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

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Disclosures

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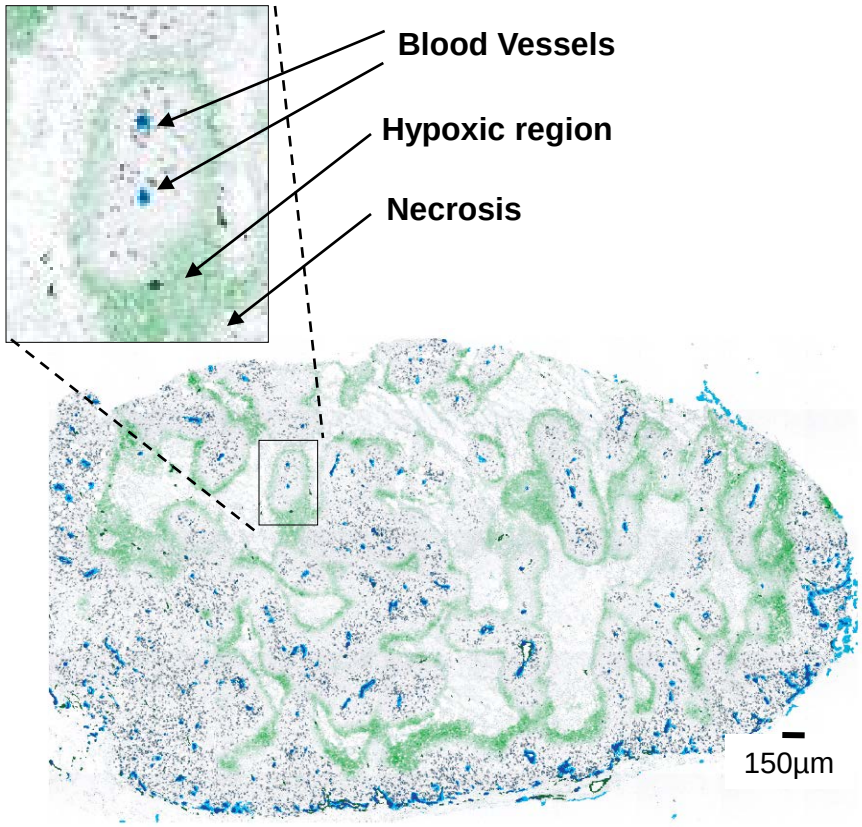
The Tumor Microenvironment

Subregional hypoxia as a defining feature



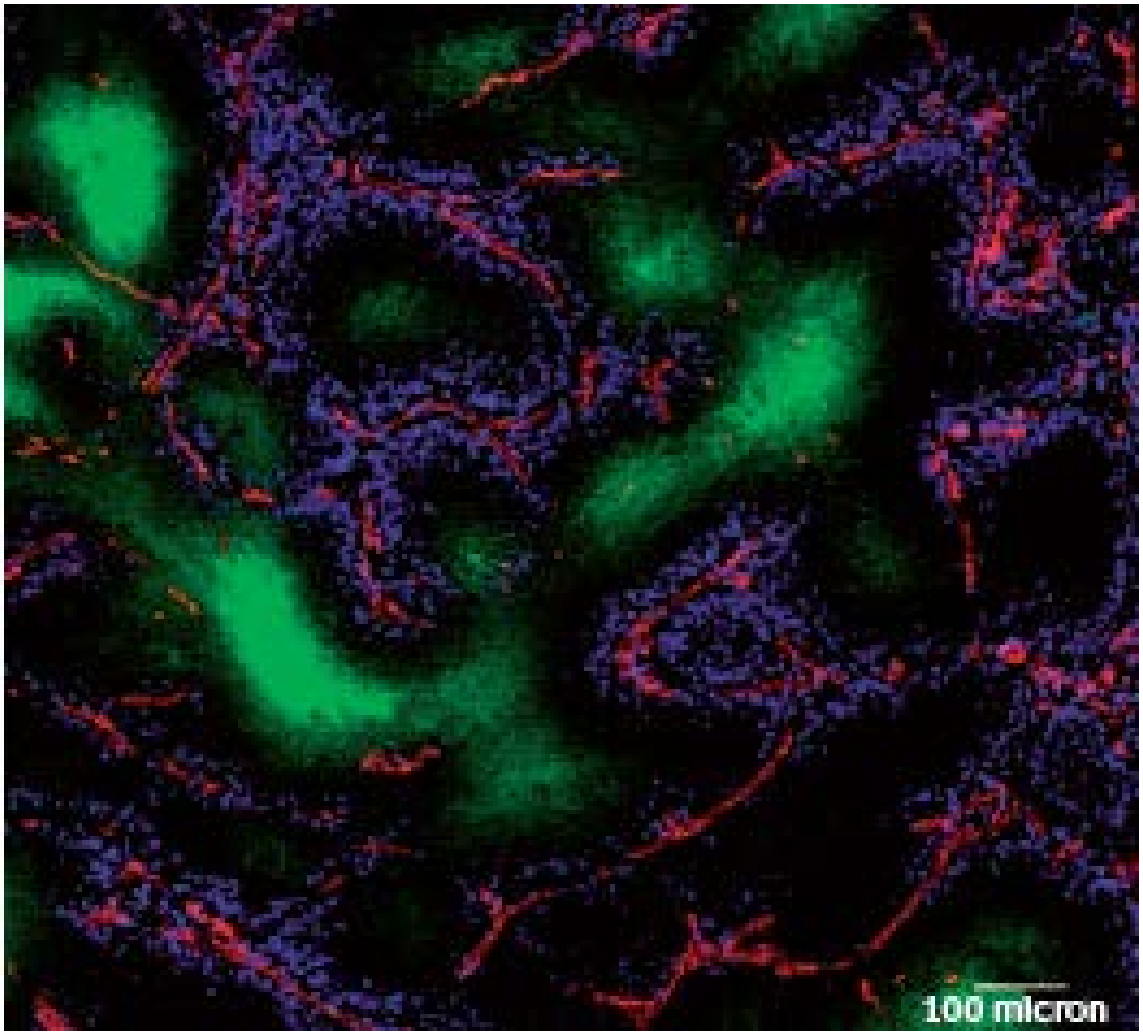
Pimonidazole staining of hypoxic regions
Blood vessels in blue

