# Magnitude of benefit

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Disclosures : amgen, roche , merck, bayer, sanofi, takeda, celgene

# Clinical benefit

## EFFICACY

## TOXICITY

## CONVENIENCE

**Setting** - curative vs palliative
- prognosis within palliative

**Endpoint**

**Size**

# Increase in median OS for different HR as a function of prognosis

| MST In control | Increase in median values as a function of HR | | | | | |
|---|---|---|---|---|---|---|
| | 0.9 | 0.8 | 0.7 | 0.6 | 0.5 | 0.4 |
| 6 | .6 | 1.5 | 2 | 4 | 6 | 9 |
| | worthless | | worthwhile | | unrealistic | |

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| 24 | 2.6 | 6 | 10 | 16 | 24 | 36 |
| | worthless | | worthwhile | | unrealistic | |

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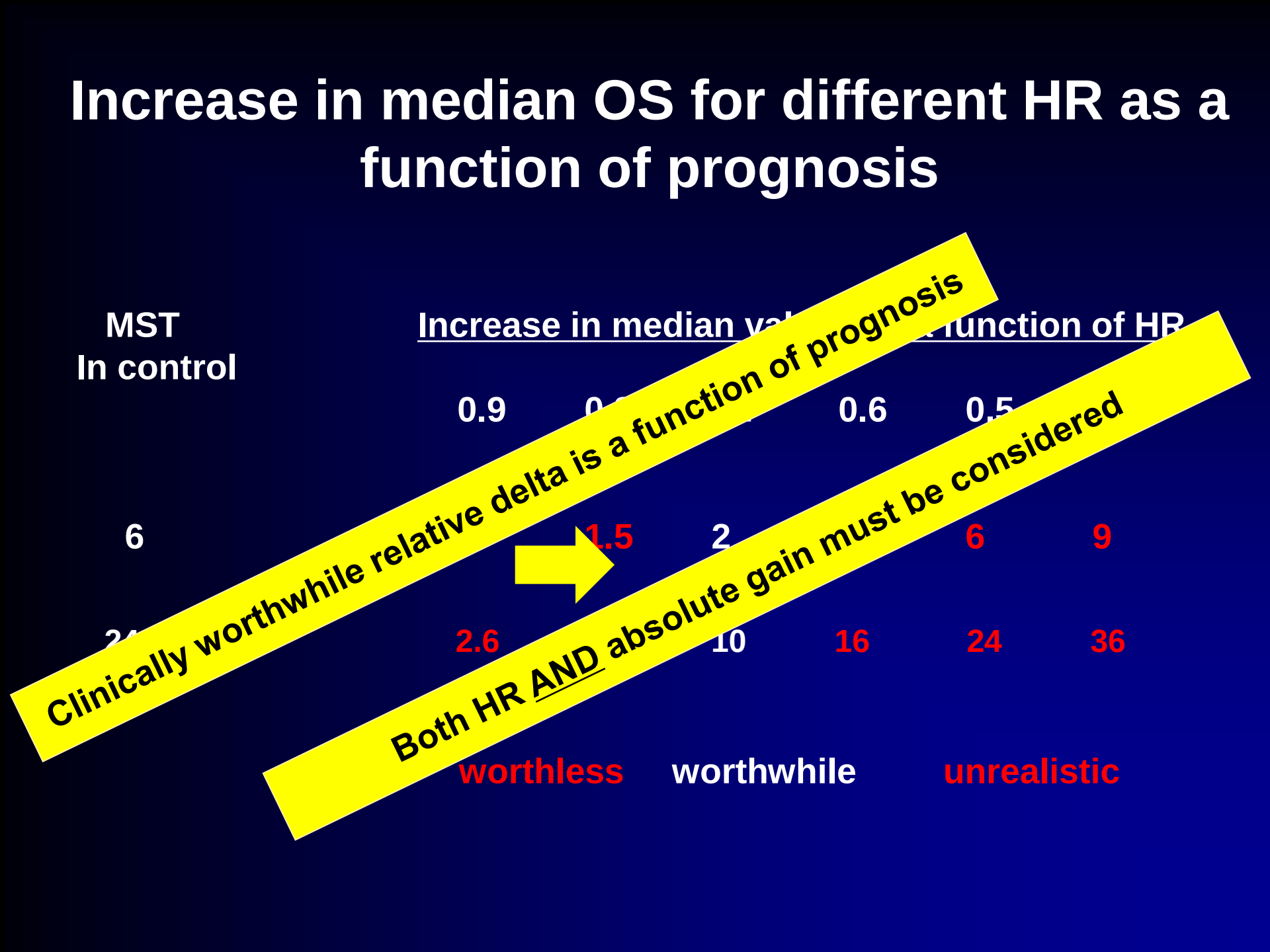
| 24 | 2.6 | 6 | 10 | 16 | 24 | 36 |

