Sustained benefits for women with HER2-positive early breast cancer

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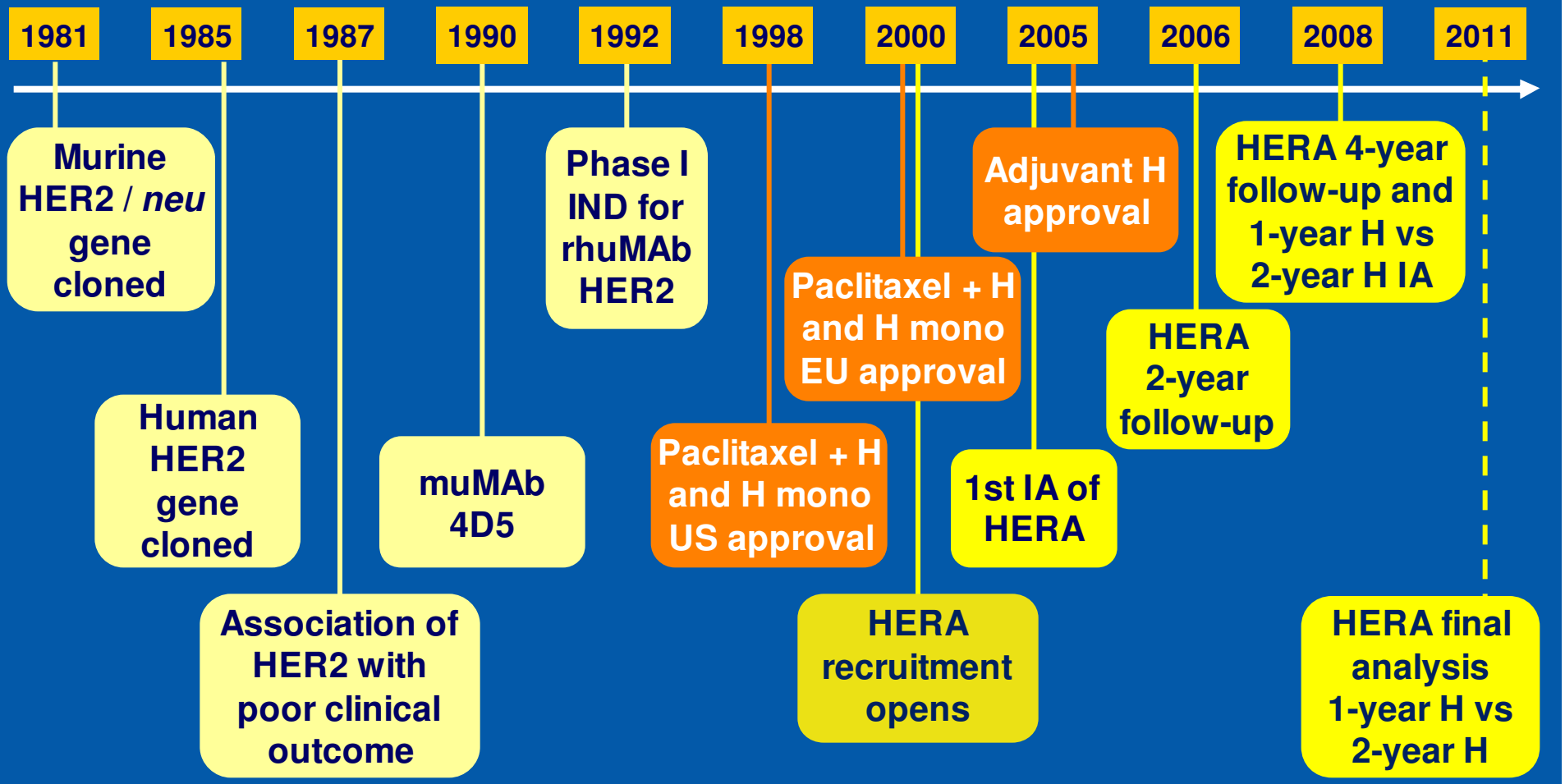
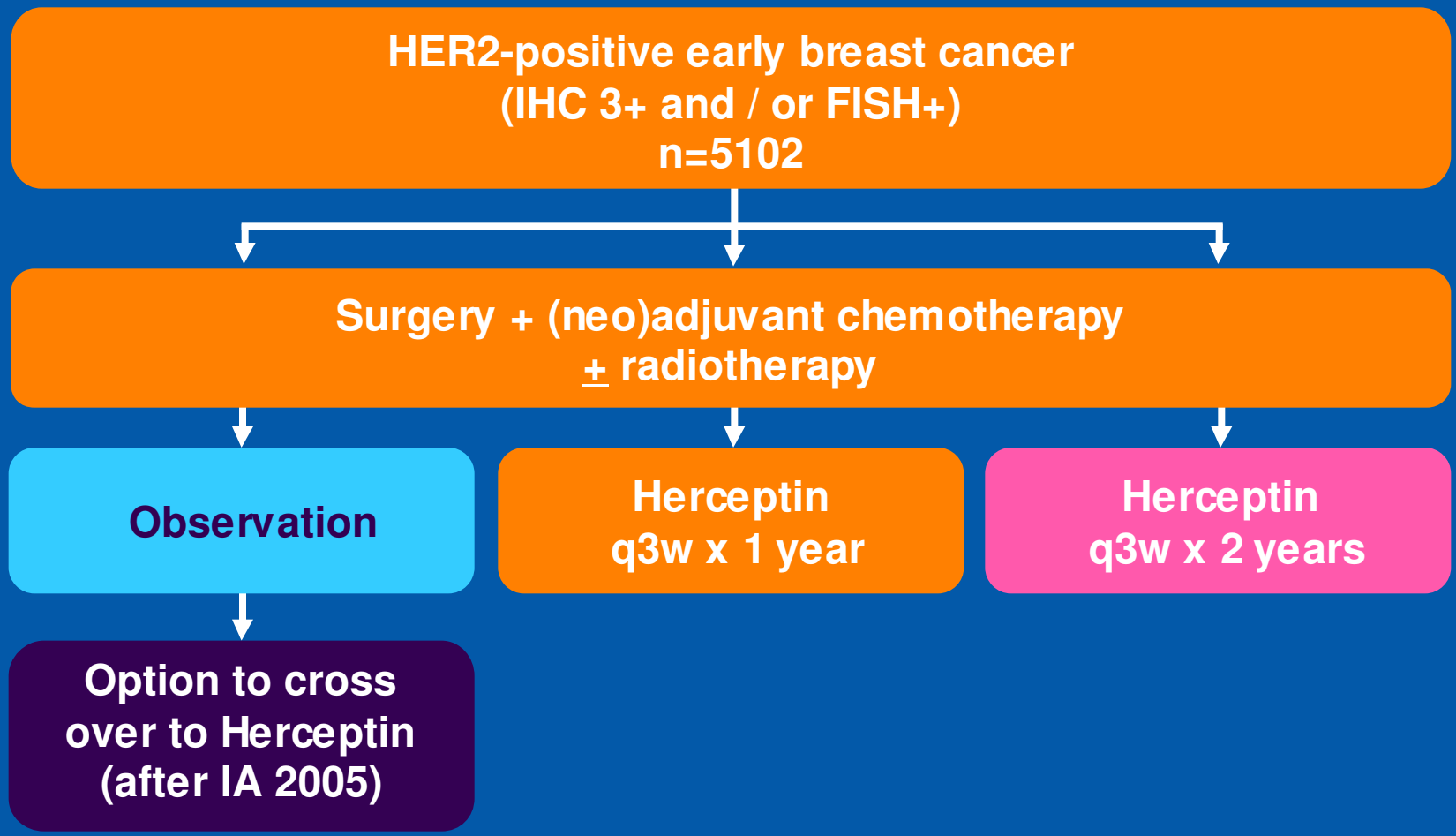
PROTOCOLO HERA

The fascinating history of Herceptin



HER2, human epidermal growth factor receptor 2; H, Herceptin; IA, interim analysis