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

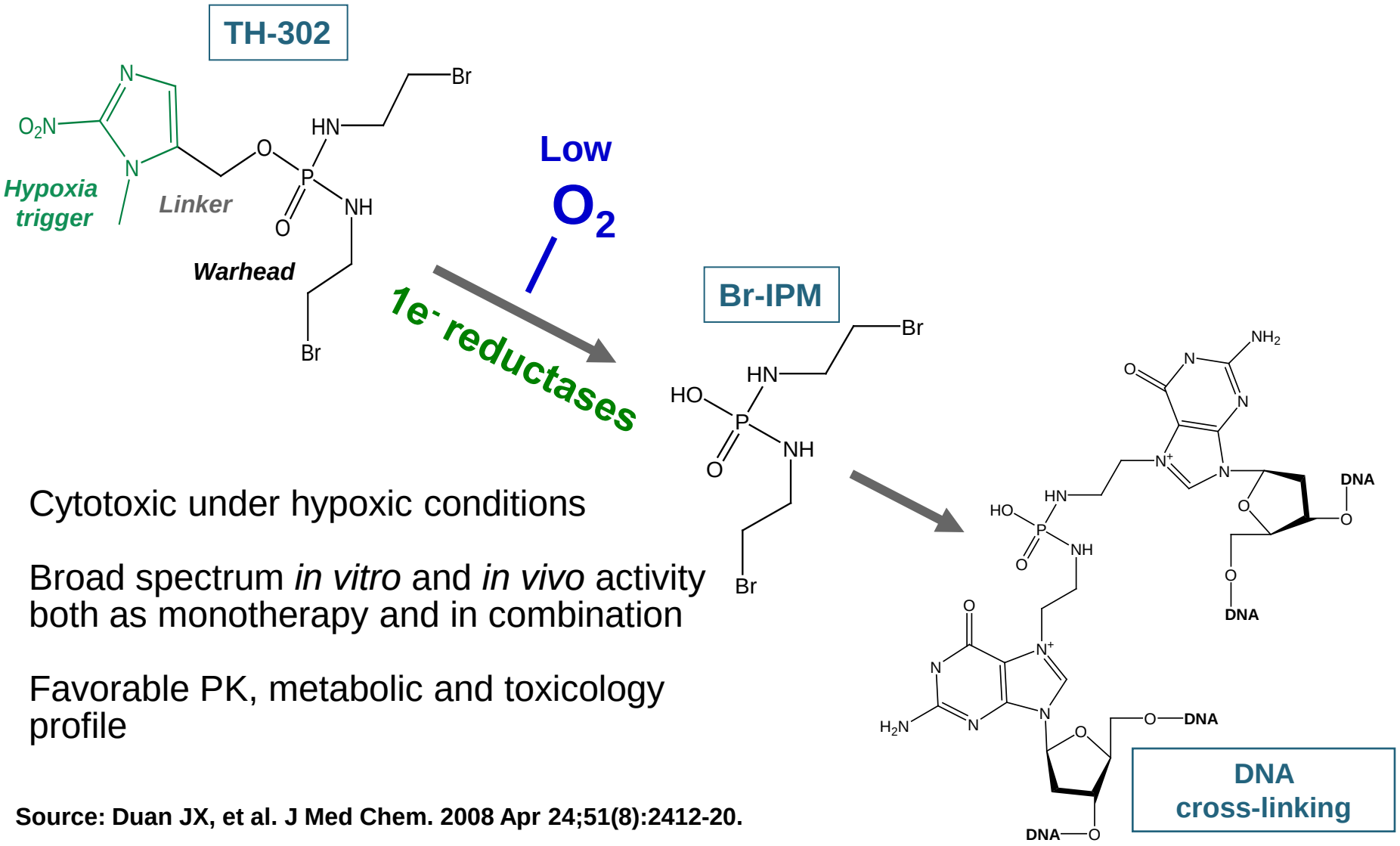


Vessels: Red
Doxorubicin: Blue
Hypoxia: Green

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

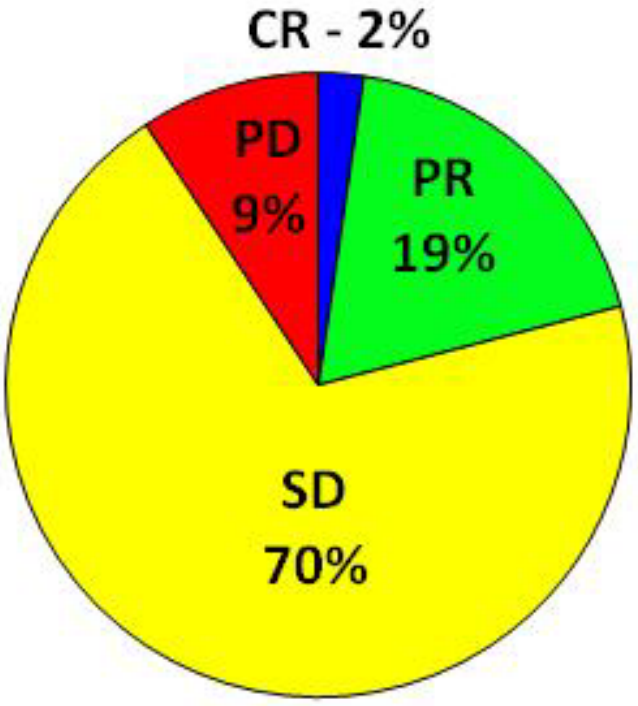


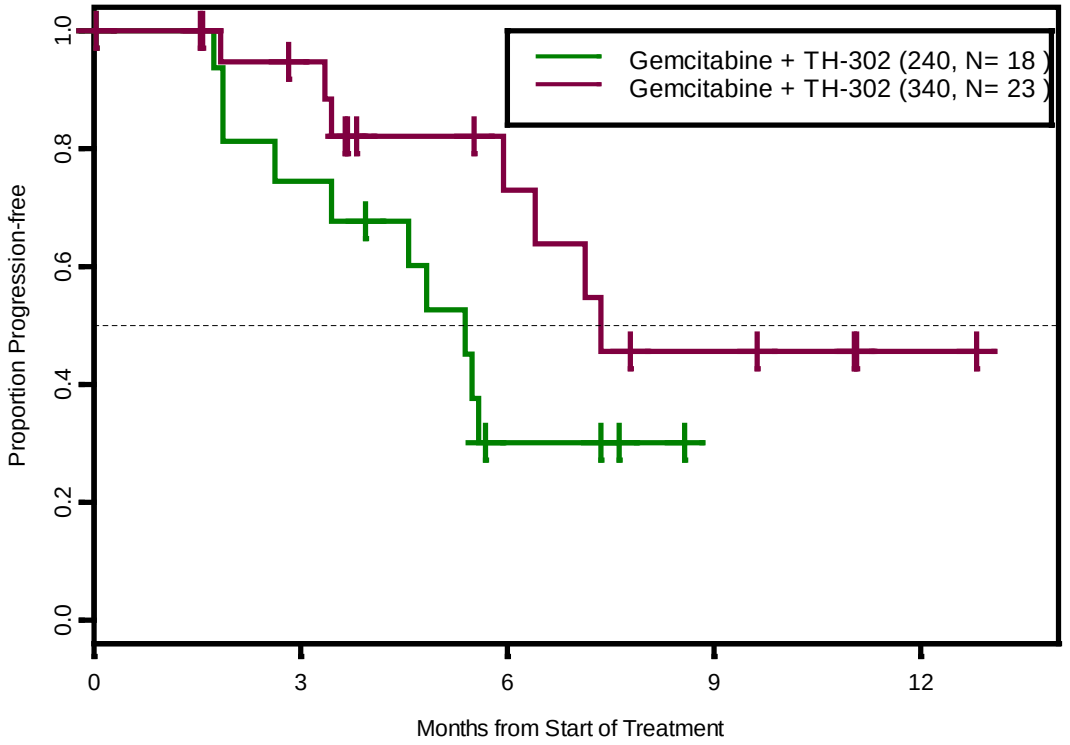
- Cytotoxic under hypoxic conditions
- Broad spectrum *in vitro* and *in vivo* activity both as monotherapy and in combination
- Favorable PK, metabolic and toxicology profile

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)

