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Module 2

Pre-considerations of regional variability when recruiting diverse populations in global drug development

ICH E17: General principles for planning and design of Multi-Regional Clinical Trials

International Council for Harmonisation of Technical Requirements
for Pharmaceuticals for Human Use

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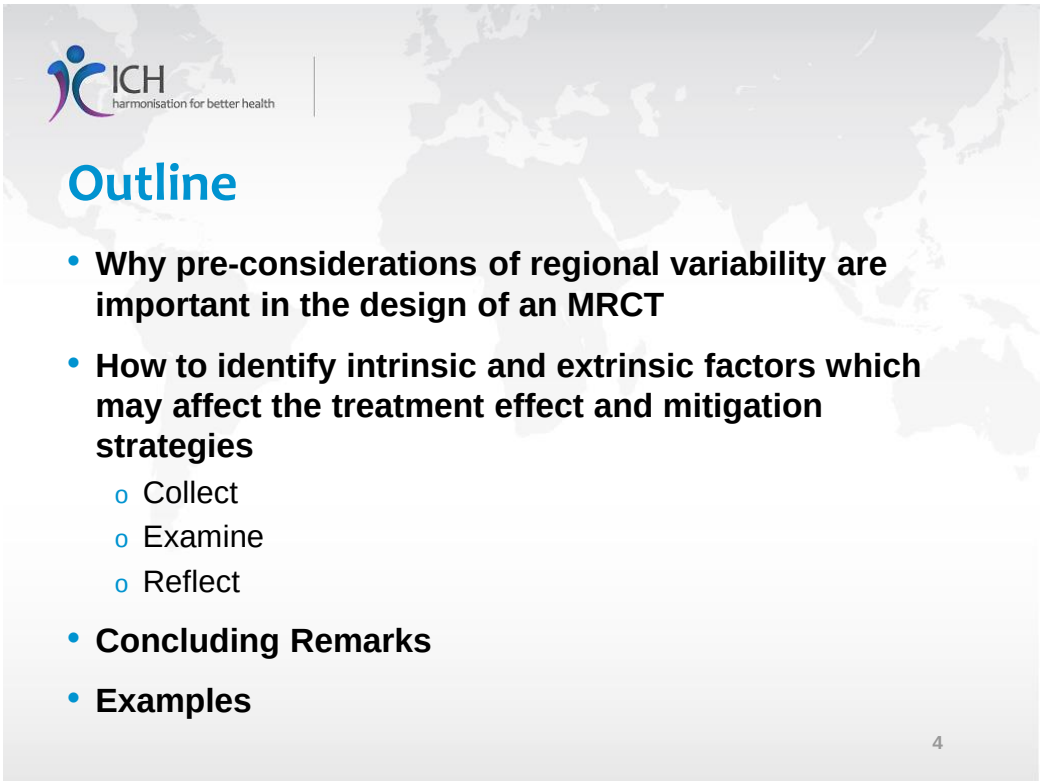
Module 2: Introduction and objectives

- **Pre-consideration of regional variability and its mitigation could affect various design perspectives.**
- **Module 2 focuses on how to ensure that the population targeted in the MRCT is relevant to all regions to support a marketing authorisation.**
  - In particular, how to identify intrinsic and extrinsic factors which may affect the treatment effect.
  - Pre-considerations of regional variability in relation to other design factors (e.g., definition of endpoints, analysis planning, use of concomitant medications) are described in the E17 guideline.



At the planning stage of an MRCT, regional variability, the extent to which it can be explained by intrinsic and extrinsic factors, and its potential to influence the study results should be carefully considered.

