TH-302 plus Gemcitabine vs. Gemcitabine in Patients with Untreated Advanced Pancreatic Adenocarcinoma

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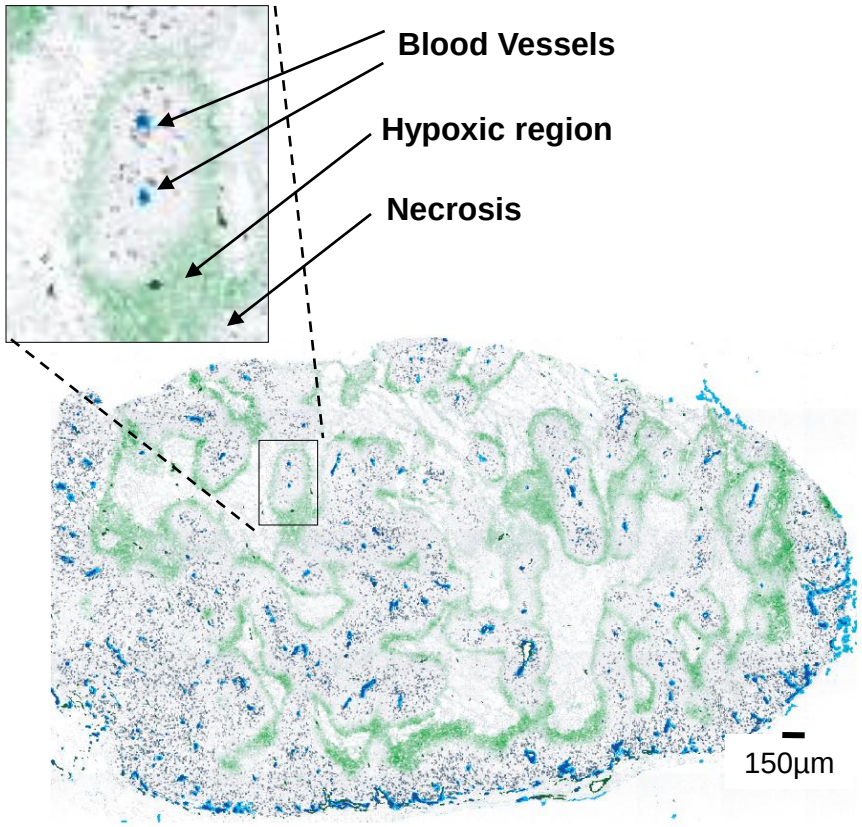
The Tumor Microenvironment

Subregional hypoxia as a defining feature



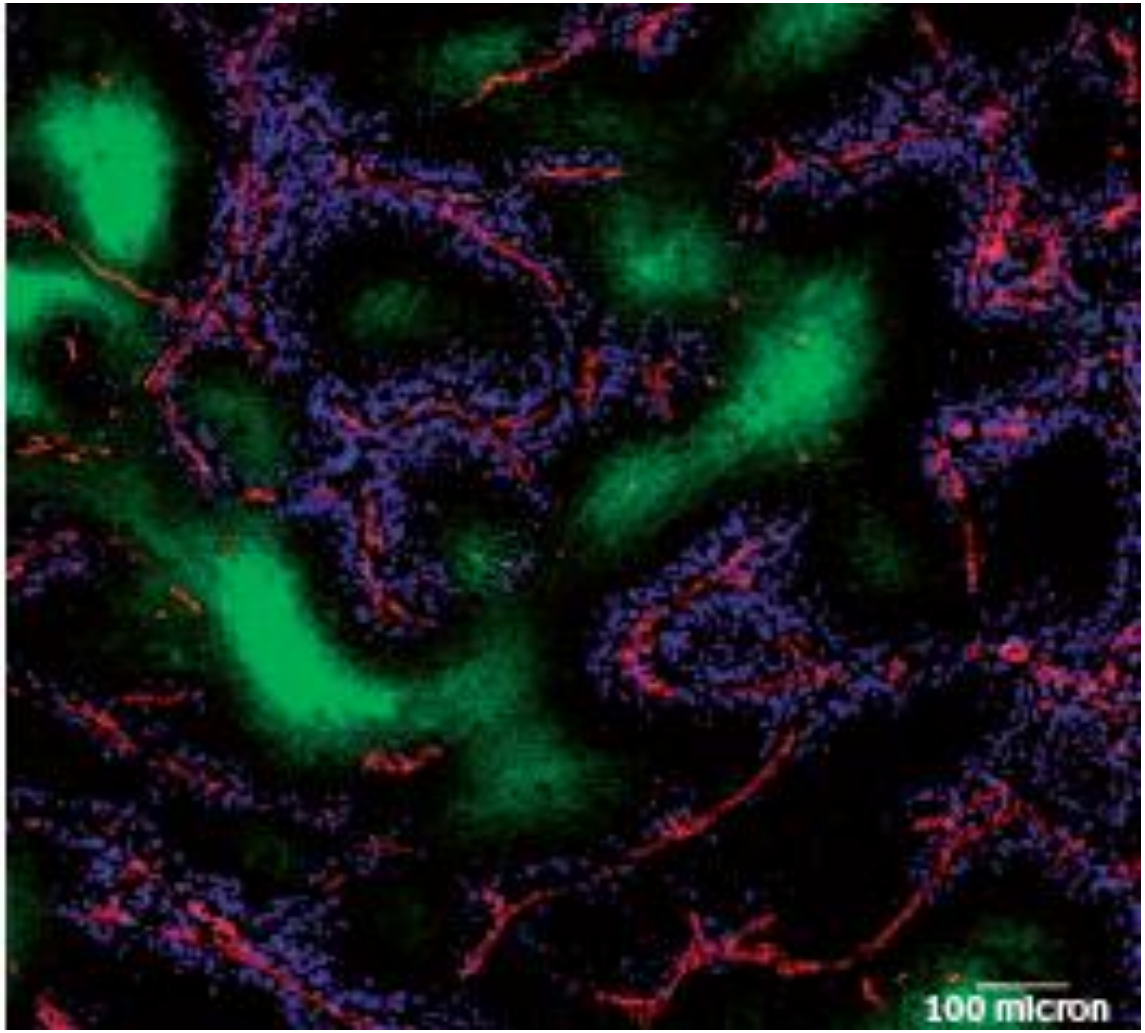
Pimonidazole staining of hypoxic regions
Blood vessels in blue

Source: Minchinton AI, Tannock IF. Nat Rev Cancer. 2006 Aug;6(8):583-92.

