Novel data visualization and unsupervised machine learning techniques to support optimal management of toxicity profiles of encorafenib plus cetuximab in patients with BRAF^{V600E} mutant metastatic colorectal cancer

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Background

Encorafenib, in combination with cetuximab (EC), is approved in US, Europe and Japan for the treatment of BRAF^{V600E} mutant mCRC after prior systemic therapy based on results of the BEACON CRC study (NCT02928224) [1, 2]. Treatment with encorafenib + cetuximab versus control resulted in improved outcomes, including overall survival (OS): median (95% confidence interval [CI]) 9.3 (8.0–11.3) months vs 5.9 (5.1–7.1) months, respectively, and a well-tolerated safety profile. [3, 4, 5]

The detailed toxicity profile of EC has been previously published and indicated that the combination is generally well tolerated in most patients with most AEI's being well tolerated in most patients and being mild-to-moderate in severity, occurring early and resolving rapidly. [6]

As the combination is the first BRAF inhibitor-based regimen approved for BRAF^{V600E} mCRC, the goal of this analysis was to explore novel and distinctive data visualization outputs to enable a potentially more practical interpretation and prediction of the safety profile of encorafenib + cetuximab and thus better management of adverse events.

Methods

Analysis were conducted on 216 patients included in the BEACON study and treated with EC.

Adverse Events (AE) of Interest (AEIs), were defined as uncommon/unique AEs or commonly occurring AEs with this combination, including dermatological AEs, arthralgia/myalgia, nausea/vomiting, diarrhea, abdominal pain, fatigue/asthenia and nephrotoxicity, as detailed in the phase 3 Beacon study [6].

AEs were grouped according to Medical Dictionary for Regulatory Activities (MedDRA)-derived terms (detailed in ref 6).

The presence of AEI, time to AEI onset and time to AEI resolution were investigated and their association with clinical characteristics (age, gender) were explored. Time to onset for an AE was defined as time from the first dose of treatment received to the first occurrence of that AE. Time to resolution was defined as the time between the start and end of the AE.

Analysis and visualization included stacked bars, multistate models' visualization, bubble timeline analysis, boxplots, heatmap graphs. An unsupervised machine learning model (Gaussian Mixture model) was used to find groups of similar AEIs based on both the onset time and the recovery time. The number of groups (k=5) was empirically determined, for minimal values of the silhouette score and of the BIC score (Bayesian Information Criterion).

Conclusion

These approaches allow a more nuanced perspective and approach to understanding AEI patterns, including linking disparate AE's.

These types of visualization can help health care givers to better predict EC side effects which is generally well tolerated in most patients, with most AEIs being mild to moderate in severity.

Visual aids are a new method to support oncologists and health care providers in daily clinical practice to help manage patients receiving EC and may improve the patient experience.

Data sources

The BEACON study (ClinicalTrials.gov: NCT02928224; EudraCT: 2015-005805-35) was a multicenter, randomized, open-label, phase 3 study in patients with BRAF ^{V600E} mut mCRC who had progressed after one or two previous regimens. The BEACON study was carried out in accordance with the Declaration of Helsinki. Ethics approval was obtained by the institutional review board or independent ethics committees at the appropriate centers. Written informed consent was provided by all patients.

References

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4) Tabernero J, Grothey A, Van Cutsem E, et al. Encorafenib plus cetuximab as a new standard of care for previously treated BRAF V600E-mutant metastatic colorectal cancer: updated survival results and subgroup analyses from the BEACON study. J Clin Oncol . 2021;39:273–284. doi: 10.1200/JCO.20.02088