HERA study design



IHC, immunohistochemistry; FISH, fluorescence *in situ* hybridisation

End points of the HERA trial

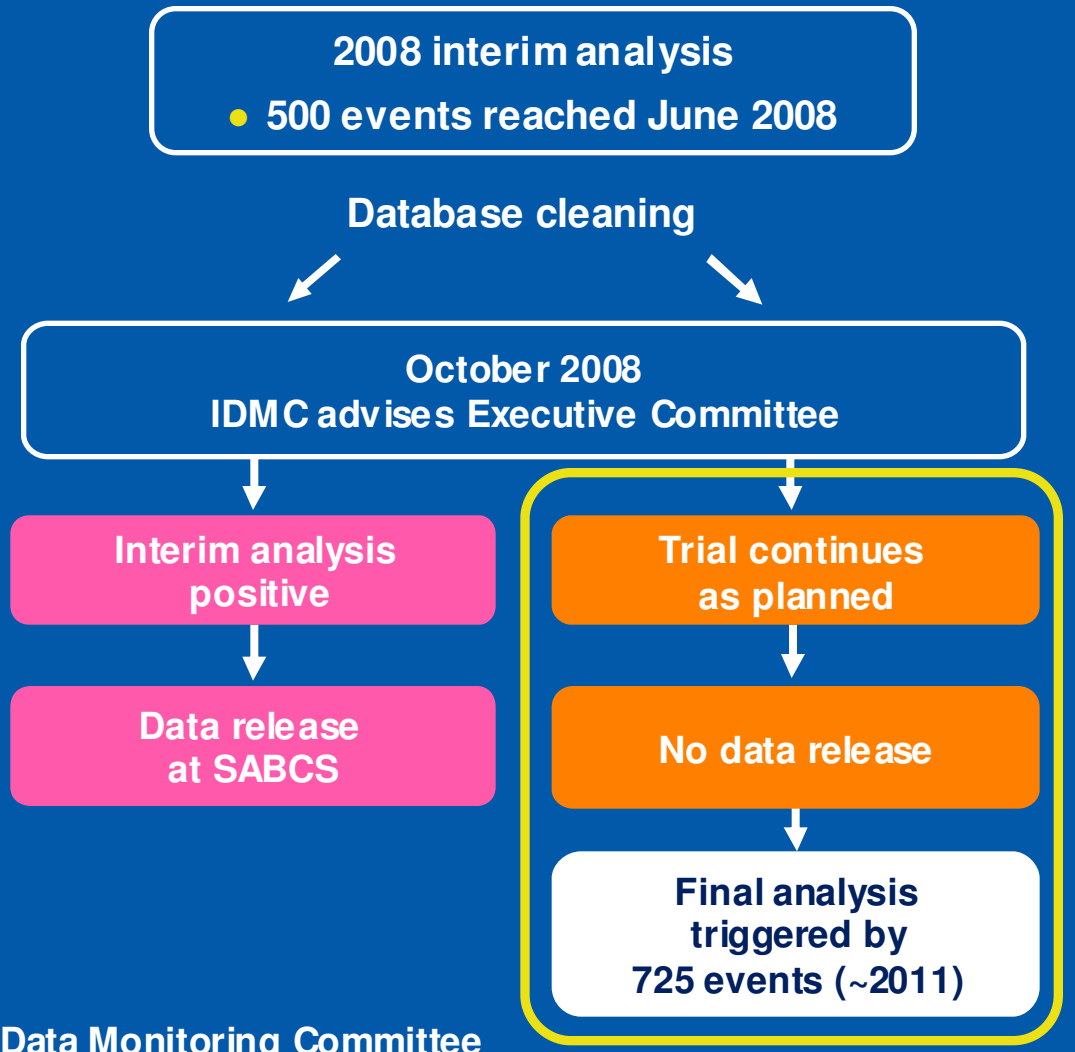
- Primary end point
  - DFS
    - 1-year Herceptin vs observation
    - 2-year Herceptin vs observation
- Secondary end points
  - OS, RFS, distant DFS, safety
    - 1-year Herceptin vs observation
    - 2-year Herceptin vs observation
  - compare DFS, OS, RFS, distant DFS and safety
    - 1-year Herceptin vs 2-year Herceptin

DFS, disease-free survival; OS, overall survival; RFS, relapse-free survival

HERA 2008 interim analysis: 2-year vs 1-year Herceptin

Statistical assumptions

- HR ≤0.80
- DFS absolute reduction 4.9%
  - 5-year DFS 1-year arm: 70%
  - 5-year DFS 2-year arm: 74.9%
- p value <0.014 for early release of results



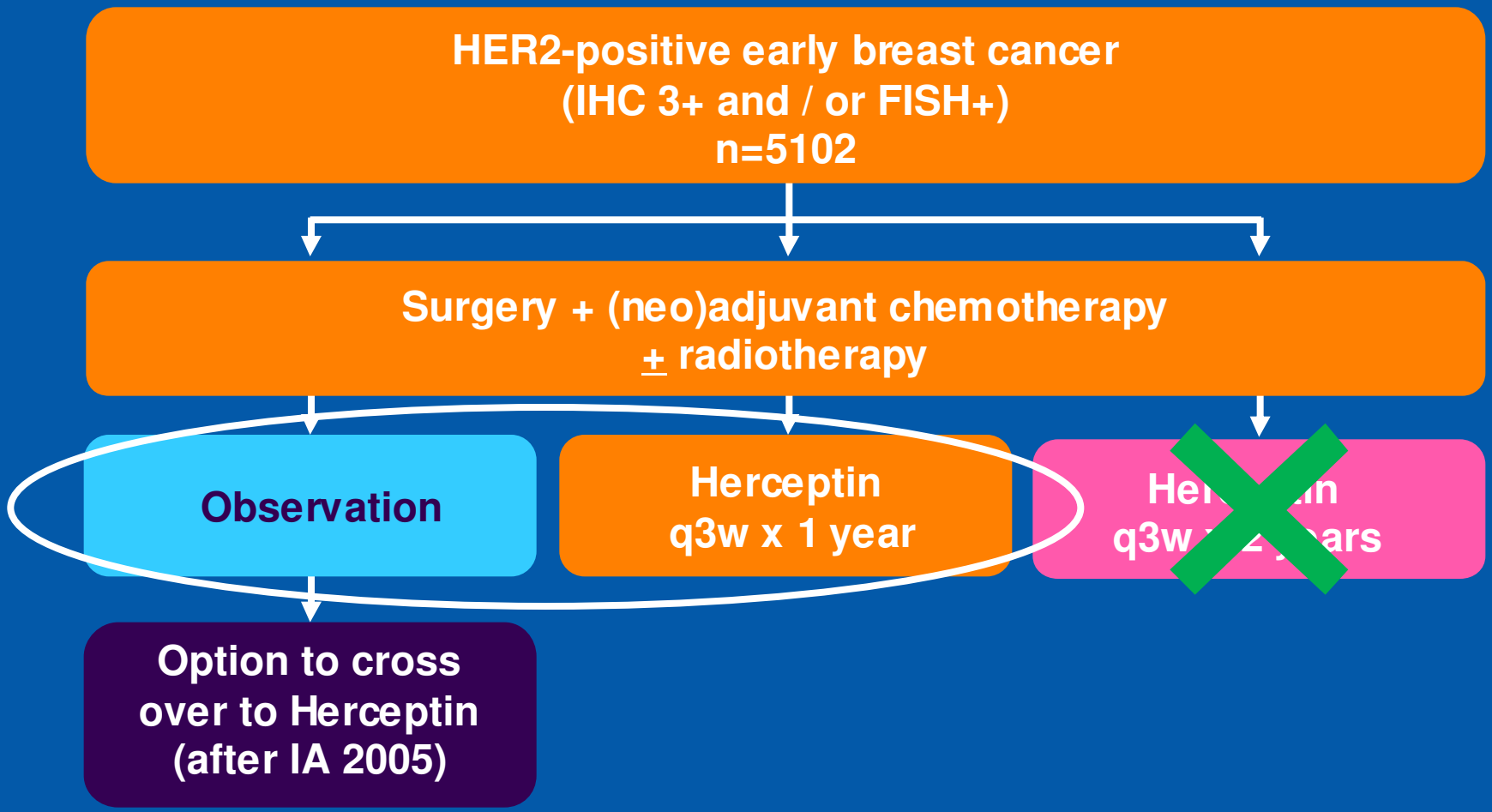
HR, hazard ratio; IDMC, Independent Data Monitoring Committee

HERA: IDMC recommendations October 2008

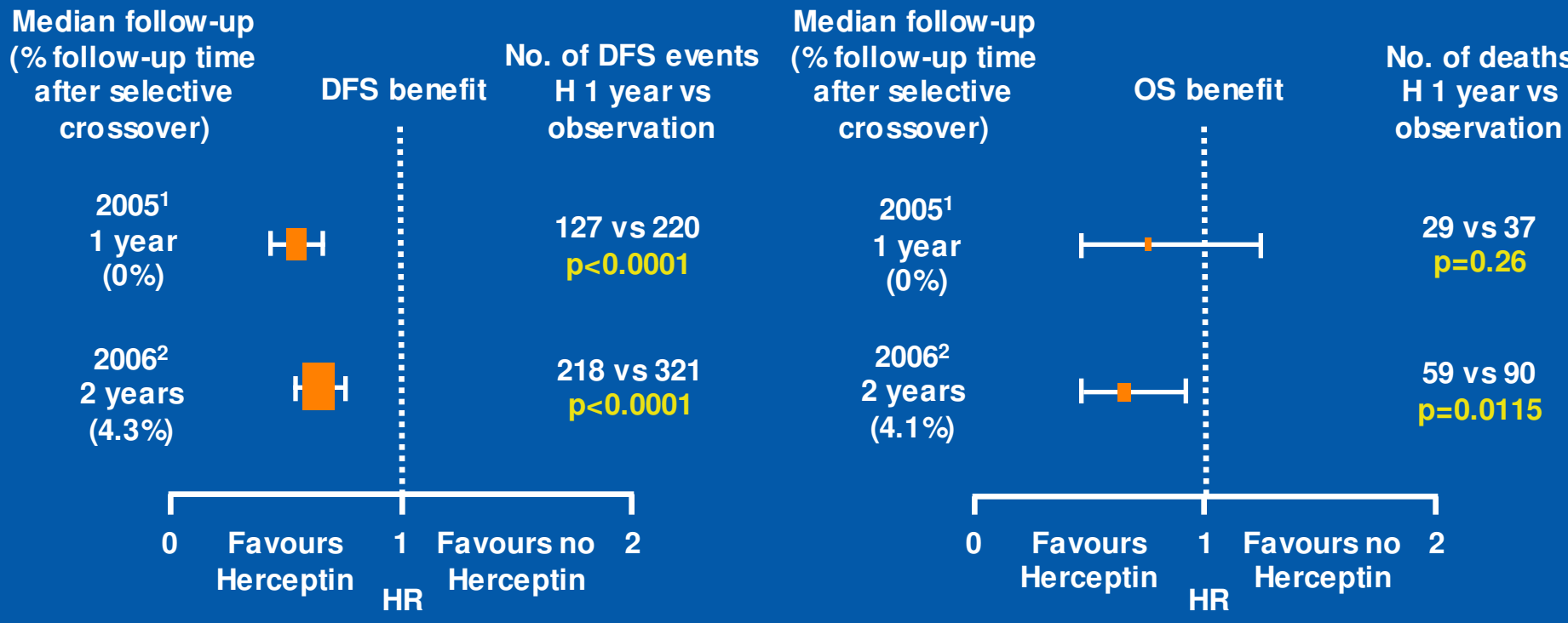
- Do not release information on the 2-year Herceptin arm
- Continue the 1-year Herceptin vs 2-year Herceptin comparison
- Release updated information on 1-year Herceptin vs observation

