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Safety Of Selpercatinib For *RET*-altered Advanced Solid Tumors: A Post Hoc Analysis Of LIBRETTO-001

Todd M Bauer[1], Benjamin Besse[2], Herbert H F Loong[3], Bruce Robinson[4], Victoria Soldatenkova[5], Catherine Elizabeth Muehlenbein[5], Bente Frimodt-Moller[5], Caroline E McCoach[6]

[61]Sarah Cannon Research Institute-Tennessee Oncology, Nashville, USA, [2]Institut Gustave Roussy, Villejuif, France, [3]The Chinese University of Hong Kong, Hong Kong, China, [4]Royal North Shore Hospital, St. Leonards, NSW, Australia, [5]Eli Lilly and Company, Indianapolis, USA, University of California, [6]San Francisco-Helen Diller Family Comprehensive Cancer Center, San Francisco, USA

Background

- Selpercatinib is a first-in-class, highly selective, and potent RET inhibitor[1] approved in multiple countries for the treatment of *RET* altered lung or thyroid cancers
- *RET* protooncogene is generally activated by one of two mechanisms, *RET* fusions or mutations
- *RET* fusions are oncogenic drivers in 1 to 2% of non–small-cell lung cancers (NSCLC)[2] and 10-20% of papillary thyroid cancers[3]
- *RET* mutations occur in 70% of medullary thyroid cancers[4]
- Selpercatinib has demonstrated clinically meaningful and durable antitumor activity in patients with *RET* fusion-positive non-small cell lung cancer[1,5-7], including patients with brain metastases[6] and in patients with *RET*-altered thyroid cancers[7]
- Highly selective selpercatinib is associated with mainly low-grade toxic effects, dose reductions were relatively uncommon [6,7], and 5% of patients discontinued treatment due to an adverse event rate[8]

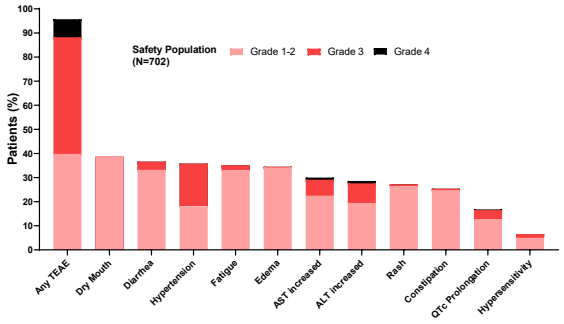
Objective: To further characterize the clinical safety profile of selpercatinib in the safety population of the LIBRETTO-001 study.

We conducted a *post hoc* safety analysis of 702 patients enrolled in LIBRETTO-001 to evaluate the safety of selpercatinib for *RET*-altered advanced solid tumors including:

- Frequency, grade and time to onset of selected all-cause, treatment-emergent adverse events (TEAEs) and associated dose adjustments in the safety population.
- Evaluation of frequency and grade of TEAEs and associated dose adjustments based on duration of treatment exposure (<12 and ≥12 months of treatment with selpercatinib)

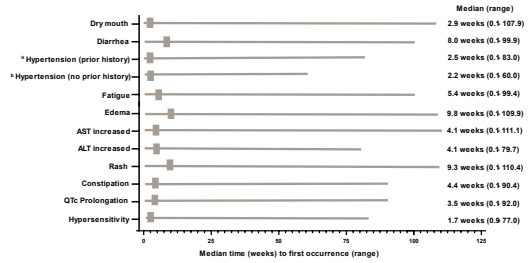
Select TEAEs by Decreasing Frequency (N=702)

- Most of the select TEAEs were low-grade
- Most common grade 3 or 4 adverse events were hypertension (18%), increase in AST (8%) and ALT (9%), QTc prolongation (4%) and diarrhea (3%) and typically were manageable with dose adjustments



