Estudio IDEA: Perspectiva Estadística

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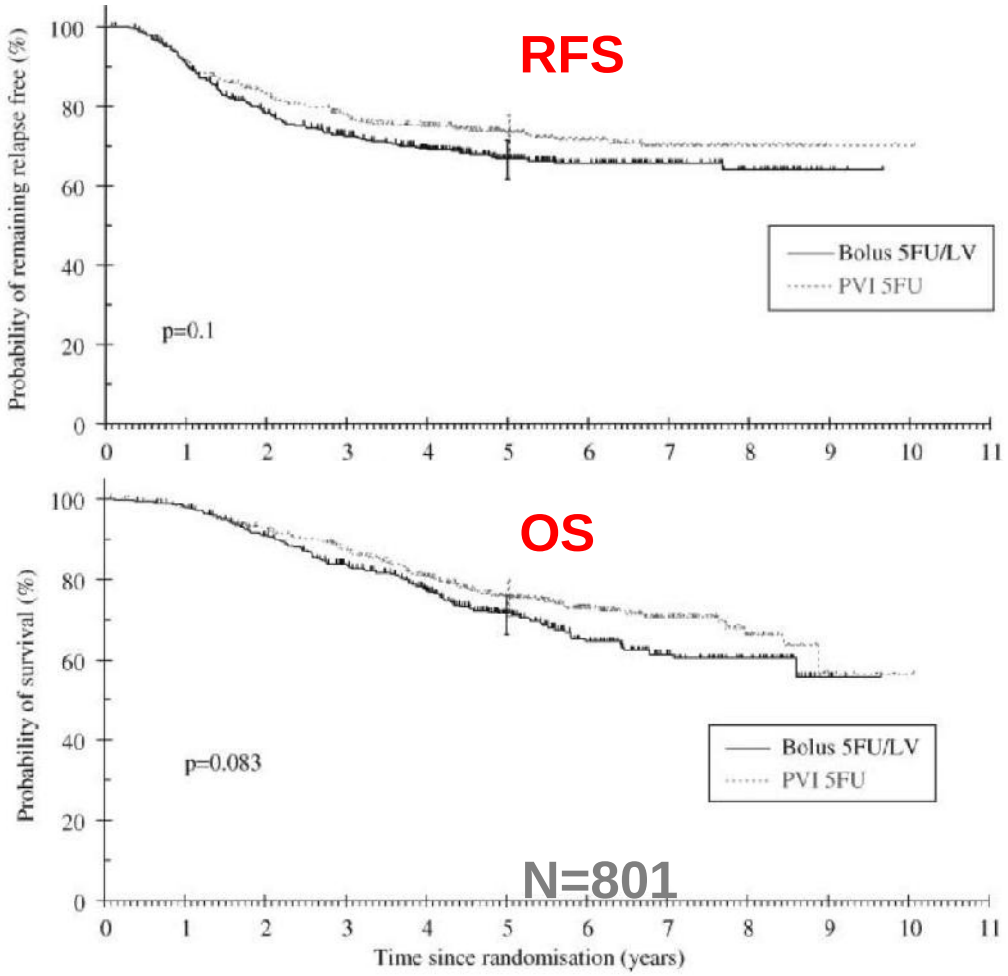
Background and Rationale

- **Current standard of care for stage III colon cancer patients: 6 months of oxaliplatin-based adjuvant therapy with FOLFOX or CAPOX (XELOX)**
- **Oxaliplatin is associated with cumulative dose-dependent neurotoxicity**
  - Debilitating for many patients, both short- and long-term
    - Nerve damage (e.g. numbness, tingling, pain) can persist long after discontinuation of therapy, sometimes permanently
  - Dose reductions and early discontinuation of therapy are common
- **Shorter duration treatment without loss of efficacy would be of benefit to patients and health care resources**

12 weeks of ci 5-FU vs 6 months of 5-FU/LV



5 Year (%)	12 wks Ci 5-FU	6 months 5-FU/LV	HR (95% CI) p-value
RFS	73.3	66.7	0.8 (0.62-1.04) p=0.10
OS	75.7	71.5	0.79 (0.61-1.03) p=0.08

Likelihood of 12 wks of ci 5-FU being inferior: P<0.005

Chau et al., Ann Oncol 2005

International Duration Evaluation of Adjuvant Chemotherapy (IDEA) Collaboration

- Academic collaboration of clinicians and statisticians from six randomized phase III trials (12 countries)
  - **SCOT** (UK, Denmark, Spain, Australia, Sweden, New Zealand), **TOSCA** (Italy), **Alliance/SWOG 80702** (US, Canada), **IDEA France**, **ACHIEVE** (Japan), **HORG** (Greece)
- Total of **12,834 patients with stage III disease** included in analysis
  - High number of patients needed to make sure with high confidence that we are not sacrificing efficacy of therapy for decreased toxicity

Study Overview

- **Objective**

  To evaluate the **non-inferiority** of 3 m compared with 6m of adjuvant oxaliplatin-based treatment in stage III colon cancer

- **Approach**

  Prospectively-designed, pooled analysis of individual patient from data from six concurrently conducted phase III randomized trials