Tumor Type	Tumor Tissue Median pO_2 *mm Hg (# of patients)*	Normal Tissue Median pO_2 *mm Hg*
Pancreas	**2** (8 pts)	**57**
Brain	**13** (104 pts)	**26**
Head & Neck	**10** (592 pts)	n/a
Lung	**16** (26 pts)	n/a
Breast	**10** (212 pts)	**52**
Cervix	**9** (730 pts)	**42**
Liver	**6** (4 pts)	**30**
Prostate	**2, 5, 10, 11, 21** (57, 55, 55, 10, 13 pts)	n/a
Sarcoma	**14** (283 pts)	**51**
Melanoma	**12** (18 pts)	**41**

Source: Vaupel P, Höckel M, Mayer A. Antioxid Redox Signal. 2007 Aug;9(8):1221-35. Review.

Chemotherapy Targets Oxygenated Tumor Compartment

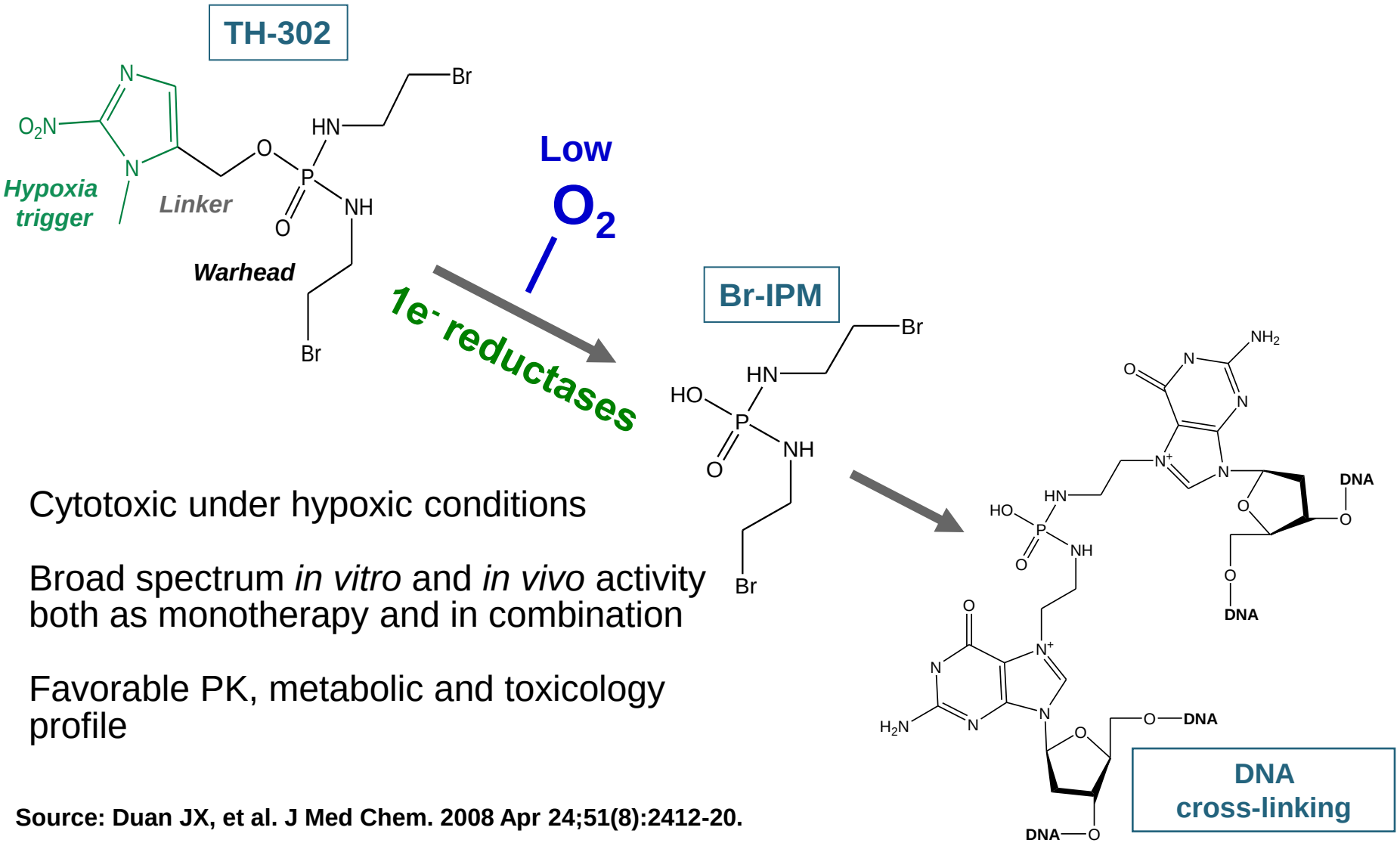


Vessels: Red
Doxorubicin: Blue
Hypoxia: Green

Source: Minchinton AI, Tannock IF. Nat Rev Cancer. 2006 Aug;6(8):583-92.

