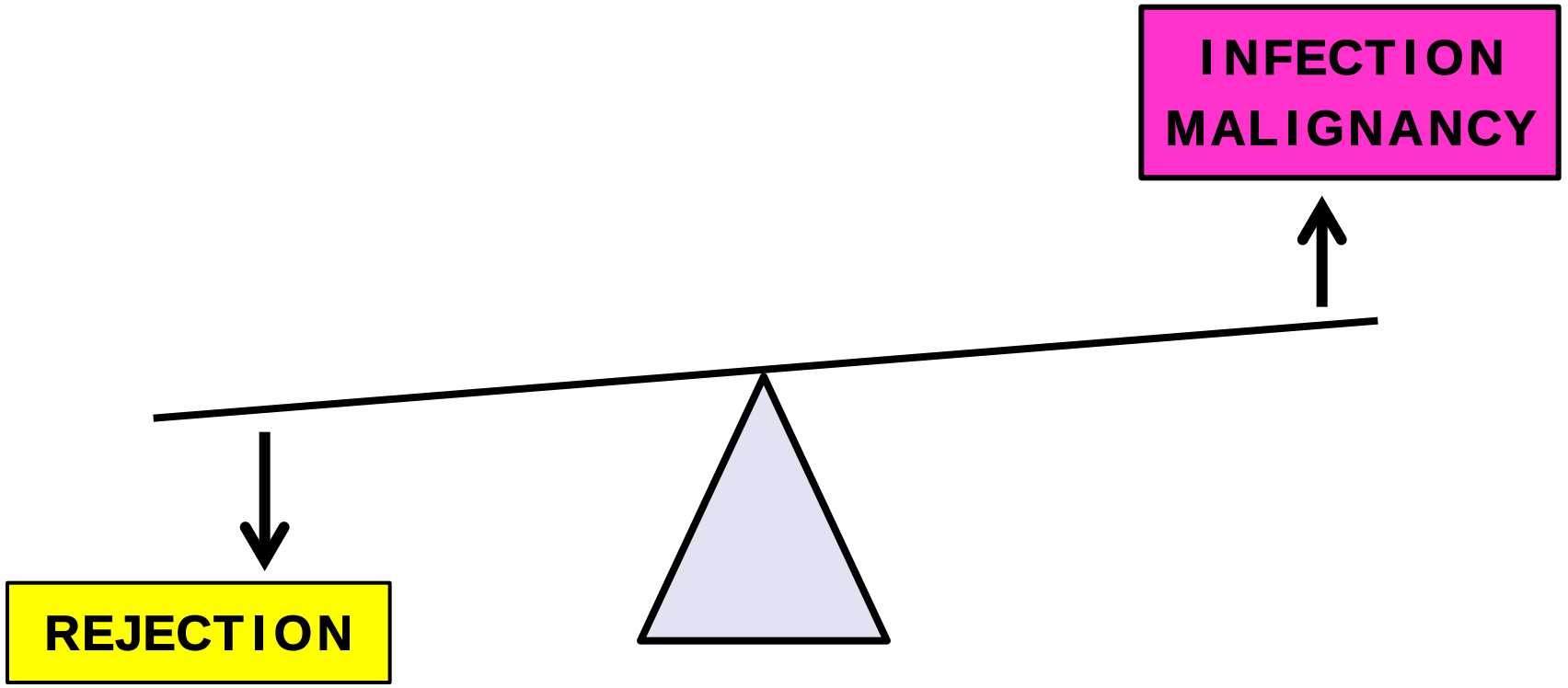
EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

EMA EFPIA Workshop
Dose Finding – Dose Selection _ Drug Development, licensing and life cycle management
2014-12-04—05

Regulatory and Physician View

Lisbeth Barkholt, EMA/SAWP and MPA

Organ transplantation



Prophylactic immunosuppression (IMS) regimens

- 'Must' to succeed in graft and patient survival
- Tx results improved over the years