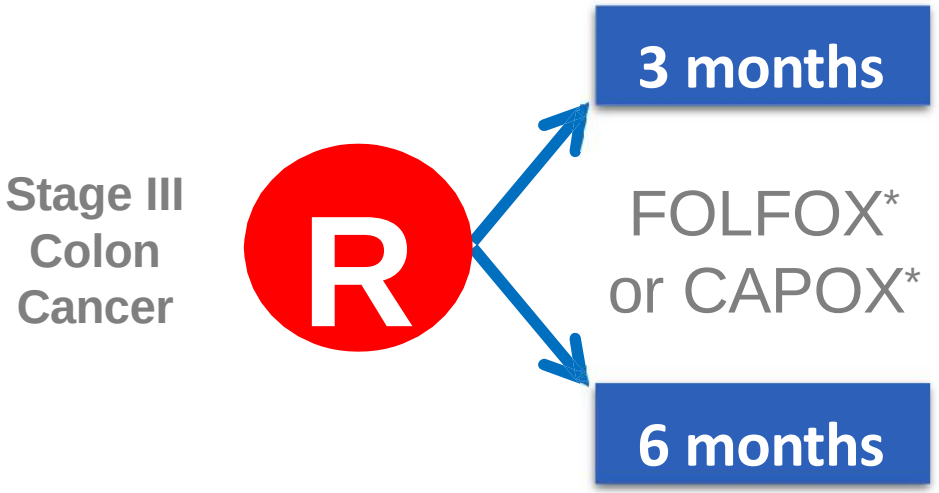
Statistical design

- **Primary Endpoint: Disease Free Survival (DFS)**

  Time from date of randomization to the earliest date of relapse, secondary colorectal primary tumor. Or death due to all causes

- **Primary Analysis Population: Modified Intent-To-Treat**
  - Randomized and received any dose of treatment
  - Analysis according to patient's original randomization assignment
- DFS Hazard Ratio (HR: 3m vs. 6 m) and two-sided 95% cpnfidence interval (CI) were estimated by Cox model **stratified by study**
- **Pre-planned Subgroup Analyses: By regimen and T/N stage**

Design



Objective:

Reduce side-effects of therapy without giving up (too much) anti-cancer efficacy of therapy

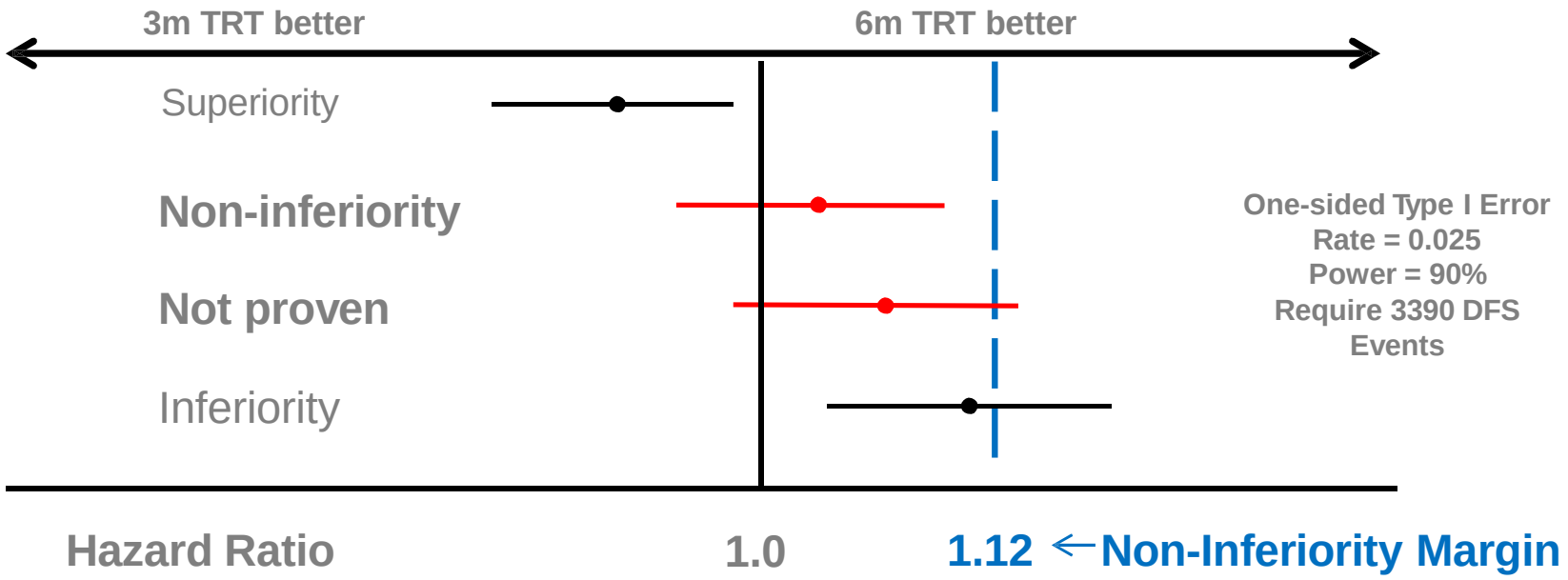
Non-inferiority design:

