Clinical Study Synopsis

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The study listed may include approved and non-approved formulations or treatment regimens. Data may differ from published or presented data and are a reflection of the limited information provided here. The results from a single trial need to be considered in the context of the totality of the available clinical research results for a drug. The results from a single study may not reflect the overall results for a drug.

Date of study report	23-Sep-2022
Study title	EPI VITRAKVI: A comparison of clinical outcomes in Infantile Fibrosarcoma (IFS) patients treated with larotrectinib in the phase I/II SCOUT study versus external historical cohorts
Sponsor:	Bayer
Sponsor's study ID	21767
NCT number	NCT05236257
Indication	Locally advanced or metastatic infantile fibrosarcoma harboring an NTRK gene fusion; Infantile fibrosarcoma
Study objectives	The objectives in this study are: • Primary objective: The primary objective was to compare the time to medical treatment failure (defined as: next systemic treatment or mutilating surgery or radiation therapy or death due to any cause) between larotrectinib and standard of care in IFS patients using externally-controlled comparison performed with phase I/II SCOUT study and eligible historical cohorts. • Secondary objectives: The secondary objectives were to compare: - Treatment outcomes (next systemic treatment, mutilating surgery, radiation therapy, death due to any cause) - Treatment discontinuation rates due to toxicity.
Name of observed product	Larotrectinib (BAY2757556)
Main inclusion criteria	Selection criteria for the sources of the external historical control cohorts: The non-arbitrary choice of the data sources to constitute the external historical control arm was ensured by a comprehensive review of the existing relevant databases in France and internationally, based on a Systematic Literature Review (SLR).Data sources were selected upon the following eligibility and feasibility criteria: *Inclusion criteria*: Cohorts with prospective enrollment and with retrospective and prospective data collection of patients with IFS from 2000 to the search date of the SLR, i.e., 30 July 2021, ✓ Cohorts containing at least clinical data allowing to assess the efficacy of the treatment and the main prognostic factors as follows: - Diagnosis and stage of the disease (locally advanced or metastatic), - Type of treatments (chemotherapy, radiotherapy, surgery: mutilating yes/no) and date of the initiation or of the procedure, - Death and date, - Localization of the tumor (axis versus limb), - Size of the tumor (< 5 cm versus > 5 cm).

	Exclusion criteria: ✓ Databases not containing patients with locally advanced or metastatic IFS, ✓ Medico-administrative databases or absence of data allowing the assessment of the efficacy of the treatment and main prognostic factors, or high rate of missing data (>10% on outcome and >25% on covariates), ✓ Cohorts with retrospective enrollment and case report, ✓ Cohorts with prospective enrollment for which all patients were included before 2000. ✓ Based on these selection criteria and on the accessibility of the database, the 2 following databases were selected: • Institute Curie database, • Database from the CWS. Selection criteria for the patients The study population comprised all patients in the SCOUT study and the eligible external historical cohorts with a diagnosis of locally advanced or metastatic IFS, regardless of their refractory or relapsed status, i.e., including treatment-naïve patients to avoid further reducing the sample size. The choice of the study population was mainly driven by feasibility/sample size considerations, in order to be able to perform a comparison based on a minimal number of patients. The study authorized the inclusion of patients with clinico-morphological findings of IFS but with unknown NTRK (neurotrophic tyrosine receptor kinase) gene fusion status to maximize sample size. The IFS population could also include patients with advanced or metastatic Congenital cellular Mesoblastic Nephroma (CMN). *Inclusion criteria:* The inclusion criteria were in line with those of the SCOUT study in terms of patients and disease characteristics: • Age ≤ 21 years old. • Locally advanced or metastatic IFS. • Patients with available information on clinical, radiological characteristics of their tumor, therapies administered and outcomes. • Patients receiving larotrectinib in the SCOUT trial. • Patients receiving at least one chemotherapy-based regimen[2] in the external historical control cohorts. *2 In order to preserve the sample size, patients were included regardless of the type of chemotherapy they received*. • No opposition from the patients and/or representatives for data use.
	Exclusion criteria: • Patients treated with TRKi in the external historical control cohorts. • Patients with documented absence of NTRK gene fusion. • Patients participating in an investigational program with interventions outside of routine clinical practice.
Study design	Retrospective, observational, externally-controlled study and Phase IV