Hypoxia-Targeted Drug TH-302

A tumor-selective, hypoxia-activated, cytotoxic prodrug

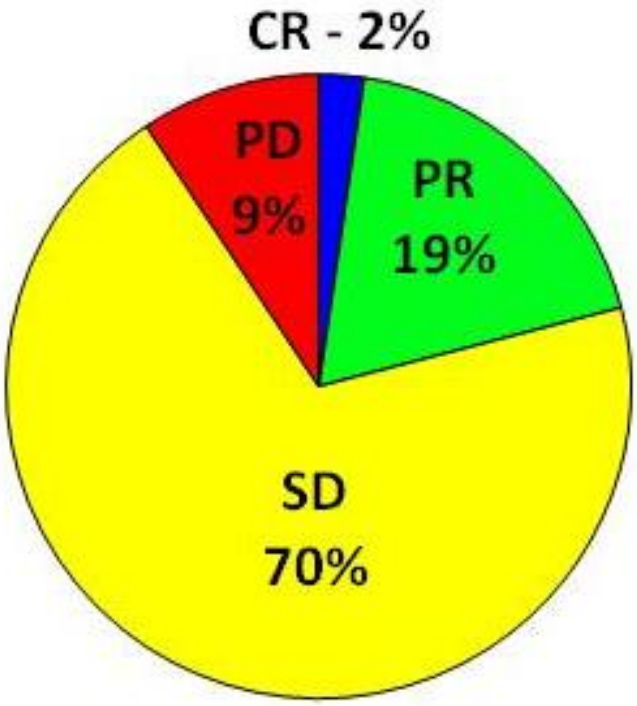


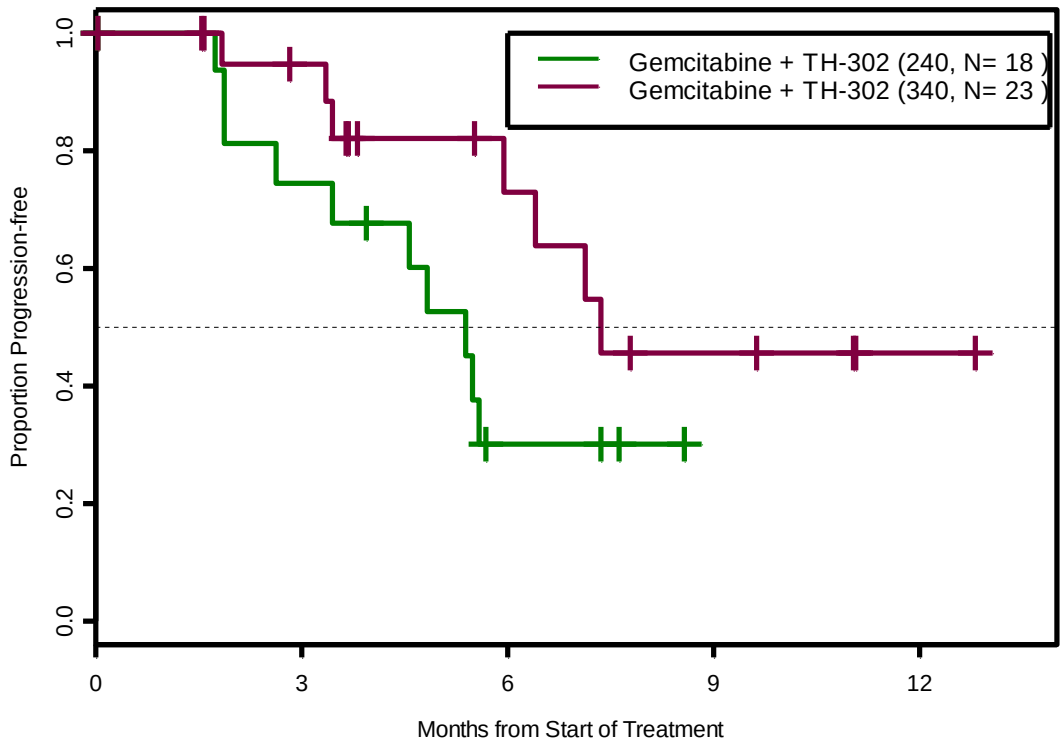
- Cytotoxic under hypoxic conditions
- Broad spectrum *in vitro* and *in vivo* activity both as monotherapy and in combination
- Favorable PK, metabolic and toxicology profile

Source: Duan JX, et al. J Med Chem. 2008 Apr 24;51(8):2412-20.

TH-302 + Gemcitabine in First-Line Pancreatic Cancer

Single Arm Dose Expansion Formed Basis for Randomized Design





- **47 patients** with advanced first-line pancreatic cancer
- Response rate of **21%** and median PFS of 5.9 months
- Greater efficacy at higher doses 240 mg/m^2: 0% Response, **5.4 mo median PFS**
- 340 mg/m^2 : **33% Response**, **7.4 mo median PFS**
- Skin and mucosal toxicity not dose limiting at these doses; single agent MTD = 575 mg/m^2
- Better dose intensity at lower doses

Source: Borad M, et al. ASCO GI 2011

Study TH-CR-404

Randomized Phase 2 Study Design (June 2010- June 2011; 45 sites)

Advanced Pancreatic Cancer

(N=214)