Median Time (weeks) to First Occurrence of Select TEAEs by Decreasing Frequency

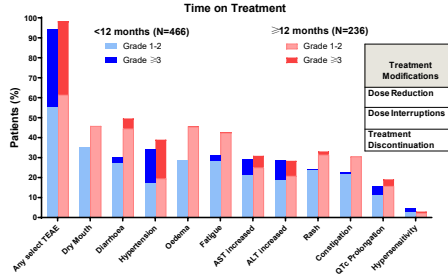
- The median times for first occurrence of select TEAEs were within 10 weeks of treatment initiation
- Median time to onset was the earliest for hypersensitivity (1.7 weeks) and the latest for rash (9.3 weeks)



Data are median (min/max range). Hypertension data was analysed based on patient's prior medical history before trial enrolment. [a] Patients had a prior history of hypertension (n=289), [b] patients had no prior history of hypertension (n=413)

Frequency of Select TEAEs in Patients on Selpercatinib Therapy <12 and ≥12 Months

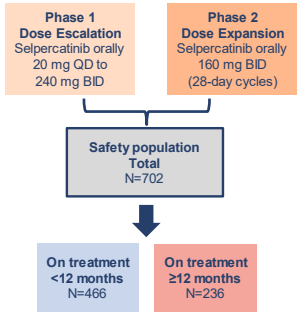
- Similar rates of grade ≥3 for select TEAEs were reported regardless of treatment duration (<12 or >12 months)
- More patients on the ≥12 months exposure group required dose adjustments due to TEAEs but treatment discontinuation rates were similar between both treatment exposure subgroups.



Treatment Modifications	<12 months N=466 n (%)	≥12 months N=236 n (%)
Dose Reduction	138 (29.6)	81 (34.3)
Dose Interruptions	259 (55.6)	153 (64.8)
Treatment Discontinuation	32 (6.9)	5 (2.1)

Study Design

The Phase 1/2 LIBRETTO-001 Trial: Selpercatinib in Patients with *RET*-altered Cancers



- The analyzed safety population in LIBRETTO-001 comprises all patients enrolled who received at least one dose and were followed up until the data cutoff (16-Dec-2019)
- Select TEAEs herein were based on frequency (≥25%) with the addition of two adverse events of clinical interest (hypersensitivity and QTc prolongation)[a]
- Median and ranges for time to onset were described[a]
- Safety analyses were also conducted on TEAEs clustered in two subgroups (<12 vs ≥12 months) based on the length of treatment exposure at the time of data cutoff (16-Dec-2019)

- An ongoing multicenter trial (NCT03157128) conducted in 12 countries and 65 sites.
- Key inclusion criteria: Age of ≥18 years or ≥12 years if permitted by regulatory authorities, diagnosis of advanced or metastatic solid tumor, ECOG PS 0 to 2, QTc of ≤470 msec, and adequate organ function. Treatment beyond progression permitted with continued benefit

[a] Calculated from safety population dataset

Clinicaltrials.gov: NCT03157128

Baseline Characteristics

Characteristic N (%) unless otherwise stated	Safety Population (N=702)
Age, median (range), years	59 (15-92)
Sex	
Female	334 (47.6)
Male	368 (52.4)
Race	
White	485 (69.1)
Black	24 (3.4)
Asian	154 (21.9)
Other	4 (0.4)
ECOG performance status	
0	256 (36.5)
1	431 (58.8)
2	33 (4.7)
Stage	
I	5 (0.7)
II	12 (1.7)
III	27 (3.8)
IV	647 (92.2)
Missing	11 (1.6)
Received prior systemic therapy	
Yes	525 (74.8)
No	177 (25.2)
Cancer Indication	
RET fusion+ NSCLC	329 (46.9)
RET-mutant MTC	299 (42.6)
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RET alteration	
Fusion	387 (55.1)
Mutation	307 (43.7)
Other/missing	8 (1.2)

Summary of Select TEAEs Leading to Treatment Modification

Select TEAEs by Decreasing Frequency (N=702)

