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Rash and Efficacy in Anaplastic Lymphoma Kinase Positive (ALK+) Non-Small Cell Lung Cancer Patients Treated with Ensartinib

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BACKGROUND

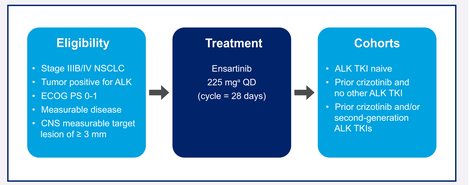
- Ensartinib is a potent ALK small-molecule tyrosine kinase inhibitor (TKI)[1,2]
- Ensartinib has additional activity against MET, ABL, AXL, EPHA2, LTK, ROS1, and SLK[1]
- Ensartinib has demonstrated significant preclinical antitumor activity in both ALK TKI–naive and ALK TKI–resistant models of *ALK*-rearranged non-small cell lung cancer (NSCLC)[1]
- Ensartinib was generally well tolerated, with rash being the most common related adverse event (AE)[2]

SKIN TOXICITY AND TKIs

- Skin toxicity is a class-specific side effect of TKIs, specifically of epidermal growth factor receptor (EGFR) TKIs[3]
- Although skin rash is considered an AE, it's presence and severity of skin rash are associated with improved clinical efficacy in patients receiving EGFR TKIs[3,4]
- EGFR TKI skin toxicity is typically manifested as papulopustular rash with nail fissuring. It is related to the inhibition of wild-type EGFR in the skin, which is crucial for the normal development and physiology of the epidermis[5]
- ALK TKIs normally have less skin toxicity than EGFR TKIs
- Ensartinib-related rash has been described as different than EGFR TKI rash in its pathogenesis, presentation, and evolution. It is possibly immune mediated and presents as a "sunburn type" of rash in appearance (without the discomfort) that tends to wane while the patient is receiving treatment
- This post hoc analysis of a phase 1/2 dose escalation and expansion study of ensartinib (eXalt2) was conducted to determine the relationship between rash and clinical benefit in patients treated with ensartinib 225 mg/day and to define its optimal management

METHODS

Figure 1. eXalt2 Study Design[2]



CNS, central nervous system; **ECOG PS**, Eastern Cooperative Oncology Group performance status; **QD**, once daily.
[a]Prior dose-escalation cohorts established 225 mg as the recommended dose for phase 2; however, *ALK*+ evaluable patients in this presentation include only those patients receiving 225 mg QD who had a post-baseline response assessment.

- In eXalt2 (**Figure 1**), patients received ensartinib until progressive disease (PD), unacceptable toxicity, or investigator discretion
- The primary endpoints were safety and tolerability, and the secondary endpoints were pharmacokinetics and preliminary biological activity
- Tumor assessments were performed locally every 8 weeks
- Patients with asymptomatic brain metastases at baseline were allowed to enroll

RESULTS

Table 1. Demographics by Rash Group (eXalt2 Study)

Baseline Characteristics for ALK+ Evaluable Patients at 225 mg QD[a]	Rash (n = 55)	No Rash (n = 25)	Total (N = 80)
Median age (range), years	54 (20-83)	56 (35-80)	54 (20-83)
Sex, female/male, n (%)	31 (56)/24 (44)	9 (36)/16 (64)	40 (50)/40 (50)
Race, n (%)			
White	38 (69)	19 (76)	57 (71)
Asian	11 (20)	3 (12)	14 (18)
Black/African American	2 (4)	1 (4)	3 (4)
Other	4 (7)	2 (8)	6 (7)
ECOG PS: 0/1, n (%)[b]	22 (40)/32 (58)	6 (24)/18 (72)	28 (35)/50 (63)
Prior ALK TKI treatment, n (%)			
ALK TKI naive	11 (20)	2 (8)	13 (16)
Prior ALK treatment	44 (80)	23 (92)	67 (84)
Prior chemotherapy treatment, n (%)			
Yes	48 (87)	22 (88)	70 (88)
No	7 (13)	3 (12)	10 (13)
Brain metastases, n (%)			
Target lesions only	7 (13)	1 (4)	8 (10)
Nontarget lesions only	15 (27)	4 (16)	19 (24)
Target and nontarget lesions	7 (13)	4 (16)	11 (14)
None	26 (47)	16 (64)	42 (53)
Median duration of ensartinib treatment, months (IQR)	8.3 (3.7-16.6)	3.6 (1.8-9.3)	6.8 (2.2-14.5)

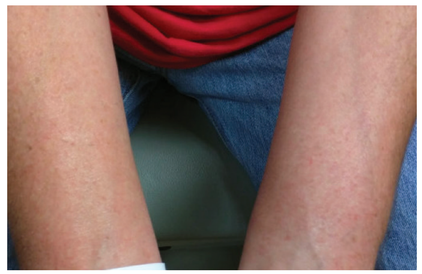
IQR, interquartile range.
[a]Information in the database as of February 7, 2019. ALK+ evaluable patients in this presentation include those receiving 225 mg QD who had a post-baseline response assessment.
[b]Baseline ECOG PS was not collected for 2 patients.