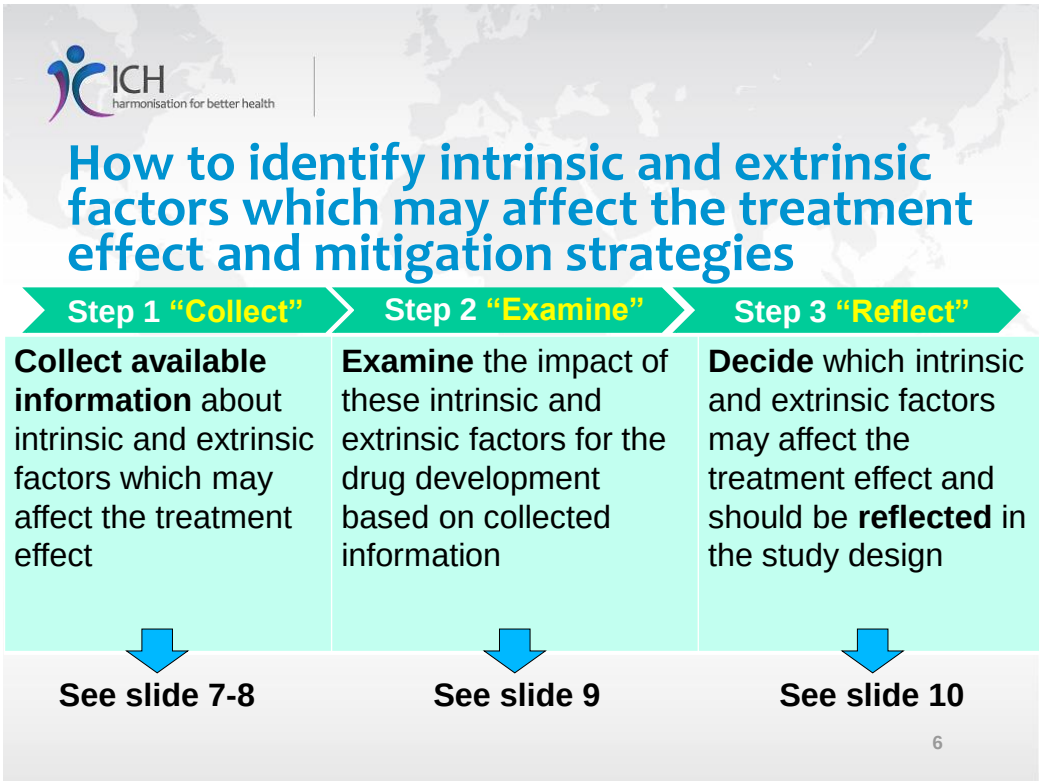
Intrinsic and extrinsic factors important to the drug development programme should be identified.

The planning of a clinical trial usually begins long before the start of subject enrolment.

When starting a new drug development programme, it is important to ensure data from an MRCT can be informative in all regions.

Why pre-considerations of regional variability are important

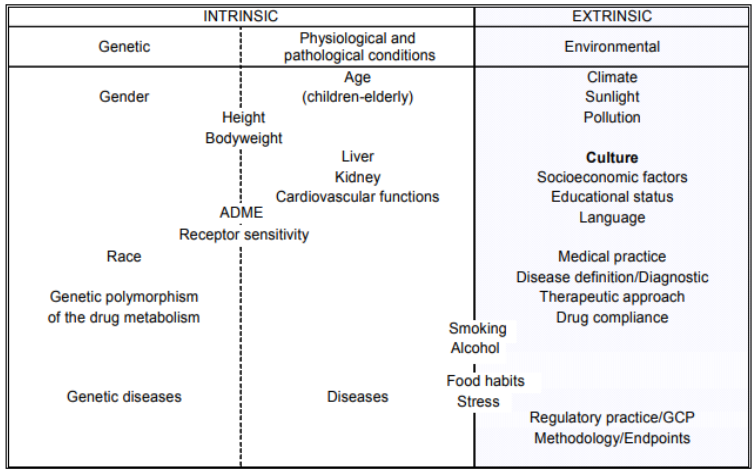
- **Intrinsic and/or extrinsic factors may impact the treatment effect**
- **Pre-consideration and mitigation of large differences across regions can support adequate interpretability of the results of an MRCT in different regions**
- **Pre-consideration of regional variability should be reflected in the trial design to lead to a successful MRCT**



This slide outlines steps that can be taken in the process of identifying intrinsic and extrinsic factors which may affect the treatment effect that can lead to variability, and how to, if appropriate, mitigate for expected large differences.

Step1 "Collect" information

Major intrinsic and extrinsic factors are described in Appendix A of ICH E5



Not only intrinsic factors but also extrinsic factors may have a potential to affect the treatment effect

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When collecting data on intrinsic and extrinsic factors, the ICH E5 guideline can help to identify the factors that may affect the treatment effect. However, in recent years, drug development has changed to some extent and many new targeted therapies are now the focus of drug development. With this, additional relevant intrinsic factors such as biomarkers may need to be considered. See also Example 2 (gefitinib) later in this module.

