POSTMARKETING STRATEGIES AND APPROACHES

REGULATORY PERSPECTIVE

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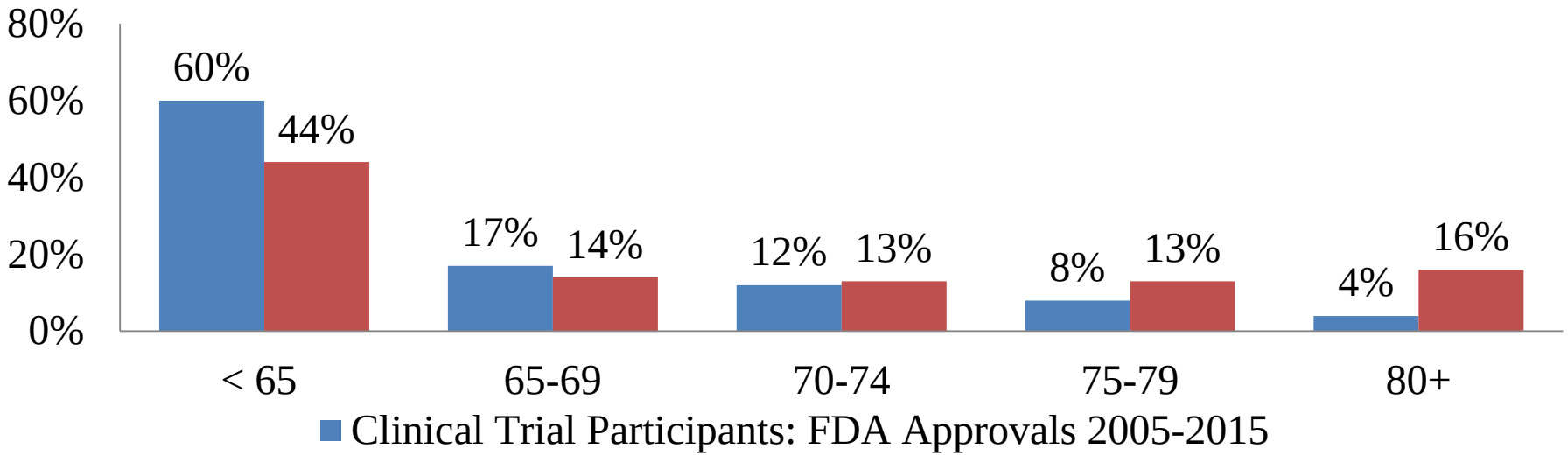
IMPROVING THE EVIDENCE BASE FOR TREATMENT DECISION-MAKING FOR OLDER ADULTS WITH CANCER

FDA Analysis of Cancer Patients Enrolled on Clinical Trials Supporting FDA Approval Compared with SEER



Disparity is Greatest for Patients Age ≥ 75

FDA Guidance & Publications

Year	Guidance
1997	Guidance for the Study of Drugs Likely to Be Used in the Elderly (FDA)
2012	Guidance for Industry: E7 Studies in Support of Special Populations (FDA)
2016	Evaluation and Reporting of Age, Race, and Ethnicity Data in Medical Device Clinical Studies (FDA)
2016	Enrollment of Older Adults on Oncology Trials: an FDA Perspective [1]
2017	Reevaluating Eligibility Criteria – Balancing Patient Protection and Participation in Oncology Trials[2]
2018	Expanding the Evidence Base in Geriatric Oncology: Action Items From an FDA-ASCO Workshop[3]
2019	Enhancing the Diversity of Clinical Trial Populations — Eligibility Criteria, Enrollment Practices, and Trial Designs (FDA)
2020	Cancer Clinical Trial Eligibility Criteria: Patients with Organ Dysfunction or Prior or Concurrent Malignancies (FDA)
2020	Older adults in hematologic malignancy trials: Representation, barriers to participation and strategies for addressing underrepresentation[4]

[1]Singh et al J Geriatr Oncol.2017, [2] Beaver et al. NEJM 2017, [3] Levit et al JNCI 2018 [4] Kanapuru et al Blood Reviews. 2020

Inclusion of Older Adults in Cancer Clinical Trials Guidance for Industry

C. Postmarket

- Ideally, adequate information on older adults should be captured in the premarket clinical trials. However, if older adults are not adequately represented in pre-market clinical trials, it may be appropriate to develop a plan to collect data on older adults in the postmarket setting. This could be accomplished with post-marketing trials examining a broader population, or through collection of real world data in an observational study or registry. In certain situations, FDA may require postmarket studies and clinical trials.[15] Sponsors should prospectively discuss their plan for collecting additional information in the postmarket setting with the CDER or CBER review division or office. Postmarket data may provide clinically useful information, that when appropriate, can be added to the geriatric use section of the labeling.

Inclusion of Older Adults in Cancer Clinical Trials Guidance for Industryhttps://www.fda.gov/media/135804/download

Addressing the Issue

- Encourage sponsors to conduct inclusive and representative trials early in development
- Demographic information on age subgroups evaluated during the review
- If it is not obtained prior to initial approval of a therapeutic, this information can be obtained in the post-marketing setting.