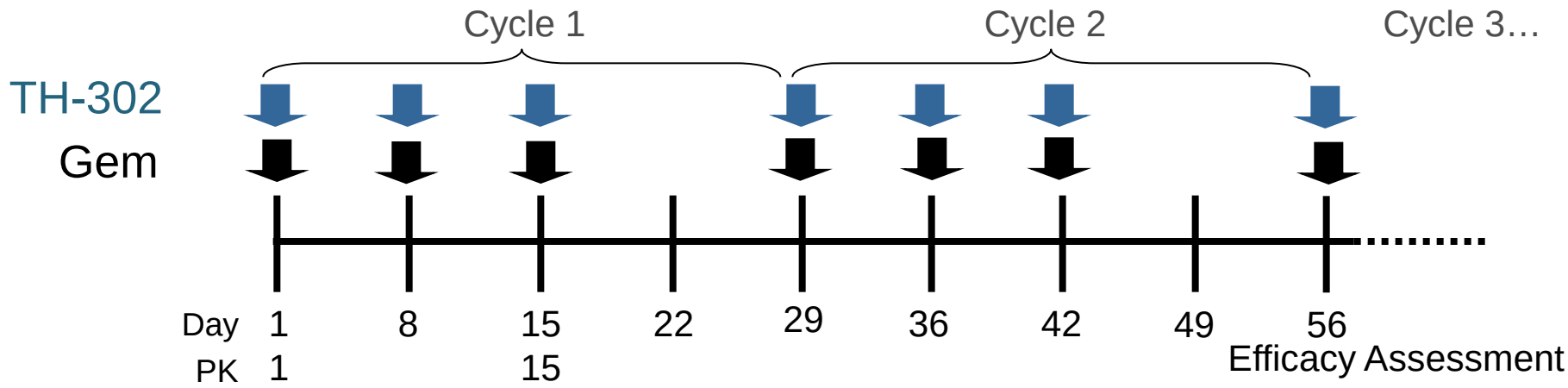
Gemcitabine + TH-302 (340 mg/m^2)

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

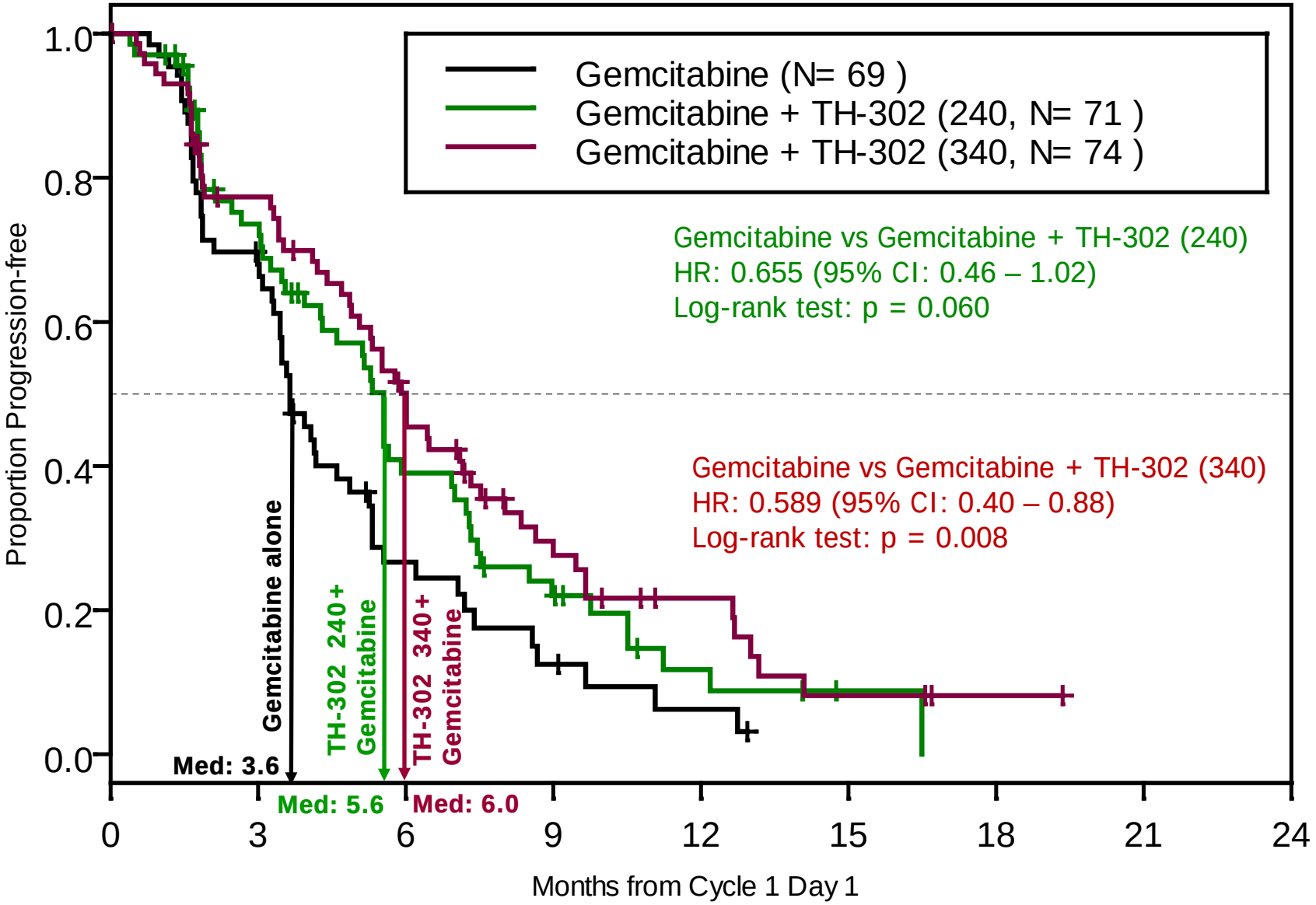
Laboratory Events

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)