Methodology	This study was a retrospective, observational, externally-controlled study. Data of patients with IFS who were treated with larotrectinib in the SCOUT study (Study ID: 20290; NCT02637687) were compared with those of an external historical control group. The historical control group was constituted of eligible cohorts of patients with IFS treated with at least one chemotherapy-based regimen, which represents the historical standard of care. The primary variable was time to treatment failure. Secondary variables were time to subsequent systemic treatment, time to mutilating surgery including limb amputation, time to radiation therapy, time to complete surgical resection, overall Survival (OS) and number of participants with treatment discontinuation due to treatment-emergent adverse events.
Statistical methods	The statistical evaluation was performed by using the software package SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) for all outputs. Descriptive analysis of the data was performed using summary statistics for categorical and quantitative (continuous) data. Continuous data were described by the number of non-missing values, median, mean, standard deviation (StD), minimum, and maximum as well as lower and upper quartiles. Frequency tables were generated for categorical data. The statistical power for the comparison of two groups under a Cox Proportional Hazards Model was calculated retrospectively.
Substantial protocol changes	None
Study period	Study Start Date: 10-Mar-2022 Study End Date: 13-Sep-2022
Study center(s)	Countries involved in SCOUT study (18 countries worldwide including France) and external historical control cohorts from the Institut Curie database and the Cooperative Weichteilsarkom Studiengruppe (CWS) database.
Number of subjects	Planned: 95 Analyzed: 93
Study endpoints	*Primary variable(s):* - Time to medical treatment failure *Secondary variable(s):* - Time to subsequent systemic treatment - Time to mutilating surgery including limb amputation - Time to radiation therapy. - Time to complete surgical resection - Overall Survival (OS) - Number of participants with treatment discontinuation due to treatment emergent adverse events

Subject disposition and baseline

In total, 93 patients were included in this study (IFS population). The larotrectinib arm of the study included 51 patients from the SCOUT study. The single comparator arm of patients that received conventional chemotherapy included in total 42 external control patients, pooled from the Institut Curie database (N=18) and the CWS database (N=24). About 60% of the patients in the IFS population were males (57 patients, 61.3%). Patients were on average 1.43 years old (StD: 2.91) at the index date, which was defined as either the first dose of larotrectinib or initiation of first line of chemotherapy. The average age was higher in the larotrectinib group (2.01 years [StD: 3.49]) than in the external control group (0.73 years [StD: 1.81]).The most common primary tumor location was

the limbs in both groups (28 patients [54.9%] in the larotrectinib group and 29 patients [69.0%] in the external control group). In the larotrectinib group, 29 patients (56.9%) had ongoing study treatment, while 22 (43.1%) discontinued study treatment by the data cut-off. Thirteen (13) patients discontinued the treatment due to surgical resection or maintained response to treatment (Table 1). In the external control group, only 1 patient (2.4%) had ongoing chemotherapy, whereas 41 (97.6%) discontinued chemotherapy. Only a slight difference was observed for the mean time from locally advanced/metastatic disease diagnosis to initiation of first line chemotherapy: 1.34 (1.91) months in patients from the Institut Curie database and 0.29 (0.48) months in patients from the CWS database.

