# Progression as an endpoint in CRC

Kevin Carroll, BSc, MSc, FRSS,
Global Statistical Leader, Oncology,
AstraZeneca Pharmaceuticals

# Progression is a meaningful endpoint in CRC trials

- AstraZeneca's phase III trial program data provide evidence to support PFS as a surrogate for survival in 1st line CRC.
- Recent literature is supportive, with improvements in PFS generally followed by improvements in survival.
- An 'event count' analysis provides a simple alternative to the analysis of PFS time and avoids concerns with respect to the determination of the time of progression.
- Progression is a meaningful endpoint in 1st line CRC[1,2], improvements in which represent a patient benefit and, as such, should be employed as the primary endpoint in clinical trials.

[1]Di Leo et al, Annals of Oncology 2004; [2]DeGramont et al, JCO, 2000

# Tomudex vs. 5FU-LV in 1st line CRC

- 3, multicenter, international randomized phase III trials in 1361 patients.
- Trials of similar design, similar incl./excl. criteria and commonly defined endpoints.
- One trial (0010[1]) conducted in North America, two trials (0003[2] and 0012[3]) predominantly in Europe and Australia.

[1]Pazdur, Proc *ASCO* 1997; [2]Cunningham, *Annals of Oncology*, 1996; [3]Cocconi, *JCO*, 1998.

# PFS and survival outcomes in the Tomudex trials

| | Progression-Free Survival | | Overall Survival | |
|---|---|---|---|---|
| Trial | Tomudex Events (%) | 5FU-LV Events (%) | Tomudex Events (%) | 5FU-LV Events (%) |
| 0003 (N=439) | 223 (94.6) | 216 (94.4) | 165 (74.0) | 152 (70.4) |
| 0010 (N=427) | 205 (94.5) | 192 (91.4) | 163 (75.1) | 136 (64.8) |
| 0012 (N=495) | 205 (84.6) | 195 (78.6) | 123 (49.8) | 119 (48.0) |
| **All (N=1361)** | **625 (91.0)** | **591 (87.7)** | **451 (65.7)** | **407 (60.4)** |
| | **HR* & 95% CI 1.30 (1.16, 1.46)** | | **HR* & 95% CI 1.17 (1.03, 1.34)** | |

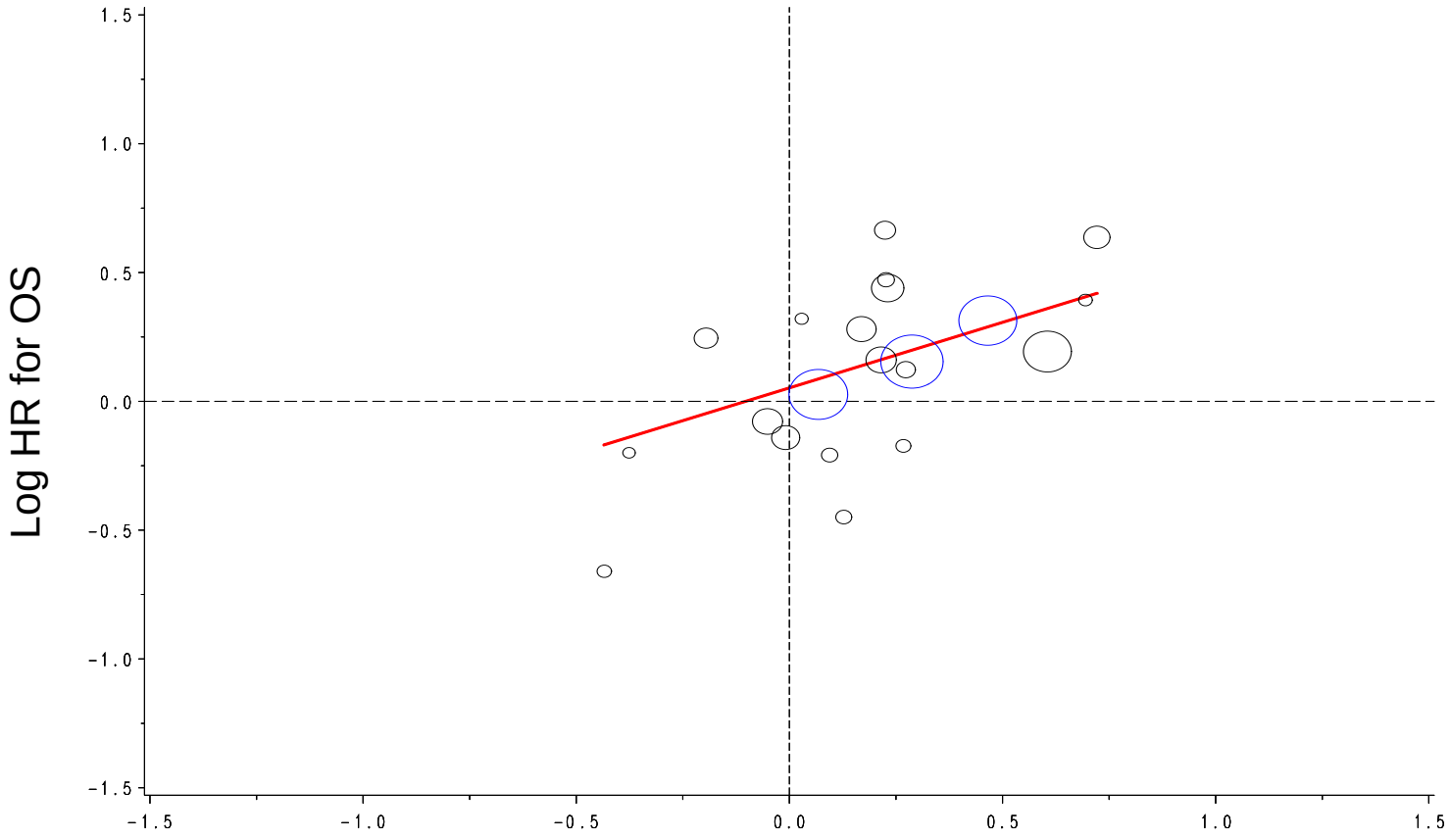
*HR=Hazard ratio from an unadjusted log rank test