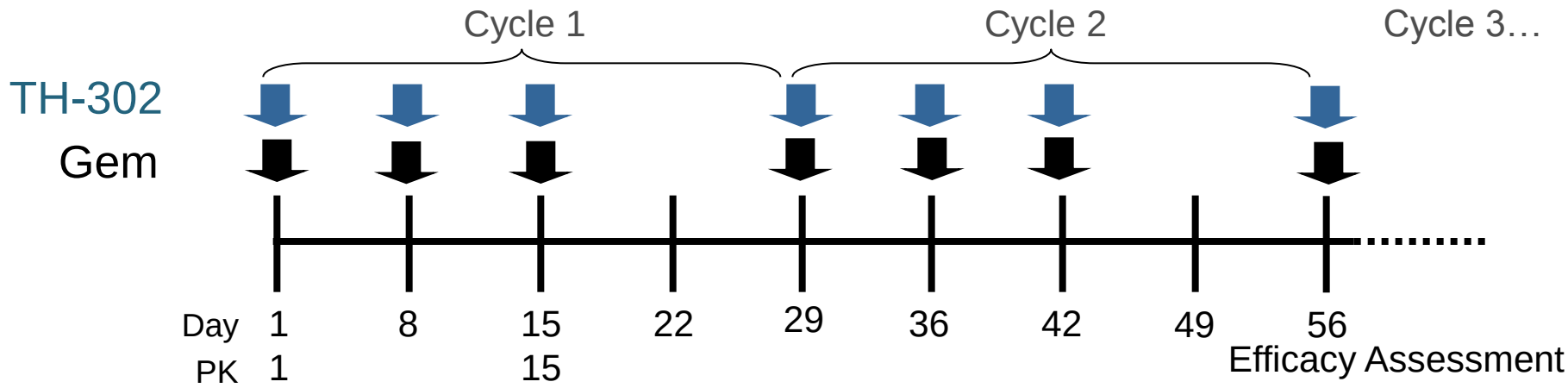
Randomize 1:1:1

- **Gemcitabine + TH-302 (240 mg/m^2)**
- **Gemcitabine + TH-302 (340 mg/m^2)**
- **Gemcitabine (1000 mg/m^2)**

Crossover (randomized to one of Gemcitabine plus TH-302 dose groups)

Gemcitabine + TH-302 (240 or 340 mg/m^2)

Stratification: Stage (Unresectable Locally Advanced vs. Distant Metastases)



Study TH-CR-404

Study Design

- Key Eligibility Criteria
  - Locally advanced or metastatic pancreatic ductal adenocarcinoma confirmed by histology or cytology
  - Measurable disease by RECIST 1.1 criteria
  - ECOG performance status of 0 or 1

- Primary
  - Progression-free Survival (PFS)
  - Safety

- Secondary
  - Response rate (RECIST 1.1)
  - Change in CA19-9 including CA19-9 response (>50% decrease)
  - Overall Survival (OS)
  - Similar endpoints following crossover (comparing the 240 mg/m^2 and 340 mg/m^2 combination treatment groups)

Study TH-CR-404

Statistical Considerations

- Primary Efficacy Analysis of PFS (conducted in February 2012)
  - **80% power** to detect a **50% improvement in PFS (hazard ratio: 0.667)**
  - With a control arm median of **3 to 4.0 months**, translates to a **1.5 to 2.0 month** improvement in median PFS
- Sample Size for Primary Efficacy Analysis
  - **200** patients required to obtain the **144** events for primary PFS efficacy analysis
  - Phase 2b **one-sided alpha = 10% (two-sided 20%)**
- No Formal Statistical Power Analysis for OS
  - Crossover contribution confounds analysis of OS
  - Phase 2b **one-sided alpha = 10% (two-sided 20%)**
    - **65% power** to detect a **33% improvement in OS** (hazard ratio: 0.750)
    - **45% power** to detect a **50% improvement in 12 mo OS rate** (20% vs. 30%)

Study TH-CR-404

Demographics

	Gemcitabine (N=69)	**Gemcitabine + TH-302 (240 mg/m²)** (N=71)	**Gemcitabine + TH-302 (340 mg/m²)** (N=74)
Age (years) Median Range ≥65 years	 67 41 – 83 41 (59%)	 63 41 – 81 28 (39%)	 65 29 – 86 38 (51%)
Gender (Male)	58%	62%	57%
Locally Advanced Unresectable N (%)	14 (20%)	17 (24%)	20 (27%)
Median months from Dx	1.1	1.1	1.2

Study TH-CR-404

Baseline Performance Status and Disease Characteristics

	Gemcitabine (N=69)	**Gemcitabine + TH-302 (240 mg/m²)** (N=71)	**Gemcitabine + TH-302 (340 mg/m²)** (N=74)
Screening ECOG 0 1	 20 (30%) 47 (70%)	 31 (45%) 38 (55%)	 28 (39%) 43 (61%)
Site of primary pancreatic tumor involves Head N (%)	41 (59%)	40 (56%)	44 (59%)
Baseline CA19-9[1] Median	(N=55) 1291	(N=53) 2575	(N=58) 2391
Metastatic Sites Liver N (%) Lung N (%)	 46 (67%) 10 (14%)	 44 (62%) 11 (15%)	 42 (57%) 15 (20%)
Baseline Hemoglobin <12 g/dL (%)	25 (37%)	26 (37%)	24 (32%)

[1] Normal CA19-9 is 35 U/mL or less

Study TH-CR-404

Drug Exposure

	Gemcitabine (N=69)	Gemcitabine + TH-302 (240 mg/m²) (N=71)	Gemcitabine + TH-302 (340 mg/m²) (N=74)
Minimum Cycles received			
Cycle One	69 (100%)	71 (100%)	74 (100%)
Cycle Two	60 (87%)	67 (94%)	66 (89%)
Cycle Three	44 (64%)	49 (69%)	55 (74%)
Cycle Four	41 (59%)	44 (62%)	50 (68%)
Cycle Five	26 (38%)	36 (51%)	48 (65%)
Cycle Six	22 (32%)	32 (45%)	41 (55%)
Cycle Seven	11 (16%)	21 (30%)	27 (36%)
Cycle Eight	11 (16%)	18 (25%)	27 (36%)
Cycle Nine or More	7 (10%)	12 (17%)	20 (27%)
Mean (Range)	4.5 (1 – 16)	5.5 (1 – 17)	6.4 (1 – 21)
Ongoing	1 (1%)	1 (1%)	2 (3%)
Mean Cumulative Gemcitabine Dose Intensity at End of Cycle 6	88%	81%	72%

Study TH-CR-404

Most Frequent Non-Laboratory AEs – Regardless of Relationship to Study Drug

	Gemcitabine (N=69)	**Gemcitabine + TH-302 (240 mg/m²)** (N=71)	**Gemcitabine + TH-302 (340 mg/m²)** (N=74)
Fatigue	30 (43%)	43 (61%)	40 (54%)
Nausea	25 (36%)	28 (39%)	35 (47%)
Peripheral edema	28 (41%)	25 (35%)	29 (39%)
Any Rash[1]	11 (16%)	30 (42%)	35 (47%)
Abdominal pain	20 (29%)	27 (38%)	27 (36%)
Constipation	22 (32%)	25 (35%)	25 (34%)
Vomiting	20 (29%)	16 (23%)	27 (36%)
Diarrhea	15 (22%)	19 (27%)	28 (38%)
Decreased Appetite	16 (23%)	18 (25%)	24 (32%)
Pyrexia	16 (23%)	19 (27%)	21 (28%)
Stomatitis[2]	5 (7%)	13 (18%)	31 (42%)

[1] Includes all AEs including the term ‘rash’; 3 subjects at 340 mg/m² had a grade 3.
[2] All Grade 1 or Grade 2.