Table 1: Demographic and baseline clinical characteristics of the IFS population

	Larotrectinib (N=51)	External Controls (N=42)	Total (N=93)
Demographic characteristics			
Sex			
Female	21 (41.2%)	15 (35.7%)	36 (38.7%)
Male	30 (58.8%)	27 (64.3%)	57 (61.3%)
Age at Index Date (years)			
Mean (StD)	2.01 (3.49)	0.73 (1.81)	1.43 (2.91)
Median	0.89	0.30	0.52
Min, Max	0.1, 17.8*	0.0, 11.7	0.0, 17.8*
Baseline cancer characteristics			
Tumor type			
IFS	49 (96.1%)	41 (97.6%)	90 (96.8%)
CMN	2 (3.9%)	1 (2.4%)	3 (3.2%)
Primary Tumor Location			
Limbs	28 (54.9%)	29 (69.0%)	57 (61.3%)
Non parameningeal head and neck	9 (17.6%)	1 (2.4%)	10 (10.8%)
Thoracic	5 (9.8%)	4 (9.5%)	9 (9.7%)
Abdomen/pelvis	2 (3.9%)	6 (14.3%)	8 (8.6%)
Orbit	3 (5.9%)	1 (2.4%)	4 (4.3%)
Kidney	2 (3.9%)	1 (2.4%)	3 (3.2%)
Spine	2 (3.9%)	0	2 (2.2%)
Disease Status			
Locally advanced	41 (80.4%)	39 (92.9%)	80 (86.0%)
Metastatic	10 (19.6%)	3 (7.1%)	13 (14.0%)
Initial IRS Group Stage at index date			
III	41 (80.4%)	39 (92.9%)	80 (86.0%)
IV	10 (19.6%)	3 (7.1%)	13 (14.0%)
Time from Locally Advanced/Metastatic Disease Diagnosis to First Dose of Larotrectinib / First Line of Chemotherapy (months)			
Mean (StD)	5.09 (8.64)	0.74 (1.39)	3.13 (6.79)
Median	1.81	0.20	0.92
Min, Max	0.0, 39.3	0.0, 8.0	0.0, 39.3
Treatment history at baseline			
Previous Surgical Resection			
No Surgery	38 (74.5%)	33 (78.6%)	71 (76.3%)
Single	6 (11.8%)	7 (16.7%)	13 (14.0%)
Multiple	7 (13.7%)	2 (4.8%)	9 (9.7%)
Received Prior Radiotherapy			
No	48 (94.1%)	42 (100.0%)	90 (96.8%)
Yes	3 (5.9%)	0	3 (3.2%)
Number of Prior Systemic Regimens			
0	19 (37.3%)	42 (100.0%)	61 (65.6%)
1-2	26 (51.0%)	0	26 (28.0%)
3 or more	6 (11.8%)	0	6 (6.5%)
Treatment disposition			
Ongoing with study treatment	29 (56.9%)	1 (2.4%)	30 (32.3%)
Discontinued study treatment	22 (43.1%)	41 (97.6%)	63 (67.7%)

Index date and baseline are defined as either the first dose of larotrectinib or initiation of first line of chemotherapy.
** The 17.8-year old patient had an original diagnosis of IFS in 2002 and relapsed in 2019.*
CMN: congenital mesoblastic nephroma, IFS: infantile fibrosarcoma, IRS: intergroup rhabdomyosarcoma study, Min: minimum, Max: maximum, StD: standard deviation

Results –

Primary variable(s):

- **Time to medical treatment failure**

Five (5) medical treatment failure events (i.e. start of new systemic treatment, radiation therapy, mutilating surgery or death) were reported in 4 patients (7.8%) in the larotrectinib group, and 23 events were reported in 15 patients (35.7%) in the external control group. Patients not recording an event were censored at the last known alive date: 47 patients (92.2%) in the larotrectinib group and 27 patients (64.3%) in the external control group. Reasons for censoring in the larotrectinib group were data cut-off (35 patients, 68.6%), lost to follow-up14 (8 patients, 15.7%), missing visit assessments (3 patients, 5.9%) or withdrawal of consent by the subject/parent (1 patient, 2.0%). The description of censoring events was unavailable for the external control group. Looking at the first medical treatment failure event since the start of treatment, 2 patients (3.9%) received a new systemic treatment and 2 patients (3.9%) underwent mutilating surgery in the larotrectinib group, whereas in the external control group 6 patients (14.3%) received a new systemic treatment, 2 patients (4.8%) radiation therapy, 5 patients (11.9%) mutilating surgery and 2 patients (4.8%) died. (table 2)