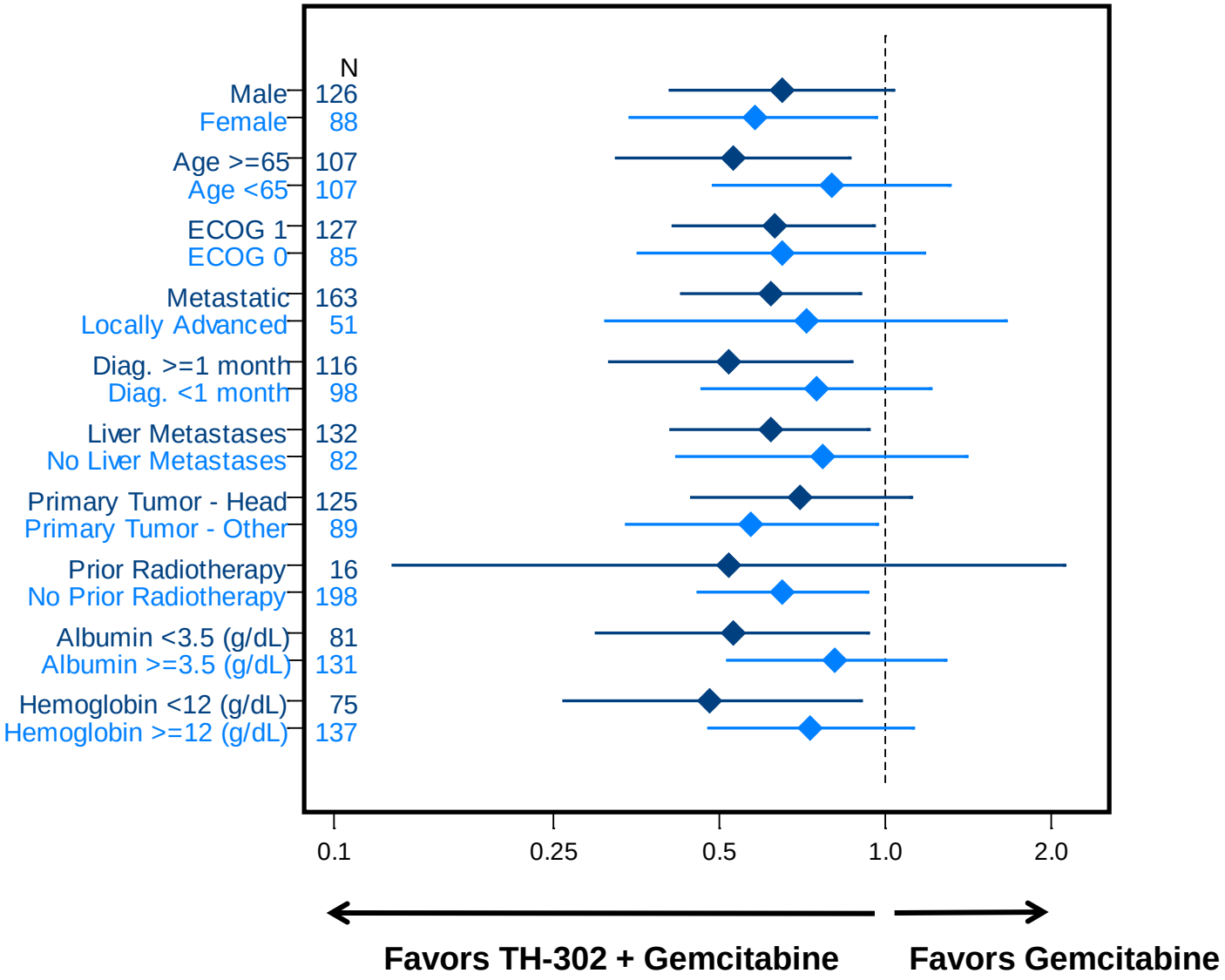
Study TH-CR-404

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

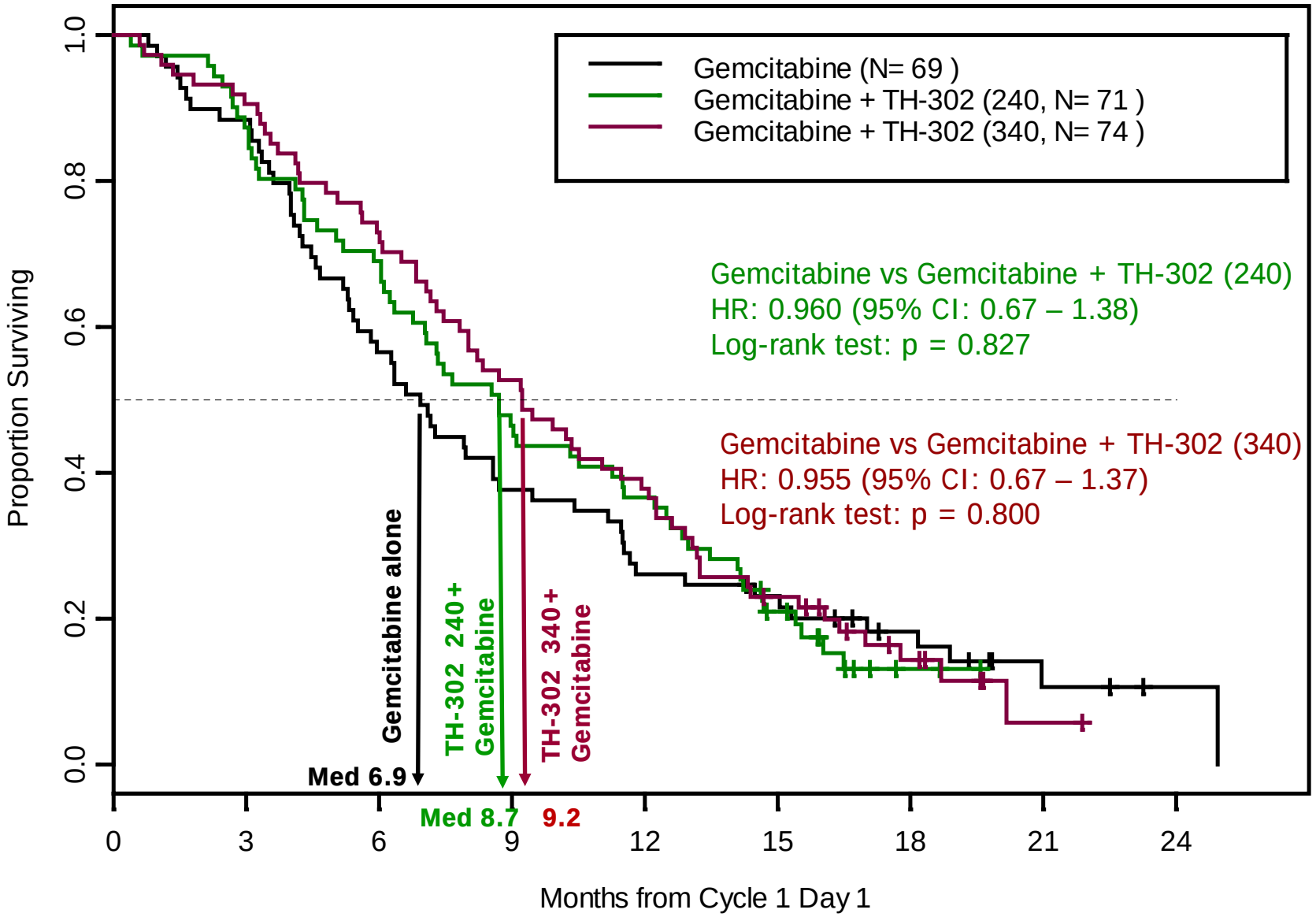
	Gemcitabine (N=50)	**Gemcitabine + TH-302 (240 mg/m²) (N=50)**	**Gemcitabine + TH-302 (340 mg/m²) (N=53)**
Mean Nadir Change (U/L) in CA19-9	-523	-3909	-5385**
Percent CA 19-9 Decrease >20% >50% >90%	 34 (68%) 26 (52%) 8 (16%)	 36 (72%) 25 (50%) 12 (24%)	 47 (89%) 37 (70%) 17 (32%)
Months to CA19-9 Response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