Steroids → AZA → CNIs → anti-T cell Abs → MMF, EVR

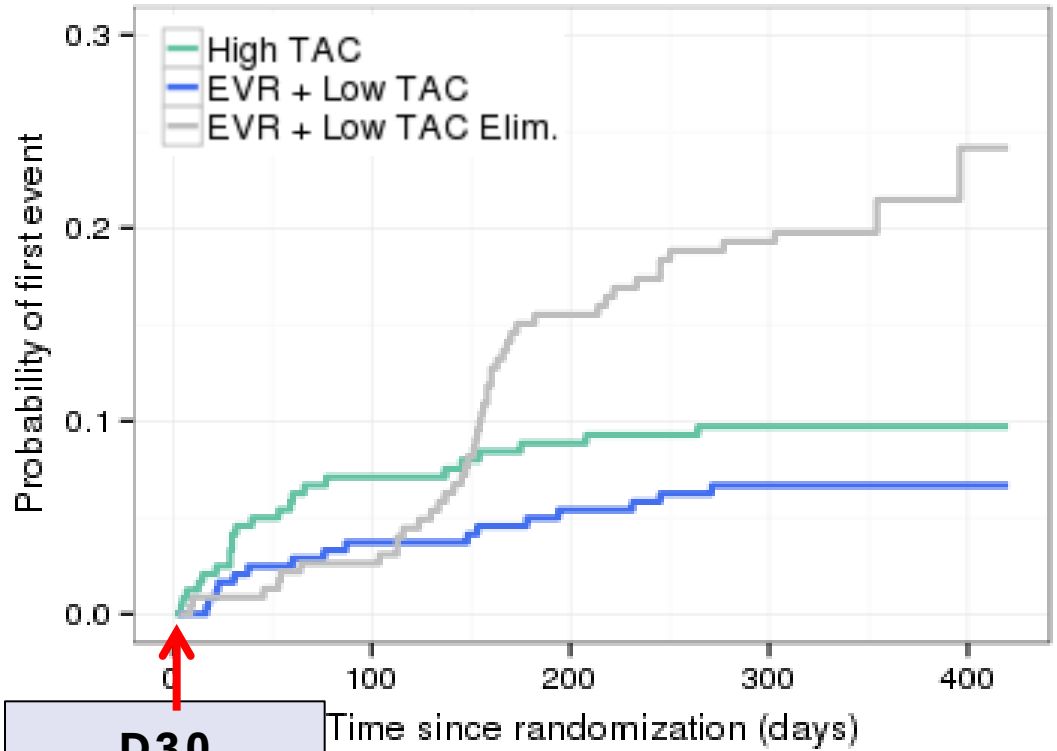
- Individualized regimens possible
  - needed due to specific risk factors
  - multipharmacy; unusual combinations
  - daily patient evaluation – multiple components
- Goal: *controlled* toxicity vs efficacy balance where … sub-optimal therapy is calculated in regimens

Case study: Efficacy results

Numerical superiority of EVR + Low TAC. But no information about efficacy contribution of EVR

Probability of first rejection event

Kaplan-Meier estimates



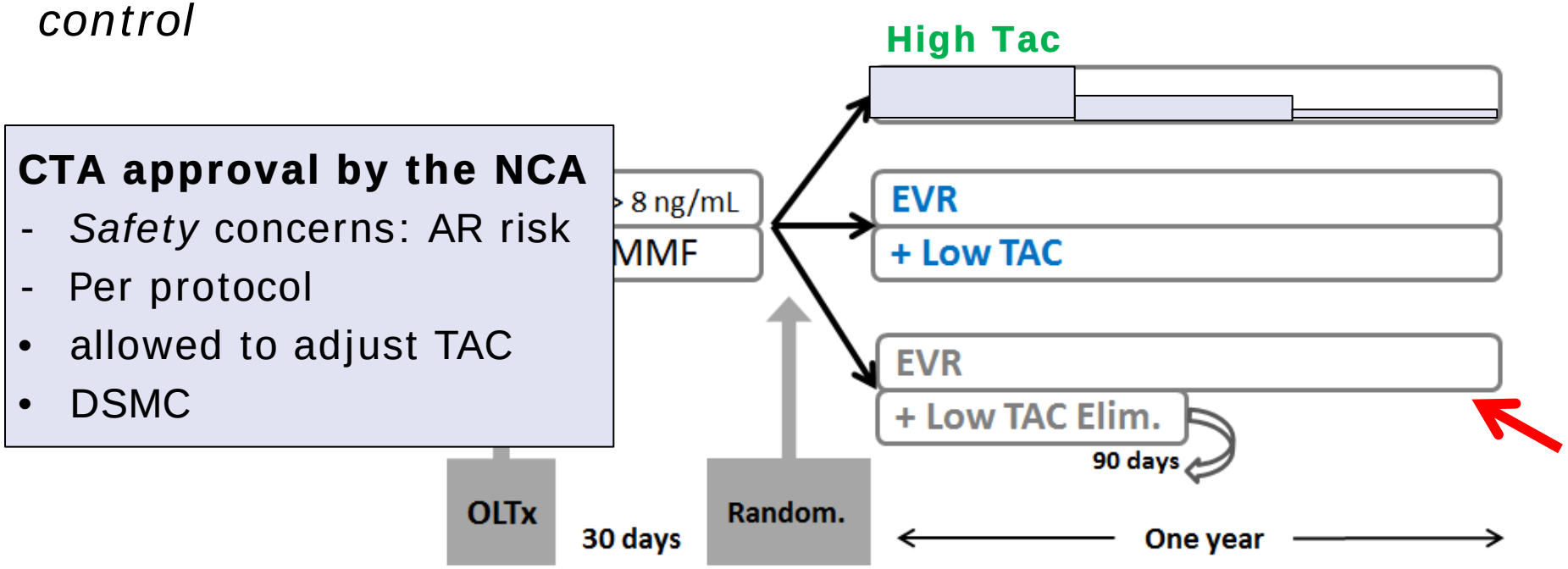
D30 postLTx

IMS regimen includes acceptance of 10-15 % acute rejections ≤ 1-3 mo

- avoid over immunesuppression
- majority managed with high-dose steroids
- liver graft - tolerance development?

Case study: Liver transplantation - Phase III CT

Non-inferiority study with 2 EVR based combinations and active control



No efficacy information for Low TAC ('placebo'); Non-inferiority margin decided based on clinical consideration

Therapeutic drug monitoring:

Low TAC: 3-5 ng/mL; **High TAC: 8-12 ng/mL till Month 3 then 6-10 ng/mL**; EVR: 3-8 ng/mL