Phase II Double-Blind Placebo-Controlled Study of Armodafinil for Brain Radiation Induced Fatigue

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Background

- Most common acute side effects of brain radiation therapy (RT) - fatigue, drowsiness, ↓physical functioning, and ↓QOL
- Modafinil
  - Wakefulness promoting drug FDA approved for excessive sleepiness associated with narcolepsy and obstructive sleep apnea; available in 150/200 mg doses
  - Reduces fatigue and ↑cognitive function in breast cancer patients receiving chemotherapy (Jean-Pierre et al, Cancer 116:3513, 2010) and breast cancer survivors (Kohli et al, Cancer 115:2605, 2009) (off-label use)
- Armodafinil – R-enantiomer of modafinil
  - For present study 150mg dose utilized

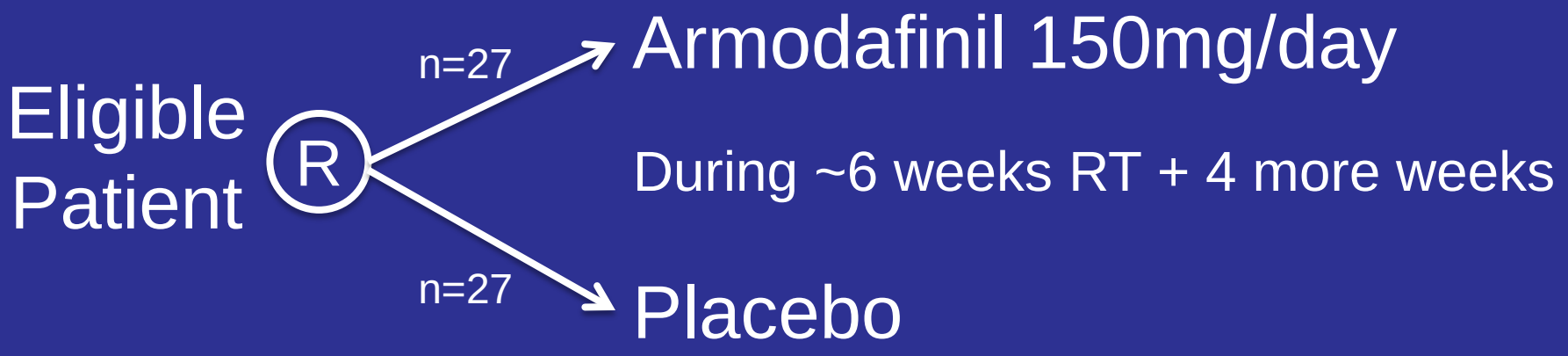
Objectives Phase II Study

- Estimate efficacy of armodafinil in 1° brain tumor patients receiving partial- or whole-brain RT
  - Fatigue – Brief Fatigue Inventory (BFI)
  - Sleepiness – Epworth Sleep Scale (ESS)
  - QOL – FACT, FACT-Brain, FACIT-Fatigue
  - Cognitive Function – Wake Forest neurocognitive function battery (subsequent report)
- Estimate toxicity
- Determine whether larger Phase III study warranted

Methods

- Eligibility Criteria
  - ≥18 years old
  - 1° brain tumor (benign, low- or high-grade)
  - Planned RT dose ≥45Gy, ≥1.5Gy per fraction
  - KPS ≥60
  - Hgb ≥10g/dL
  - No severe headaches
  - Concurrent chemotherapy allowed

Study Schema



- Patients stratified by KPS (60-80 vs. 90-100) and +/- chemotherapy
- Patient assessments:
  - Baseline, end RT, 4 weeks after end RT – BFI, ESS, FACT, FACT-Brain, FACIT-Fatigue
  - Weekly during RT – BFI

Results – Patient Characteristics

- Median age 59yo
- 54% female
- 93% white
- KPS: 41% 90-100, 59% 60-80
- 1° brain tumor type
  - 74% malignant glioma
  - 26% low-grade glioma or benign (meningioma, pituitary adenoma)