TEAE (Consolidated Terms)	Any Grade TEAE n (%)	Grade ≥3 TEAE n (%)	Leading to Dose Reduction n (%)	Leading to Drug Interruption n (%)	Leading to Drug Discontinuation n (%)
Any event	694 (98.8)	415 (59.1)	219 (31.2)	294 (41.9)	37 (5.3)
Dry Mouth	273 (38.9)	0 (0.0)	5 (0.7)	2 (0.3)	0 (0.0)
Diarrhea	257 (36.6)	24 (3.4)	11 (1.6)	18 (2.6)	0 (0.0)
Hypertension	252 (35.9)	120 (17.1)	9 (1.3)	33 (4.6)	0 (0.0)
***History of hypertension**	114 (39.4)	70 (24.2)	5 (1.7)	17 (5.9)	0 (0.0)
***No history of hypertension**	138 (33.4)	55 (13.3)	4 (1.0)	16 (1.7)	0 (0.0)
Fatigue	246 (35.0)	14 (2.0)	18 (2.6)	19 (2.7)	2 (0.3)
Edema	242 (34.5)	2 (0.3)	7 (1.0)	7 (1.0)	0 (0.0)
AST increased	210 (29.9)	52 (7.4)	39 (5.6)	34 (4.8)	2 (0.3)
ALT increased	201 (28.6)	64 (9.1)	45 (6.4)	36 (5.1)	3 (0.4)
Rash	191 (27.2)	5 (0.7)	15 (2.1)	14 (2.0)	1 (0.1)
Constipation	178 (25.4)	4 (0.6)	2 (0.3)	2 (0.3)	0 (0.0)
QTc Prolongation	118 (16.8)	28 (4.0)	16 (2.3)	15 (2.1)	0 (0.0)
Hypersensitivity	30 (4.3)	11 (1.6)	20 (2.8)	6 (0.9)	3 (0.4)

N, total number of patients in the population; n, number of patients; TEAE, treatment-emergent adverse event. AST, aspartate transaminase; ALT, alanine aminotransferase. No grade 5 events were documented for TEAEs in table. *Patients with hypertension were separated by prior history and percentages were calculated from each subpopulation total; prior history of hypertension (n=289), no prior history of hypertension (n=413).

Summary and Conclusion

In this *post-hoc* analysis of the safety population of LIBRETTO-001 (N=702):

- Most TEAEs were low grade
- Select adverse events emerged early on during treatment (median onset within 10 weeks of treatment initiation) and were manageable with dose adjustments
- TEAEs were associated with low rates of discontinuation
- The safety profile in the two exposure subgroups were consistent with previous reports[6,7] and no new safety signals were identified

References [1]Subbiah V, Velcheti V, Tuch BB et al: Selective RET kinase inhibition for patients with RET-altered cancers. Ann Oncol 2018.
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[4]Cancer Genome Atlas Research Network. Integrated genomic characterization of papillary thyroid carcinoma. Cell 2014.
[5]Markham A, Selpercatinib: First Approval, Springer Nature Switzerland AG 2020.
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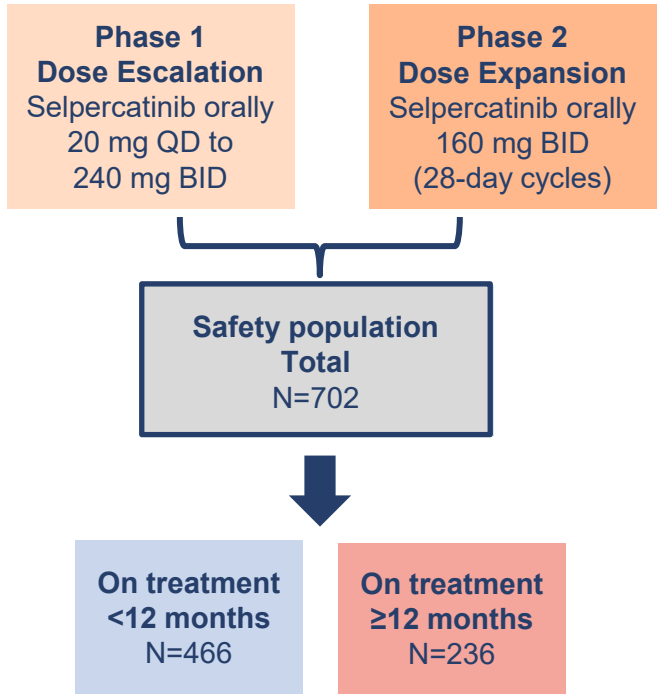