No conclusions can be drawn regarding the efficacy of Herceptin therapy for 2 years vs 1 year

HERA study design

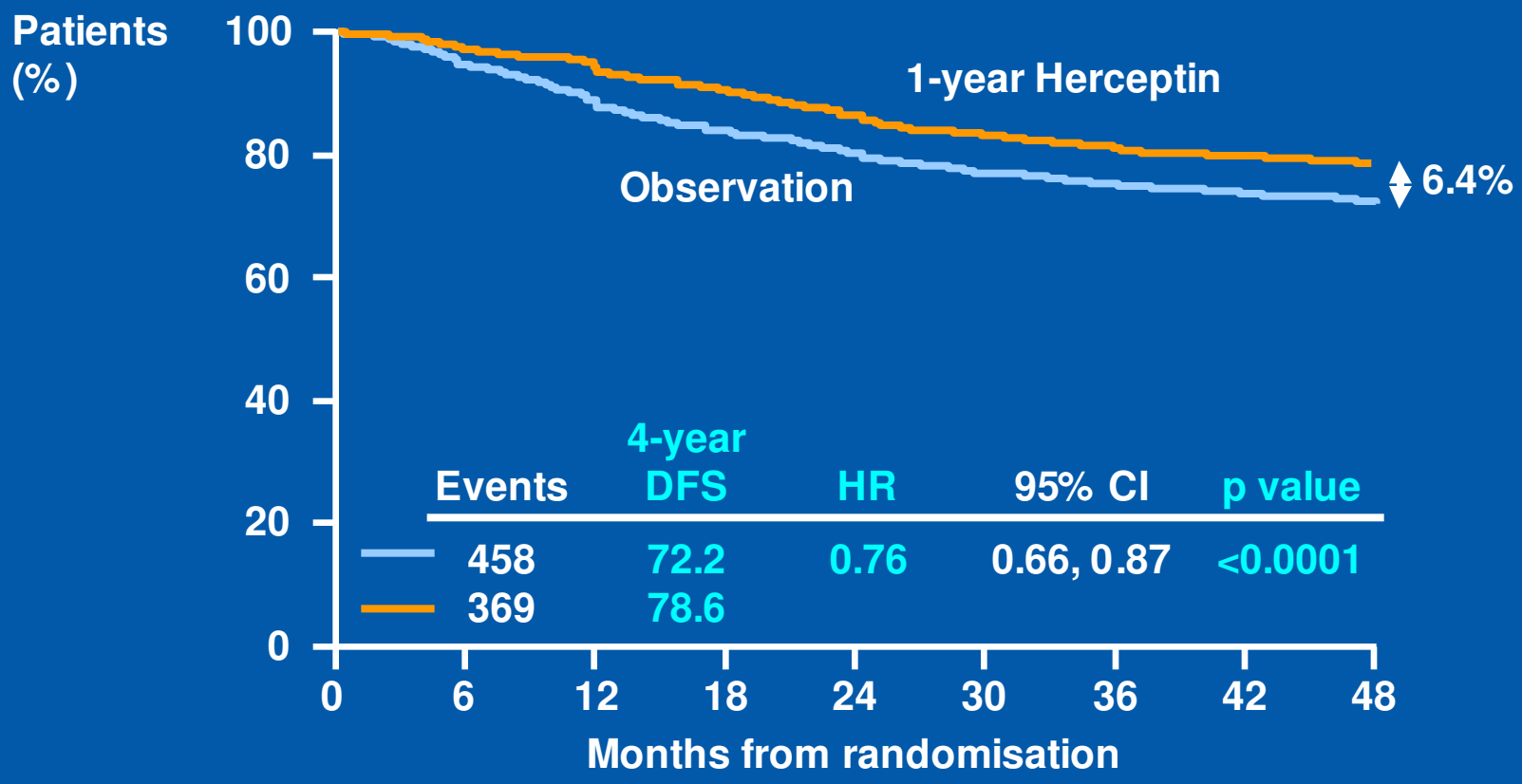


HERA: DFS and OS over time
1 and 2 years' follow-up

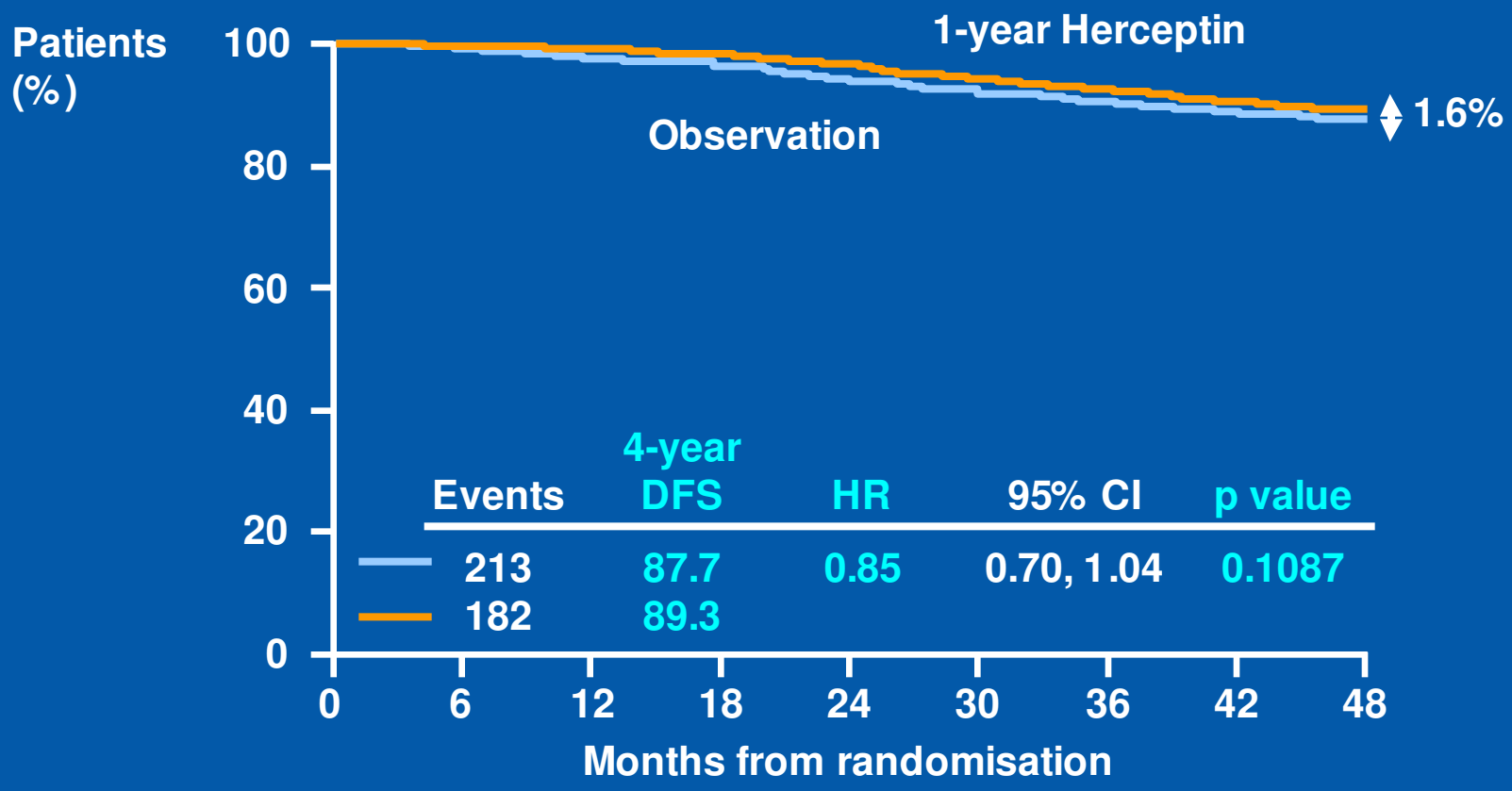


[1]Piccart-Gebhart et al 2005;
[2]Smith et al 2007

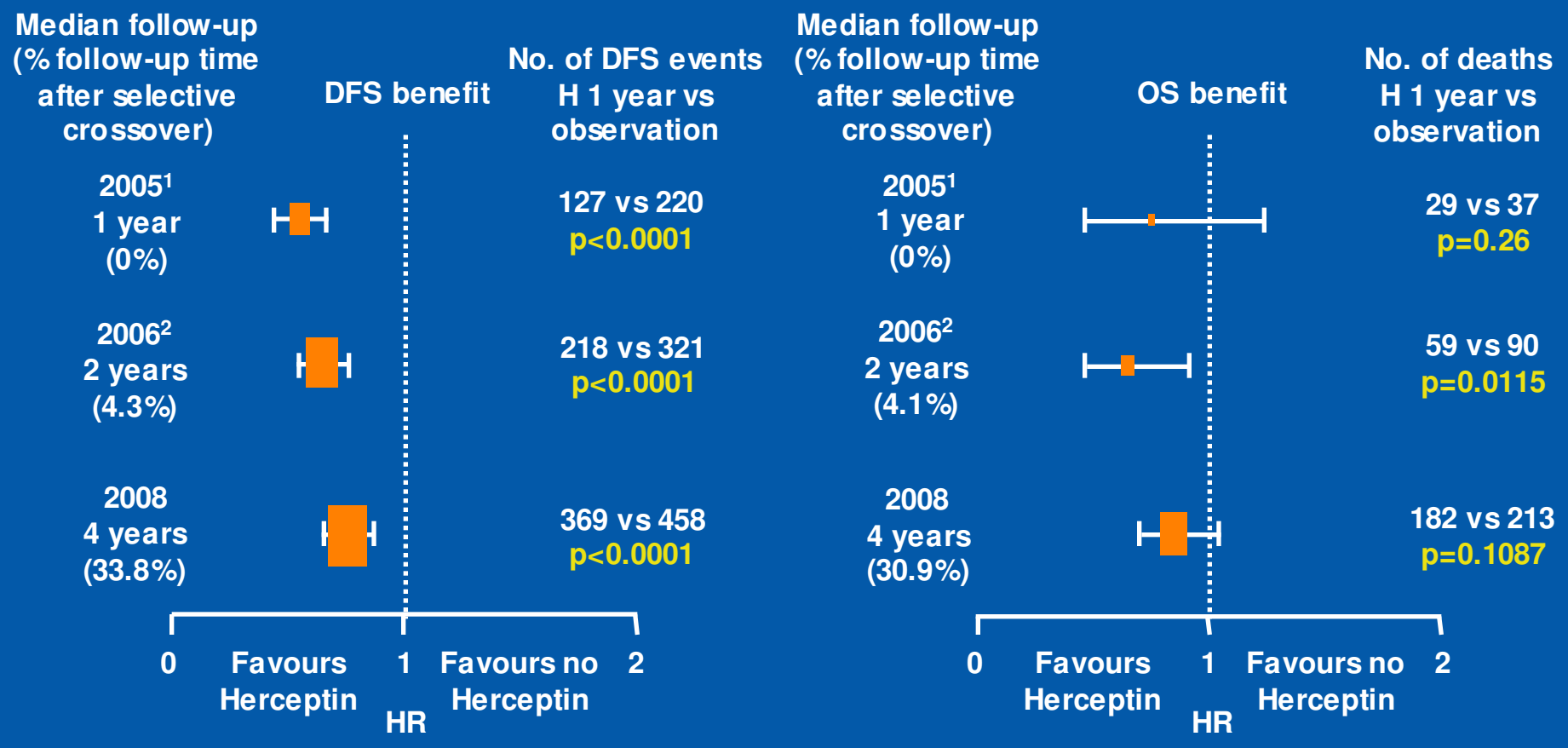
DFS (ITT): 4-year median follow-up