As agreed upon by patient advocates and oncologists, shorter duration of therapy should not sacrifice more than 12% of benefit of adjuvant therapy

In statistical terms: upper 95% confidence interval of Hazard Ratio (HR) of disease free survival (DFS) should not exceed *1.12*

Non-Inferiority Hypothesis Testing

Statistical Conclusions Under Different Scenarios



Piaggio et al. JAMA 2012;308(24):2594-2604

TRT: treatment

IDEA Trials Summary

Trial	Regimen(s)	Stage III Colon Cancer Patients*	Enrolling Country
TOSCA	CAPOX or FOLFOX4	2402	Italy
SCOT	CAPOX or mFOLFOX6	3983	UK, Denmark, Spain, Australia, Sweden, New Zealand
IDEA France	CAPOX or mFOLFOX6	2010	France
C80702	mFOLFOX6	2440	US, Canada
HORG	CAPOX or FOLFOX4	708	Greece
ACHIEVE	CAPOX or mFOLFOX6	1291	Japan

*Only stage III colon cancer patients were included in the pooled primary analysis

Presented by: Qian Shi, PhD on behalf of IDEA collaborators

Patient Characteristics	TOSCA (N=2402)	SCOT (N=3983)	IDEA France (N=2010)	C80702 (N=2440)	HORG (N=708)	ACHIEVE (N=1291)
Median Age, years	64	65	64	61	67	66
ECOG PS*						
0	95%		74%	71%	82%	
1	5%		25%	28%	18%	
T4	**12%**	**29%**	**18%**	**15%**	**14%**	**28%**
N Stage						
N1	73%	69%	75%		67%	
N2	27%	31%	25%		33%	
Median follow-up time, m	**62**	**37**	**51**	**35**	**48**	**37**

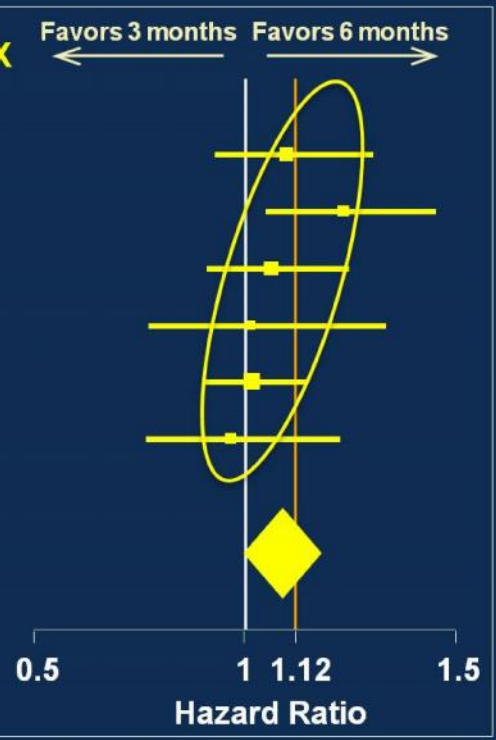
Regimens and Patient Characteristics

	CAPOX	FOLFOX	P-value
Age, yrs (range)	65.0 (18-85)	64.0 (19-88)	<0.0001
Gender (%male)	57.2	56.0	0.17
ECOG 0 / 1 / 2 (%)	81.1 / **18.8** / 0.1	77.6 / **21.8** / 0.7	**<0.0001**
T stage 1-2 / 3 / 4 (%)	12.5 / 63.2 / **24.3**	13.7 / 67.7 / **18.6**	**<0.0001**
N stage 1 / 2 (%)	71.4 / 28.6	72.4 / 27.6	0.47
Risk group (%) T1-3 N1	56.4	60.2	**<0.0001**
T4 and / or N2	**43.6**	**39.8**	
# LNs examined (range)	19 (1-122)	19 (1-132)	0.33
Grade (%) 1-2 / 3-4	88.2 / **11.8**	84.9 / **15.1**	**0.0002**

Primary Efficacy Analysis

	Patients 3m arm	Patients 6m arm	HR (3m/6m)	%CAPOX
C80702	1232	1208	1.10	0.0
IDEA France	1002	1008	1.24	10.0
TOSCA	1194	1208	1.07	35.0
HORG	354	354	1.02	58.2
SCOT	1992	1991	1.02	66.5
ACHIEVE	650	641	0.97	75.1
Overall	**6424**	**6410**	**1.07**	**39.5**

