Regional Matters on the Road to Global Approvals

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I am an employee of F. Hoffmann La-Roche Ltd

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Regional Matters on the Road to Global Approvals

- **From ICH E5** «Ethnic Factors in the acceptability of Foreign data» to
  ICH E17 «General principals for planning and design of multi regional clinical trial»
- **Inclusive research** takes a closer look at ethnic factors
- **Avastin plus Tarceva in NSCLC - Case Study**
- **Further avenues and future state**
- **Conclusion**

ICH Framework and beyond

Tripatriate guideline **ICH E5** from **1998** provides sound and robust framework to assess ethnic factors

- Wants to avoid dublication of clinical data
- Aims for one bridging study

Q&A for **ICH E5, 2006** reflects ICH membership expansion

- Emphasizes that each region can still have individual requests if there is a rational
- Introduces the concept of MRCTs

ICH 17 on multi-regional clinical trials (MRCTs) issued **2017** wants to enhance global relevance of MRCT protocols

Inclusive research shines increasingly brighter light on ethnic factors

- Socioeconomic factors and differences in disease biology contribute to a specific outcome (ASH 2020 Paper on "Young African American patients with poor outcome in AML" Cancer Discov. 2020 Dec 4;CD-20-1579. doi: 10.1158/2159-8290.CD-20-1579.).
- Clinical tools for decision making use racial factors influencing access to treatments (Hidden in plain sight – Reconsidering the use of race correction in clinical algorithms, N Engl J Med 2020; 383:874-882; DOI: 10.1056/NEJMms2004740).
- Population changes over time in specific regions (Impact of US population demographic changes on projected incident cancer cases from 2019 to 2045, J Clin Oncol 38: 2020 (suppl; abstr e19044).

Avastin & Tarceva Case study 1/3

Global Regulatory Approvals in NSCLC based on pivotal data from Japanese study

Study JO25567: Erlotinib alone or with bevacizumab as first-line therapy in patients with advanced non-squamous NSCLC harbouring EGFR mutations: an open-label, randomised, multicentre, phase 2 study with Japanese patients

- Clinically meaningful PFS
- Extension of Indication EMEA/H/C/000582/II/0086

Many Regulatory approvals «from Argentina, Brazil, Canada to Zimbawe»

- Regulatory feedback was sought on proposed data package prior to submission
- Proposed package met expectations of most, but not all agencies

Case study 2/3 EPAR extracts on extrapolation

EU-SMPC 4.1 Bevacizumab, in combination with erlotinib, is indicated for first-line treatment of adult patients with unresectable advanced, metastatic or recurrent non-squamous non-small cell lung cancer with Epidermal Growth Factor Receptor (EGFR) activating mutations (see Section 5.1).

Based on the data submitted, it is expected that the effect of Erl+Bv observed in the Japanese population in study JO25567 could be extrapolated to an European population. The Population PK model for Erlotinib indicates no clinical significant relationship between predicted apparent clearance and ethnicity

There is robust scientific evidence to support the claim that **EGFR activating mutations (exon 19 deletions and L858R) in tumours of Asian and Caucasian NSCLC patients are sufficiently similar** to justify extrapolation of the results from the Japanese study JO25567 to Caucasians. **The effect of bevacizumab in different ethnic groups** has been investigated in several clinical trials. So far there has not been any indication of a treatment difference depending on ethnicity. **Erlotnib studies OPTIMAL, EURTAC and ENSURE have previously demonstrated that the EGFR mutations is the main driver** of treatment effect, thus, allowing an extrapolation between Japanese (Asians) and Caucasian patients.