OS (ITT): 4-year median follow-up



HERA: DFS and OS over time



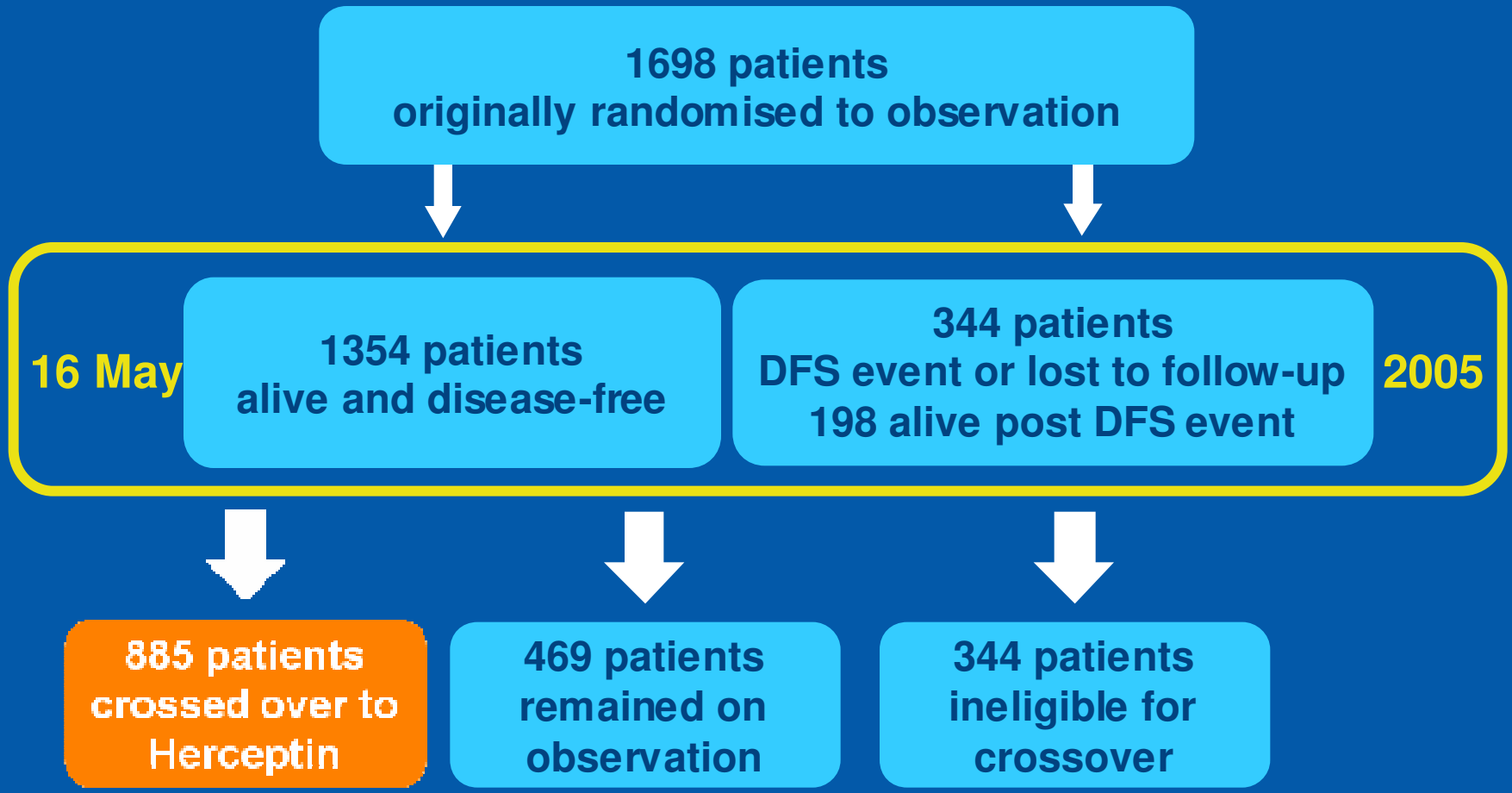
[1]Piccart-Gebhart et al 2005;
[2]Smith et al 2007

Specific question 1

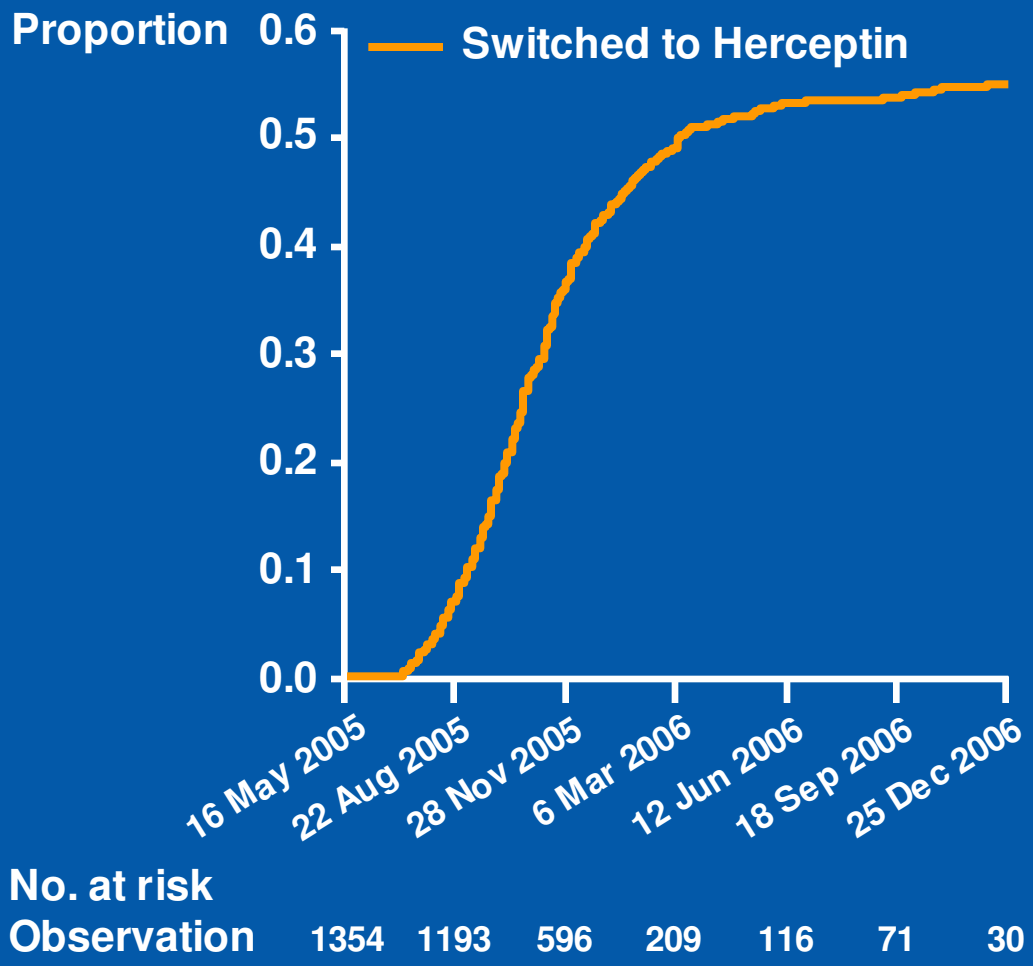
- **Crossover to Herceptin of 52% of the patients originally allocated to observation disrupted the randomised comparison between 1-year Herceptin and observation**
- *Question:*