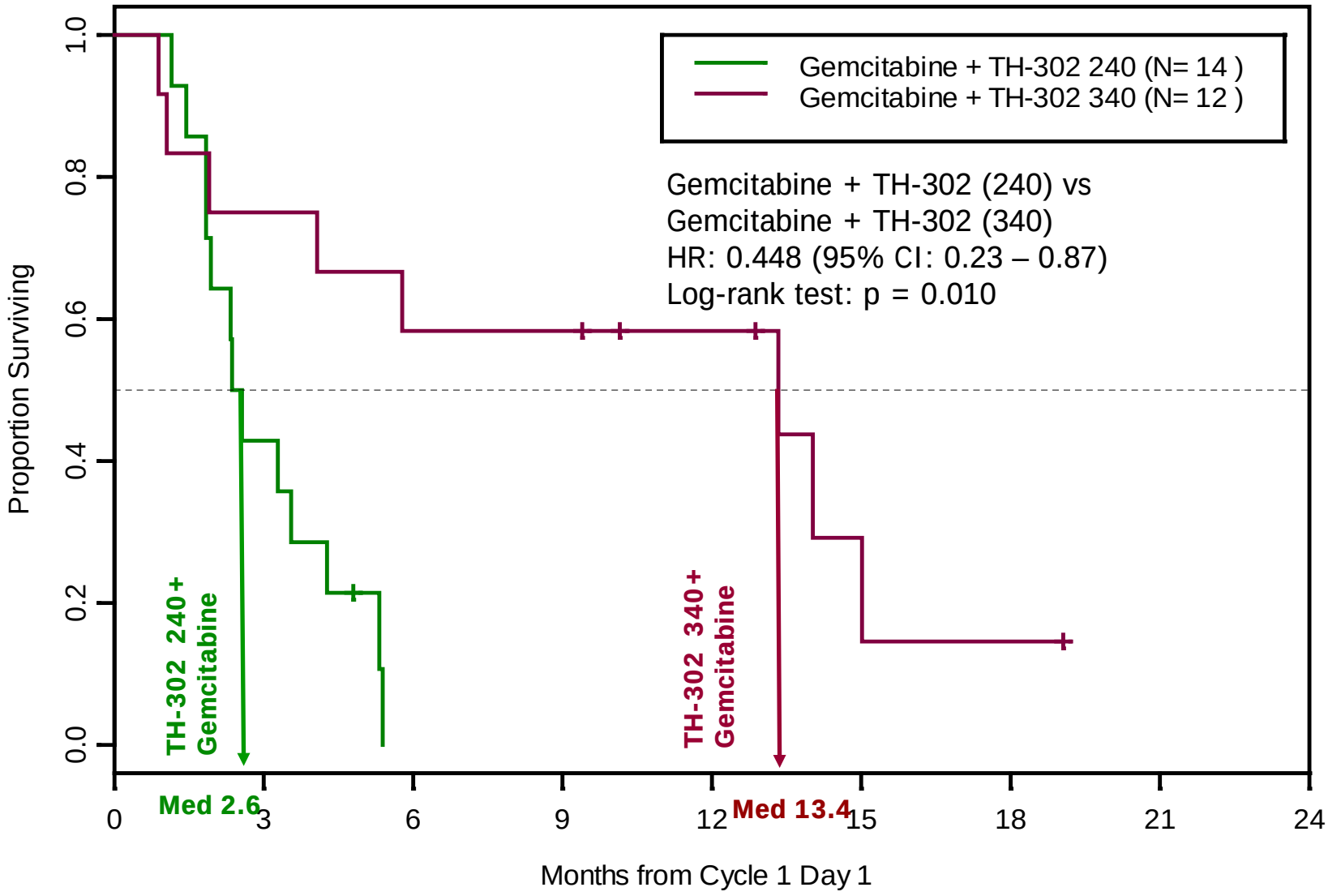
Randomized Crossover Efficacy Summary

	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**
- **Investigators and their teams**

MJ Borad, Mayo Clinic Arizona, Scottsdale, AZ; N Bahary, University of Pittsburgh Medical Center, Pittsburgh, PA; S Reddy, Louisiana State University Health Sciences Center, Shreveport, LA; H Uronis, Duke University Medical Center, Durham, NC; DS Sigal, Scripps Cancer Center, La Jolla, CA; AL Cohn, Rocky Mountain Cancer Centers, Denver, CO; WR Schelman, University of Wisconsin Hospital and Clinics, Madison, WI; J Stephenson, Jr., Institute for Translational Oncology Research, Greenville, SC; EG Chiorean, Indiana University Melvin and Bren Simon Cancer Center, Indianapolis, IN; S Del Prete, Hematology Oncology, PC, Stamford, CT; T Dragovich, T Brown, Arizona Cancer Center, Tucson, AZ; PJ Rosen, Providence Saint Joseph Medical Center, Burbank, CA; B Ulrich, Texas Oncology-Wichita Falls Texoma Cancer Center, Wichita Falls, TX; MJ Rarick, Kaiser Permanente Northwest Region, Portland, OR; E Anderes, Loyola University Medical Center, Maywood, IL; LC DeMarco, New York Oncology Hematology, P.C., Hudson, NY; J Muscato, Missouri Cancer Associates, Columbia, MO; J Raymond, Allegheny Cancer Center; Allegheny General Hospital, Pittsburgh, PA; J Seng, Minnesota Oncology, Minneapolis, MN; A Spira, Virginia Cancer Specialists, PC, Fairfax, VA; K Windsor, Birmingham Hematology and Oncology Associates, LLC, Birmingham, AL; VJM Cline-Burkhardt, Texas Oncology-Seton Williamson, Round Rock, TX; C Croot, North Mississippi Hematology and Oncology Associates, Ltd., Tupelo, MS; T Finnegan, Alamance Regional Medical Center Cancer Center, Burlington, NC; W Ma, Roswell Park Cancer Institute, Buffalo, NY; P Piperdi, VG Bathini, University of Massachusetts Medical Center, Worcester, MA; R Ruxer, Texas Oncology-Fort Worth 12th Ave., Fort Worth, TX; P Beatty, Montana Cancer Institute Foundation, Missoula, MT; V Harish, Emerywood Hematology/Oncology, High Point, NC; T Rado, Columbia Basin Hematology and Oncology, Kennewick, WA; LS Wilfong, Texas Oncology-Dallas Presbyterian Hospital, Dallas, TX; P Yu, Palo Alto Medical Foundation, Mountain View, CA; G Abesada-Terk, Martin Memorial Cancer Center, Stuart, FL; A Baron, Pacific Hematology Oncology Associates, San Francisco, CA; R Belani, Sharp Clinical Oncology Research, San Diego, CA; F Braiteh, Comprehensive Cancer Centers of Nevada, Las Vegas, NV; W Conkright, Oncology Hematology Cunsulants d/b/a Purchase Cancer Group, Paducah, KY; E Garon, University of California -- Los Angeles, Los Angeles, CA; P Haghighat, Los Palos Oncology and Hematology, Salinas, CA; P Jiang, Providence Regional Medical Center Everett/Providence Regional Cancer Partnership, Everett, WA; S McKenney, Texas Oncology-Beaumont, Mamie McFaddin Ward Cancer Center, Beaumont, TX; S Shao, Northwest Cancer Specialists, P.C., Portland, OR; F Sinicrope, Mayo Clinic, Rochester, MN; M Stagg, II, Medical Oncology, LLC, Baton Rouge, LA; D Ryan, Massachusetts General Hospital, Boston, MA

Threshold Pharmaceuticals, Inc.

Supplemental Information on Study TH-CR-404 Overall Survival Analysis

September 29, 2012

Forward-Looking Statements

These slides contain "forward-looking" statements within the meaning of the Private Securities Litigation Reform Act of 1995. These statements may be identified by the use of forward looking terminology such as "anticipate", "believe", "continue", "could", "estimate", "expect", "intend", "may", "might", "plan", "potential", "predict", "should" or "will" and include statements regarding Threshold's product candidates and clinical trial progress and results. These forward-looking statements are based on our current expectations, speak only of the date of this presentation and involve risks and uncertainties, many of which are outside of our control, that can cause actual results to differ materially from those in the forward-looking statements. Potential risks and uncertainties include, but are not limited to, our ability to complete our anticipated clinical trials, the time and expense required to conduct such clinical trials, the ability to manufacture clinical or commercial product, issues arising in the regulatory process and the results of such clinical trials (including product safety issues and efficacy results). Further information is included in Threshold's periodic reports filed with the SEC at www.sec.gov.

We disclaim any duty to update any forward-looking statements.