- Patient demographics by rash group are shown in **Table 1**
- The most common treatment-related AEs occurring in ≥ 10% of the population were mostly Grade 1/2 and included rash, nausea, pruritus, fatigue, and vomiting
- Rash was the most prominent AE
- Of the 130 patients treated in eXalt2, 80 *ALK*+ evaluable patients were treated at 225 mg QD. The incidence of rash in these 80 patients was 69%

Rash Clinical Features

- The type of rash was predominantly generalized rash, rash maculopapular, and rash erythematous (**Figure 2**)

Figure 2. Example of Ensartinib-Associated Rash

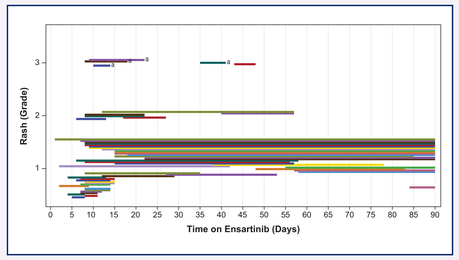


- 43-year-old man; never smoker; ALK FISH negative/NGS ALK EML4-ALK fusion (variant 5 a/b)
- Developed Grade 1 macular rash at 8 weeks; no dose modification required; treated with hydrocortisone; rash duration of 6.5 months
- PR in CNS and SD in lung; still on study in Cycle 28

FISH, fluorescence in situ hybridization; **NGS**, next-generation sequencing; **PR**, partial response; **SD**, stable disease.

- Of patients with rash (**Figure 3**), 73% presented with Grade ≤ 2 and 27% presented with Grade 3 rash. No Grade 4 rash was reported. Rash grading was determined mostly by total body surface area and not by severity
- Median time to initial onset of rash by patient: day 9 after first dose (IQR, 7-22 days; range, 1-226 days)
- Median rash duration: 21.5 days (IQR, 8-59 days; range, 2-389 days)
- 81% of rash cases were resolved at the time of data cut
- 10% of rash cases led to dose reduction (225 to 200 mg)
- Rash was treated predominantly with topical steroids, antihistamines, emollients, and occasionally topical or systemic antibiotics
- 2% of patients discontinued due to rash

Figure 3. Rash Onset and Duration by Grade



Each horizontal bar represents one patient with rash.
[a]Rash leading to dose reduction.

- Overall response rate (ORR) and median progression-free survival (mPFS) were better in ensartinib-treated patients with rash vs those without rash (**Table 2**)
- The evaluable population (n = 80) consisted of 13 patients (16%) who were ALK TKI naive, 37 patients (46%) who received prior crizotinib only, and 30 patients (38%) who received prior second-generation ALK TKI(s)

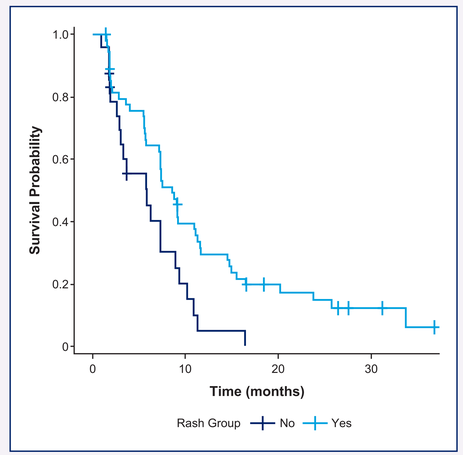
Table 2. Pooled Efficacy in 1L, 2L, and 3L+ Patients Treated with Ensartinib 225 mg QD

	ALK+ Evaluable Patients (n = 80)[a]	
	Rash (n = 55)	No Rash (n = 25)
ORR, n (%)	29 (52.7)	10 (40.0)
mPFS (95% CI), months	8.6 (5.8-11.3)	5.7 (2.9-7.3)
Log-rank *P* value	.0044	

CI, confidence interval.
[a]Evaluable patients in this study were *ALK*+, treated with ensartinib 225 mg QD, and had a postbaseline response assessment.

- A multivariate Cox proportional hazards model (**Figure 4**, **Table 3**) controlling for baseline factors revealed a correlation between rash and PFS (HR, 0.53; *P* = .0285)

Figure 4. Survival Probability in Patients with NSCLC Treated with Ensartinib 225 mg QD: with Rash and without Rash



- Baseline factors such as rash, age, sex, ethnicity, ECOG PS, prior ALK TKI, and presence of CNS metastases at baseline were considered for the model
- The final reduced model included rash group and prior ALK TKI through stepwise variable selection

Table 3. HR of PFS by Multivariate Cox Proportional Hazards Model

HR (95% CI)	0.53 (0.30-0.94)
***P* value**	.0285

HR, hazard ratio.

CONCLUSIONS

- Ensartinib has shown promising activity in patients with *ALK*+ NSCLC, including patients previously treated with ALK TKIs
- Ensartinib is well tolerated, with mild to moderate rash being the most common drug-related AE at 225 mg QD (recommended phase 2 dose)
- The ensartinib-related rash is clinically distinct from the typical EGFR TKI–related rash
- The rash was manageable with topical treatments; it was transient and required discontinuation in only 2% of patients
- Despite dose reduction in 10% of the patients, rash was potentially associated with better clinical benefit from ensartinib in a mixed population of *ALK*+ patients in first or greater lines of treatment

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