Clinically worthwhile relative delta is a function of prognosis

worthless worthwhile unrealistic

# Increase in median OS for different HR as a function of prognosis



# Clinical benefit

## EFFICACY

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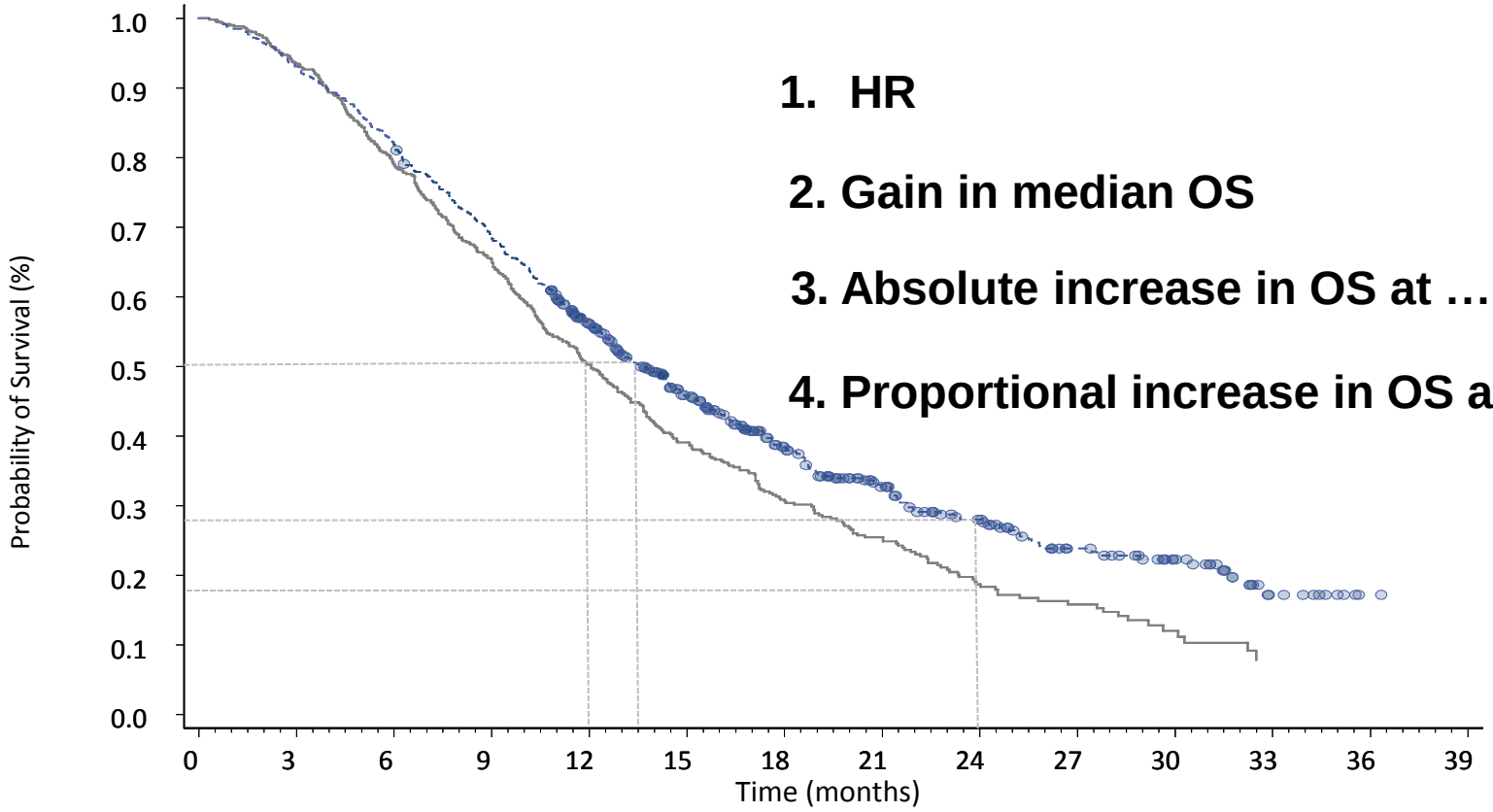
**Setting**
- curative vs palliative
- prognosis within palliative