THRESHOLD PHARMACEUTICALS

Supplemental Information on TH-CR-404

Outline

TH-302 Hypoxia-Targeted Drug

Drug Profile

- Novel small molecule with patent protection through 2029
- Favorable PK, metabolic, and preclinical profile
- Demonstrated clinical activity in multiple tumor types
  - Both as monotherapy and in combination with several different approved and widely used anti-cancer therapies
- Safety profile established in more than 700 patients
  - Rare single agent dose limiting bone marrow suppression
    - DLTs predominantly skin irritation or mucositis
  - In combination, DLTs mainly related to bone marrow suppression
- Straightforward regulatory paths initiated
- Nine ongoing/pending clinical studies in multiple indications and drug combinations

PK=pharmacokinetics; DLT=dose-limiting toxicity

THRESHOLD PHARMACEUTICALS

Study TH-CR-404
Objectives

- Primary Objectives
  - Efficacy of TH-302 + gemcitabine as measured by PFS compared to gemcitabine alone
  - Safety of TH-302 and gemcitabine compared to gemcitabine alone
- Secondary Objectives
  - Efficacy of TH-302 + gemcitabine as measured by ORR, duration of response, OS including 6 and 12 mo OS, changes in performance status, changes in VAS pain score, changes in CA19-9 and CA19-9 response rate compared to gemcitabine alone
  - To select the most suitable TH-302 dose for Phase 3
  - To compare crossover efficacy and safety to that on initial gemcitabine
  - To investigate PK of TH-302 and Br-IPM including influence of covariates
- Exploratory Objective
  - Explore the association of serum and tumor hypoxia biomarkers with efficacy endpoints

PFS=Progression-free Survival; ORR=Overall Response Rate; OS=Overall Survival; VAS=visual analog scale; PK=pharmacokinetics; Br-IPM=bromo-isophosphoramide mustard

Source: Borad M., et al. ESMO 2012 Congress (Abstract 666O)

Study TH-CR-404
Highest Enrolling Sites

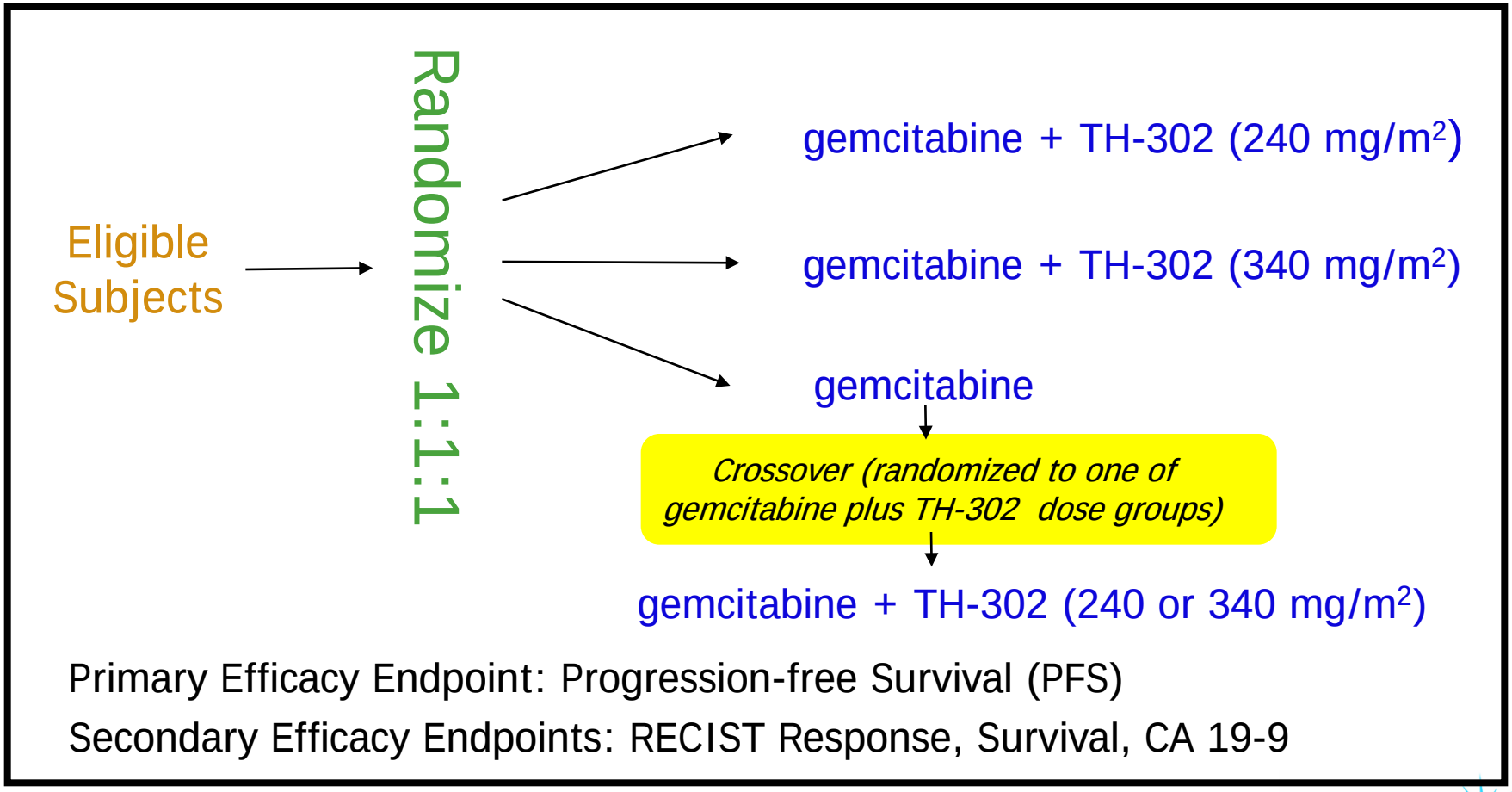
214 patients were enrolled and treated at 45 sites in the United States

Investigator	Pts	Site	Location	
Borad, Mitesh	18	Mayo Clinic Cancer Center--Arizona	Scottsdale	AZ
Ryan, David	17	Mass. General Hospital	Boston	MA
Reddy, Shantan	14	Louisiana State University Health Sciences Center	Shreveport	LA
Bahary, Nathan	14	University of Pittsburgh Medical Center	Pittsburgh	PA
Uronis, Hope	13	Duke University Medical Center	Durham	NC
Sigal, Darren S.	11	Scripps Clinical Research Services	La Jolla	CA
Cohn, Allen L	10	Rocky Mountain Cancer Centers	Denver	CO
Stephenson, Jr., Joe	7	Institute for Translational Oncology Research (ITOR)	Greenville	SC
Schelman, William	7	University of Wisconsin	Madison	WI
Chiorean, Elena	6	Indiana Univ Melvin and Bren Simon Cancer Center	Indianapolis	IN
Del Prete, Salvatore	6	Hematology Oncology Associates, PC	Stamford	CT
Dragovich, Thomas	6	Arizona Cancer Center	Tucson	AZ
Rosen, Peter	6	Disney Family Cancer Center	Burbank	CA
Ulrich, Brian	6	Texas Oncology-Wichita Falls Texoma Cancer Center	Wichita Falls	TX

Study TH-CR-404

Randomized Phase 2 Study Design

Randomized, open-label crossover study of previously untreated patients with locally advanced unresectable or metastatic pancreatic adenocarcinoma