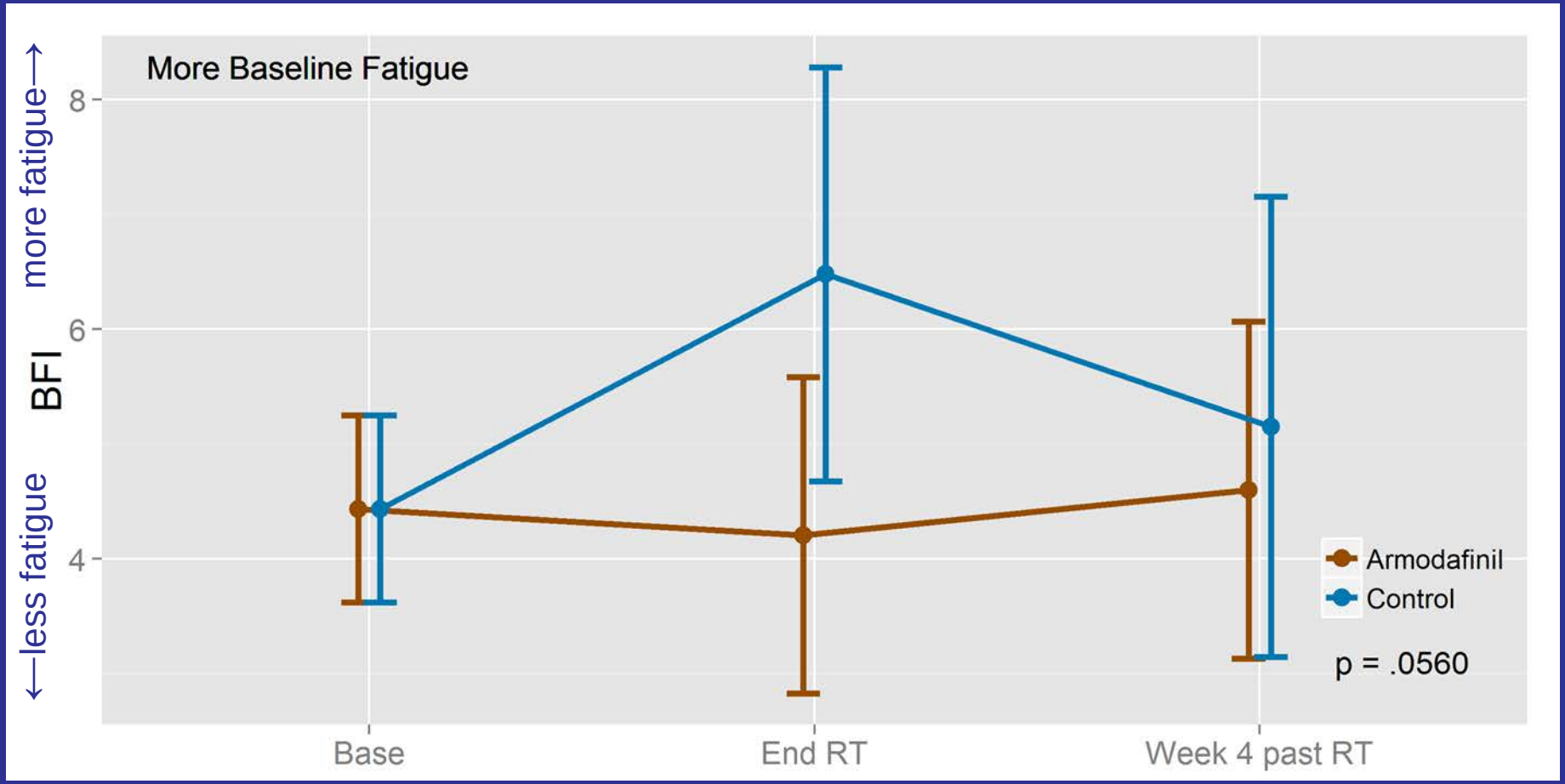
Results – Recruitment/Retention

- 54 patients enrolled 9/2010-10/2012
  - 52/54 patients received chemotherapy
- Retention 80%
  - 85% Armodafinil arm
  - 75% Placebo arm
- Overall self-reported compliance 94%