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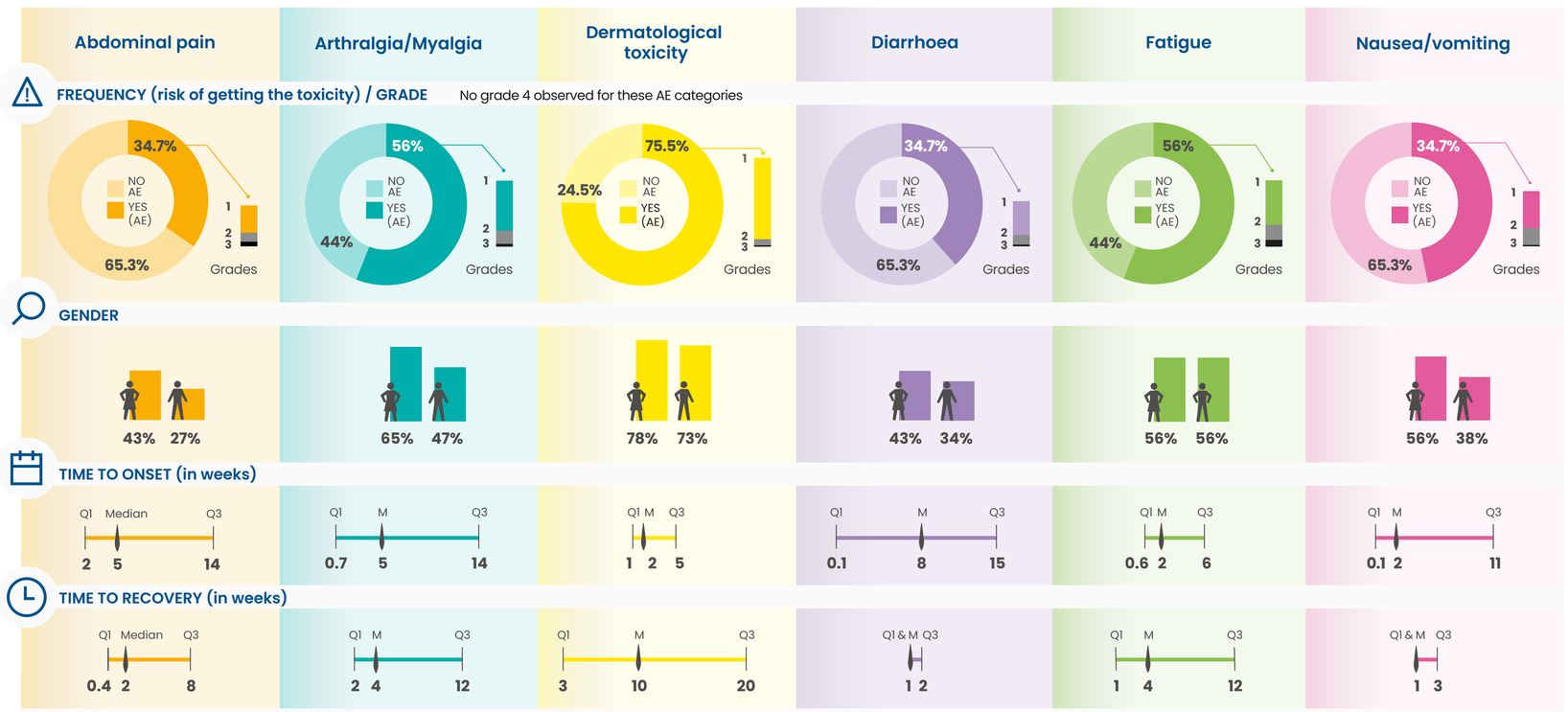
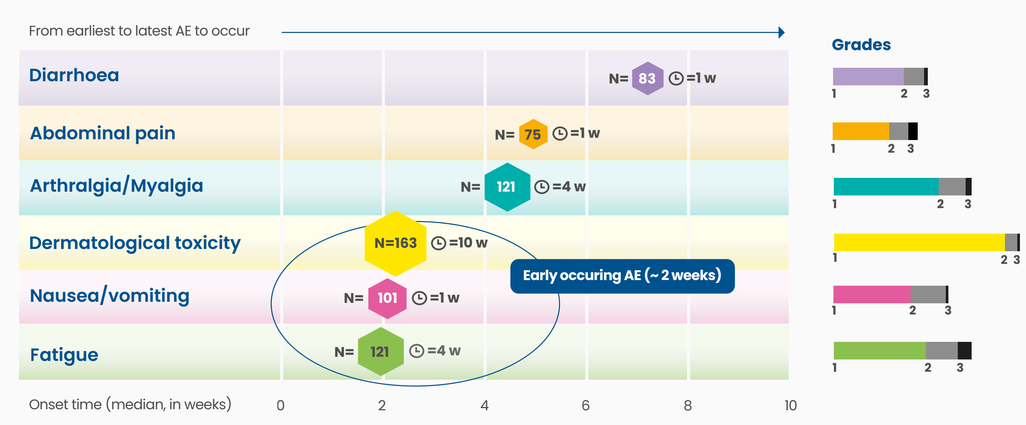
Results

Fig 1. Overview of the probability of having an AEI following treatment initiation with encorafenib + cetuximab



Q1 (quartile 1): 25% of the patients experienced the AE in less than XX weeks / Q3: 25% of the patients experienced the AE in more than XX weeks.