Step1 “Collect” information

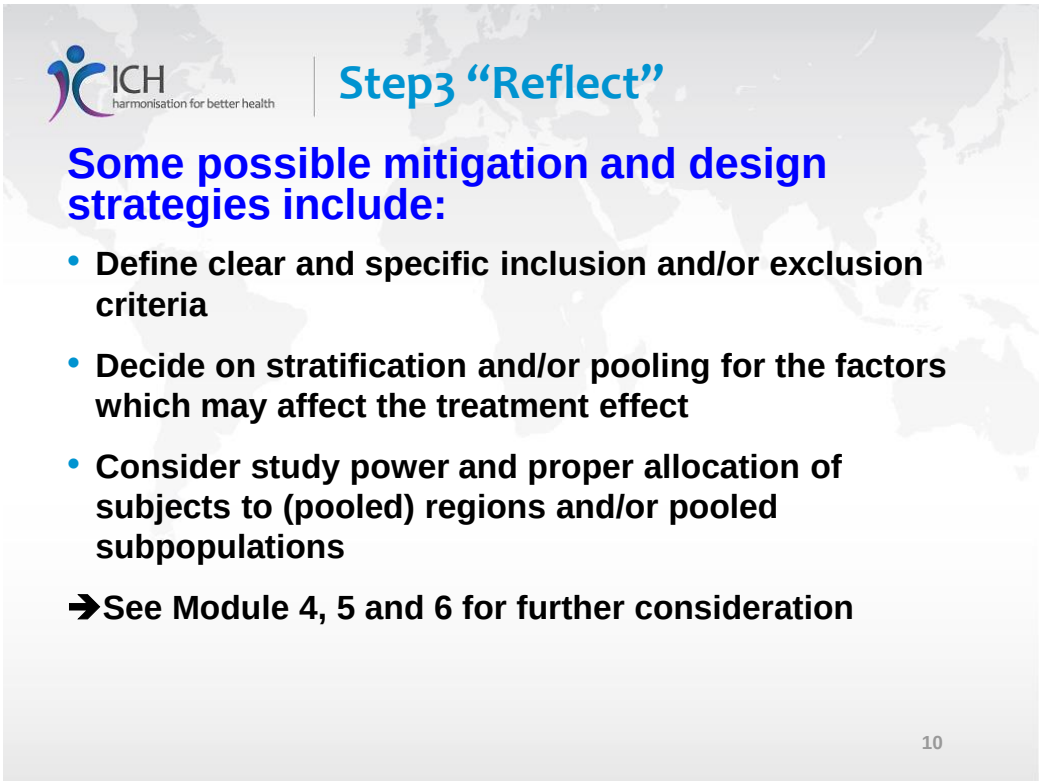
- **Search medical and scientific literature, guidelines and other publicly available information**
  - disease information
  - genetic information
- **Search databases (e.g., WHO disease database, registries)**
  - epidemiological data
  - historical data
- **Consult local healthcare professionals**
  - clinical practice, therapeutic approach in their region

WHO: World Health Organization

Step2 “Examine”

- Examine the impact of intrinsic and extrinsic factors based on collected information about the drug and from studies, literature, databases, local healthcare professionals
- If needed, collect more information by conducting studies or use modeling and extrapolations, e.g., PK-PD studies, exploratory studies
- Intrinsic and extrinsic factors which may affect the treatment effect can be identified based on the information above

PK: pharmacokinetics
PD: pharmacodynamics



One set of inclusion and/or exclusion criteria is ideally preferred and local amendments should be avoided. If necessary, the number of local amendments should be reduced to a minimum.

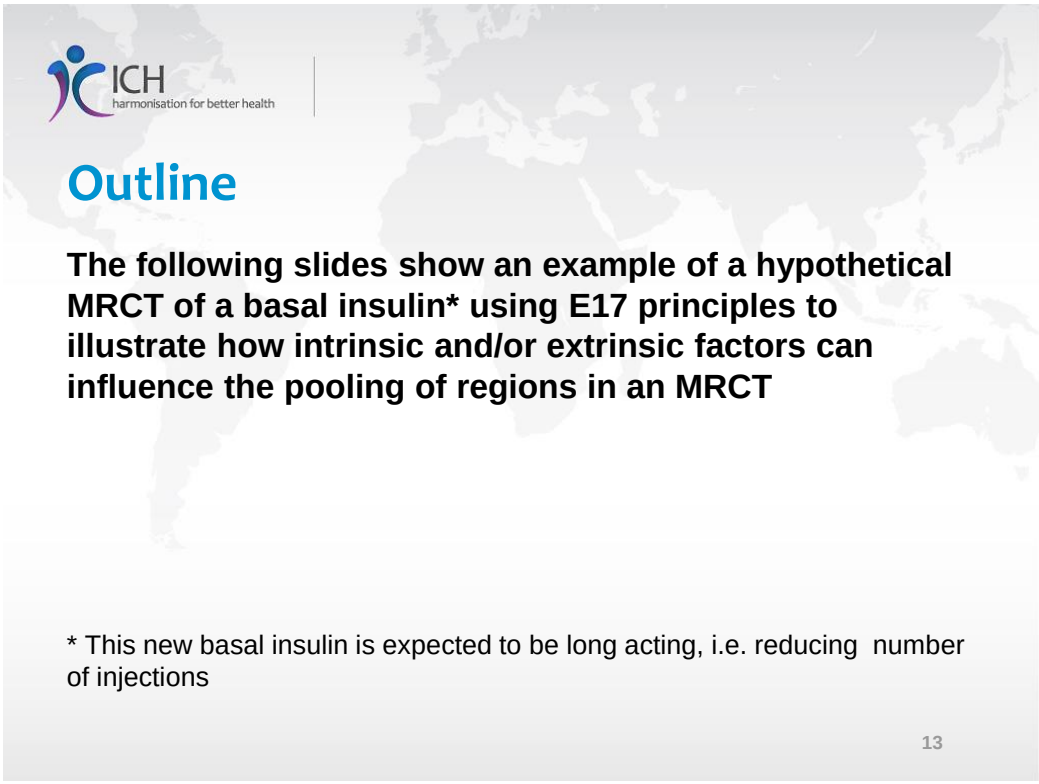
With respect to mitigation, there are some caveats. For example, too much mitigation (e.g., narrowing of study population) may help to demonstrate a treatment effect, but may reduce the external validity of the study results in certain regions.