Study TH-CR-404

Most Frequent Non-Hematologic SAEs – Regardless of Relationship to Study Drug

	Gemcitabine (N=69)	**Gemcitabine + TH-302 (240 mg/m²)** (N=71)	**Gemcitabine + TH-302 (340 mg/m²)** (N=74)
Any SAE	37 (54%)	35 (49%)	43 (58%)
Abdominal pain	2 (3%)	4 (6%)	6 (8%)
Bile duct obstruction	4 (6%)	4 (6%)	3 (4%)
Pulmonary embolism	3 (4%)	2 (3%)	6 (8%)
Vomiting	2 (3%)	3 (4%)	5 (7%)
Nausea	2 (3%)	4 (6%)	4 (5%)
Cholangitis	5 (7%)	2 (3%)	2 (3%)
Pneumonia	4 (6%)	3 (4%)	2 (3%)

Study TH-CR-404

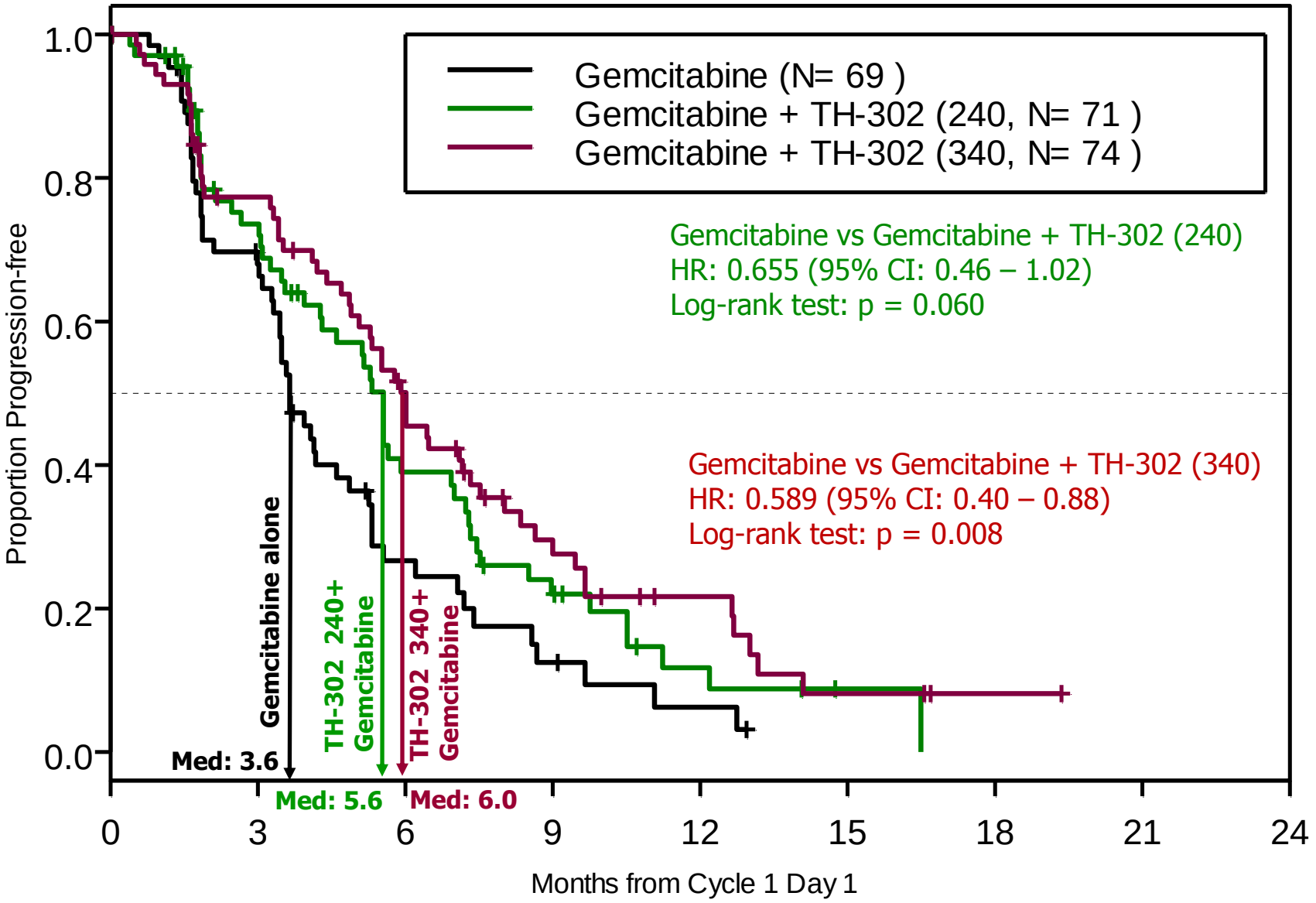
Laboratory Events

Laboratory Maximum Grade	**Gemcitabine** (N=69)	**Gemcitabine + TH-302 (240 mg/m²)** (N=71)	**Gemcitabine + TH-302 (340 mg/m²)** (N=74)
Platelets Grade 3/4	5/2 (11%)	11/16 (39%)	23/23 (63%)
ANC Grade 3/4	19/2 (31%)	31/8 (56%)	26/18 (60%)
Hemoglobin Grade 3/4	6/0 (9%)	15/2 (24%)	20/0 (27%)
Creatinine (N) Grade 3/4 (increase)	0/0 (0%)	0/0 (0%)	1/0 (1%)
Bilirubin (N) Grade 3/4 (increase)	3/1 (6%)	9/1 (13%)	5/1 (8%)