  To what extent might crossover have biased the ITT analysis?

Flow chart of observation patients: by status on 16 May 2005



Time to selective crossover by calendar date (n=885)



	Median time (range), months
Randomisation to 1st dose	22.8 (<1-52.7)
Diagnosis to 1st dose	30.9 (9.1-58.3)
Follow-up from 1st dose	29.1 (0.8-34.5)

Baseline characteristics of observation patients alive and disease free on 16 May 2005

- Compared to patients who did not selectively cross over to Herceptin, those who did were more likely to:
  - be younger
  - have received anthracyclines and anthracyclines plus taxanes
  - be diagnosed with node-positive disease
  - have hormone receptor-positive tumours

Specific question 2

- **885 of 1354 patients (65%) in the observation group who were alive and disease free on May 16 2005 crossed over and received Herceptin**
- *Questions:*

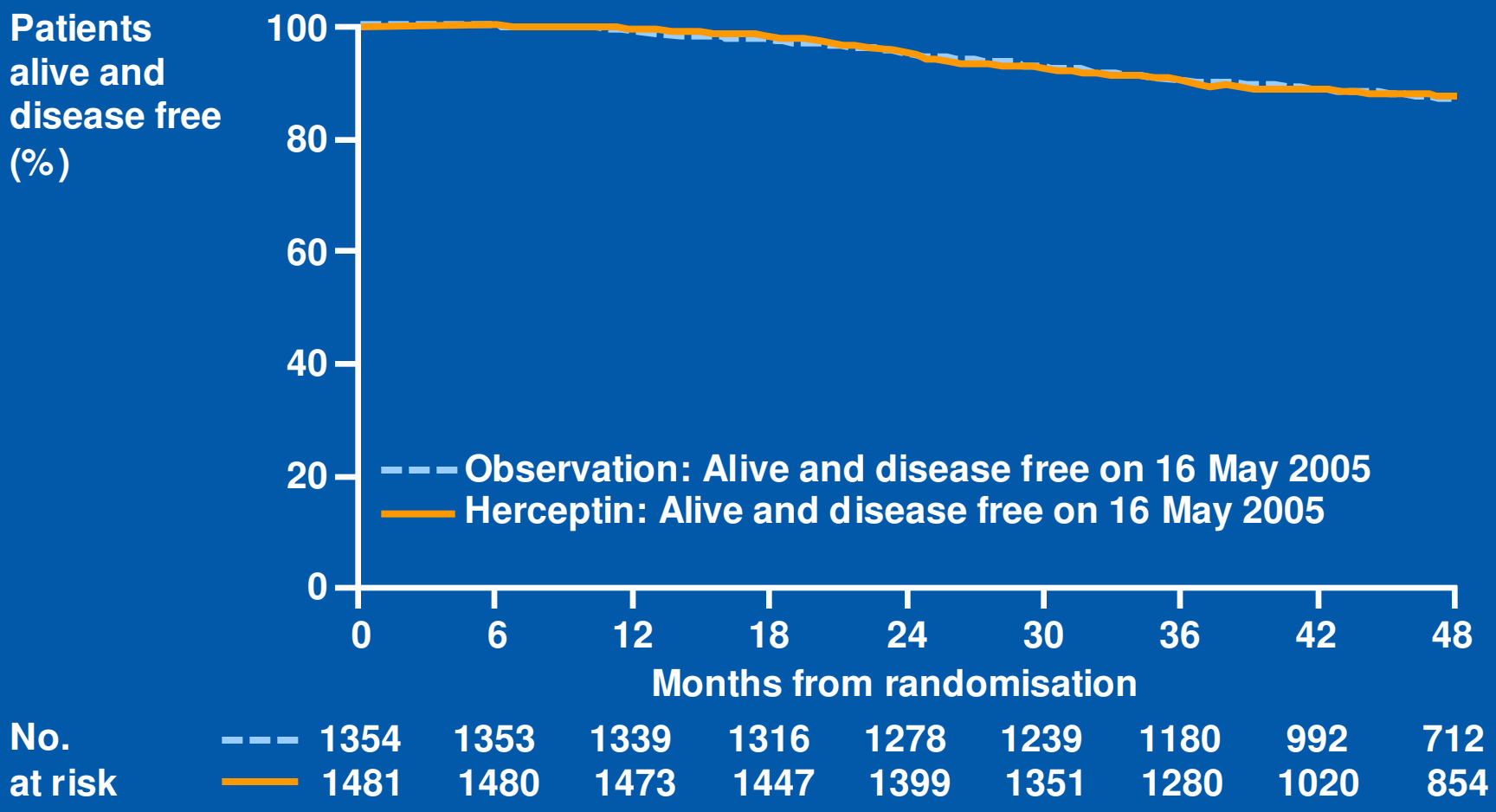
  What was the course of disease in the subgroups of observation patients who did or did not cross over to active therapy?

  Is there any effect of the late introduction of Herceptin?

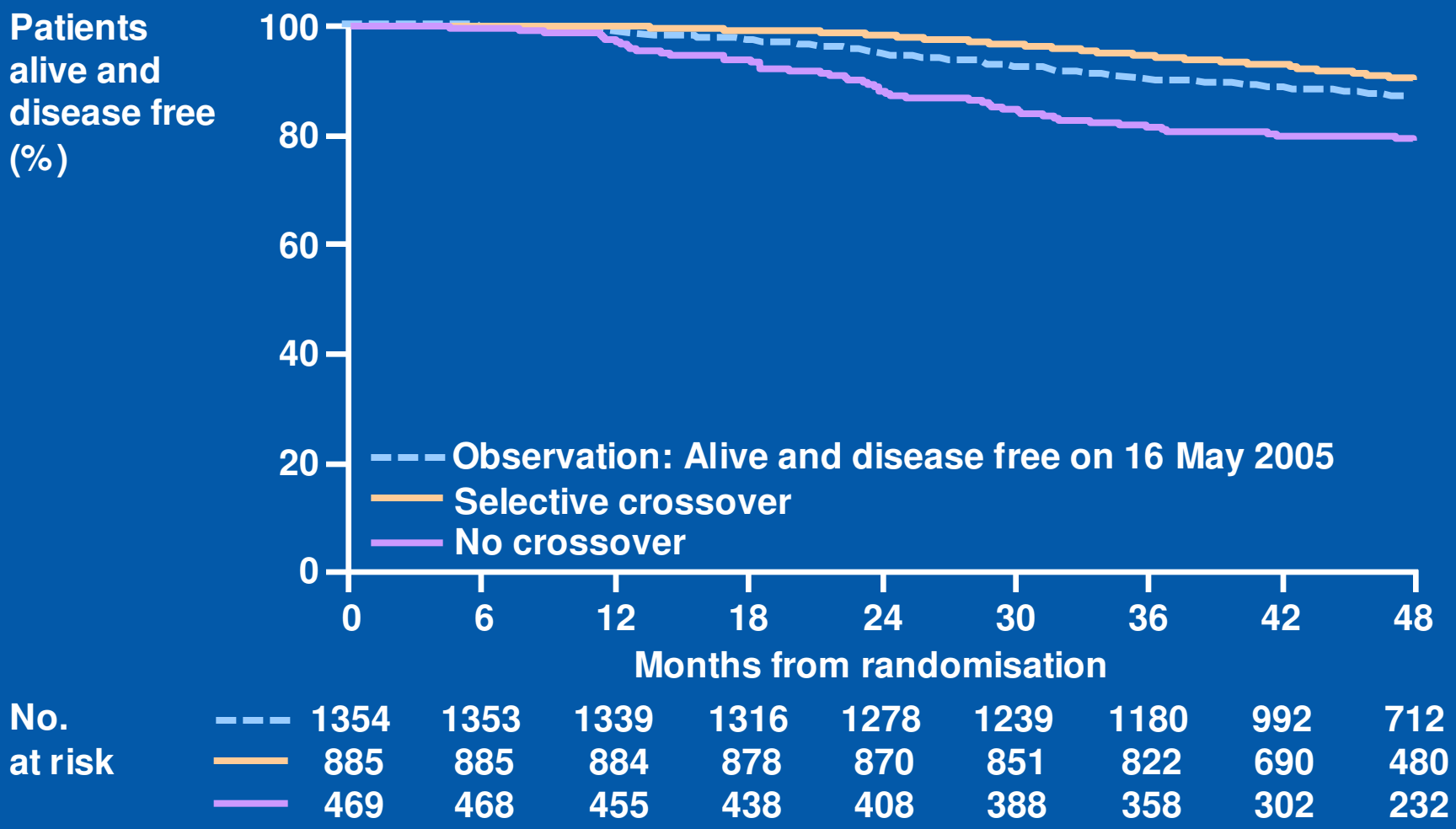
Landmark of 16 May 2005

- The landmark analysis considers only patients who were alive and disease free on 16 May 2005

