Study TH-CR-404

A Randomized Crossover Phase 2 Study of the Safety and Efficacy of Two Dose Levels of TH-302 in Combination with Gemcitabine Compared with Gemcitabine Alone in Previously Untreated Patients with Locally Advanced Unresectable or Metastatic Pancreatic Adenocarcinoma

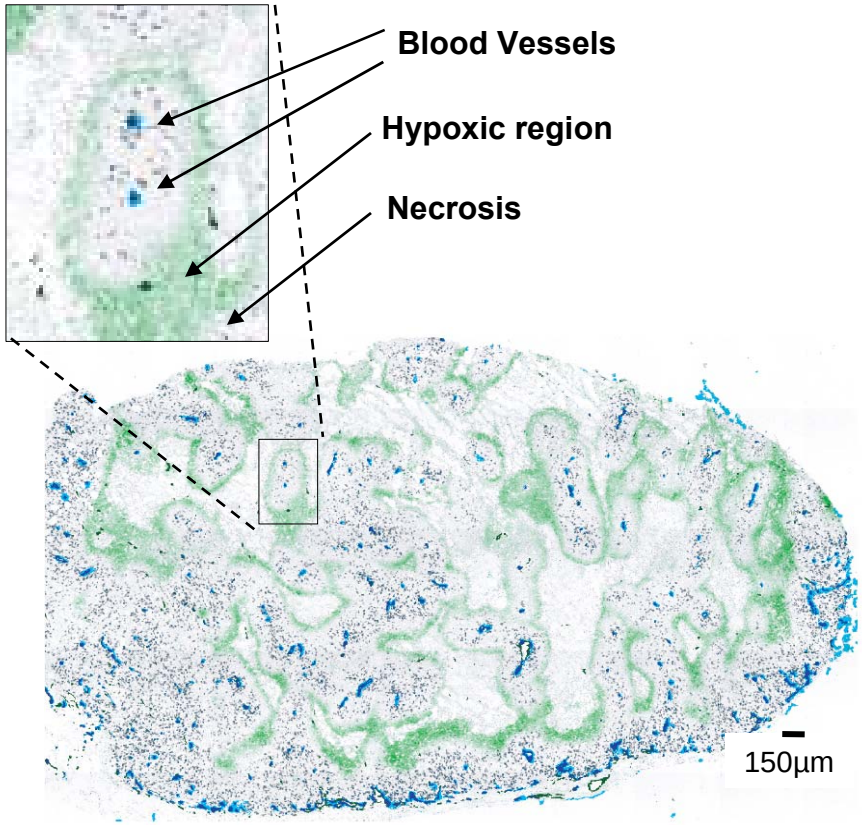
MJ Borad, Mayo Clinic, Scottsdale, AZ
S Reddy, Louisiana State University Health Sciences Center, Shreveport, LA
N Bahary, University of Pittsburgh Medical Center, Pittsburgh, PA
H Uronis, Duke University Medical Center, Durham, NC
DS Sigal, Scripps Clinical Medical Group, La Jolla, CA
AL Cohn, Rocky Mountain Cancer Centers, Denver, CO
WR Schelman, University of Wisconsin Hospital and Clinics, Madison, WI
J Stephenson, Inst for Translational Oncology Research, Greenville, SC
EG Chiorean, Indiana University Simon Cancer Center, Indianapolis, IN
PJ Rosen, Providence Saint Joseph Medical Center, Burbank, CA
B Ulrich, Texas Oncology, Wichita Falls, TX
T Dragovich, Arizona Cancer Center, Tucson, AZ
S Del Prete, Hematology Oncology, PC, Stamford, CT
M Rarick, Kaiser Permanente Northwest Region Oncology Hematology, Portland, OR
C Eng, S Kroll, Threshold Pharmaceuticals, South San Francisco, CA
D Ryan, Massachusetts General Hospital, Boston, MA

Disclosures

- My institution has received financial support from Threshold Pharmaceuticals to conduct clinical trial related activities