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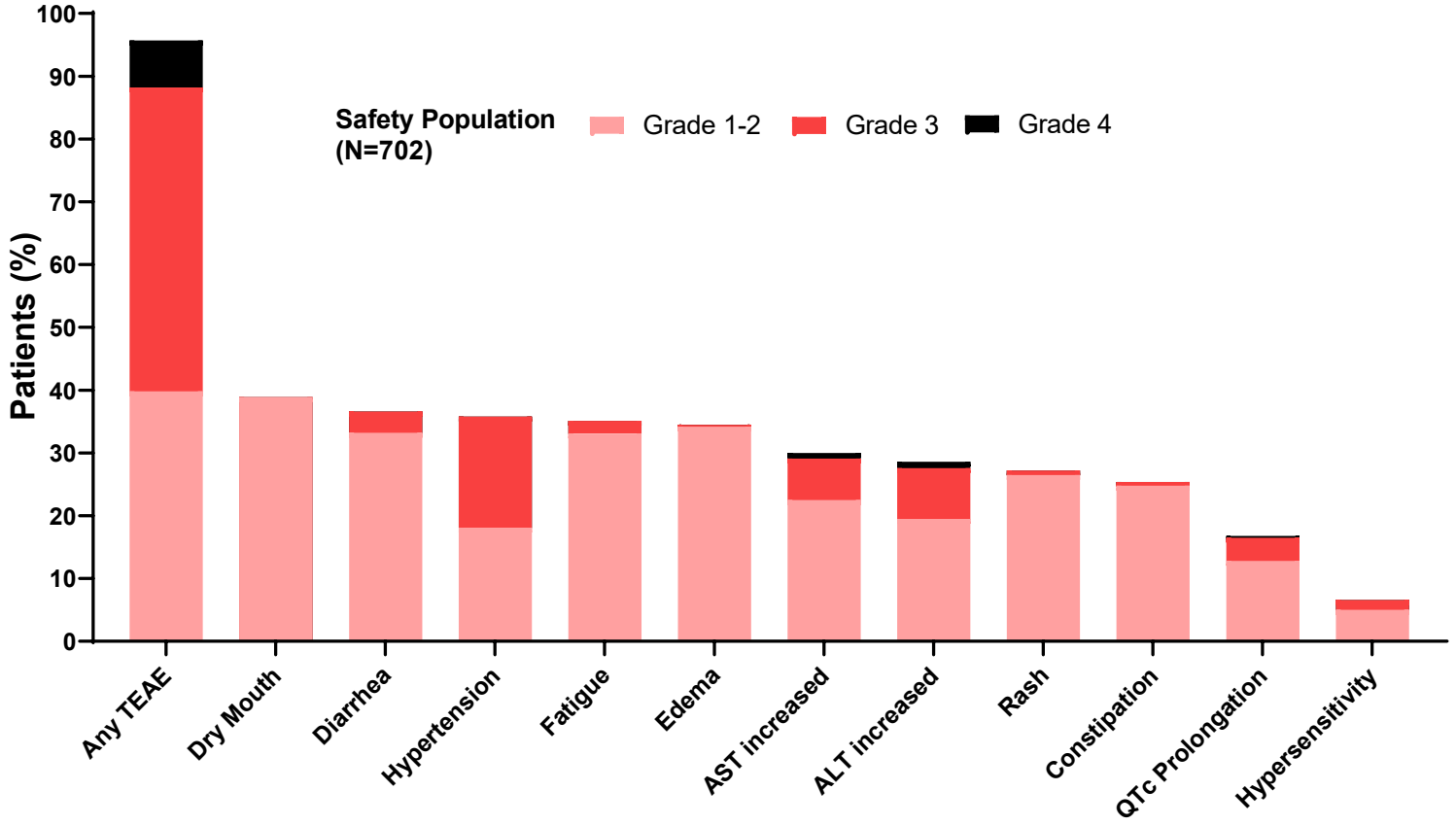