Concluding remarks

- **Pre-considerations of regional variability are important in the design of an MRCT because intrinsic and extrinsic factors may affect the treatment effect and the interpretation of the trial.**
- **A stepwise approach to identify these factors as well as some mitigation and design strategies are proposed.**

It is important to collect information about the subjects to be included in a development programme, so that researchers have the possibility to evaluate the effect of drugs across different ethnic groups. Conducting MRCTs may allow researchers to explore potential differences among ethnic groups.

For example, researchers have learned that African Americans have reduced blood pressure responses to monotherapy with beta-blockers, angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARB) when compared to responses to diuretics or calcium channel blockers.



Both intrinsic and extrinsic factors are important for the development of type 2 diabetes, and the prevalence of several complications of diabetes vary among diabetic populations across regions*

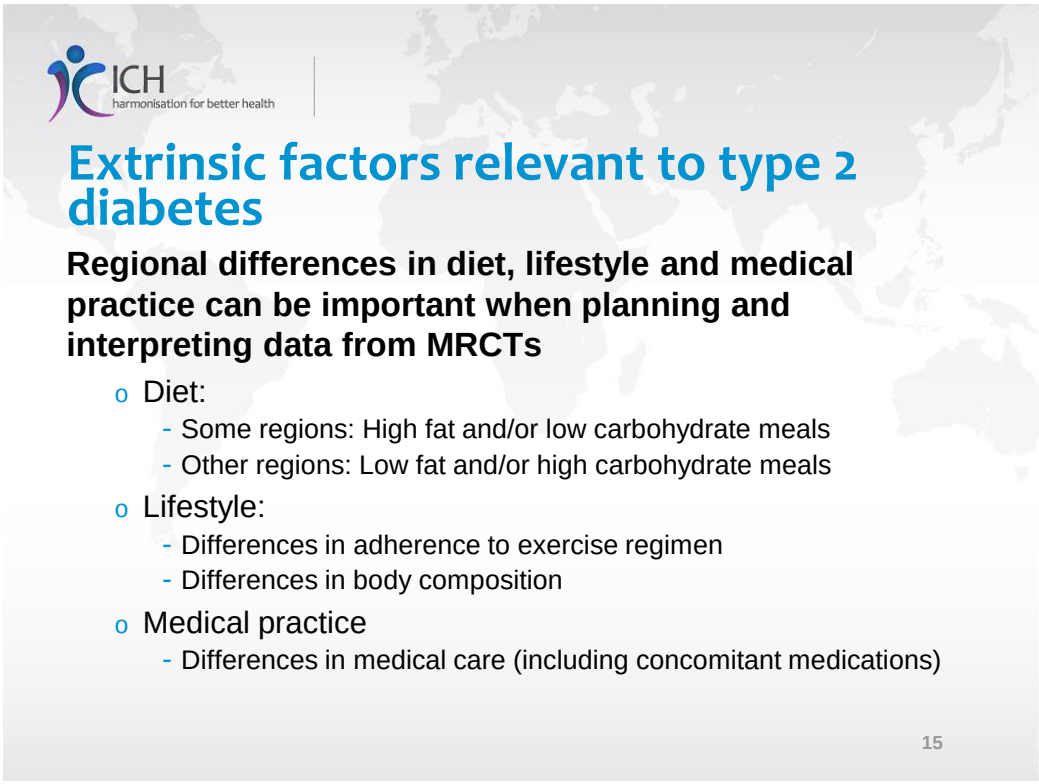
Risk factors for type 2 (DM) associated with lifestyle are the factors that matter most for the increasing prevalence of the disease and these may differ between ethnic populations.

**Kenealy T, Elley CR, Collins JF, Moyes SA, Metcalf PA, Drury PL. Increased prevalence of albuminuria among non-European peoples with type 2 diabetes. Nephrol Dial Transplant 2012; 27:1840–1846.*

Type 1 Diabetes Mellitus is characterised by complete lack of endogenous insulin production. The insulin regimen required to treat subjects with type 1 DM is called "basal-bolus". Basal insulin is long-acting and covers the need for insulin between meals; bolus insulin is rapid-acting and covers the need for insulin due to meals. Ethnic factors are not of major importance in the treatment of type 1 Diabetes Mellitus, except for factors associated with diet where a high carbohydrate content of meals leads to a higher meal-time insulin need.