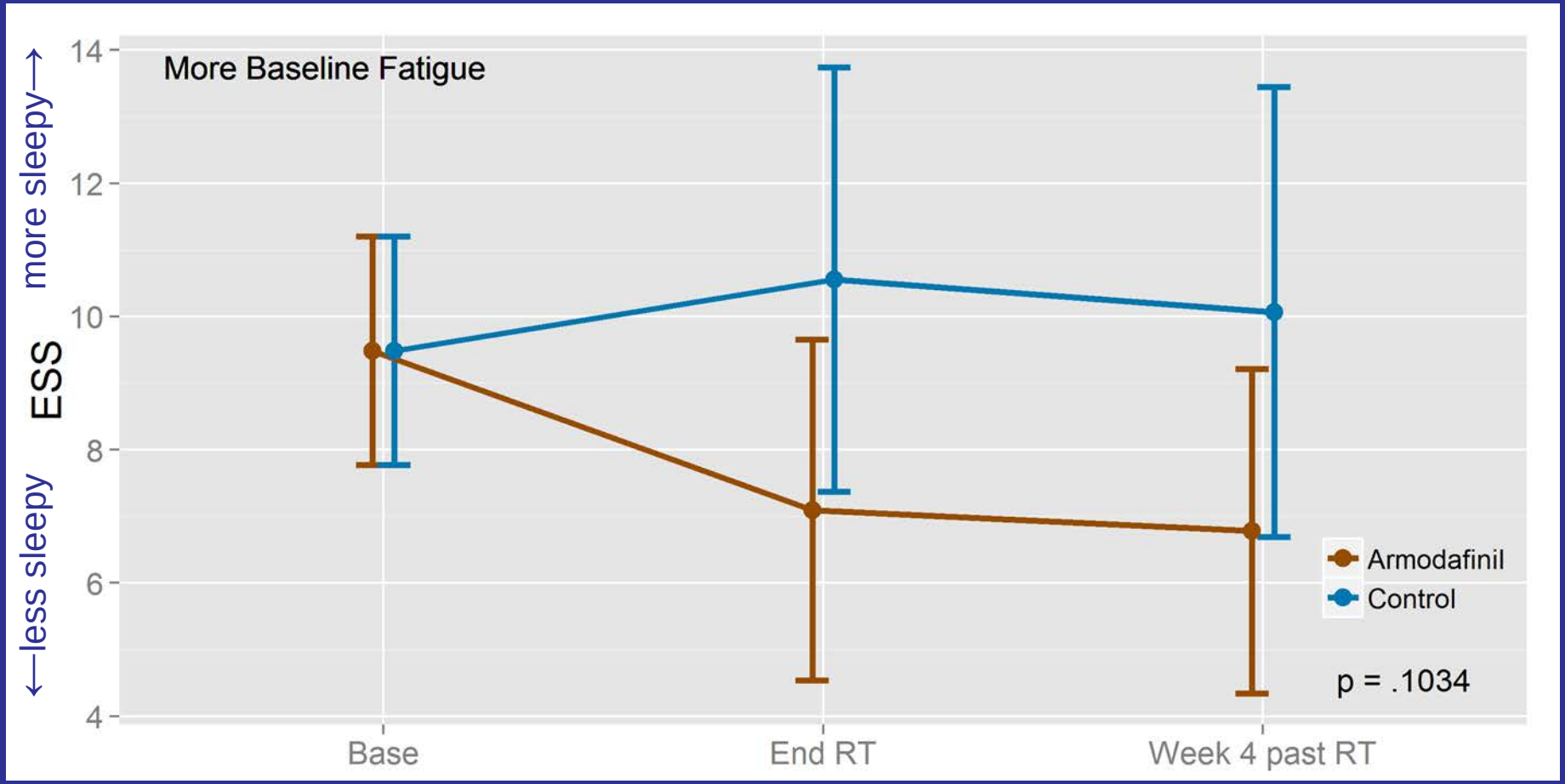
Results - More Fatigued Patients

- No statistically significant differences in outcomes (baseline vs. end RT or 4 week after end RT) between armodafinil and placebo-treated patients in any outcome (BFI, ESS, FACT, FACT-Brain, and FACIT-Fatigue)
- However, in more fatigued patients (FACIT-Fatigue subscale score >median), statistically significant ($p<0.05$) or suggestive ($p=0.05$-0.1) differences in were identified comparing baseline to end RT
  - No significant differences in patient character-istics between more/less fatigued patients