$I^2 = 0\%$



PRESENTED AT: ASCO ANNUAL MEETING '17 | #ASCO17

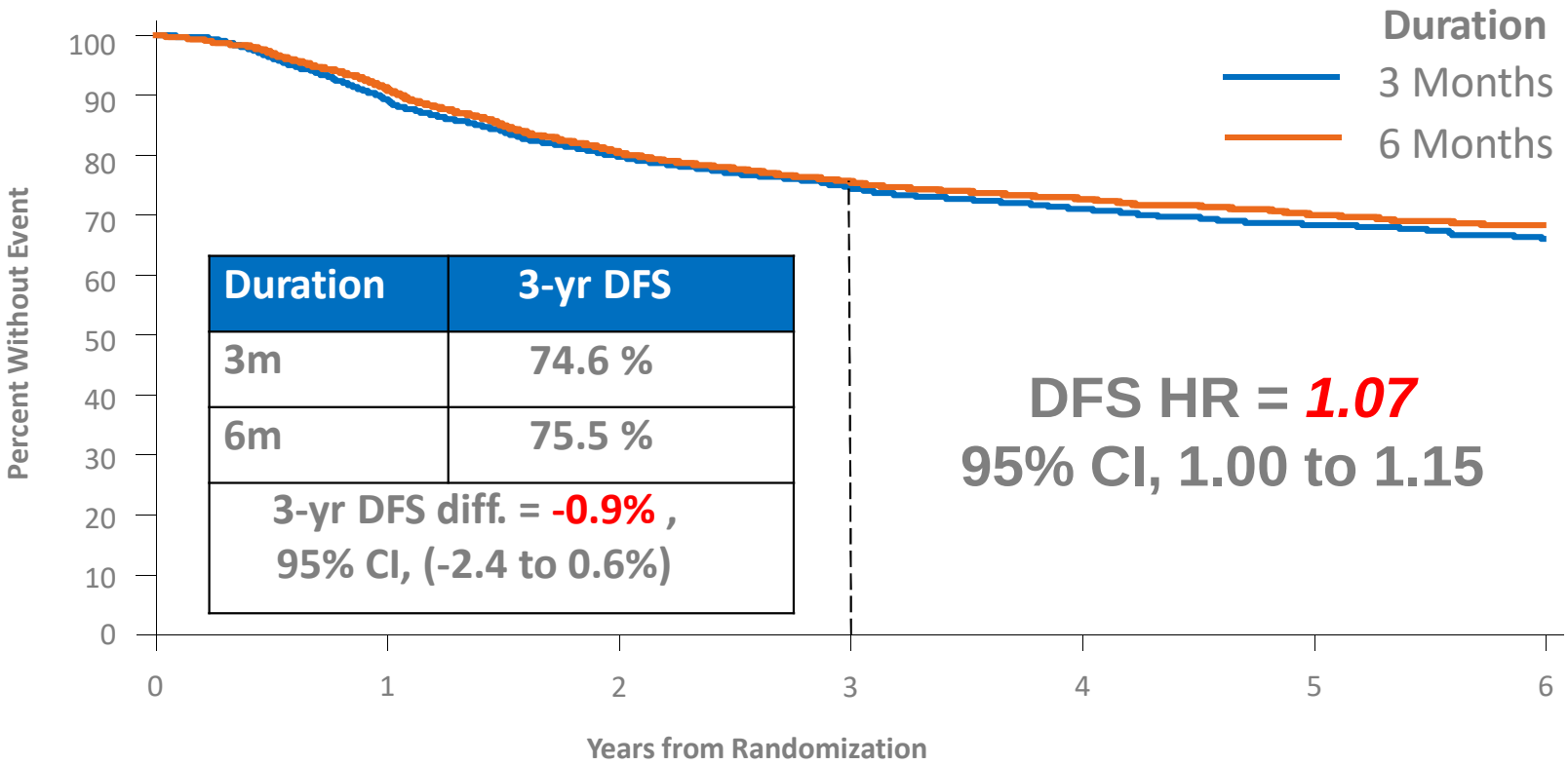
Presented by: Qian Shi, PhD on behalf of IDEA collaborators

Presented By Qian Shi at 2017 ASCO Annual Meeting

STATISTICAL ANALYSIS PLAN

- The primary IDEA efficacy analysis will consist of estimating the hazard ratio for DFS comparing 3 versus 6 months of therapy using a Cox proportional hazards regression model.
- Interaction testing will be performed between treatment assignment and N-stage, T-stage and the choices of initial therapy (FOLFOX vs. CAPOX).
- The primary endpoint of DFS will be compared between treatment groups in the modified per-protocol population, defined as all patients randomized and who received at least 3 months of therapy.