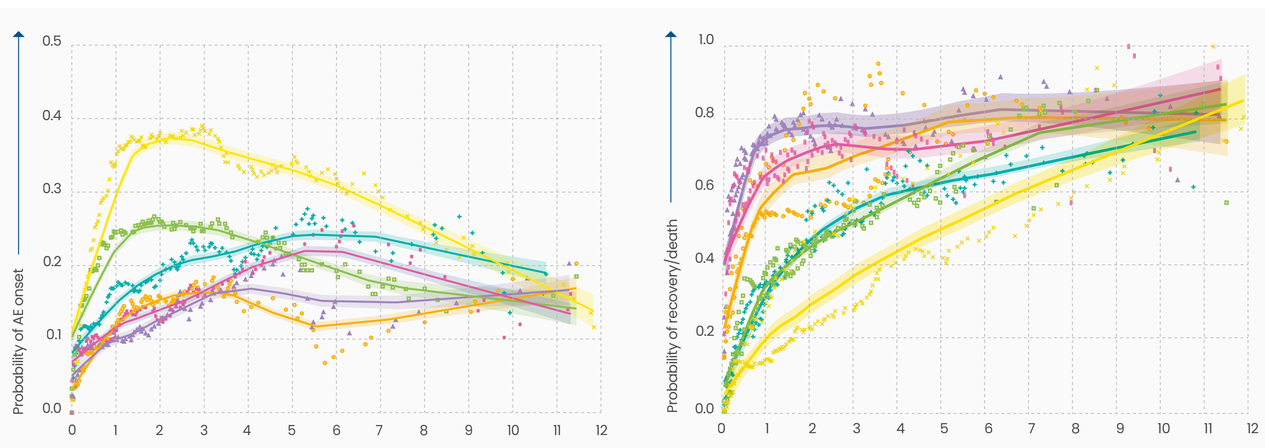
Fig 2. Vizualisation of AEI time to onset with bubble timeline analysis



Representation with a bubble timeline analysis provides visual advantages to ease interpretation, within the same graph:

- the frequency of AEIs occurrence (size of the bubble representing the number of patients who experienced the AE (N)),
- grades of AEIs (color),
- time to onset (y-axe),
- and time to resolution (), depending on each AEI category (y-axe).

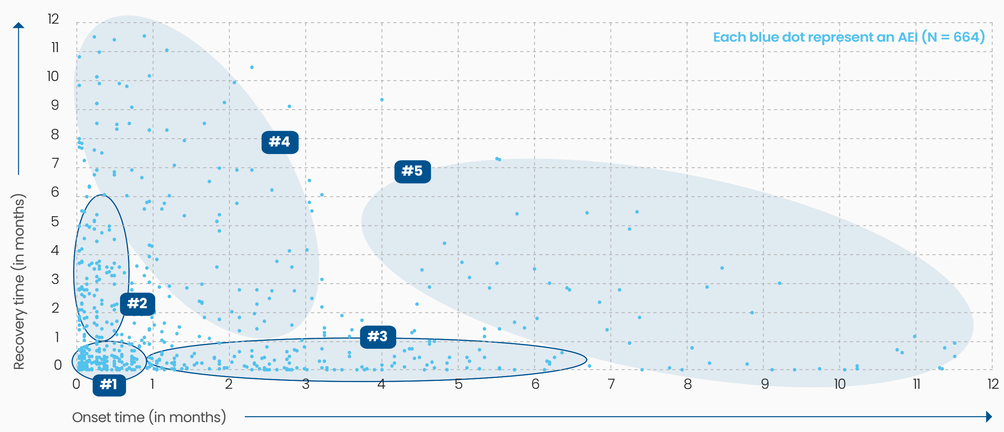
Fig 3. Visualization of the evolution of probability of onset and probability of recovery for each AEI groups since the inclusion with multistate models



Provides a visualization of the evolution of probability of onset and probability of recovery for each AEI group since the inclusion.

- Abdominal pain
- Diarrhoea
- Arthralgia/Myalgia
- Fatigue
- Dermatological toxicity
- Nausea/vomiting

Fig 4. Identification of typical patients' clusters with unsupervised machine learning



Most AEs occur within 2 months (clusters n°1, 2) and recover within 2 months (clusters n°1, 3).

	Proportion of AEs in the cluster	Gender (% of female)	Age (median, +/-std)
Cluster #1	23%	51%	60 (+/-12)
Cluster #2	23%	47%	62 (+/-11)
Cluster #3	24%	51%	61 (+/-11)
Cluster #4	17%	57%	60 (+/-13)
Cluster #5	12%	55%	61 (+/-12)

Provides a quick overview of the typical safety profiles.