUc (N=213)	All (N=389)
Lung	N (%)	86 (48.9)	96 (45.1)	182 (46.8)
Brain	N (%)	42 (23.9)	56 (26.3)	98 (25.2)
Bone	N (%)	46 (26.1)	49 (23)	95 (24.4)
Mediastinum	N (%)	47 (26.7)	31 (14.6)	78 (20.1)
Liver	N (%)	27 (15.3)	32 (15)	59 (15.2)
Pleura	N (%)	28 (15.9)	28 (13.1)	56 (14.4)
Adrenals	N (%)	26 (14.8)	25 (11.7)	51 (13.1)

Description of last treatment before sotorasib

	All (N=456)
Antineoplastic	431 (94.5)
Radiotherapy	143 (31.4)
Surgery	42 (9.2)

Antineoplastic	N=431	
Single agent chemotherapy	n=110 (25.5)	Paclitaxel +/- Bevacizumab 57 Gemcitabine 23 Docetaxel 18 Pemetrexed 10 Vinorelbine 2
Platin-based doublet	n=64 (14.8)	Platin-Paclitaxel+/- Bevacizumab 29 Platin-Pemetrexed+/- Bevacizumab 28 Other 7
Immunotherapy	n=72 (16.7)	
Immunotherapy + Chemotherapy	n=166 (38.5)	
Immunotherapy + Other	n=5 (1.2)	
Targeted therapy	n=1 (0.2)	Crizotinib
Other	n=13 (3.0)	

Causes of sotorasib discontinuation

	ATUn (N=180)	ATUc (N=220)	All (N=400)
Progressive disease	136 (75.6)	144 (65.5)	280 (70)
Toxicity	22 (12.2)	44 (20)	66 (16.5)
Death	21 (11.7)	26 (11.8)	47 (11.8)
Intercurrent event	1 (0.6)	3 (1.4)	4 (1)
Patient decision	0	3 (1.4)	3 (0.8)

Toxicities that led to sotorasib discontinuation

	All (N=66)
Hepatic toxicity	35 (53.0)
Diarrhea	12 (18.2)
Digestive toxicity	6 (9.1)
Diarrhea and altered general status	2 (3.0)
Diarrhea and vomiting	2 (3.0)
Hepatic toxicity and diarrhea	2 (3.0)
Asthenia and chest pain	1 (1.5)
Hepatic toxicity and abdominal pain	1 (1.5)
Hepatic toxicity and digestive toxicity	1 (1.5)
Hepatic toxicity and thrombocytopenia	1 (1.5)
Hepatic toxicity, diarrhea, vomiting, hyperleukocytosis	1 (1.5)
Interstitial lung disease	1 (1.5)
Thrombocytopenia	1 (1.5)

Maximal hepatic toxicity of sotorasib

	All (N=458)			
SOC CTCAE V5.0	Any Grade	Grade 2	Grade 3	Grade 4
Any adverse event	29 (6.3%)	5 (1.1%)	18 (3.9%)	6 (1.3%)
- Gamma-glutamyltransferase increased	21 (4.6%)	3 (0.7%)	14 (3.1%)	4 (0.9%)
- Alanine aminotransferase increased	19 (4.1%)	6 (1.3%)	12 (2.6%)	1 (0.2%)
- Aspartate aminotransferase increased	16 (3.5%)	7 (1.5%)	9 (2%)	0 (0%)
- Blood alkaline phosphatase increased	10 (2.2%)	5 (1.1%)	5 (1.1%)	0 (0%)
- Blood bilirubin increased	5 (1.1%)	3 (0.7%)	1 (0.2%)	1 (0.2%)

Conclusion

IFCT-2102 study confirms the effectiveness of sotorasib in pretreated *KRAS G12C*-NSCLC pts and its safety profile is manageable with hepatic grade 3 or 4 treatment-related adverse events occurring in 7% of pts. Our findings support the use of sotorasib as a treatment option in this population. The results of rwPFS were lower than those of CodeBreaK 200 phase III study but the population was more heavily pretreated. Further analysis according to treatment lines are planned.

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