# Evidence PFS is a surrogate for survival in the Tomudex program

- 53% of the treatment effect on survival is explained by the effect of treatment on PFS[1,2].
  - Survival is not significant after adjustment for PFS; HR = 1.08 (0.94, 1.23), p=0.27.
- The relative effect[3] of treatment on survival vs. PFS is estimated to be 0.51 (0.11, 0.91).
  - If PFS increases by 50%, expect survival to increase by 29% 95% CI (13%, 48%).

[1]Prentice, Stat in Med, 1989; [2]Freedman et al, Stat in Med, 1992; [2]Buyse and Molenbergs, 1998.

# Positive association between treatment effects on survival and PFS in 1st line Tomudex CRC trials




r=0.48, p=0.0247

Size of circle proportional to N pts in region/trial.

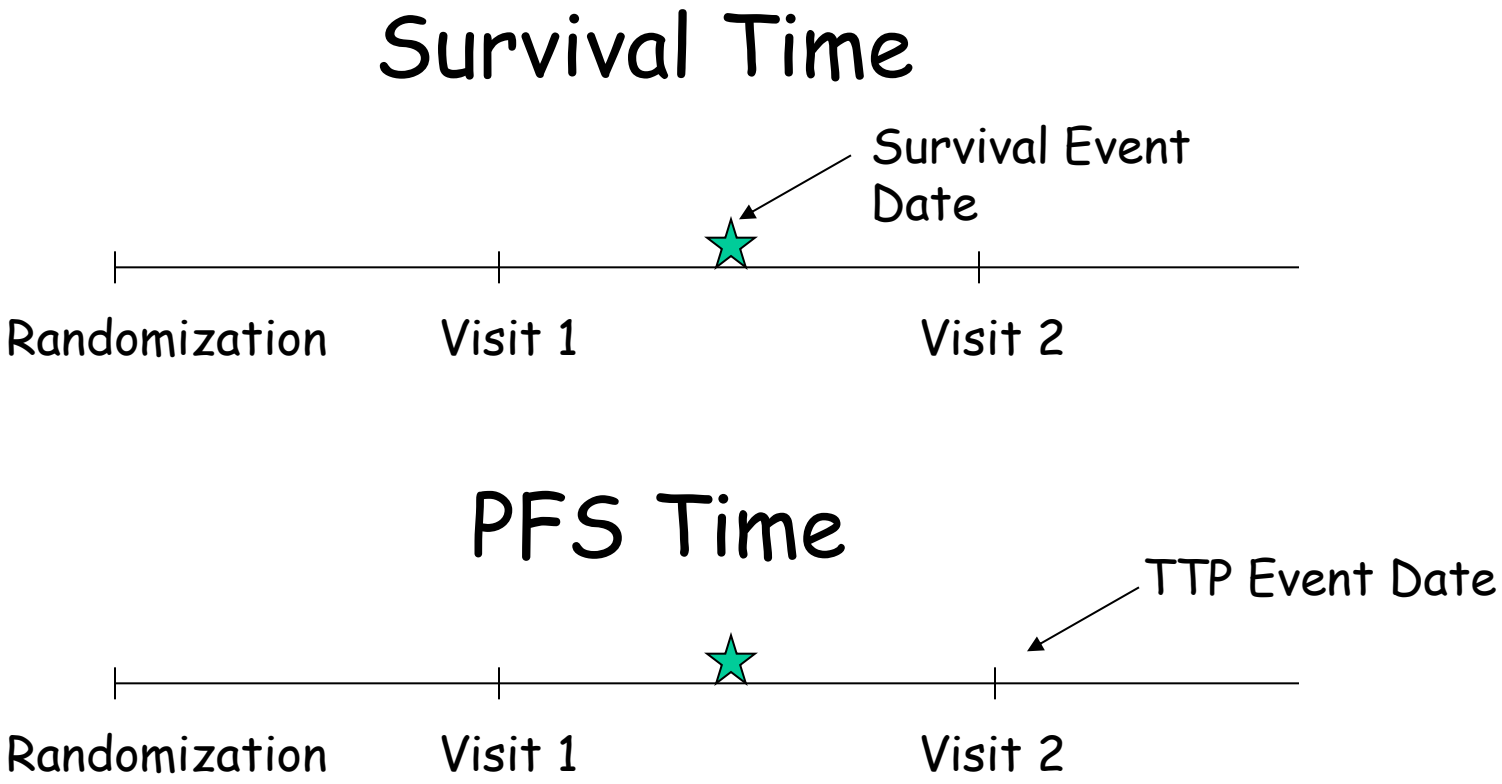
# PFS and survival data from recently completed trials in 1st line CRC

| Comparison | Reference | Total No. of patients | Effect† on PFS | Effect† on survival |
|---|---|---|---|---|
| IFL v FL | Saltz[1] | 457 | +56%* | +28%* |
| IFL v FL | Douillard[2] | 385 | +69%* | +23%*# |
| Oxali +FL v FL | DeGramont[3] | 420 | +72%* | +25%* |
| Oxali +FL v FL | Giacchetti[4] | 200 | +43%*# | -3%NS# |
| Bevac +IFL v IFL | Hurwitz[5] | 815 | +85%* | +54%* |
| Oxali +FL vs. IFL | Goldberg[6] | 531 | +35%* | +52%* |
| Oxali +FL vs. IrOx | Goldberg[6] | 528 | +39%* | +20%NS |

*2p<0.05. #ratio of medians. †Inverse hazard ratio.

[1]NEJM, 2000; [2]Lancet, 2000; [3]*JCO*, 2000; [4]*JCO*, 2000; [5]Proc *ASCO*, 2003; [6]*JCO*, 2004;