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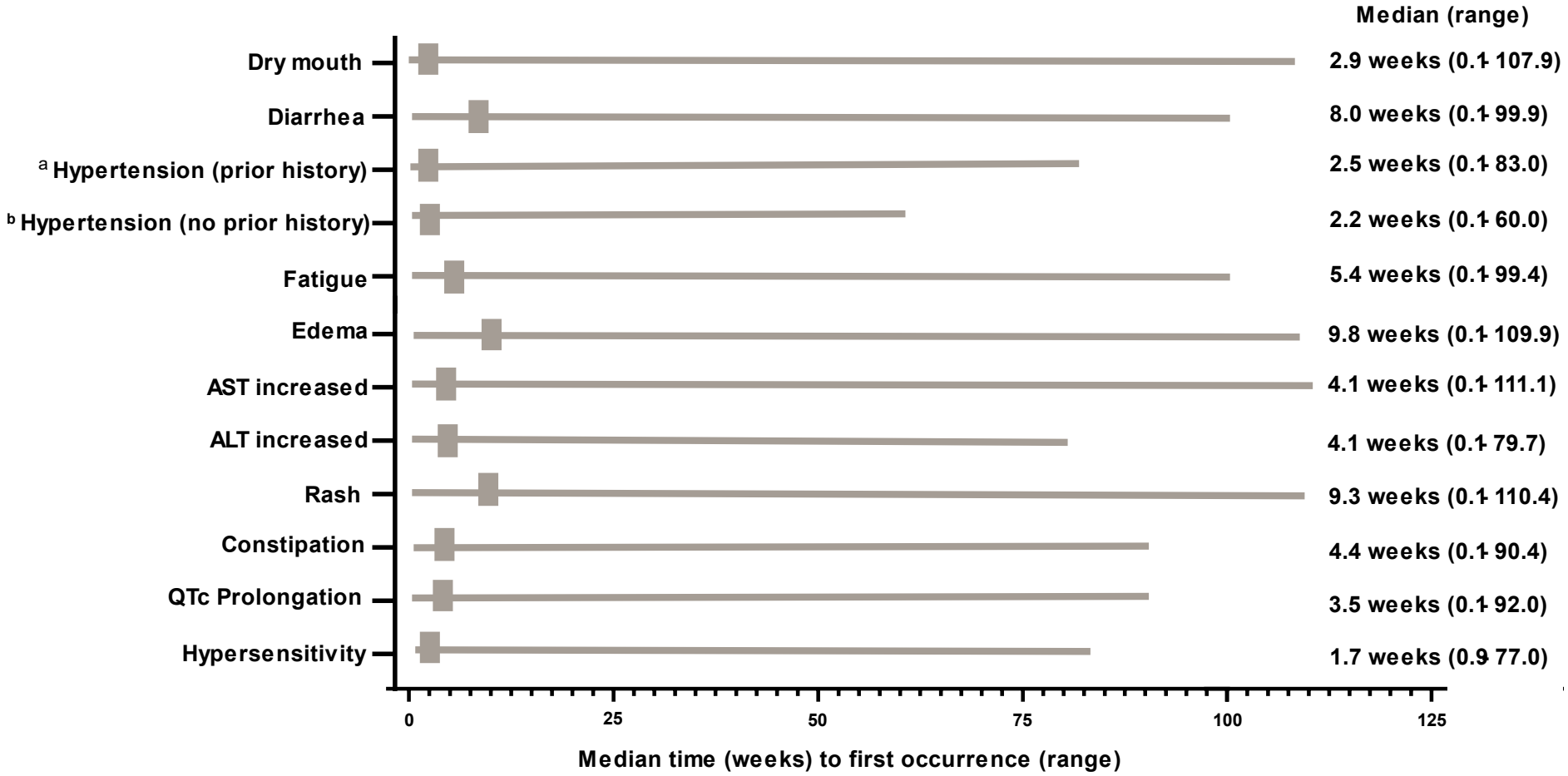