Type 2 Diabetes Mellitus is characterized by relative insulin deficiency, i.e, the excreted insulin does not exert its full effect on the tissues. In the later stages of type 2 DM, endogenous insulin production will decline.

Type 2 Diabetes is initially treated with oral antihyperglycaemic agents followed by basal insulin and later meal-time insulin. Ethnic factors affect the treatment of type 2 DM to a higher degree than the treatment of type 1 DM. This is mostly due to differences in diet composition, exercise patterns and body composition, that vary from region to region.



This example is about developing a new long acting (basal) insulin. This new basal insulin must still be supplemented with the usual antidiabetic treatment (e.g., bolus insulin) which takes care of the meal-related need for treatment.

Potentially important differences between ethnic populations include carbohydrate content of meals (may be higher in Asia compared to other regions) and sensitivity to insulin.

In insulin development programmes, studies are conducted with a "treat-to-target" concept. This means that all subjects are followed closely and insulin dosing is optimised so that all subjects will reach the same level of glycaemic control (fasting blood glucose).

In dividing subjects into the above mentioned regions the most relevant factors that potentially may impact the treatment effect have been considered. These include differences in diet composition; for example, Asian populations generally ingest more carbohydrates during their meals compared to the other populations. This has implications on the split between bolus insulin and basal insulin doses. Another factor to consider is the body composition, as measured by body mass index (BMI) of the population; for example, populations of the Americas tend to have higher BMIs than populations in other regions. This has implications on the absolute number of units of insulin needed to treat a patient to reach a glycaemic target (fasting blood glucose).

Example 1: Conclusion

- **For some drugs the response to treatment may be affected by extrinsic factors**
- **Therefore, it is important to understand:**
  - the extrinsic factors that may impact the treatment effect
  - the prevalence of these factors across geographic regions
- **Subjects with similar extrinsic factors can be pooled**
- **Differences in some factors may be mitigated, but the degree of mitigation should not impact the generalisability of study results**
- **Sufficient number of subjects from different regions should be enrolled to support the evaluation of the consistency of treatment effects among regions**

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Module 2: example 2

Treatment of non-small cell lung cancer with gefitinib; an example where intrinsic factors matter

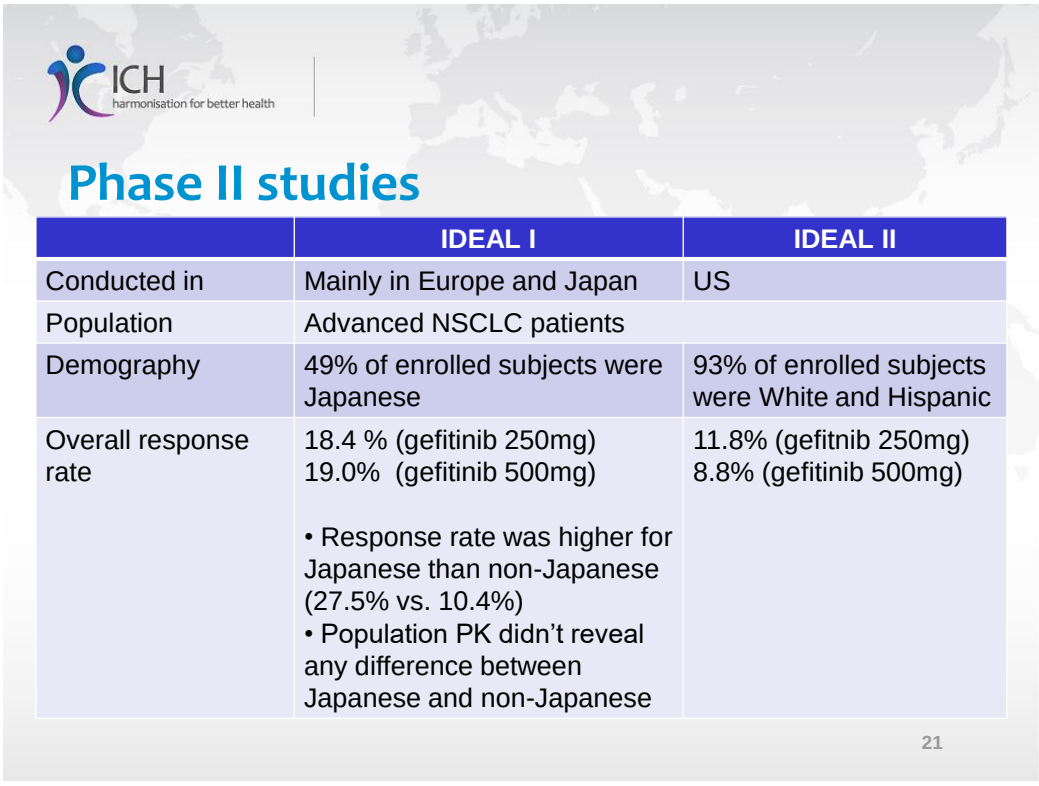
Outline

The following drug development example illustrates how intrinsic factors can impact the treatment effect and how this can be informative for identifying appropriate target populations.