Primary Outcomes Analysis



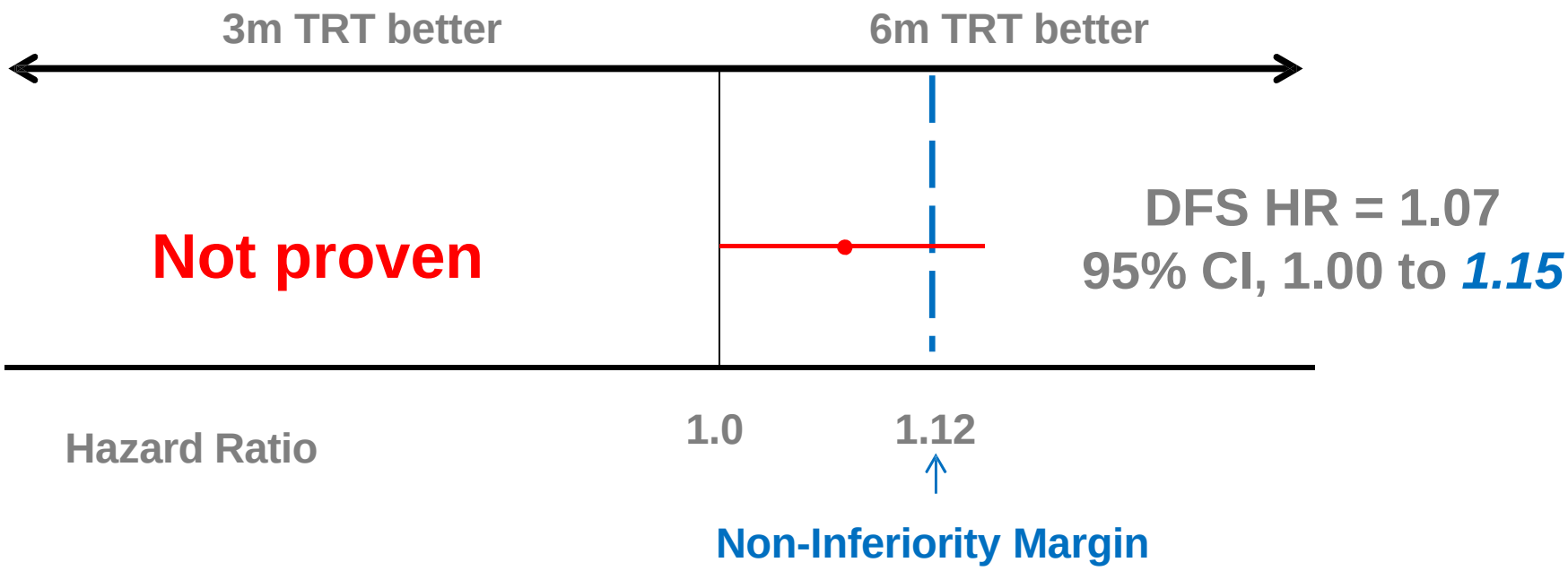
N Patients	6424	5446	4464	3000	1609	826	321
At risk	6410	5530	4477	3065	1679	873	334

IDEA RESULTS: Global

HR 3 vs. 6 mos (95% CI)	CAPOX	FOLFOX	ALL
LOW RISK (T1-3 N1)	**0.85** (0.71 – 1.01)	**1.10** (0.96 – 1.26)	**1.01** (0.90 – 1.12)
HIGH RISK (T4 or N2)	**1.02** (0.89 – 1.17)	**1.20** (1.07 – 1.35)	**1.12** (1.03 – 1.23)
ALL	**0.95** (0.85 – 1.06)	**1.16** (1.06 – 1.26)	1.07 (1.00 – 1.15)

3 mos not inferior | inconclusive | 3 mos inferior

Primary DFS Analysis (mITT), cont.