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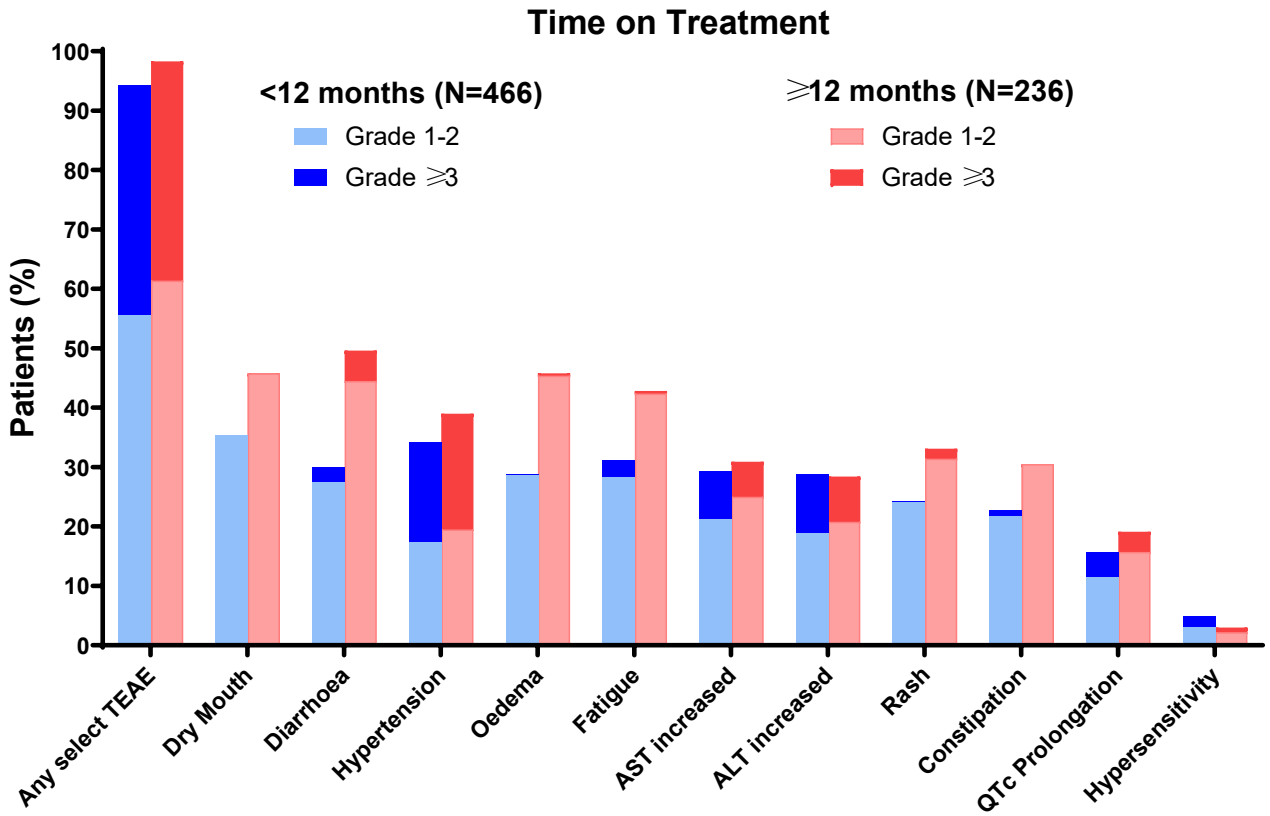

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