Gefitinib

- **Small molecule inhibitor of EGFR tyrosine kinase**
- **Target population: patients with NSCLC**
- **During drug development, the science behind the potential predictive biomarker for EGFR TKIs in NSCLC was unclear**
- **Two phase II studies (IDEAL I & II) in advanced NSCLC patients showed different response rates in different regions and populations**

EGFR: epidermal growth factor receptor
TKI: tyrosine kinase inhibitor
NSCLC: non–small cell lung cancer



The IDEAL 1 and 2 data suggested a difference in treatment response between populations, with a higher response rate shown in Asian patients. At that time, the reason for the better treatment response in Asians was not known.

References:

1. Fukuoka et al, J Clin Oncol 2003; 21:2237-2246 (IDEAL I)
2. US FDA 021399 Medical Review Part 1 (IDEAL I & II)
3. Iressa US FDA label 2003 (IDEAL II)
4. EMEA Assessment Report for Iressa, EMEA/CHMP/563746/2008, page 23-24/86 (IDEAL I and II)

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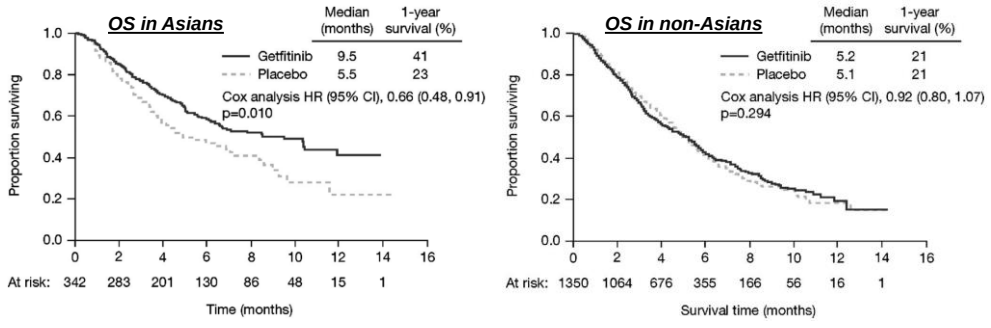
Phase III study (ISEL): survival effect was seen only in Asians

- **ISEL was conducted in advanced NSCLC patients**
- **75% of enrolled subjects were Caucasians and 20% were Asian**



(Both subgroup analyses were pre-planned)

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ISEL was a Phase III survival study comparing gefitinib plus best supportive care (BSC) with placebo plus BSC, in patients with advanced NSCLC. The primary endpoint was overall survival.

Gefitinib did not prolong survival in the overall population, with a hazard ratio (HR) of 0.89 (95% CI 0.77 to 1.02, p=0.0871). But survival outcomes differed by ethnic origin, with gefitinib shown to be effective only in Asians.

Thus, the differences in treatment responses observed in the phase II IDEAL I and II studies were confirmed in the phase III ISEL study, with significant treatment effect in Asians**,** but not in non-Asians.