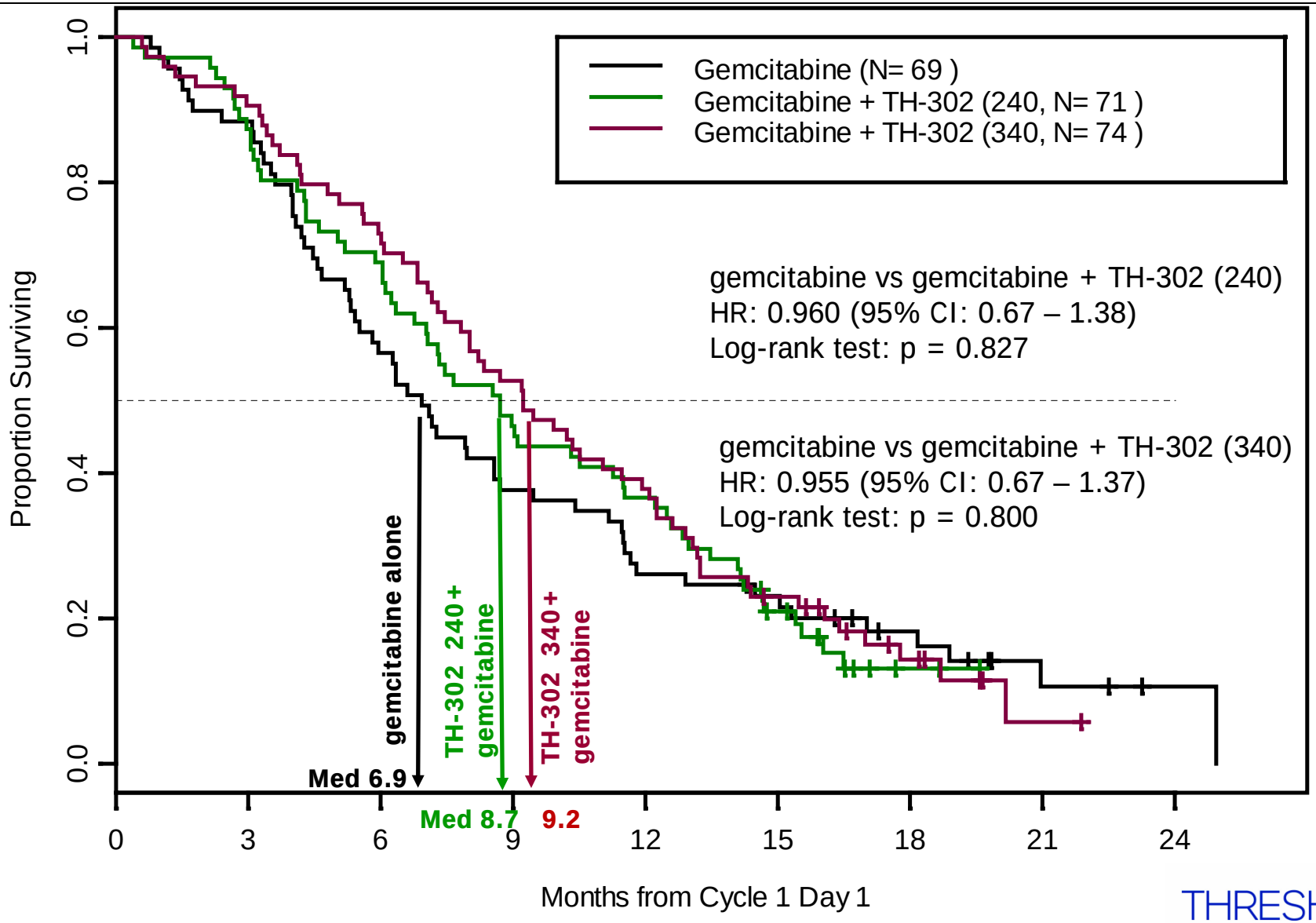


Source: Borad M., et al. ESMO 2012 Congress (Abstract 666O)

THRESHOLD PHARMACEUTICALS

Study TH-CR-404

Overall Survival by Treatment Arm: All Patients Including Crossover



Source: Borad M., et al. ESMO 2012 Congress (Abstract 666O)

THRESHOLD PHARMACEUTICALS

Study TH-CR-404

Survival at 6 and 12 months by Treatment Arm: All Patients Including Crossover

	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

Source: Borad M., et al. ESMO 2012 Congress (Abstract 666O)

THRESHOLD PHARMACEUTICALS

Impact of Crossover on Overall Survival Analysis

Example from Sunitinib in Gastrointestinal Stromal Tumors (GIST)

- "Sunitinib is recommended, within its licensed indication, as a treatment option for people with unresectable and/or metastatic malignant GIST…"
- "The main clinical-effectiveness evidence came from one randomised controlled trial (RCT). The RCT, A6181004, compared the effect of sunitinib (SU) plus best supportive care (n = 207) with placebo (PL) plus best supportive care (n = 105)."
- "A total of 84% of people randomised to receive placebo plus best supportive care crossed over and received sunitinib plus best supportive care."
- "During the blinded phase of the study, more than half of the people in both study arms of the trial were alive. However, the interim ITT analysis showed that overall survival was significantly longer for those who received sunitinib compared with those who received placebo (HR 0.491; 95% CI 0.290 to 0.831, p = 0.007)."
- "The ITT NICE technology appraisal guidance 179 analysis of the entire study (that is, blinded plus open-label phase) showed that there was no statistically significant difference in overall survival for people who received sunitinib plus best supportive care (overall survival 73 weeks) compared with people who received placebo plus best supportive care (overall survival 65 weeks) (HR 0.876; 95% CI 0.679 to 1.129, p = 0.306)."

Source: NICE technology appraisal guidance 179 http://www.nice.org.uk/nicemedia/pdf/TA179Guidance.pdf