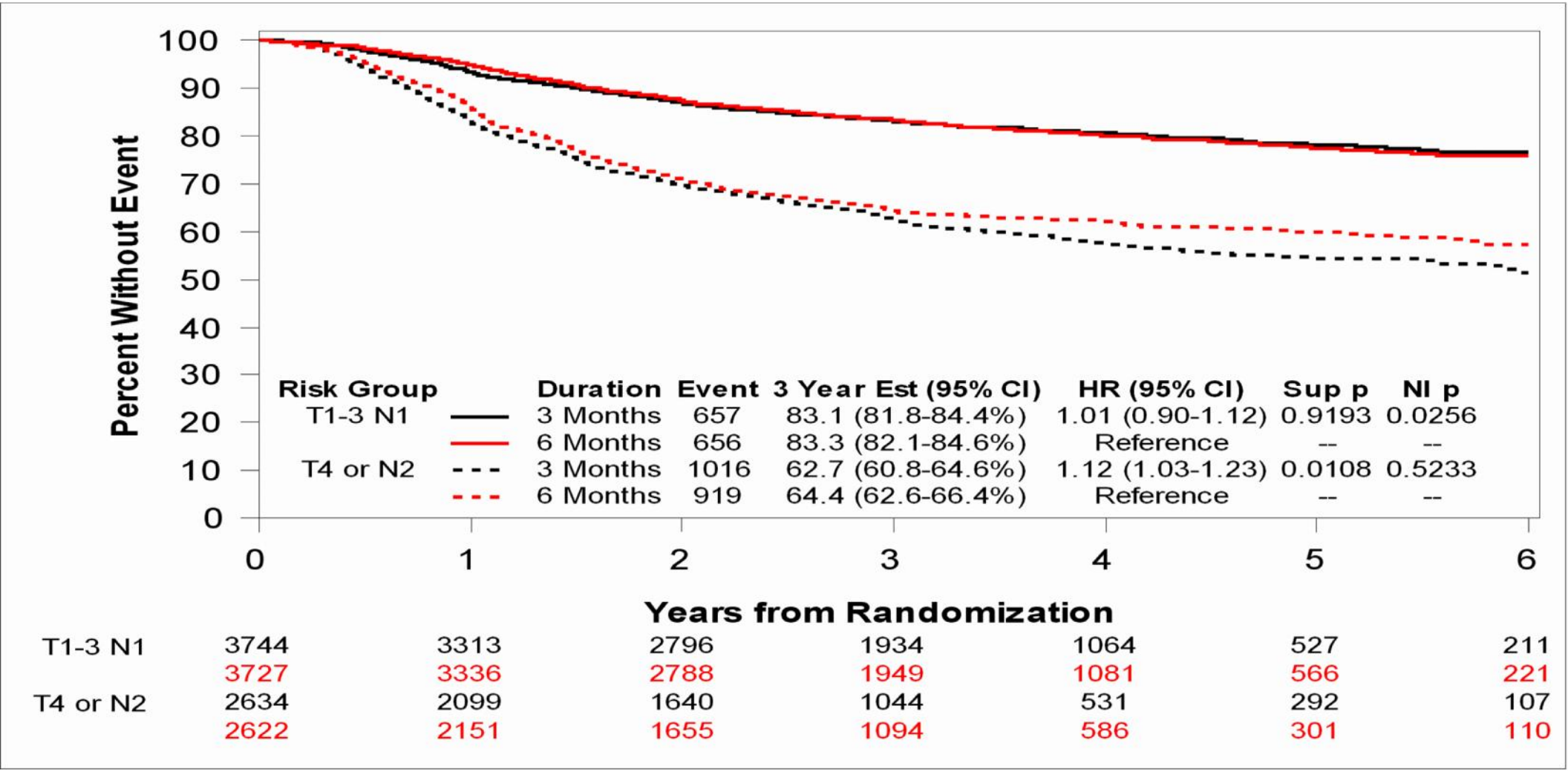
TRT: treatment

Analysis by Risk Groups and Regimens

- **Large difference in overall prognosis observed between (T1-3 N1) and (T4 and/or N2) cancers**
  - 3-year DFS Δ 20% 80% vs 60%

  Preplanned subgroup analysis for T and N
  - Analysis of 3m vs 6m adjuvant therapy by risk groups
- **Two different adjuvant regimens used, FOLFOX (N=7763) and CAPOX (N=5071)**
  - Preplanned analysis of 3m vs 6m based on regimen

Analysis by Risk Groups and Regimens



SUMMARY OF IDEA RESULTS

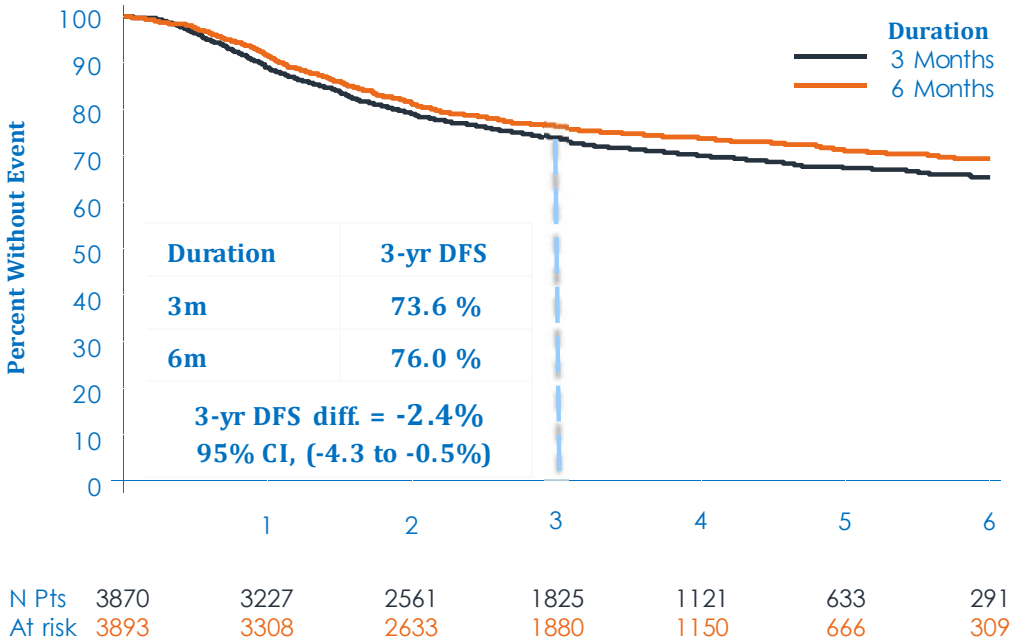
HR 3 vs. 6 mos (95% CI)	ALL
LOW RISK (T1-3 N1)	1.01 (0.90 – 1.12)
HIGH RISK (T4 or N2)	1.12 (1.03 – 1.23)
ALL	1.07 (1.00 – 1.15)

Interaction test
P-value = 0.11
(moderate interaction)