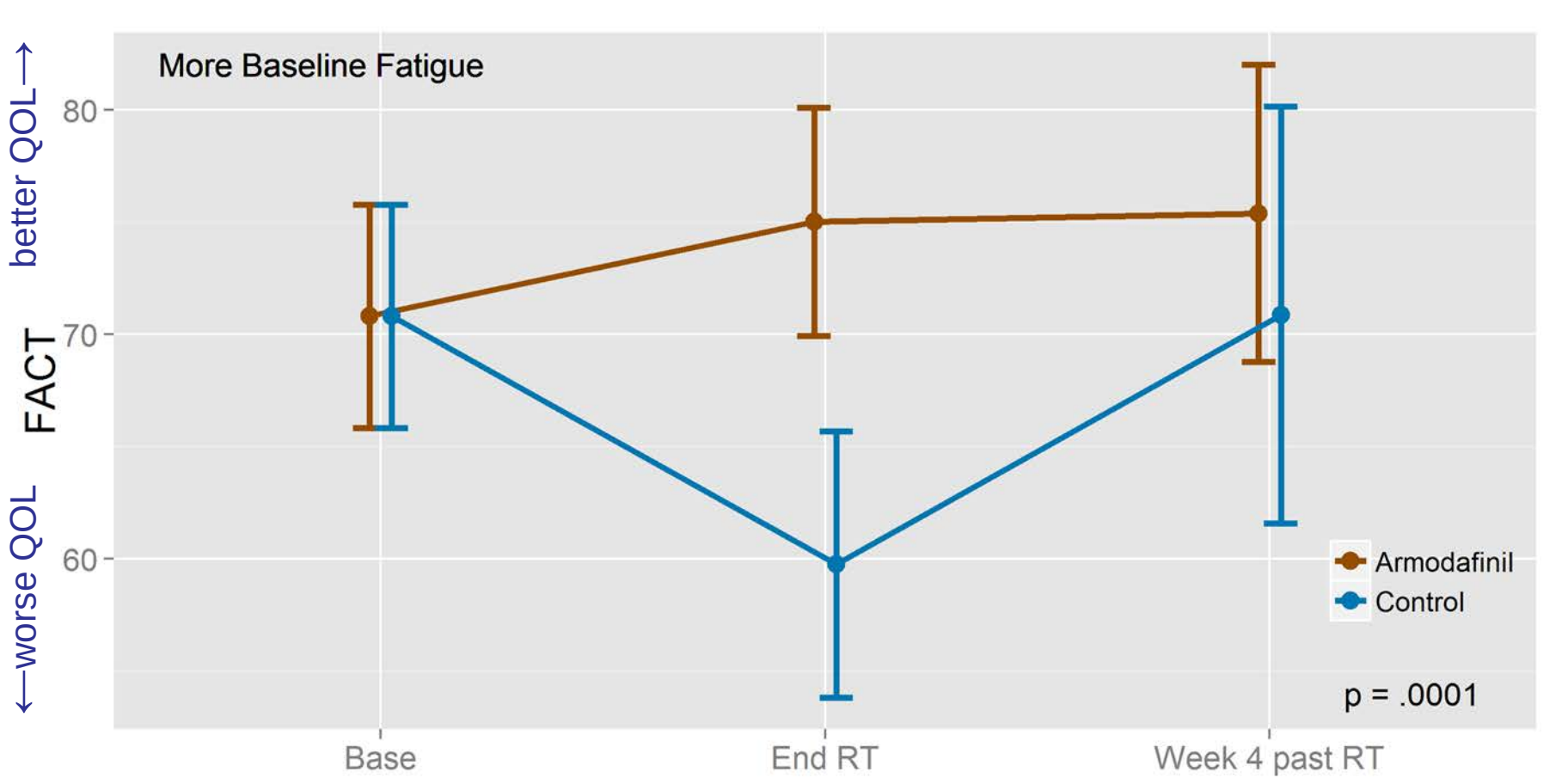
BFI in More Fatigued Patients



ESS in More Fatigued Patients

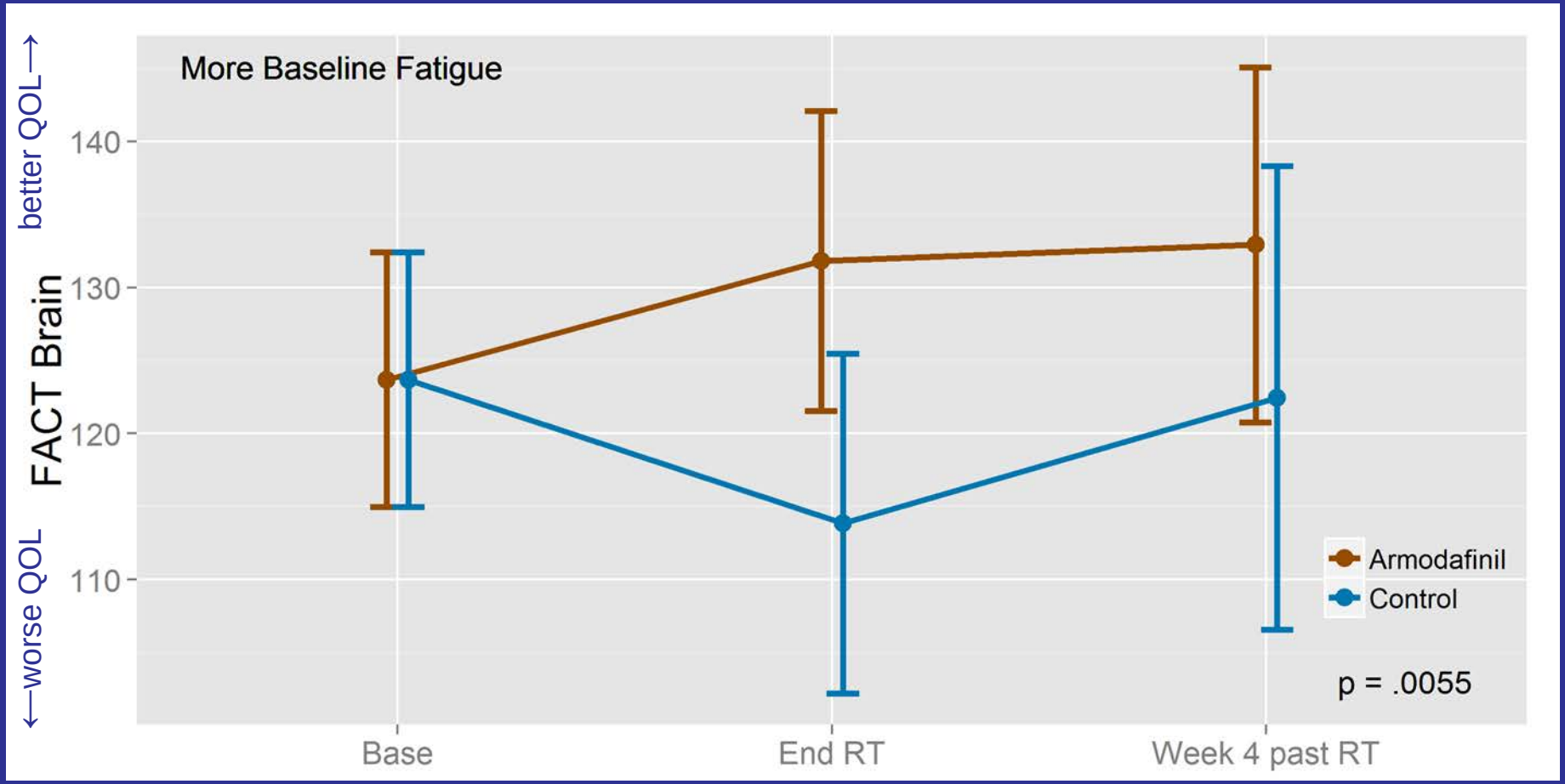


FACT in More Fatigued Patients*

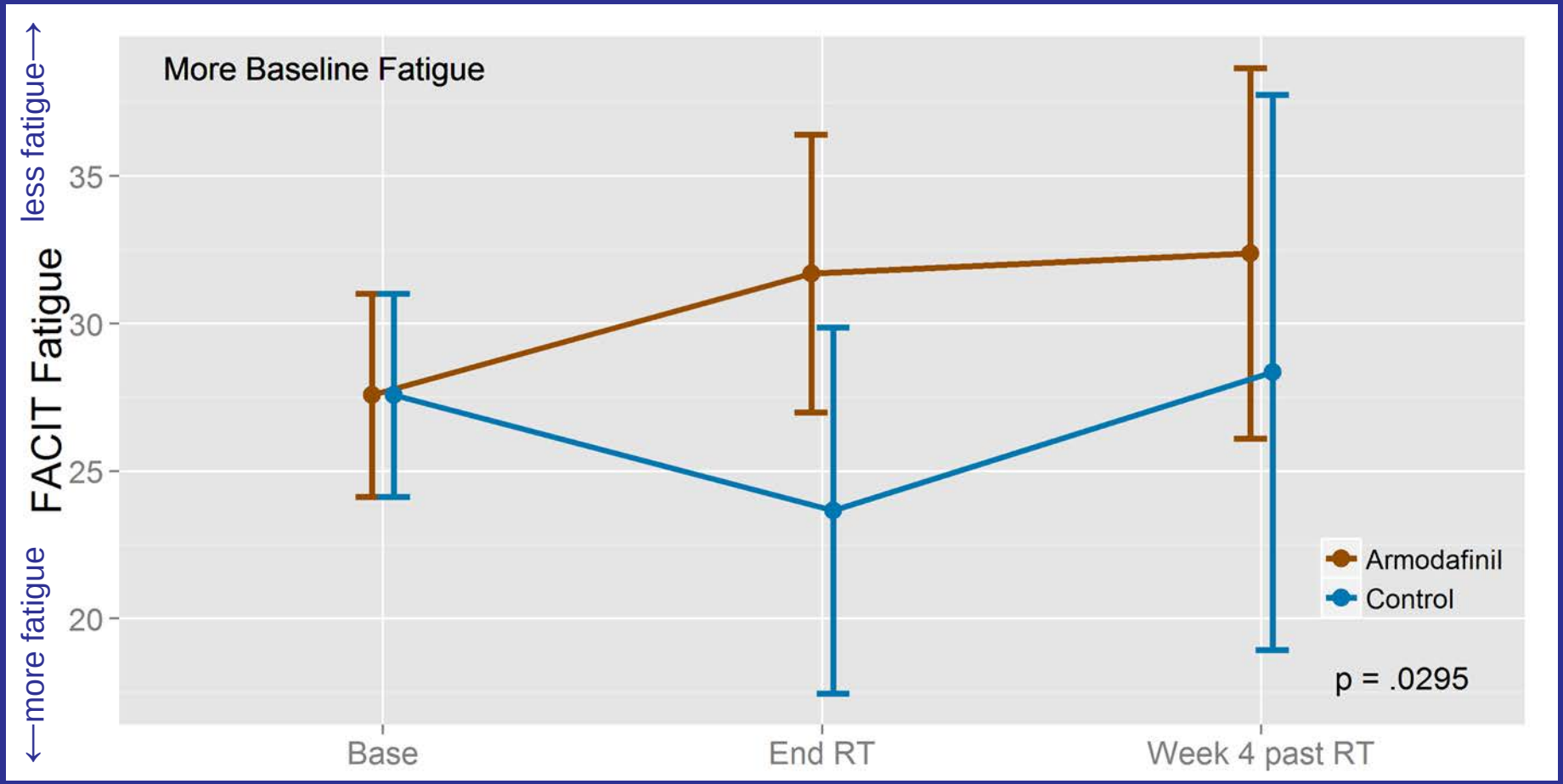


*Improvement mostly due to improved physical well-being

FACT-Brain in More Fatigued Patients



FACIT-Fatigue in More Fatigued Patients



Results - Toxicity

- No grade 4 or 5 toxicities; incidence grade 2 and 3 toxicities similar between treatment arms
- 10 SAEs; 4 possibly related to treatment
  - 3 on placebo arm: grade 2 seizure, grade 3 ↑LFTs, grade 4 agitation/personality change,
  - 1 on armodafinil arm: grade 3 headache/chest pain
- Most common grade 2+3 toxicities reported:
  - 15% each, anxiety and nausea
  - 19% headaches (HA)
  - 20% insomnia

Conclusions

- In 1° brain tumor patients undergoing RT, those with greater baseline fatigue experienced less fatigue/sleepiness and better QOL using armodafinil 150md/day vs. placebo
- Toxicity acceptable: 15-20% incidence grade 2+3 toxicities – insomnia, HA, anxiety, nausea
- The data warrant a Phase III prospective double-blind placebo-controlled study *in patients with greater baseline fatigue*