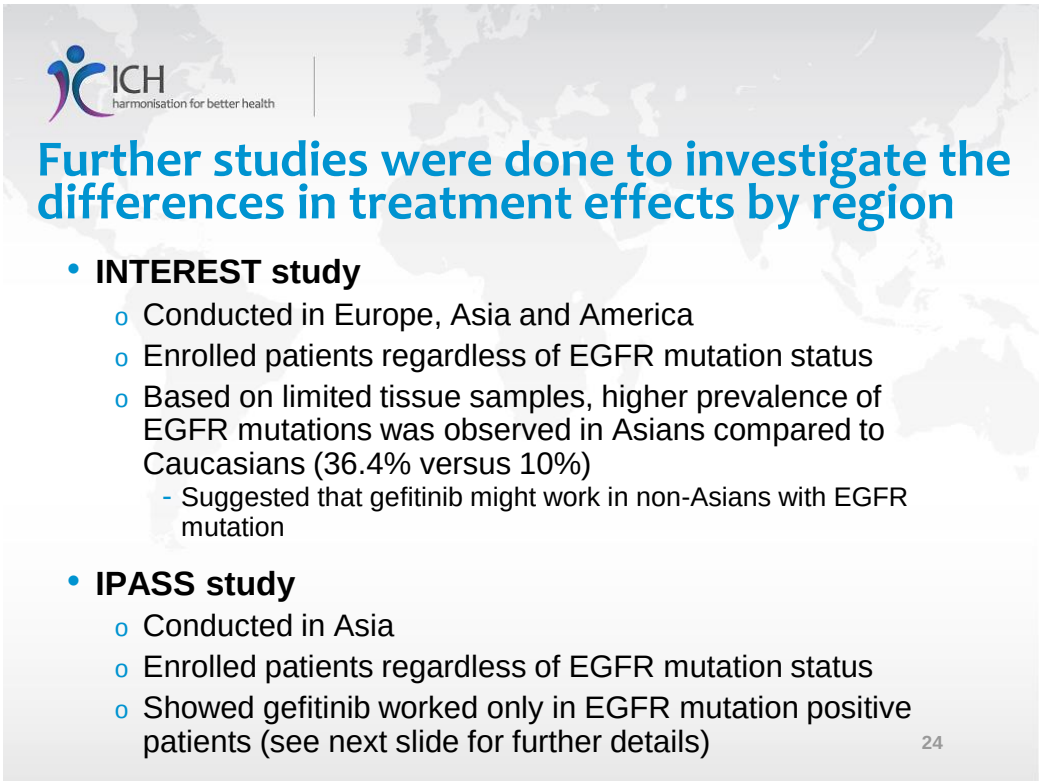
References:

1. Change A, et al. J Thorac Oncol. 2006;1: 847–855
2. EMEA Assessment Report for Iressa, EMEA/CHMP/563746/2008

Why did gefitinib work in Asians?

No obvious explanation for the lack of treatment effect on overall survival in Caucasian patients

- **The importance of tumour genetics such as EGFR mutation status was considered**



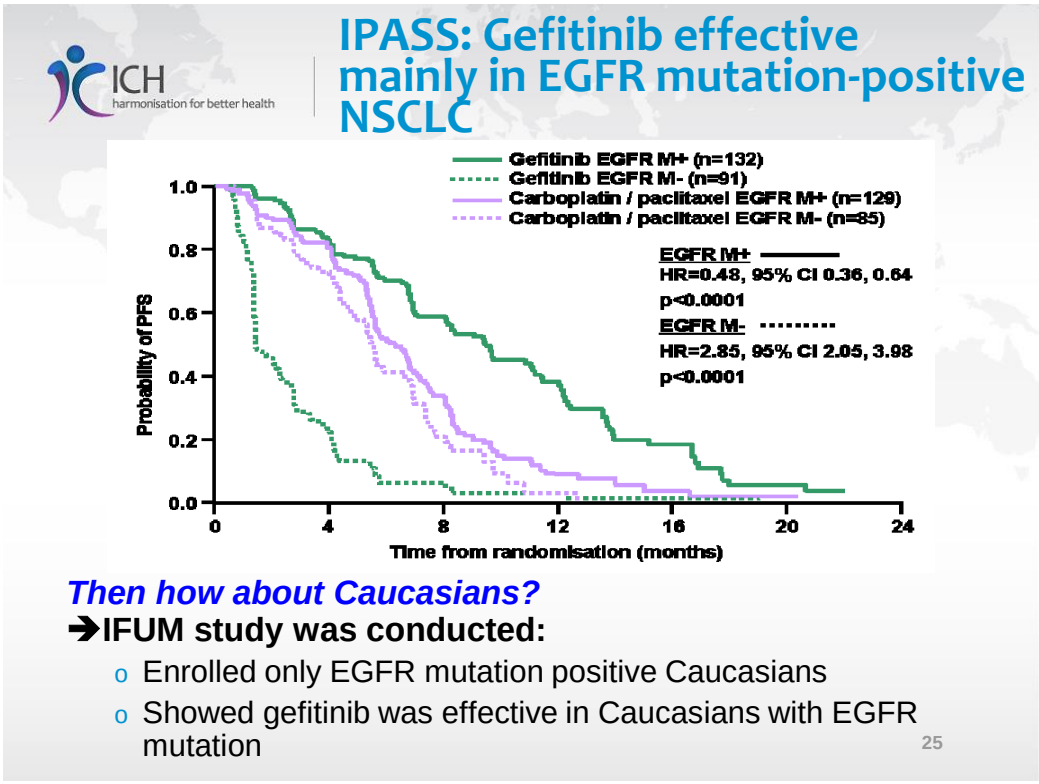
INTEREST was a phase III study of gefitinib versus intravenous docetaxel (TAXOTERE) in patients with advanced.

IPASS was a Phase III study to assess efficacy, safety and tolerability of gefitinib versus carboplatin-paclitaxel doublet chemotherapy in patients with NSCLC.