Postmarketing requirement (PMR) if there is a specific safety issue (including lack of efficacy) or, Postmarketing Commitments (PMC) to understand the safety and efficacy in a representative U.S patient population

Considerations for requiring Postmarketing data

Postmarketing Requirements

Under Section 505(o)(3) of the Food Drug and Cosmetics (FD&C) Act for

- Serious risk or signals of serious risk
- Identify an unexpected serious risk if there is a potential for serious risk

FDA can require postmarketing studies and clinical trials for the above purposes

Example

Evaluate a new signal that a subgroup of patients (e.g., defined by age, sex, race, biomarker) with a life-threatening cancer may not respond to a drug that had been approved based on a clinically meaningful effect in the overall population with the cancer, such that certain patients may be exposed to toxicity with less prospect for benefit

Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act Guidance for Industry https://www.fda.gov/media/131980/download

Considerations for Postmarketing Commitments

- Postmarketing Commitments

- No serious safety signal or potential reduced effectiveness but there is a lack of data on a particular under-represented group
- To understand the safety and efficacy in a representative U.S patient population

Agreed -upon postmarketing studies and clinical trials:
• 21 CFR 312.85

Data and Design Considerations

- Clinical Trials

- Considerations to enrich planned or ongoing (with no/blinded data looks) at the time of the NDA or BLA submission for the subgroup(s) of interest to obtain post-marketing data
- An open-label safety study can enroll and analyze an older adult population separately in a parallel arm of a trial. In some cases, the older adult arm(s) can be actively accruing at the time of NDA or BLA submission

- Post marketing Studies

- Observational pharmacoepidemiologic studies- Administrative health care claims data, electronic medical records[1], registries, prospectively collected observational data, or other sources of observational information.

- Meta-analysis[2]

Recommend early interaction with the Agency regarding need for post marketing data and design

1 Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data
2 Meta-Analyses of Randomized Controlled Clinical Trials to Evaluate the Safety of Human Drugs or Biological Products (November 2018) Guidance for Industry

Belantamab Mafodotin

- Efficacy:
  - ORR 31% (95% CI: 20.8, 42.6)
- Safety:
  - Ocular Toxicity, Boxed Warning, REMS with ETASU

	2.5 mg/kg (N=95)		3.4 mg/kg (N=99)	
	n	%	n	%
Keratopathy~	67	71	77	76
Thrombocytopenia*^	33	35	58	59
Anemia*	23	24	37	37
Nausea	23	24	32	32
Pyrexia	21	22	25	25
Vision blurred^	21	22	30	30
Infusion related reaction	20	21	16	16
Fatigue*	19	20	34	34
Dry Eye^	13	14	21	21
AST increased*^	19	20	24	24
Lymphopenia*^	19	20	17	17
Upper Respiratory tract infection^	10	11	25	25
Neutropenia*^	13	14	26	26
Vomiting	7	7	20	20

Source: FDA Analysis (Treatment emergent adverse events≥20% of Patients in either dose) data cut-off June 21,2019;
^ FDA Grouped preferred terms; ~ Based on ocular exams and study specific Keratopathy Visual Acuity (KVA) scale
**Rates based on laboratory dataset (2.5mg/kg,3.4 mg/kg): Platelets decreased:62%,74%; hemoglobin decreased:32%,44%; AST increased:57%,69%;neutrophils decreased:28%,46%; lymphocytes decreased:49%,46%*

Belantamab Mafodotin

Demographics DREAMM-2

Age	2.5 mg/kg N=97 N (%)
Median (range), years	65 (39-85)
Age Subgroup	
<65 years	45 (46)
65-74 years	39 (40)
≥75 years	13 (13)

Keratopathy Rates by Age Subgroup

Adverse Event Age Subgroup	2.5 mg/kg (N=95), n (%)*
Keratopathy† (all ages)	67 (71)
18 to <65 years	29 (67)
65 to <75 years	31 (79)
75 years and above	7 (54)
Change in BCVA† (all ages)	50 (53)
18 to <65 years	20 (47)
65 to <75 years	23 (59)
75 years and above	7 (54)
Vision blurred• (all ages)	21 (22)
18 to <65 years	8 (19)
65 to <75 years	11 (28)
75 years and above	2 (15)
Dry eye• (all ages)	13 (14)
18 to <65 years	6 (14)
65 to <75 years	4 (10)
75 years and above	3 (23)

- ORR 8% (1/13) in patients ≥75 years
- Higher rates of keratopathy and visual acuity changes in patients ≥65 years

Belanatamab mafodotin Post Marketing Requirement

Accelerated Approval PMR

Submit the final study report and datasets from a randomized phase 3 clinical trial that verifies and describes the clinical benefit of belantamab mafodotin in patients with relapsed or refractory multiple myeloma. Patients should be randomized to receive belantamab mafodotin compared to standard therapy for relapsed or refractory multiple myeloma. The primary endpoint should be progression-free survival and secondary endpoints that include overall survival and overall response rate, as well as patient-reported outcomes. **This trial should include a sufficient number of older patients (ages 65-74 and ≥75)** and patients with extramedullary disease.

Belanatamab mafodotin Post Marketing Commitment

Submit an interim and a final integrated report containing data from clinical trials and other data sources such as, expanded access treatment protocols, post marketing reports and real world data, to further characterize the ocular toxicity, including keratopathy, changes in visual acuity, and other ocular symptoms, with belantamab mafodotin in older age subgroups of patients, age 65-74 years and ≥75 years, with relapsed or refractory multiple myeloma, compared to patients <65 years to provide longer-term data to further characterize the benefit-risk profile in older age subgroups. The results from this study may inform product labeling.

Summary

- Sponsors should make every effort to conduct inclusive and representative trials
- FDA will evaluate demographic information on age subgroups during the review of marketing applications
- A PMR or PMC may be issued to understand the safety and efficacy in a representative U.S patient population
- Discussion for a post marketing trial or data collection in the appropriate population should be discussed at the pre-NDA or BLA meeting
- Post market data may provide clinically useful information, that when appropriate, can be added to drug labeling.

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