Number of Grade 3 / Number of Grade 4
Percents (% Grade 3 or 4) based on evaluable subjects (subjects with post-baseline assessment)

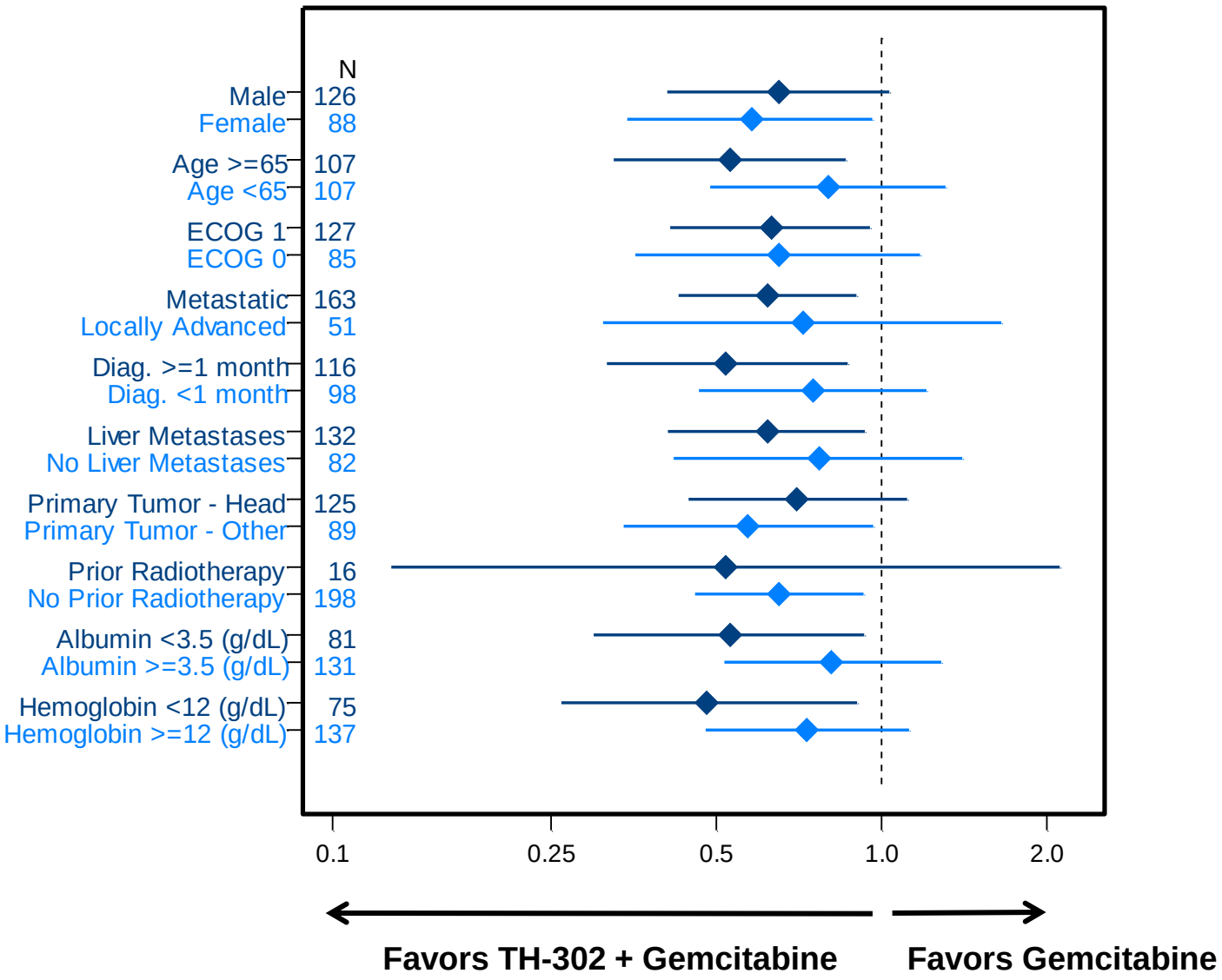
Study TH-CR-404

Progression-free Survival by Treatment Arm



Study TH-CR-404

Progression-free Survival – Primary Efficacy Endpoint Analysis



Study TH-CR-404

RECIST Best Response

	Gemcitabine (N=69)	**Gemcitabine + TH-302 (240 mg/m²)** (N=71)	**Gemcitabine + TH-302 (340 mg/m²)** (N=74)
Response			
CR	0 (0%)	0 (0%)	2 (3%)
PR	7 (10%)	12 (17%)	17 (23%)
SD	39 (57%)	41 (58%)	37 (50%)
PD	12 (17%)	13 (18%)	12 (16%)
NA*	11 (16%)	5 (7%)	6 (8%)
Response	7 (10%)	12 (17%)	19 (26%)
P-value** vs. Gemcitabine		0.220	0.021

* No Response assessment on study. Unless specified, subject is classified as PD for analysis.