3 mos not inferior | 3 mos inferior

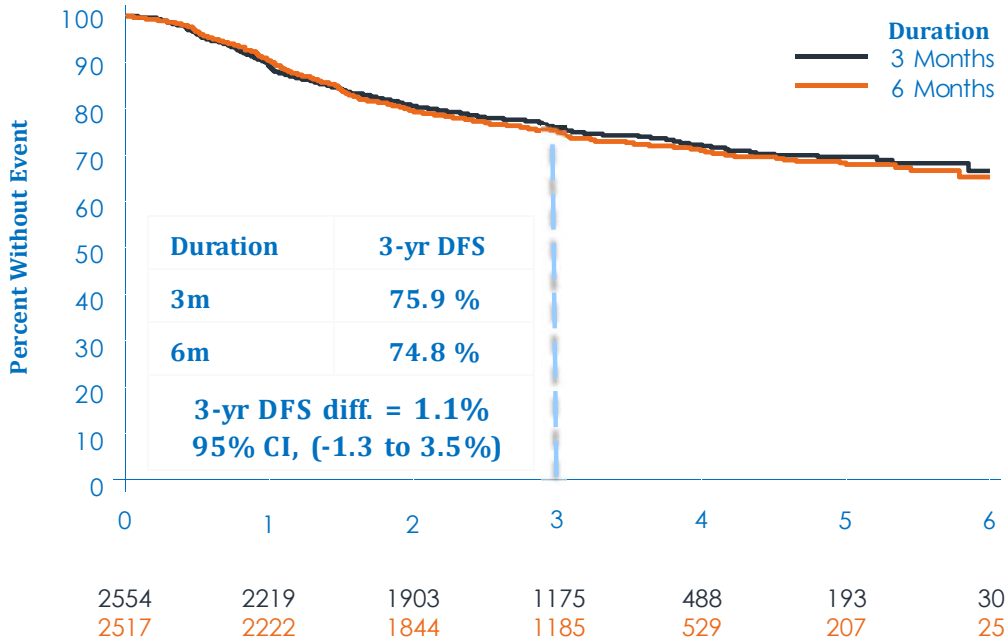
DFS Comparison by Regimen

FOLFOX



N Pts	3870	3227	2561	1825	1121	633	291
At risk	3893	3308	2633	1880	1150	666	309

CAPOX



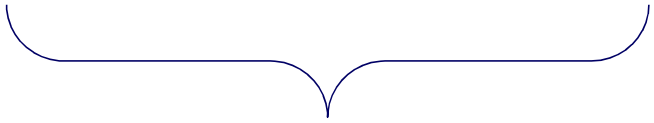
N Pts	2554	2219	1903	1175	488	193	30
At risk	2517	2222	1844	1185	529	207	25

Interaction p-value = 0.0051

Presented by: Qian Shi, PhD on behalf of IDEA collaborators

SUMMARY OF IDEA RESULTS

HR 3 vs. 6 mos (95% CI)	CAPOX	FOLFOX	ALL
ALL	0.95 (0.85 – 1.06)	1.16 (1.06 – 1.26)	1.07 (1.00 – 1.15)



Interaction test
P-value = 0.0051
(strong interaction)

3 mos not inferior | 3 mos inferior

IDEA RESULTS: All subgroups

HR 3 vs. 6 mos (95% CI)	CAPOX	FOLFOX	ALL
LOW RISK (T1-3 N1)	0.85 (0.71 – 1.01)	1.10 (0.96 – 1.26)	1.01 (0.90 – 1.12)
HIGH RISK (T4 or N2)	1.02 (0.89 – 1.17)	1.20 (1.07 – 1.35)	1.12 (1.03 – 1.23)
ALL	0.95 (0.85 – 1.06)	1.16 (1.06 – 1.26)	1.07 (1.00 – 1.15)

3 mos not inferior | inconclusive | 3 mos inferior

Statistical Conclusions

The significant duration x treatment interaction supports giving

- 3 mos of CAPOX (assuming this is the preferred treatment)
- 6 mos of FOLFOX (assuming this is the preferred treatment)

BUT how does CAPOX 3 mos compare with FOLFOX 6 mos?

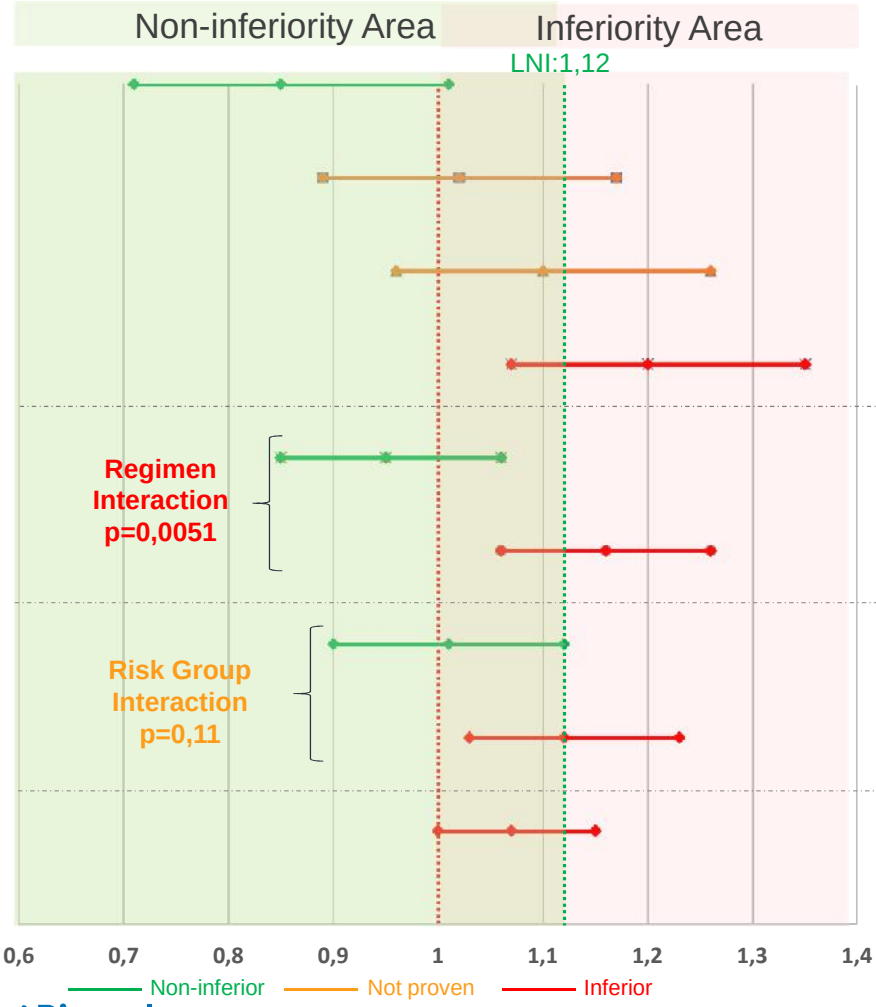
Despite its large size and prospective design, IDEA provides no direct evidence on the efficacy of CAPOX compared with that of FOLFOX.