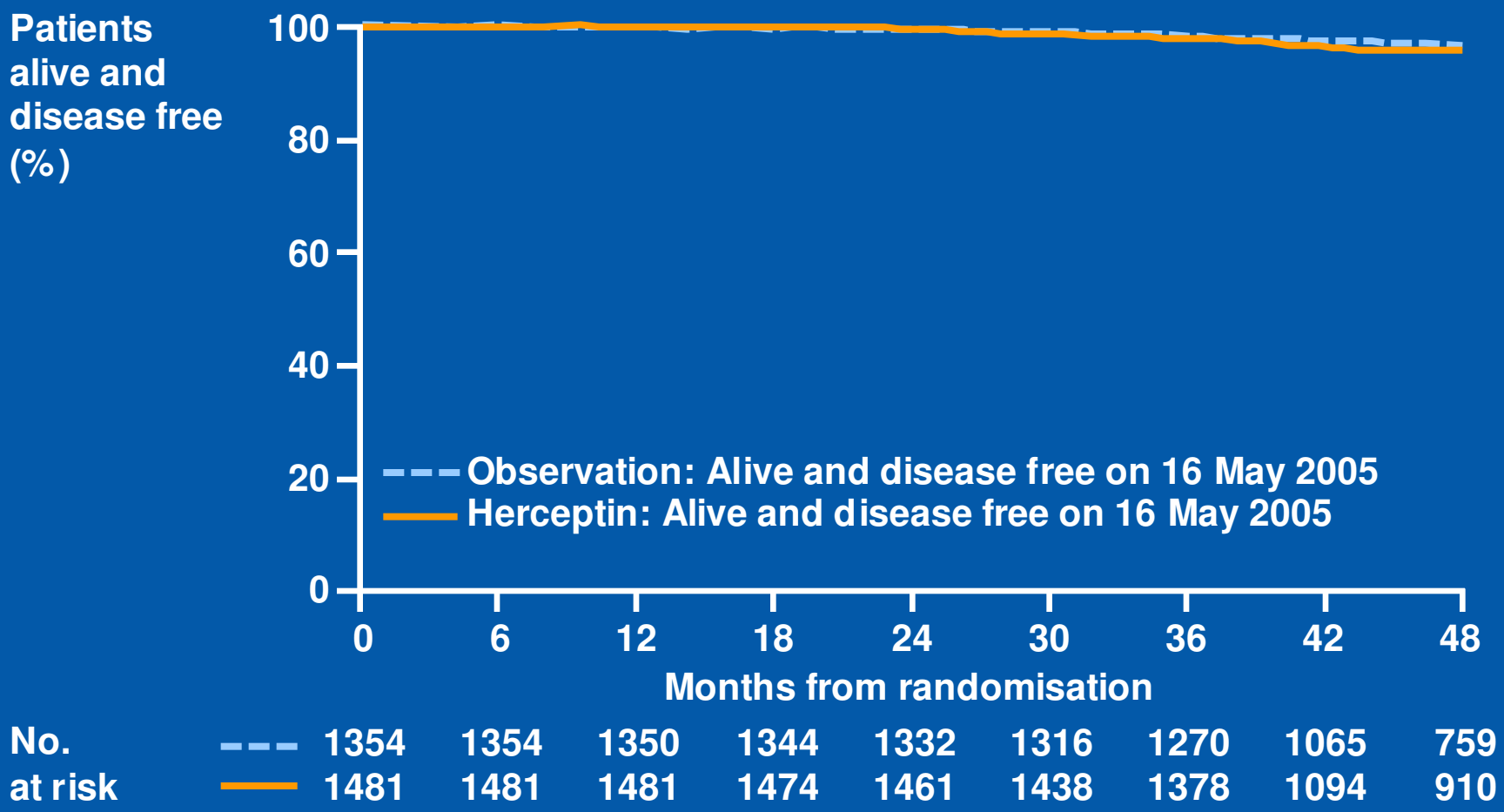
DFS (landmark analysis): Herceptin vs observation



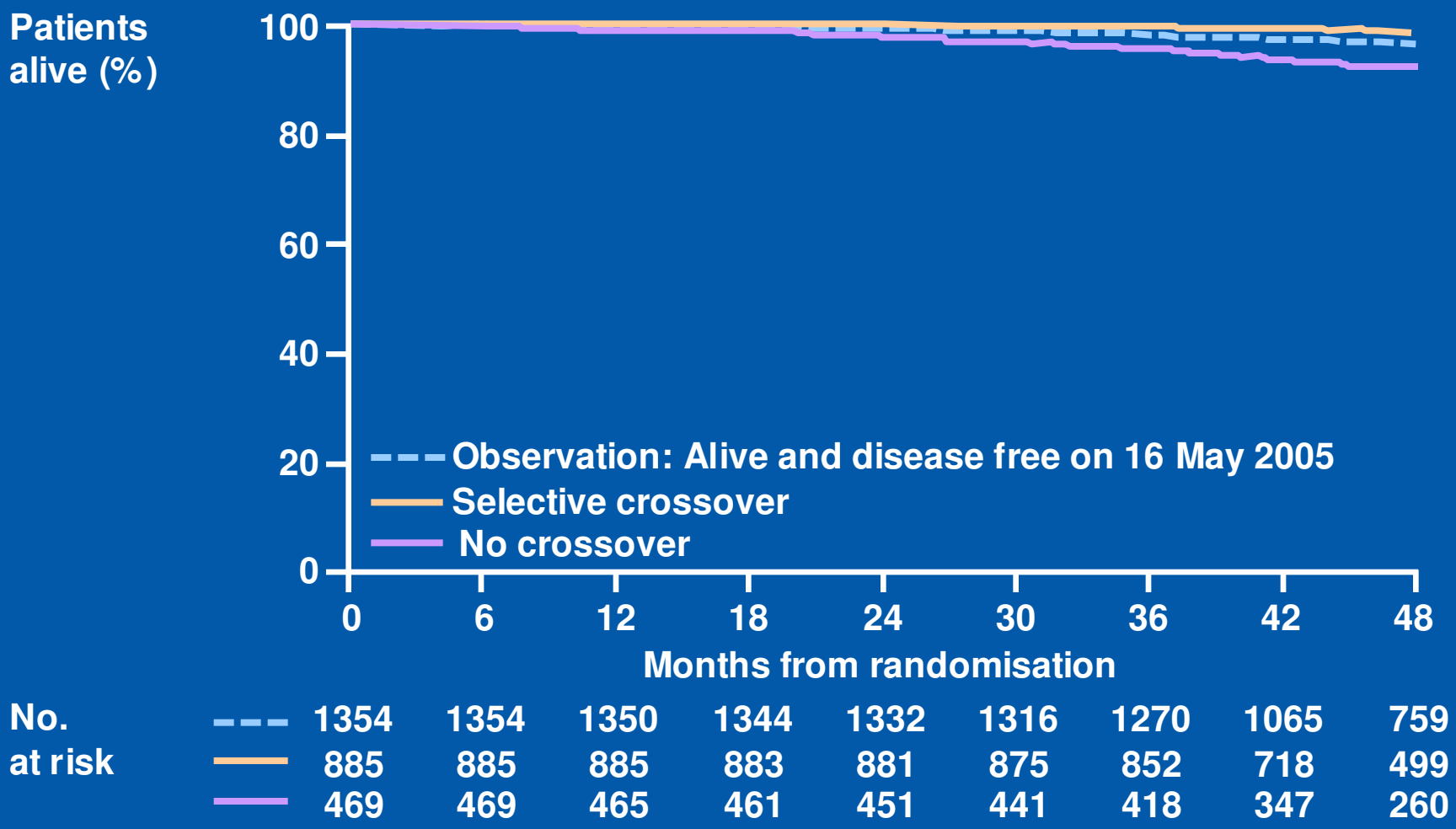
DFS (landmark analysis): observation (alive, no DFS event), selective crossover and no crossover



OS (landmark analysis): Herceptin vs observation



OS (landmark analysis): crossover vs no-crossover



Cardiac safety: safety analysis population[a]