Case study 3/3 ***What helped***

- Pro-active discussion of ICH E5 topics in pre-submission meetings and in the dossier
- Various supportive studies included in the dossier
- Robust population PK model

- Effect on PFS was considered clinically meaningful
- Mature OS data available post approval
- Avastin and Tarceva have been globally approved and have well described safety profiles

Further Avenues to facilitate global approvals

Local guidelines supplement ICH framework

October 2020 , China CDE issues local guidance on «Drugs marketed overseas but not marketed in China”

- References ICH E5 and ICH E17
- Defines criteria where local data is needed

Globally orchestrated reviews

- Confidentiality agreements among regulatory agencies facilitate e.g. exchange of assessment reports
- Project like Orbis provides framework for parallel review
- ASSC ^{plus} goes further and allows for a shared review among definied health authorities

Future State

- **Study designs keep evolving -** from classical MRCTs to decentralized MRCTs and to platform trials generating registrational data using digital tools and RWD comparator arms

- **Vision for integrating cloud enabling practices in drug regulation** is pursued by many Industry- and multi stakeholder collaborations and may further facilitate global approvals
(Ref. Nature Reviews Drug Discovery ISSN1474-1784 , Accumulus Synergy Inc website as current example)

Conclusion

Regional matters should not delay global approvals

Pre-requisit

- GCP data
- ICH framework addressed in dossier
- Ethnic factors defined under ICH E5 should be scrutinized against concept of inclusive research

Ambition

- Carefully designed clinical development programs allow the risk benefit assessment of innovative oncology treatments globally without delay
- Globally orchestrated submissions and reviews to be further enhanced by new technology

Back- up slides

Table 1 extracted from "Hidden in Plain Sight" — Reconsidering the Use of Race Correction in Clinical Algorithms" Darshali A. Vyas, M.D.,Leo G. Eisenstein, M.D.,and David S. Jones, M.D., Ph.D. August 27, 2020 N Engl J Med 2020; 383:874-882 DOI: 10.1056/NEJMms2004740.

Table 1. Examples of Race Correction in Clinical Medicine.*

Tool and Clinical Utility	Input Variables	Use of Race	Equity Concern
Oncology			
Rectal Cancer Survival Calculator[18] (http://www3.mdanderson.org/app/medcalc/index.cfm?pagename=rectumcancer) *Estimates conditional survival 1–5 yr after diagnosis with rectal cancer*	Age and sex Race: white, black, other Grade Stage Surgical history	White patients are assigned a regression coefficient of 1, with higher coefficients (depending on stage) assigned to black patients (1.18–1.72).	The calculator predicts that black patients will have shorter cancer-specific survival from rectal cancer than white patients. Clinicians might be more or less likely to offer interventions to patients with lower predicted survival rates.
National Cancer Institute Breast Cancer Risk Assessment Tool (https://bcrisktool.cancer.gov/calculator.html) *Estimates 5-yr and lifetime risk of developing breast cancer, for women without prior history of breast cancer, DCIS, or LCIS.*	Current age, age at menarche, and age at first live birth First-degree relatives with breast cancer Prior benign biopsies, atypical biopsies Race/ethnicity: white, African American, Hispanic/Latina, Asian American, American Indian/Alaska Native, unknown	The calculator returns lower risk estimates for women who are African American, Hispanic/Latina, or Asian American (e.g., Chinese).	Though the model is intended to help conceptualize risk and guide screening decisions, it may inappropriately discourage more aggressive screening among some groups of nonwhite women.
Breast Cancer Surveillance Consortium Risk Calculator[19] (https://tools.bcsc-scc.org/BC5yearRisk/calculator.htm) *Estimates 5- and 10-yr risk of developing breast cancer in women with no previous diagnosis of breast cancer, DCIS, prior breast augmentation, or prior mastectomy*	Age Race/ethnicity: white, black, Asian, Native American, other/multiple races, unknown BIRADS breast density score First-degree relative with breast cancer Pathology results from prior biopsies	The coefficients rank the race/ethnicity categories in the following descending order of risk: white, American Indian, black, Hispanic, Asian.	Returns lower risk estimates for all nonwhite race/ethnicity categories, potentially reducing the likelihood of close surveillance in these patients.