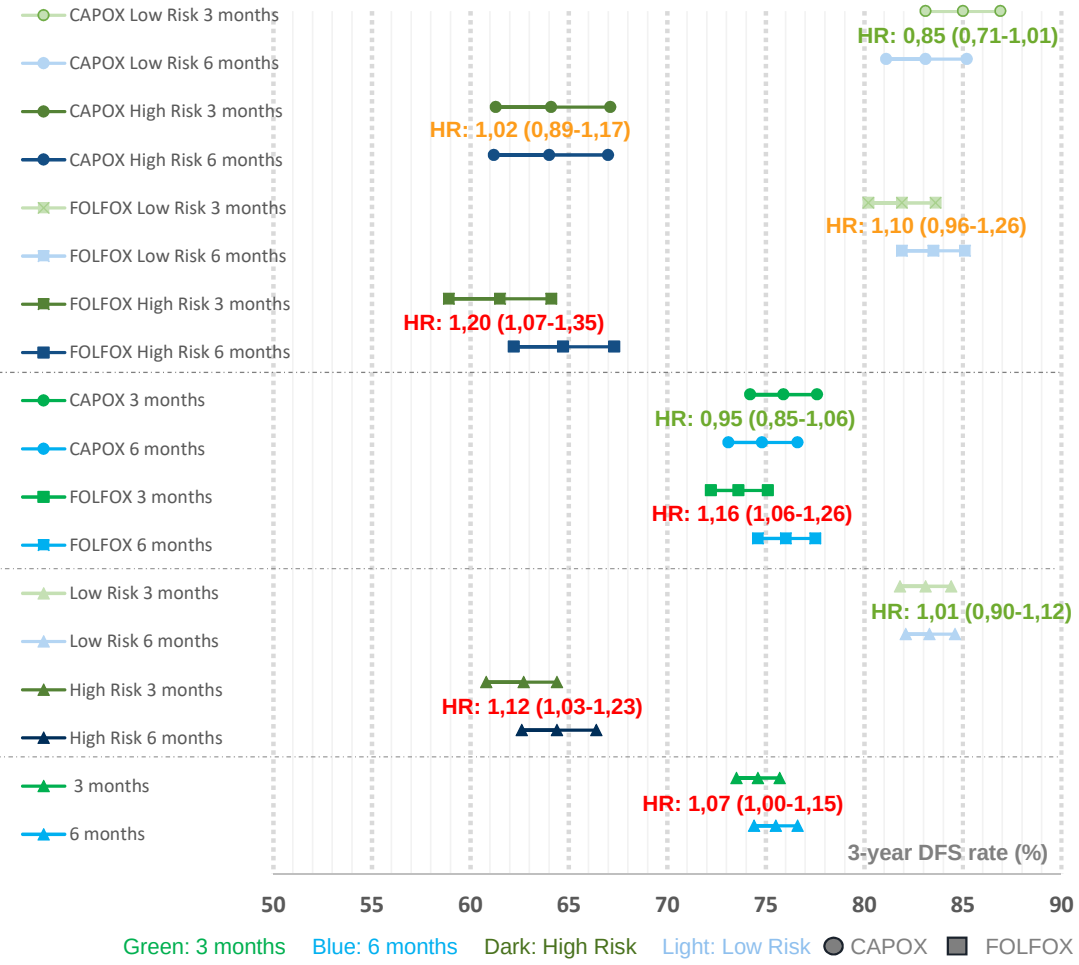
Patients could have been randomized to CAPOX vs. FOLFOX in addition to being randomized to 3 vs. 6 mos.

Conclusions

- IDEA data provide a framework for discussions on risks and benefits of **individualized adjuvant therapy** approaches
- Shorter duration of therapy associated with remarkable reduction in (neuro)toxicity
- For patients treated with **CAPOX**, 3 months was as good as 6 months, particularly in the low-risk population.
- For patients treated with **FOLFOX**, 6 months treatment added extra benefit in terms of DFS, particularly in the high-risk population

Results summary





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