	No. patients (%)	
	Observation[a] n=1719	1-year Herceptin n=1682
Cardiac death	1 (0.1)	0 (0.0)
Severe CHF (NYHA III and IV)	0 (0.0)	13 (0.8)
Symptomatic CHF (II, III and IV)	3 (0.2)	33 (2.0)
Confirmed significant LVEF drop	13 (0.8)	62 (3.7)
Herceptin discontinued due to cardiac problems		87 (5.2)

[a]Patients who crossed over are censored from the date of starting Herceptin treatment

CHF, congestive heart failure; NYHA, New York Heart Association;
LVEF, left ventricular ejection fraction

Cardiac safety: observation group

	No crossover after 16 May 05 n=469	Crossover n=885
Cardiac death	0 (0.0)	0 (0.0)
Severe CHF (NYHA III and IV)	0 (0.0)	0 (0.0)
Symptomatic CHF (II, III and IV)	1 (0.2)	9 (1.0)
Confirmed significant LVEF drop	5[a] (1.1)	26 (2.9)
Herceptin discontinued due to cardiac problems		43 (4.9)

[a]For 3 of the patients, the LVEF drop occurred between 16 May 05 and the date of the patient decision and may have influenced the patient decision

HERA 4-year follow-up data: summary (1)

- The updated analysis at 4 years was limited to 1-year Herceptin vs observation as recommended by IDMC
- Extensive selective crossover of observation patients to active therapy biased the ITT comparison
- Landmark analysis of observation patients who were disease free on 16 May 2005 explored the effects of later introduction of Herceptin
- Lack of randomisation limits the interpretation of the landmark analysis
  - different outcome due to drug effect or patient characteristics?

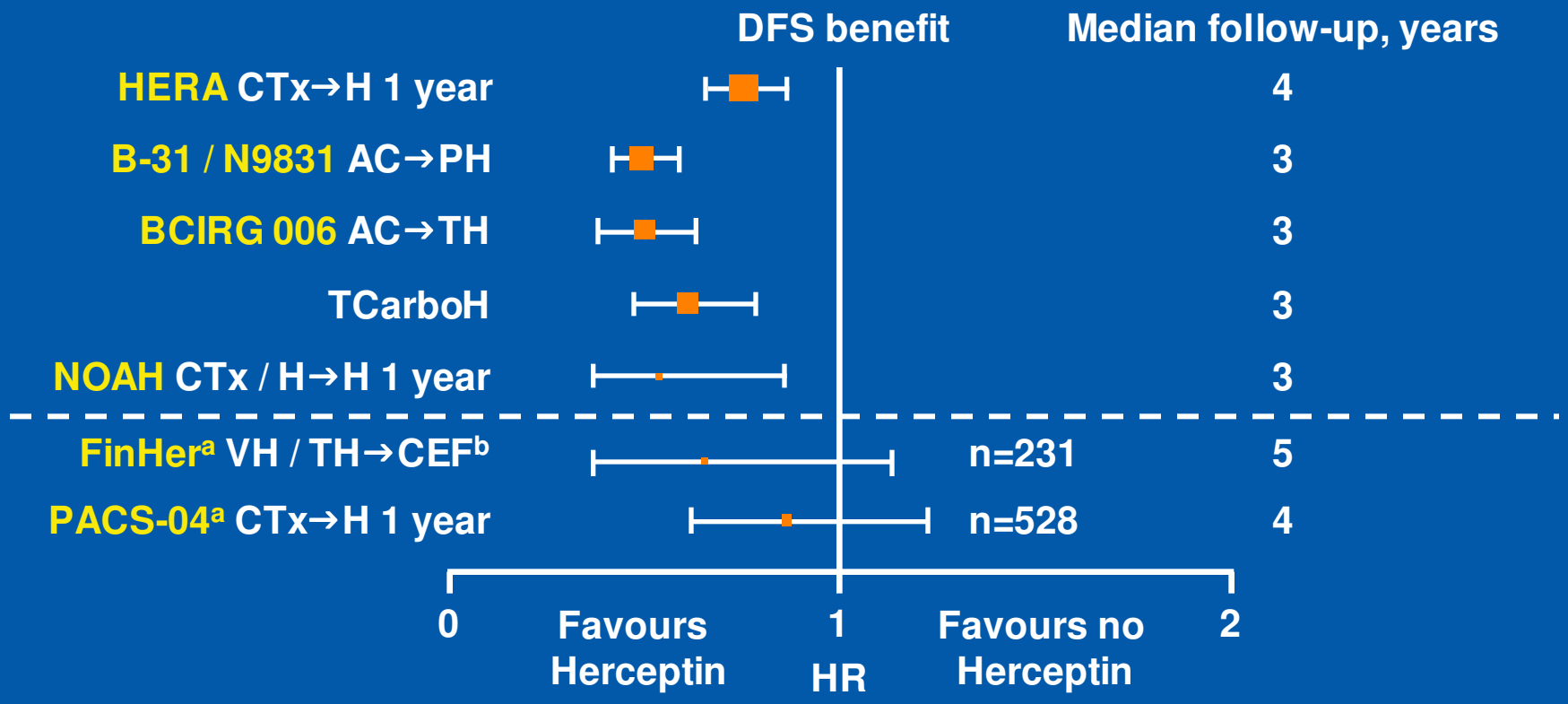
HERA 4-year follow-up data: summary (2)

- In HERA, the DFS benefit associated with Herceptin is maintained at 4-year median follow-up
- 50% of patients in the observation arm crossed over to Herceptin treatment, therefore the OS benefit is no longer statistically significant
- Patients crossing over at a later date appear to benefit from 1 year of Herceptin

HERA: conclusions and next steps

- 4-year follow-up data support the hypothesis that the risk of relapse in HER2-positive early breast cancer persists over time
- Prolonged exposure to the Herceptin antibody may improve efficacy
- This is being tested in the comparison of the 1-year and 2-year groups in the HERA study

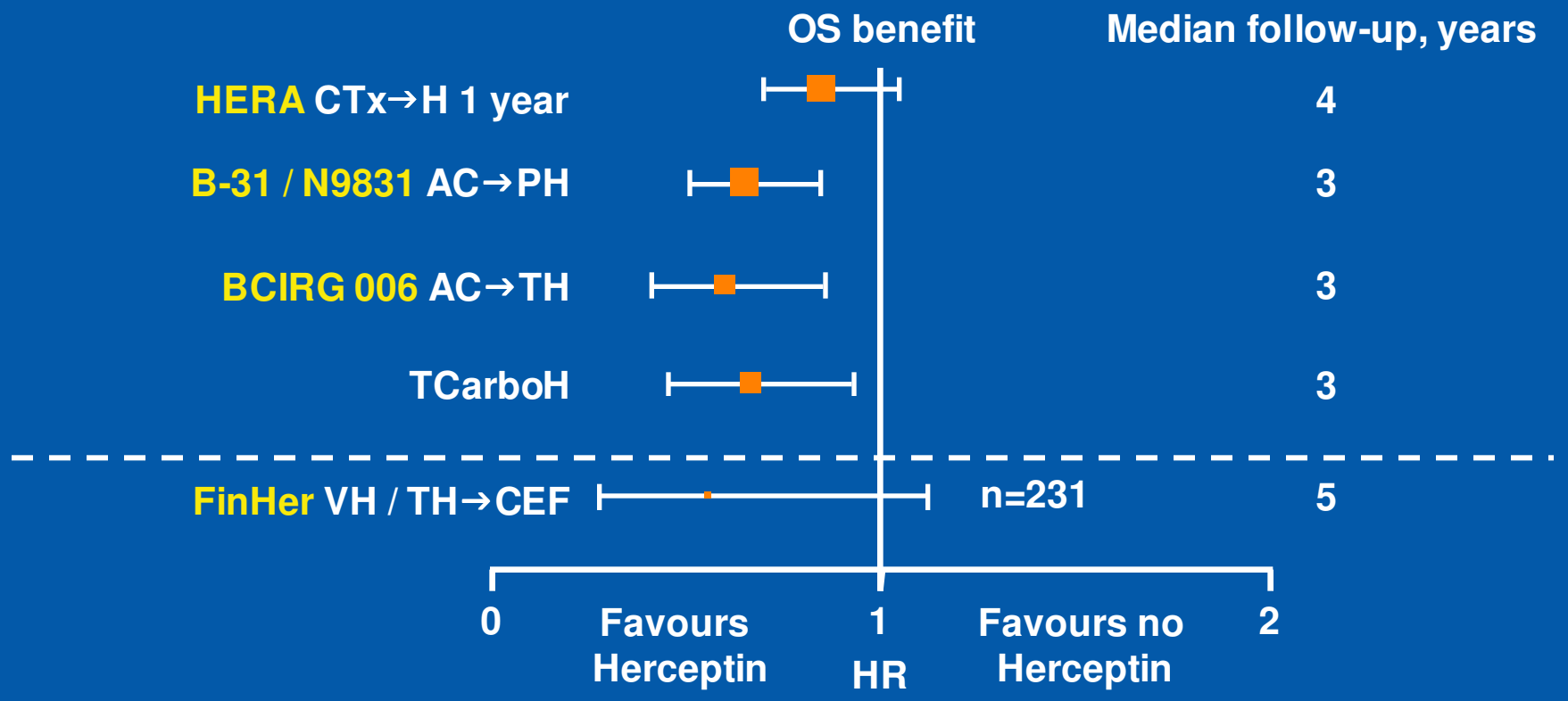
Additional studies demonstrate consistent DFS benefit for Herceptin