**Endpoint**
- type
- ways to summarize the efficacy endpoint

**Size**

# The 4 ways to interpret OS curves




1. HR
2. Gain in median OS
3. Absolute increase in OS at …
4. Proportional increase in OS at …

| Number At Risk | | | | | | | |
|---|---|---|---|---|---|---|---|
| | 614 | 485 | 286 | 131 | 51 | 14 | |
| | 612 | 498 | 311 | 148 | 75 | 33 | |

# Clinical benefit

## EFFICACY  TOXICITY  CONVENIENCE

| | |
|---|---|
| **Setting** | **- curative vs palliative**<br>**- prognosis within palliative** |
| **Endpoint** | **- type**<br>**- ways to summarize the efficacy endpoint** |
| **Size** | **- extent of efficacy → magnitude of 'benefit '** |

# Size of benefit (target delta) : a compromise

1. plausible to achieve
2. worthwhile if achieved

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# N. of rials meeting the low required benefit for mCMO out of 43 pivotal randomized studies analyzed.

| | | CRITERIA | | NUMBER OF POSITIVE TRIALS | | | |
|---|---|---|---|---|---|---|---|
| Prognosis in control | N of trials | Hazard Ratio | gain in OS | Hazard Ratio | gain in OS | "either" parameter | "both" prameters |
| < 9 mo | 9 | | | | | | |
| 9-12 mo | 8 | | | | | | |
| 12-18 mo | 9 | | | | | | |
| >18 mo | 17 | | | | | | |
| TOT | 43 | | | | | | |

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| < 9 mo | 9 | 0,70 | 2 mo | | | | |
| 9-12 mo | 8 | 0,75 | 2,5 mo | | | | |
| 12-18 mo | 9 | 0,75 | 3 mo | | | | |
| >18 mo | 17 | 0,80 | 3,5 mo | | | | |
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| Prognosis in control | N of trials | Hazard Ratio | gain in OS | Hazard Ratio | gain in OS | "either" parameter | "both" prameters |
| < 9 mo | 9 | 0,70 | 2 mo | 4 | 5 | 5 | 4 |
| 9-12 mo | 8 | 0,75 | 2,5 mo | 5 | 4 | 5 | 4 |
| 12-18 mo | 9 | 0,75 | 3 mo | 4 | 5 | 6 | 3 |
| >18 mo | 17 | 0,80 | 3,5 mo | 4 | 7 | 7 | 4 |
| TOT | 43 | | | 17 | 21 | 23 | 15 |

# Trials, drugs and indications meeting the high required benefit for mCMO out of 43 pivotal randomized studies analyzed.

| | | CRITERIA | | NUMBER OF POSITIVE TRIALS | | | |
|---|---|---|---|---|---|---|---|
| Prognosis in control | N of trials | Hazard Ratio | gain in OS | Hazard Ratio | gain in OS | "either" parameter | "both" prameters |
| < 9 mo | 9 | 0,60 | 3 mo | | | | |
| 9-12 mo | 8 | 0,65 | 4 mo | | | | |
| 12-18 mo | 9 | 0,65 | 5 mo | | | | |
| >18 mo | 17 | 0,70 | 6 mo | | | | |
| TOT | 43 | | | | | | |

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| Prognosis in control | N of trials | Hazard Ratio | gain in OS | Hazard Ratio | gain in OS | "either" parameter | "both" prameters |
| < 9 mo | 9 | 0,60 | 3 mo | 1 | 3 | 3 | 1 |
| 9-12 mo | 8 | 0,65 | 4 mo | 0 | 1 | 1 | 0 |
| 12-18 mo | 9 | 0,65 | 5 mo | 1 | 0 | 1 | 0 |
| >18 mo | 17 | 0,70 | 6 mo | 2 | 2 | 3 | 1 |
| TOT | 43 | | | 4 | 6 | 8 | 2 |

**Temsirolimus**-kidney **vs IFN**
**Ipilimumab**-melanoma
**Cetuximab**-colon vs BSC
**Abiraterone**-prostate vs pred
**Enzalutamide**-prostate vs BSC
**Tdm1**-breast **vs cape lapatinib**
**Cetuximab**-head and neck **vs RT**
**Bevacizumab**-ovarian vs carbopaclitaxel

**Cetuximab**-colon
**Bevacizumab**-ovarian

# Conclusions

1. Tox and convenience hard to rank
2. Complexity of summarizing  efficacy
3. Relevance of prognosis on magnitude of benefit
4. Too few data on long term OS
5. Effects of raising the bar