References:

INTEREST study - EMEA Assessment Report for Iressa, Kim ES, et al. Lancet 2008;372:1809-1818

IPASS study - EMEA Assessment Report for Iressa, J Clin Oncol 29:2866-2874.



In the subgroup of patients with EGFR mutation positive tumors, progression-free survival (PFS) was significantly longer for gefitinib versus carboplatin-paclitaxel (HR, 0.48; 95% CI, 0.36 to 0.64; P<0.0001; median PFS, 9.5 vs. 6.3 months). Conversely, carboplatin-paclitaxel was superior in the EGFR mutation negative subgroup (HR, 2.85; 95% CI, 2.05 to 3.98; P<0.0001; median PFS, 5.5 v 1.5 months).

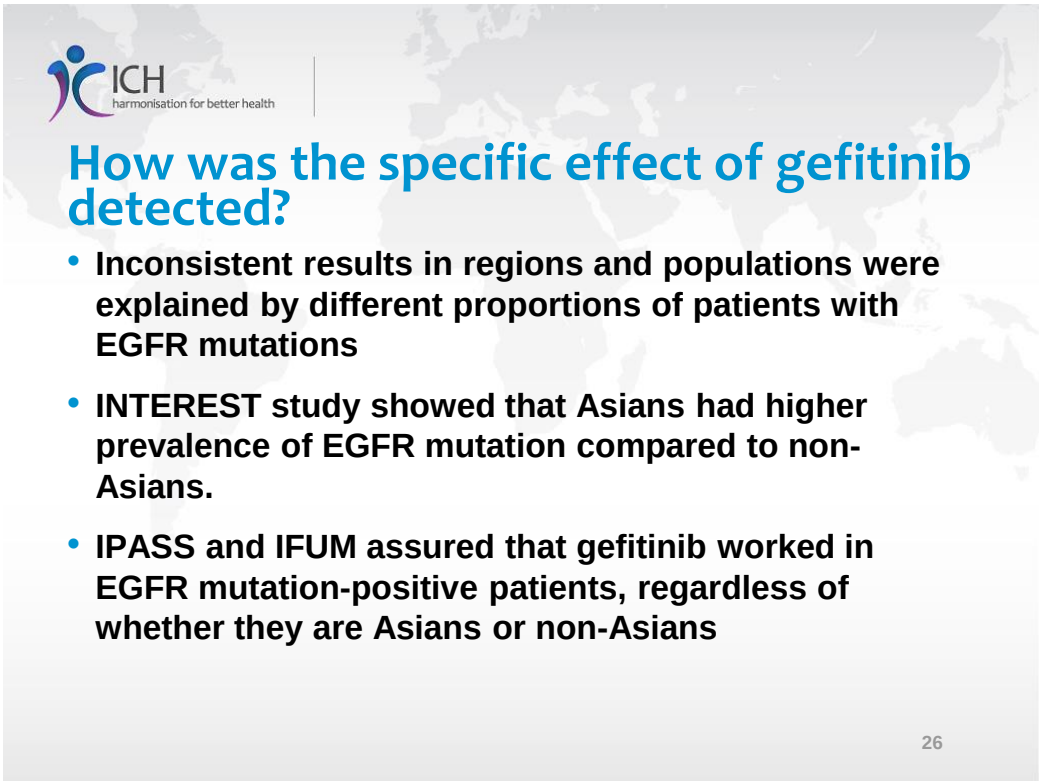
Therefore, gefitinib did not work for all Asians, it worked only in Asians with EGFR mutation positive tumors.

IFUM, a phase II study, was designed to characterize the efficacy and safety of gefitinib in Caucasian patients with EGFR mutation-positive advanced NSCLC. The major efficacy outcome measure was objective response rate (ORR) based on investigator assessment and Blinded Independent Central Review (BICR). The ORR was 70% by investigator and 50% by BICR.

Reference:

IPASS - EMEA Assessment Report for Iressa, J Clin Oncol 29:2866-2874.

IFUM study - US FDA Iressa 206995 Medical Review



It took several years and many large studies before the target patient population for gefitinib treatment in advanced NSCLC became clear.

Advances in scientific understanding of the target biology during the clinical development enabled the eventual identification of a biomarker to define patients most likely to derive benefit from gefitinib.

If the clinical trial had initially been done only in Caucasians, this very effective drug may not have been developed further. Scientists would not have known that the treatment effect differs between Caucasians and Asians, and that the treatment effect is driven by EGFR mutation status. Conducting global MRCTs may facilitate the understanding of regional differences and provide new knowledge about important intrinsic factors, such as EGFR mutation status.

Example 2: Conclusion

- **Consider if the treatment effect is sensitive to an intrinsic factor**
- **When an intrinsic factor is suspected to potentially impact the drug response it is recommended to stratify randomization based on the suspected intrinsic factor**