The time to medical treatment failure was significantly longer in the larotrectinib group than in the external control group in both the unweighted (log-rank test: p=0.0023) and the weighted analysis (logrank test: p=0.0161). The HR (hazard reduction) was 0.21 (95% CI: 0.07, 0.63; p=0.0058) in the unweighted sample and 0.15 (95% CI (confidence interval): 0.05, 0.42; p=0.0004) in the weighted sample. The weighted HR stratified by IRS group stage was 0.20 (95% CI: 0.06, 0.63; p=0.0060). The results were in favor of larotrectinib and indicated that, in patients with IFS, there was a longer time to medical treatment failure corresponding to an 80% reduced likelihood of encountering a medical treatment failure event in the larotrectinib group when compared to the external control group that received conventional chemotherapy.

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Table 2: Event and Censor Description for Medical Treatment Failure (IFS Subjects)

	Larotrectinib	External Controls	Total
Censoring or Event Description			
n	51 (100.0%)	42 (100.0%)	93 (100.0%)
Censored at last known alive date	47 (92.2%)	27 (64.3%)	74 (79.6%)
Death	0	2 (4.8%)	2 (2.2%)
Mutilating Surgery	2 (3.9%)	5 (11.9%)	7 (7.5%)
Radiation Therapy	0	2 (4.8%)	2 (2.2%)
Start of new Systemic Treatment	2 (3.9%)	6 (14.3%)	8 (8.6%)

Secondary variable(s)

- **Time to subsequent systemic treatment**

Two (2) patients (3.9%) of the larotrectinib group received a new line of systemic treatment (1 Vincristine /Actinomycin D/Cyclophosphamide [VAC], 1 entrectinib) versus 8 patients (19.0%) in the external control group (4 VAC, 3 anthracycline/alkylating agent based regimen, 1 alkylating agent based regimen with high dose chemotherapy, stem cell transplantation and regional hyperthermia). The other patients were censored at the last known alive date (49 patients [96.1%] in the larotrectinib group and 34 patients [81.0%] in the external control group). The weighted median time to subsequent systemic treatment was not estimable in the larotrectinib group due to the censored data and was 24.0 months (95% CI: 24.0, A) in the external control group. The weighted event-free rate at 24 months was 0.961 (95% CI: 0.883, 0.998) in the larotrectinib group versus 0.895 (95% CI: 0.538, 1.000) in the external control group. The time to subsequent systemic treatment was significantly longer in the larotrectinib group than in the external control group (weighted log-rank test: p=0.0041). The weighted HR stratified by IRS group stage was 0.14 (95% CI: 0.03, 0.63; p=0.0109), which

corresponds to an 86% lower likelihood of receiving a new line of systemic treatment in the larotrectinib group compared with the external control group.

- **Time to mutilating surgery including limb amputation**

Two (2) patients (3.9%) of the larotrectinib group underwent a mutilating surgery (1 thumb amputation and 1 tumor resection with functional impairment considered as mutilating surgery by the investigator), versus 8 patients (19.0%) in the external control group (including 4 limb amputations, 1 orbital exenteration, 1 shoulder disarticulation and 2 surgical interventions with location not documented in the database but with functional impairment considered as mutilating surgery by the investigator). The other patients were censored at the last known alive date (49 patients [96.1%] in the larotrectinib group and 34 patients [81.0%] in the external control group). The weighted median time to mutilating surgery was not estimable in either the larotrectinib or the external control group due to the censored data. The weighted event-free rate at 24 months was 0.982 (95% CI: 0.906, 1.000) in the larotrectinib group versus 0.903 (95% CI: 0.549, 1.000) in the external control group. The time to mutilating surgery was significantly longer in the larotrectinib group than in the external control group (unweighted log-rank test: p=0.0476), but the difference was not statistically significant when adjusted for confounding factors (weighted log-rank test: p=0.6923). The weighted HR stratified by IRS group stage was not significant (HR: 0.35; 95% CI: 0.06, 2.24; p=0.2683).