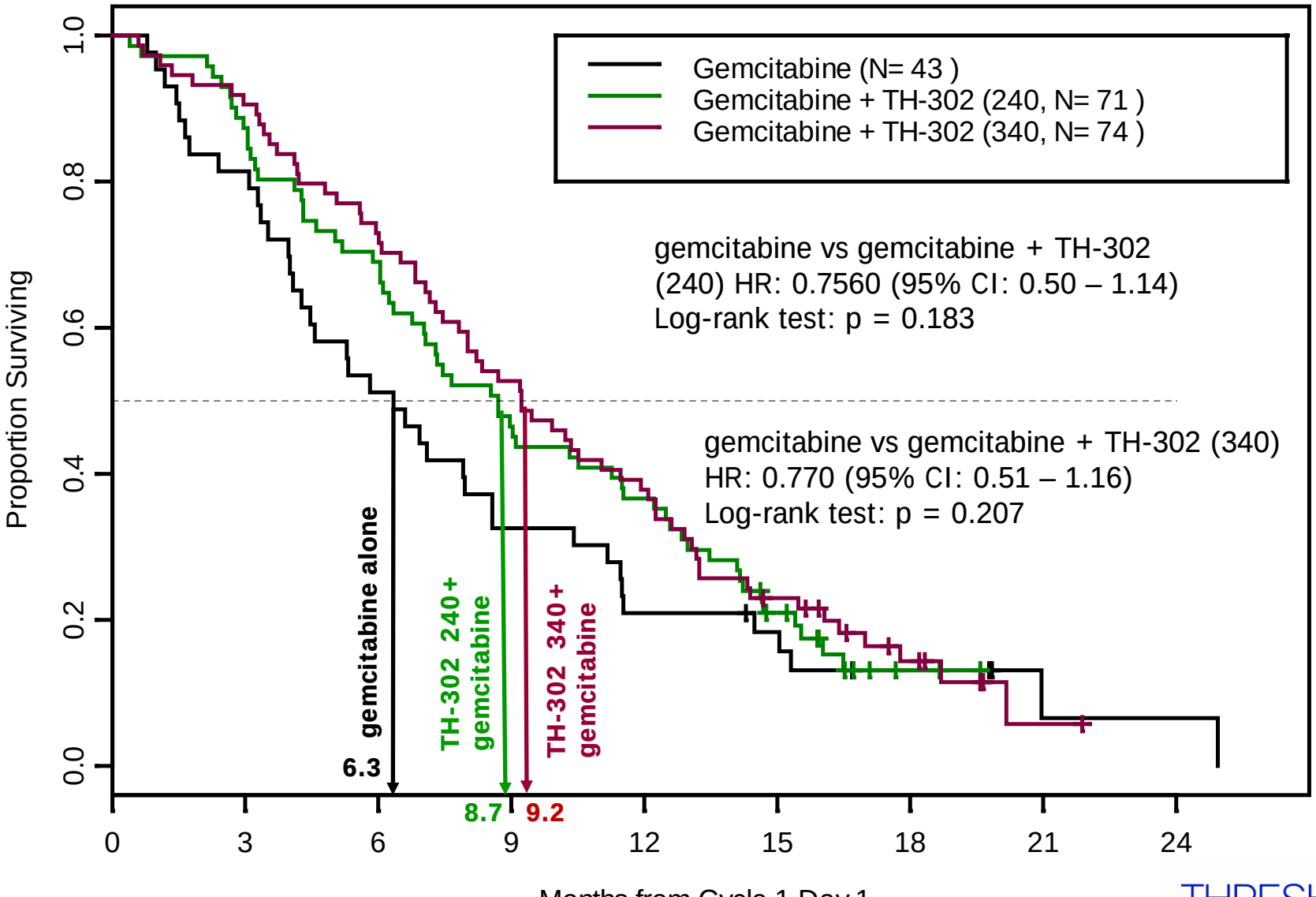
Study TH-CR-404

Crossover Randomization

- 26 of 69 patients (38%) on the active control group crossed over to treatment with TH-302+Gemcitabine
  - 14 patients were randomized to T240+G
  - 12 patients were randomized to T340+G

Study TH-CR-404

Overall Survival by Treatment Arm – Not Including Crossover



Source: Threshold data on file

THRESHOLD PHARMACEUTICALS

Study TH-CR-404

Survival at 6 and 12 months by Treatment Arm – Not Including Crossover

	gemcitabine (N=43)	**gemcitabine + TH-302 (240 mg/m²)** (N=71)	**gemcitabine + TH-302 (340 mg/m²)** (N=74)
6-month Survival (95% CI)	51% (35% - 65%)	69% (57% - 78%)	73% (61% - 82%)
P-value versus gemcitabine		0.057	0.018

	gemcitabine (N=43)	**gemcitabine + TH-302 (240 mg/m²)** (N=71)	**gemcitabine + TH-302 (340 mg/m²)** (N=74)
12-month Survival (95% CI)	21% (10% - 34%)	37% (26% - 48%)	38% (27% - 49%)
P-value versus gemcitabine		0.063	0.044

Source: Threshold data on file

THRESHOLD PHARMACEUTICALS

Caveats About Excluding Crossover from OS Analysis

- Small sample size
- Post–hoc analysis
- OS analysis is from time of randomization and patients who crossover are not identified at randomization
- Selection bias (some favorable and some not favorable)
  - Patients need to survive long enough to progress on gemcitabine and initiate crossover
  - Patients had to discontinue gemcitabine with progressive disease
    - Patients discontinuing for safety reasons could not crossover
  - Patients could select other therapies

Comparing Overall Survival After Crossover

- Randomization of patients after disease progression on gemcitabine enables a comparison of T240+G vs T340+G on post-crossover OS

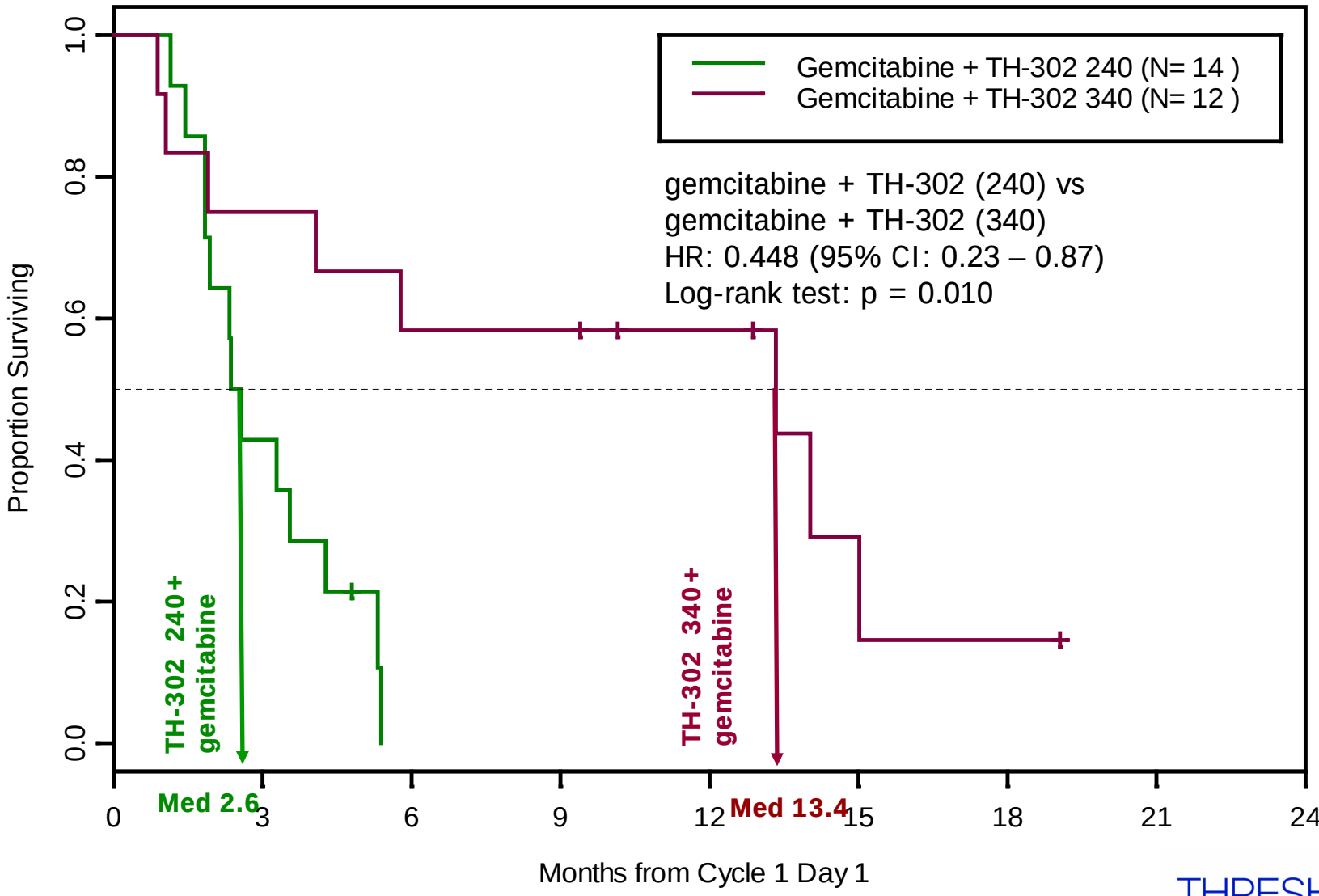
- A statistically significant difference in OS was observed: median post-crossover OS was 2.6 months in T240+G versus 13.4 months in T340+G (p=0.01) (please see survival curves on next slide)

- There is an apparent dose-dependent OS improvement following crossover with patients receiving T340+G having significantly longer OS than patients receiving T240+G.

THRESHOLD PHARMACEUTICALS

Study TH-CR-404

Randomized Comparison of Overall Survival after Crossover



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THRESHOLD PHARMACEUTICALS

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***)

*240 mg/m² crossover *vs.* 340 mg/m² crossover

- **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**

Source: Borad M., et al. ESMO 2012 Congress (Abstract 666O)

THRESHOLD PHARMACEUTICALS