[a]Based on small subgroups of patients with HER2-positive breast cancer; [b]DDFS; CTx, chemotherapy; AC, doxorubicin, cyclophosphamide; P, paclitaxel; T, docetaxel; Carbo, carboplatin; V, vinorelbine; CEF, cyclophosphamide, epirubicin, 5-fluorouracil

Gianni et al 2008; Gianni et al 2009; Joensuu et al 2009; Slamon et al 2006; Perez et al 2007; Smith et al 2007; Spielmann et al 2007

1-year Herceptin treatment consistently reduces the risk of death by one-third



Gianni et al 2009;
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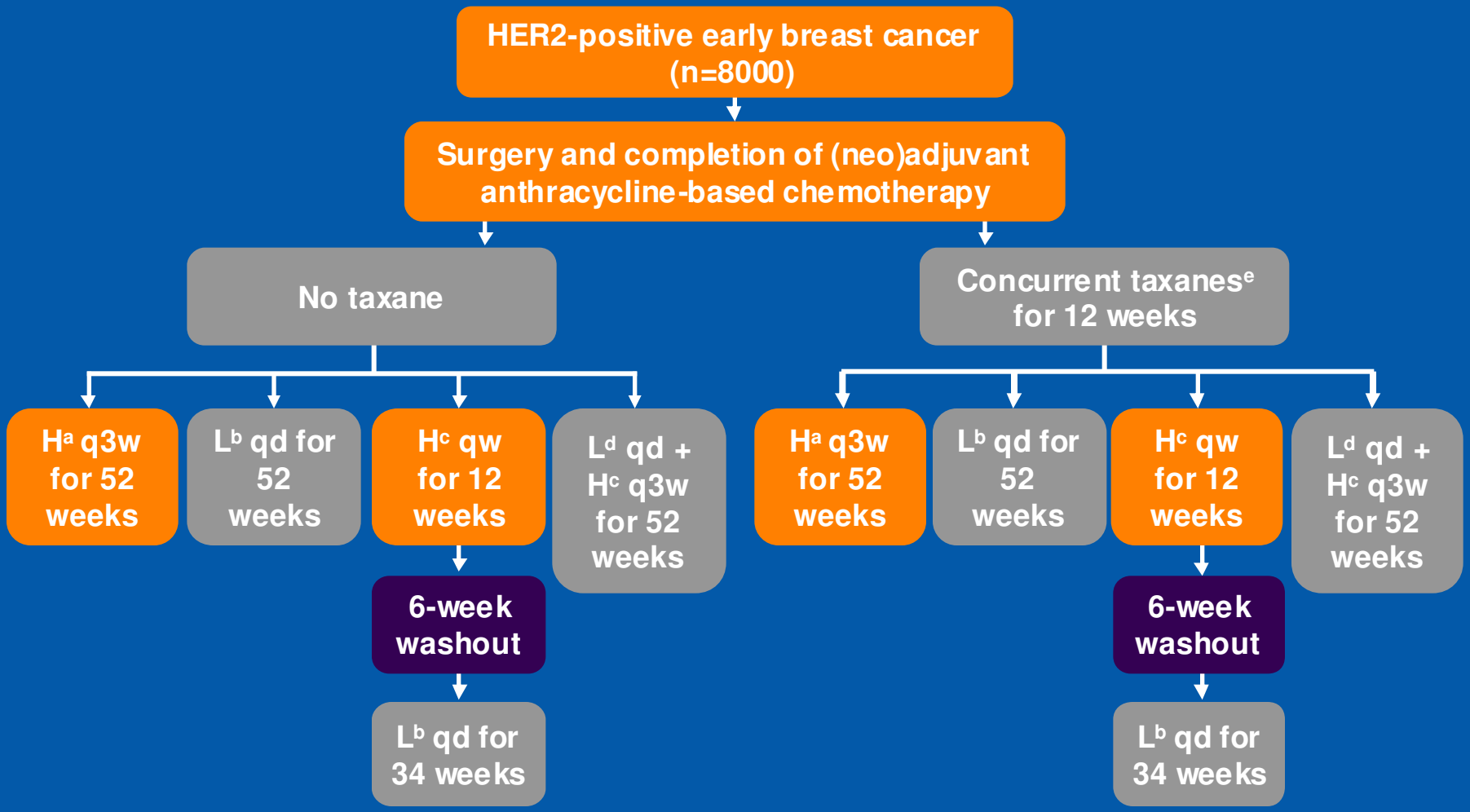
Perez et al 2007; Smith et al 2007

HER2-positive breast cancer: outstanding questions

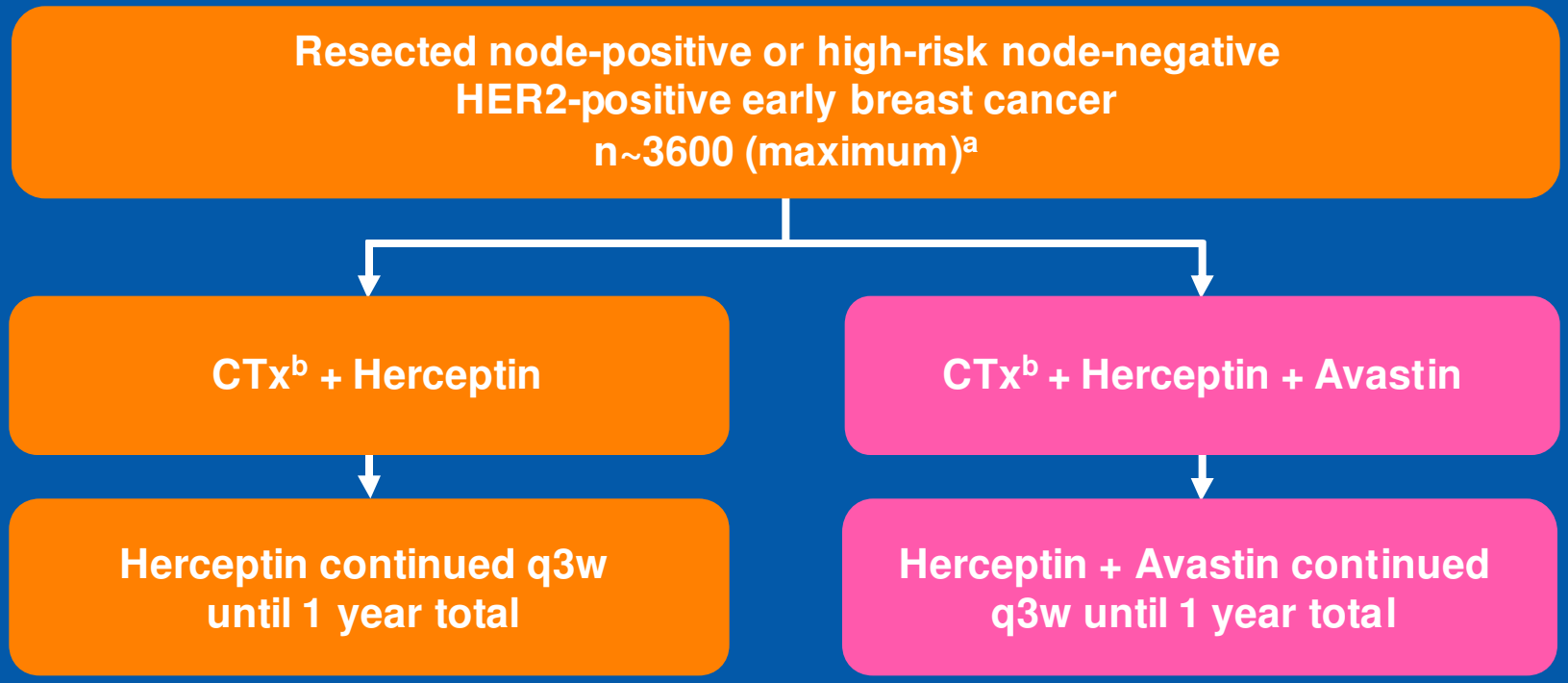
- Concurrent or sequential Herceptin therapy?
- Herceptin efficacy in lower-risk patients?
- Optimal treatment duration?
- Translational research?
- New combinations?
  - ALTTO (Herceptin + lapatinib)
  - BETH (Herceptin + Avastin)

ALTTO: Phase III randomised open-label trial comparing adjuvant lapatinib +/– Herceptin



[a]Herceptin 8 mg/kg iv loading dose followed by 6 mg/kg q3w; [b]Lapatinib 1500 mg; [c]Herceptin 4 mg/kg iv loading dose followed by 2 mg/kg qw; [d]Lapatinib 1000 mg; [e]Paclitaxel 80 mg/m^2 qw or docetaxel q3w

BETH: Phase III randomised trial comparing Herceptin-containing adjuvant regimens +/– Avastin



Primary endpoint: DFS
Secondary endpoints: OS; RFS; distant recurrence-free interval; safety; biomarker analysis

[a]Actual recruitment to date ~300;
[b]Docetaxel 75 mg/m^2 q3w + carboplatin AUC 6 q3w or docetaxel 100 mg/m^2 →FEC;
CTx, chemotherapy; q3w, three weekly

Conclusions

- 1 year of Herceptin remains the most appropriate and evidence-based approach for patients with HER2-positive early breast cancer
- Studies are ongoing to address optimal treatment duration
- Development of new anti-HER2 treatment regimens will lead to greater patient benefits