** Cochran-Mantel-Haenzel test stratifying for extent of disease.

Study TH-CR-404

CA19-9* Maximum Decrease and Response

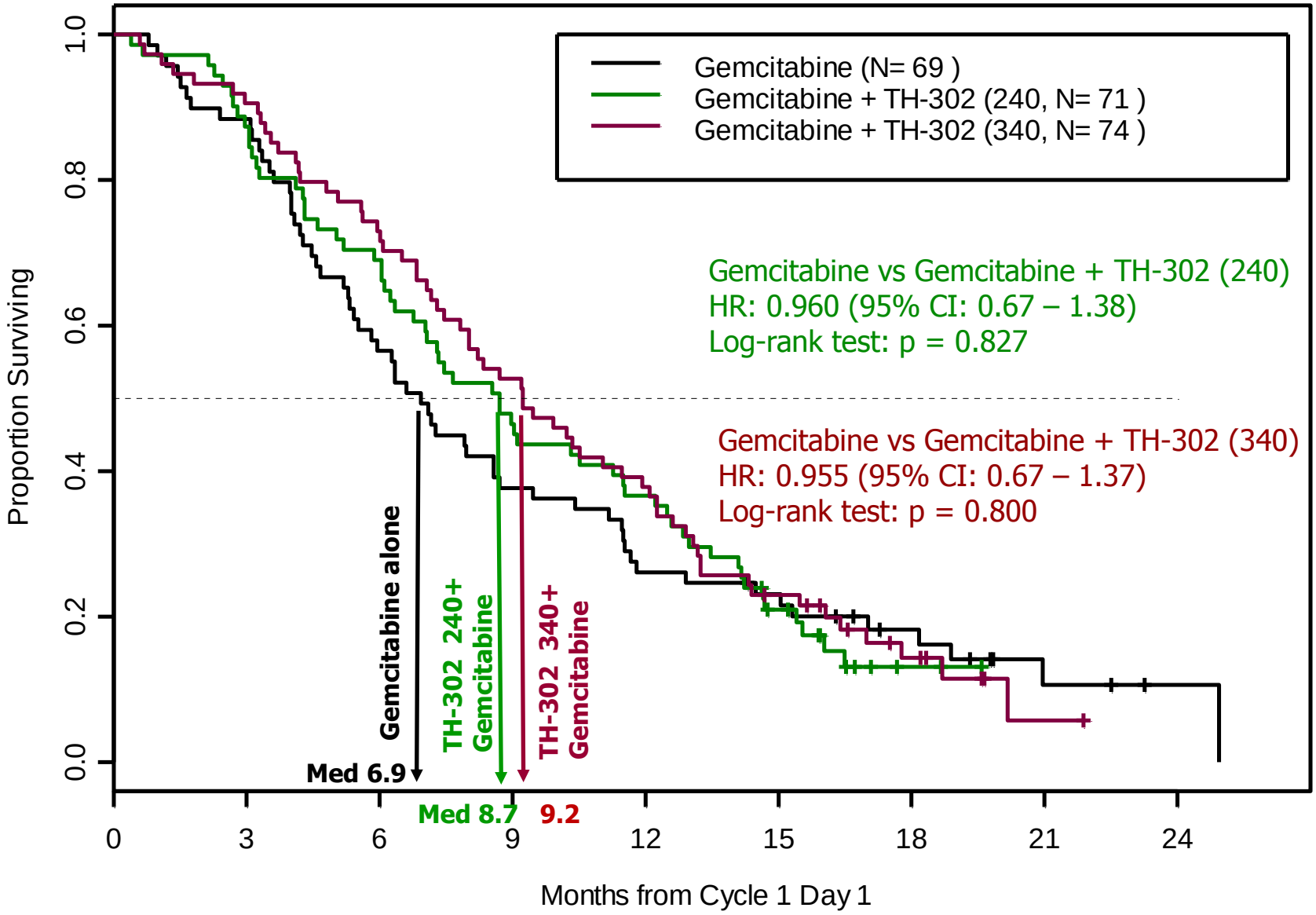
	Gemcitabine (N=50)	**Gemcitabine + TH-302 (240 mg/m²) (N=50)**	**Gemcitabine + TH-302 (340 mg/m²) (N=53)**
Mean Nadir Change (U/L) in CA19-9	-523	-3909	-5385**
Percent CA 19-9 Decrease >20% >50% >90%	 34 (68%) 26 (52%) 8 (16%)	 36 (72%) 25 (50%) 12 (24%)	 47 (89%) 37 (70%) 17 (32%)
Months to CA19-9 Response Median (range)	1.8 (0.9 – 5.6)	0.9 (0.8 – 2.8)	0.9 (0.7 – 4.6)

* Subjects with baseline assessment > ULN and at least one post-baseline CA19-9 assessment.

** Two-sample t-test of change from baseline with log transformed data: p-value = 0.008.

Study TH-CR-404

Overall Survival by Treatment Arm



Study TH-CR-404

Survival at 6 and 12 months by Treatment Arm

	Gemcitabine (N=69)	**Gemcitabine + TH-302 (240 mg/m²)** (N=71)	**Gemcitabine + TH-302 (340 mg/m²)** (N=74)
6-month Survival (95% CI)	57% (44% - 67%)	69% (57% - 78%)	73% (61% - 82%)
P-value versus Gemcitabine		0.123	0.037

	Gemcitabine (N=69)	**Gemcitabine + TH-302 (240 mg/m²)** (N=71)	**Gemcitabine + TH-302 (340 mg/m²)** (N=74)
12-month Survival (95% CI)	26% (16% - 35%)	37% (26% - 48%)	38% (27% - 49%)
P-value versus Gemcitabine		0.178	0.130

Study TH-CR-404

Subsequent Therapy – Number of Patients by Treatment Arm

Subsequent Therapy (may be more than one therapy per patient)	**Gemcitabine** (N=69)	**Gemcitabine + TH-302 (240 mg/m²)** (N=71)	**Gemcitabine + TH-302 (340 mg/m²)** (N=74)
None	25	27	28
TH-302 + Gemcitabine	26	0	0
Gem or Gem+	4	4	9
5FU/Cap or 5FU/Cap+	10	13	15
FOLFOX/FOLFIRI/etc	3	10	10
FOLFIRINOX	5	14	5
Abraxane / Gem+Abraxane	7	13	12
Other Systemic Therapy	6	4	6
Radiotherapy	5	5	6
Ongoing	1	1	2
Unknown	2	4	2
More than One Regimen	18	17	18