- **Time to radiation therapy**.

None of the patients in the larotrectinib group reported a radiation therapy event, versus 4 patients (9.5%) in the external control group. The other patients were censored at the last known alive date (51 patients [100%] in the larotrectinib group and 38 patients [90.5%] in the external control group). The weighted median time to radiation therapy was not estimable in either the larotrectinib or the external control group due to the censored data. The weighted event-free rate at 24 months was 1.000 (95% CI: 1.000, 1.000) in the larotrectinib group versus 0.941 (95% CI: 0.616, 1.000) in the external control group. The log-rank test and HR for the Kaplan-Meier curves of both groups (Figure 8) could not be calculated due to the lack of events in the larotrectinib group.

- **Time to complete surgical resection**

Twelve (12) patients (23.5%) of the larotrectinib group and 12 (28.6%) patients of the external control group underwent complete surgical resection. The other patients were censored at the last known alive date (39 patients [76.5%] in the larotrectinib group and 30 patients [71.4%] in the external control group). The weighted median time to complete surgical resection was not estimable in the larotrectinib group due to the censored data and was 6.1 months (95% CI: 5.1, A) in the external control group. The weighted event-free rate at 24 months was 0.720 (95% CI: 0.574, 0.845) in the larotrectinib group versus 0.437 (95% CI: 0.128, 0.777) in the external control group. The time to complete surgical resection was significantly longer in the larotrectinib group than in the external control group only when adjusted for confounding factors (weighted log-rank test: p=0.0369; unweighted logrank test: p=0.5695). However, the weighted HR (HR: 0.42; 95% CI: 0.16, 1.08; p=0.0707) and the weighted HR stratified by IRS group stage (HR: 0.59; 95% CI: 0.30, 1.14; p=0.1146) were not significant.

- **Overall Survival (OS)**

One (1) patient (2.0%) of the larotrectinib group died (of disease progression) versus 3 patients (7.1%) in the external control group (2 of disease progression and 1 from toxic death). The other patients were censored at the last known alive date (50 patients [98.0%] in the larotrectinib group and 39 patients [92.9%] in the external control group). The weighted median OS was not estimable in either the larotrectinib or the external control group due to the censored data. The weighted OS rate at 24 months was 0.985 (95% CI: 0.916, 1.000) in the larotrectinib group versus 0.972 (95% CI: 0.706, 1.000) in the external control group. No significant difference in OS was observed between both groups (weighted log-rank test: p=0.6172; weighted and stratified HR: 0.21; 95% CI: 0.02, 2.84; p=0.2388).

- **Number of participants with treatment discontinuation due to treatment- emergent adverse events**
  No patients permanently discontinued treatment due to TEAEs in the larotrectinib arm. One patient in the external control arm experienced a toxic death after a vincristine and actinomycin-D overdosage.

Adverse events/adverse reactions

As it is stated in the protocol of the study, this retrospective observational study used secondary data collection from a previous clinical trial (SCOUT study) and from eligible databases used to select external historical control cohorts. Therefore, no new AEs or adverse drug reactions were expected to be reported besides the ones already described during the conduct of the initial clinical trial. Furthermore, individual reporting of adverse reactions is not required for non-interventional study designs that are based on secondary use of data as per the EMA guideline on Good Pharmacovigilance Practices.

Overall conclusions

In conclusion, in this retrospective analysis using real-world data as a control arm, larotrectinib reduced the need of subsequent systemic aggressive therapy when compared to the standard of care, regardless of the line of treatment, and especially by improving local tumor control in these very young patients with IFS. These findings confirmed the potentially important role of this drug in the overall treatment strategy of patients with IFS.

Publication(s) based on the study

None at the time of finalization of this report.