# Actual PFS time is often unknown in clinical trials[1,2]



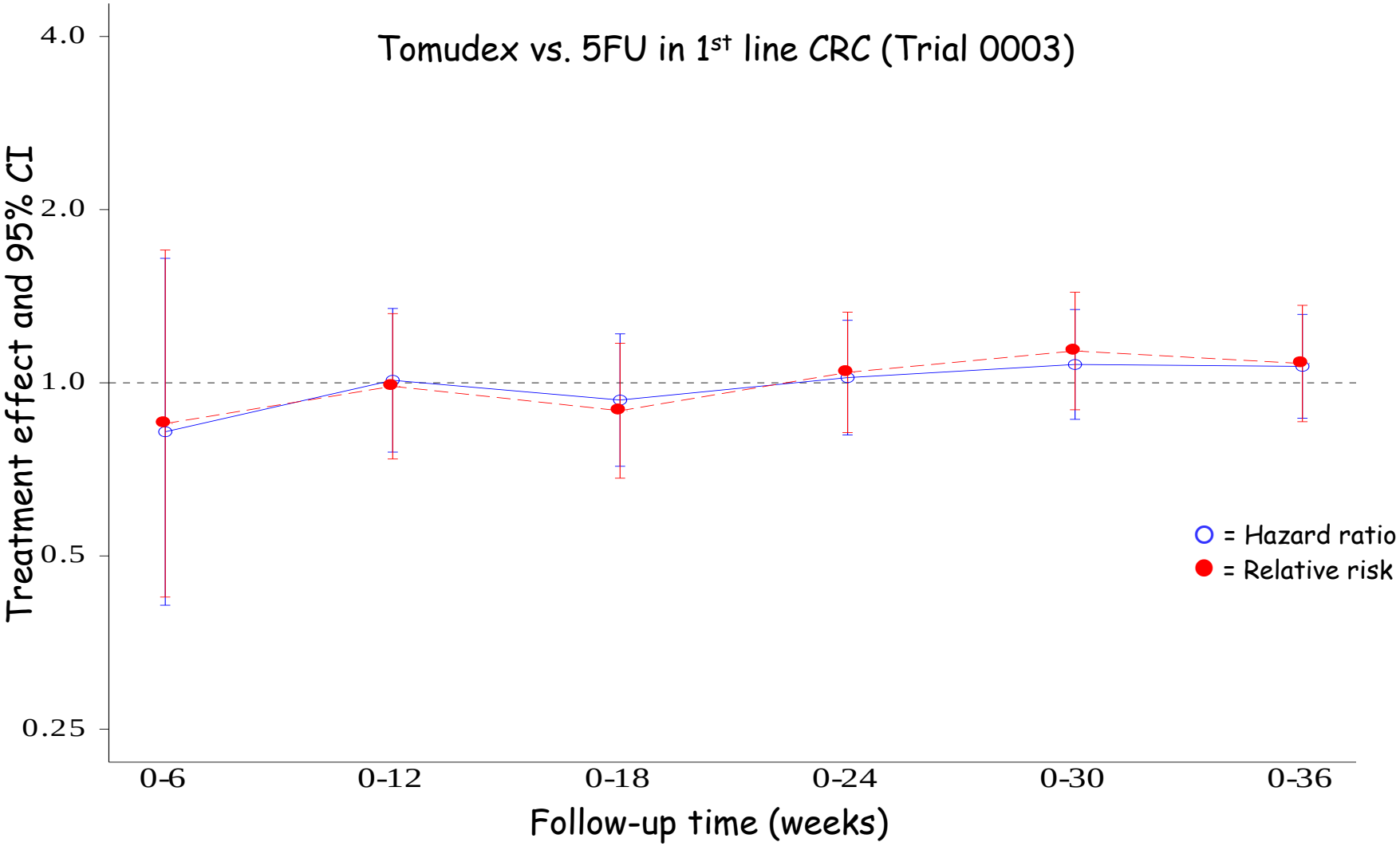

[1] Slide adapted from Dr G Williams, web link; [2] Williams et al, Proc ASCO, 2002.

# Using overall 'event count' to compare treatments for progression outcome[1,2,3]

- As an alternative to PFS time, treatments could be compared on the overall event count over the trial follow-up period
  - free from concerns and potential biases associated with the timing of the event.
  - can derive the relative risk (RR) of progression between treatments.
  - Little loss in statistical power under most circumstances providing fewer than 75-80% of patients have progressed.
  - Is more powerful if treatment effect is delayed.

[1] Cuzick, Biometrics, 1982; [2] Gail, Cont Clinical Trials, 1985; [3] Carroll, Clinical Trials, submitted 2004.

# Overall event count analysis provides similar results compared to conventional PFS time, log rank analyses



# Summary

- AstraZeneca's phase III trial program data provide evidence to support PFS as a surrogate for survival in 1st line CRC.
- Recent literature is supportive, with improvements in PFS generally followed by improvements in survival.
- An 'event count' analysis provides a simple alternative to the analysis of PFS time and avoids concerns with respect to the determination of the time of progression.
- Progression is a meaningful endpoint in 1st line CRC[1,2], improvements in which represent a patient benefit and, as such, should be employed as the primary endpoint in clinical trials.

[1]Di Leo et al, Annals of Oncology 2004; [2]DeGramont et al, JCO, 2000