Study TH-CR-404

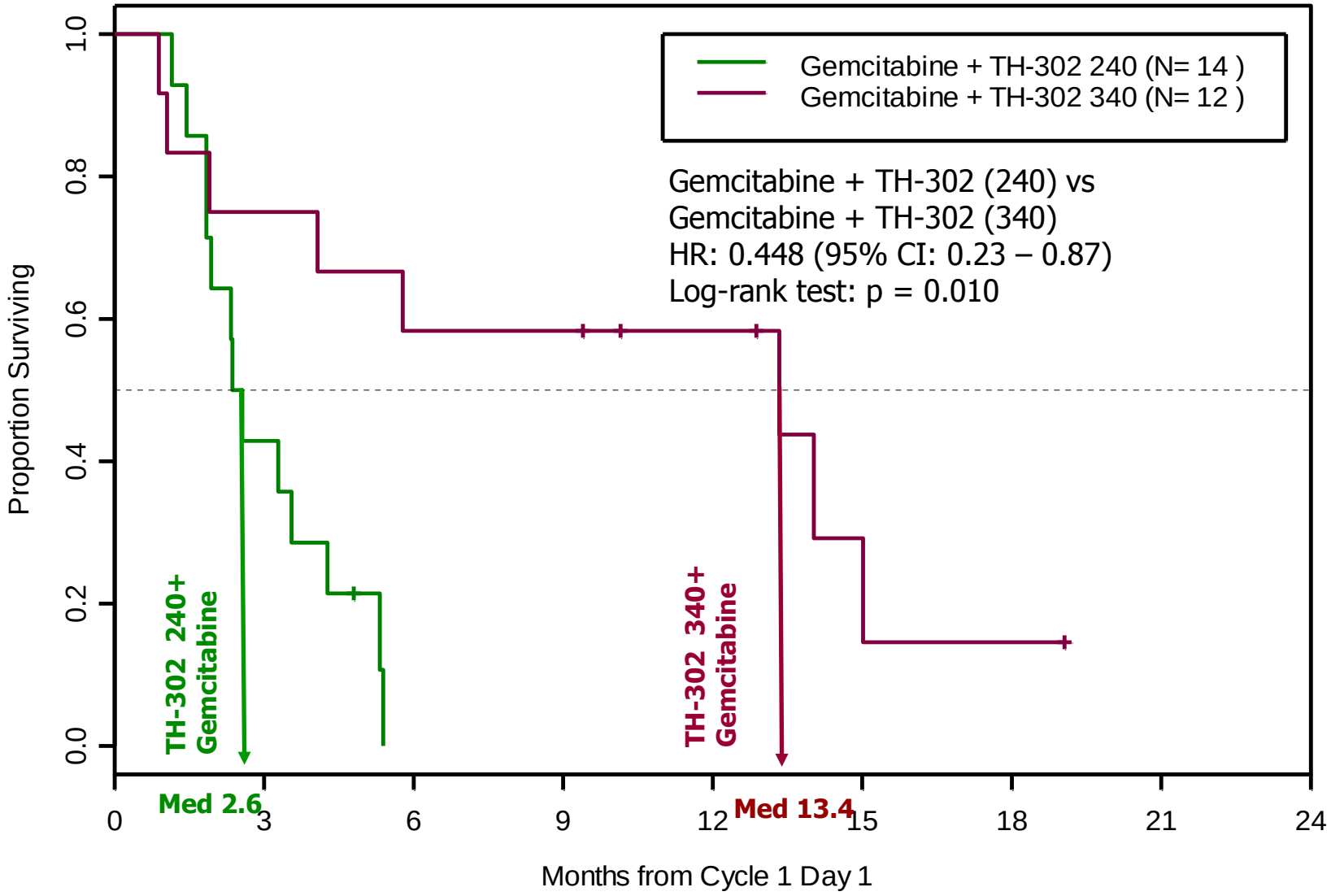
Randomized Crossover Efficacy Summary

	Gemcitabine + TH-302 (240 mg/m²) (N=14)	Gemcitabine + TH-302 (340 mg/m²) (N=12)
Median PFS (mo)	1.8 (95% CI: 1.6-2.3)	2.9 (95% CI: 1.8-NR)
Best Response	0%	0%
Median OS (mo)	2.6 (95% CI: 1.9-4.3)	13.4 (95% CI: 4.1-15.0)
CA19-9 Response	0% (0/12)	25% (2/8)

- Median PFS prior to crossover was 3.2 mo in G+T240 and 3.6 mo in G+T340
- 11 subjects received subsequent therapy after crossover

Study TH-CR-404

Randomized Comparison of Overall Survival after Crossover



Study TH-CR-404

Summary: **Gemcitabine** versus **Gemcitabine + TH-302 (340 mg/m²)**

Consistent TH-302 Dose Effect

- **Efficacy**
  - PFS primary efficacy endpoint reached (median **3.6 mo** to **6.0 mo**)
  - Increase in response rate (**10%** to **26%**)
  - Greater mean decrease in CA19-9 (**523 U/L** versus **5385 U/L**)
  - Open label crossover study not designed for estimating OS treatment effect
    - Increase in median OS (**6.9 mo** to **9.2 mo**)
  - Longer survival after crossover randomization (**2.6 mo** to **13.4 mo***)

- **Safety**
  - Increase in rash (**16%** to **47%**; 4% Grade 3)
  - Increase in stomatitis (**7%** to **42%**; no Grade 3)
  - Increase in Grade 3/4 thrombocytopenia (**11%** to **63%**)
  - Increase in Grade 3/4 neutropenia (**31%** to **60%**)
  - No increase in study discontinuations for AE (**16%** to **12%**)

- **Initiating Phase 3 Study**

*__240 mg/m²__ crossover *vs.* __340 mg/m²__ crossover

Study TH-CR-404

Acknowledgments

- **We would like to acknowledge and thank all of the patients that participated in the study and their families**
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