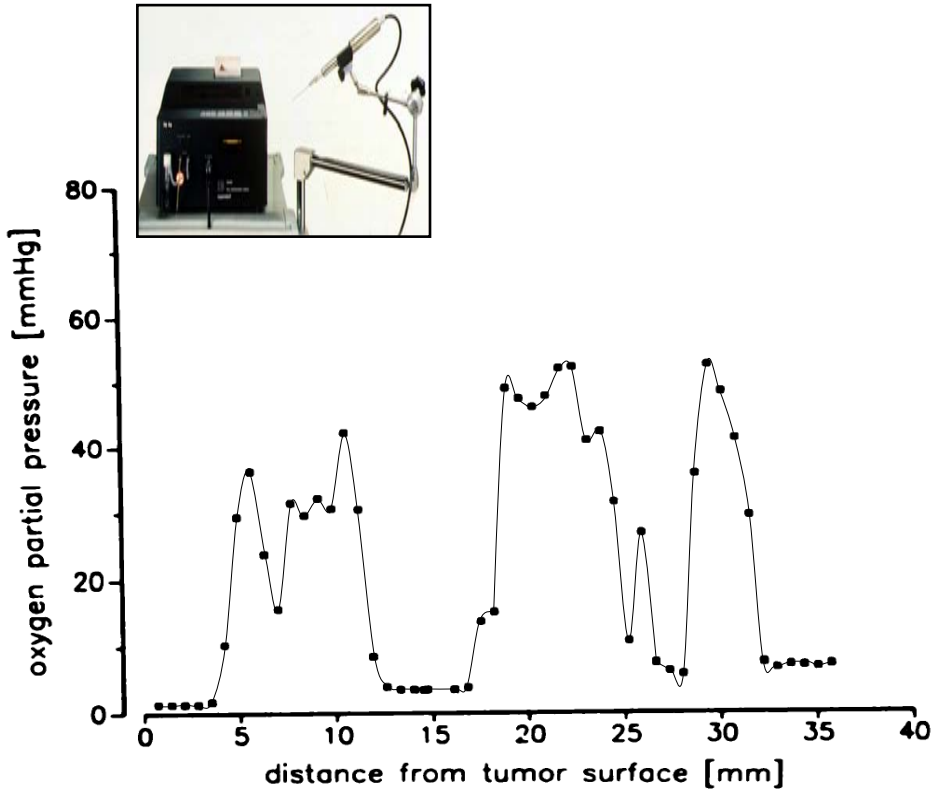
The Tumor Microenvironment

Subregional hypoxia as a defining feature



Pimonidazole staining
of hypoxic regions
Blood vessels in blue

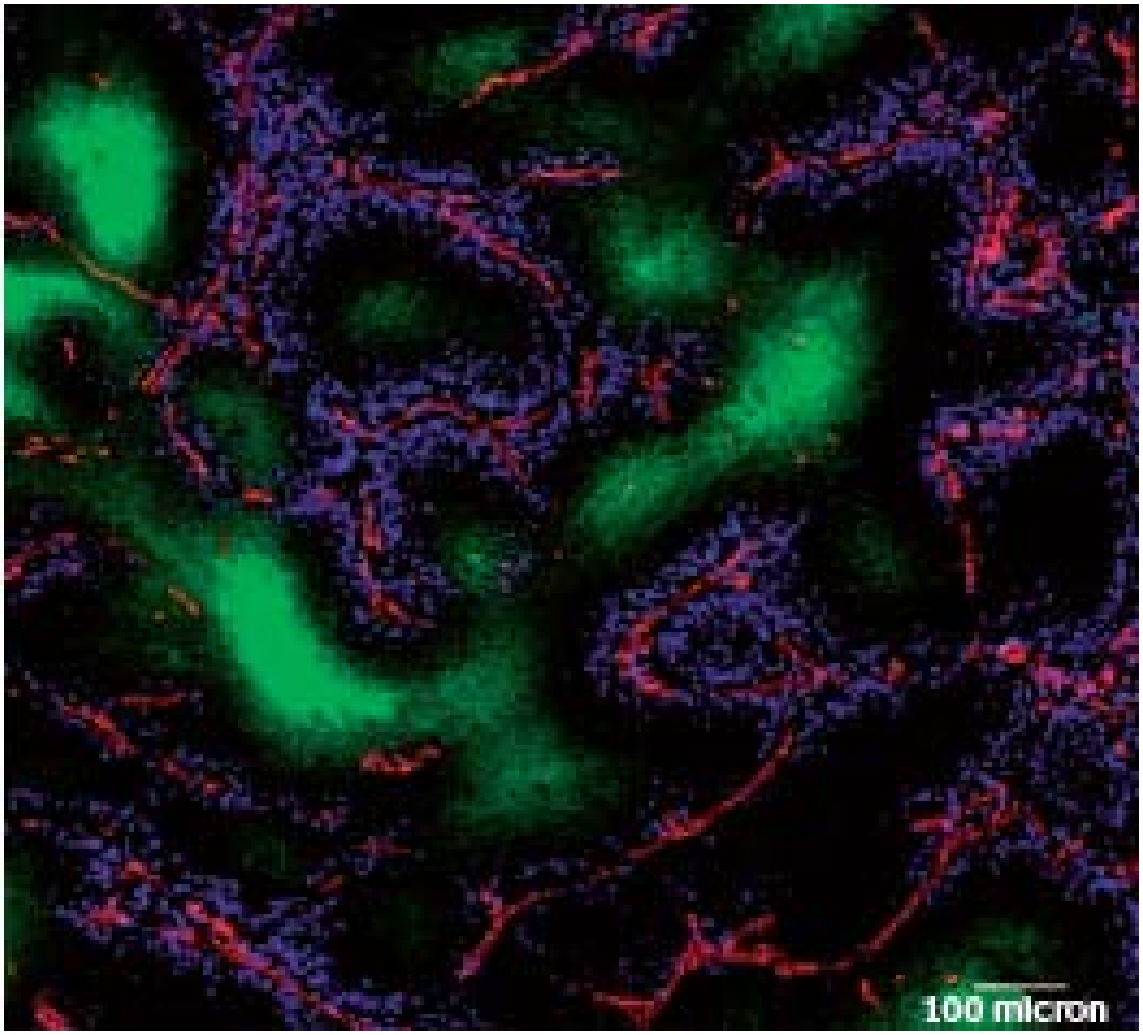
Minchinton, A. and Tannock, I. Nat. Rev. Cancer. 6: 583-92, 2006



Eppendorf electrode O_2 profiling
50 discrete measurements with ~0.7mm spacing

Vaupel, P. *et al.* Cancer Res. 51: 3316-22, 1991

Chemotherapy Targets Oxygenated Tumor Compartment

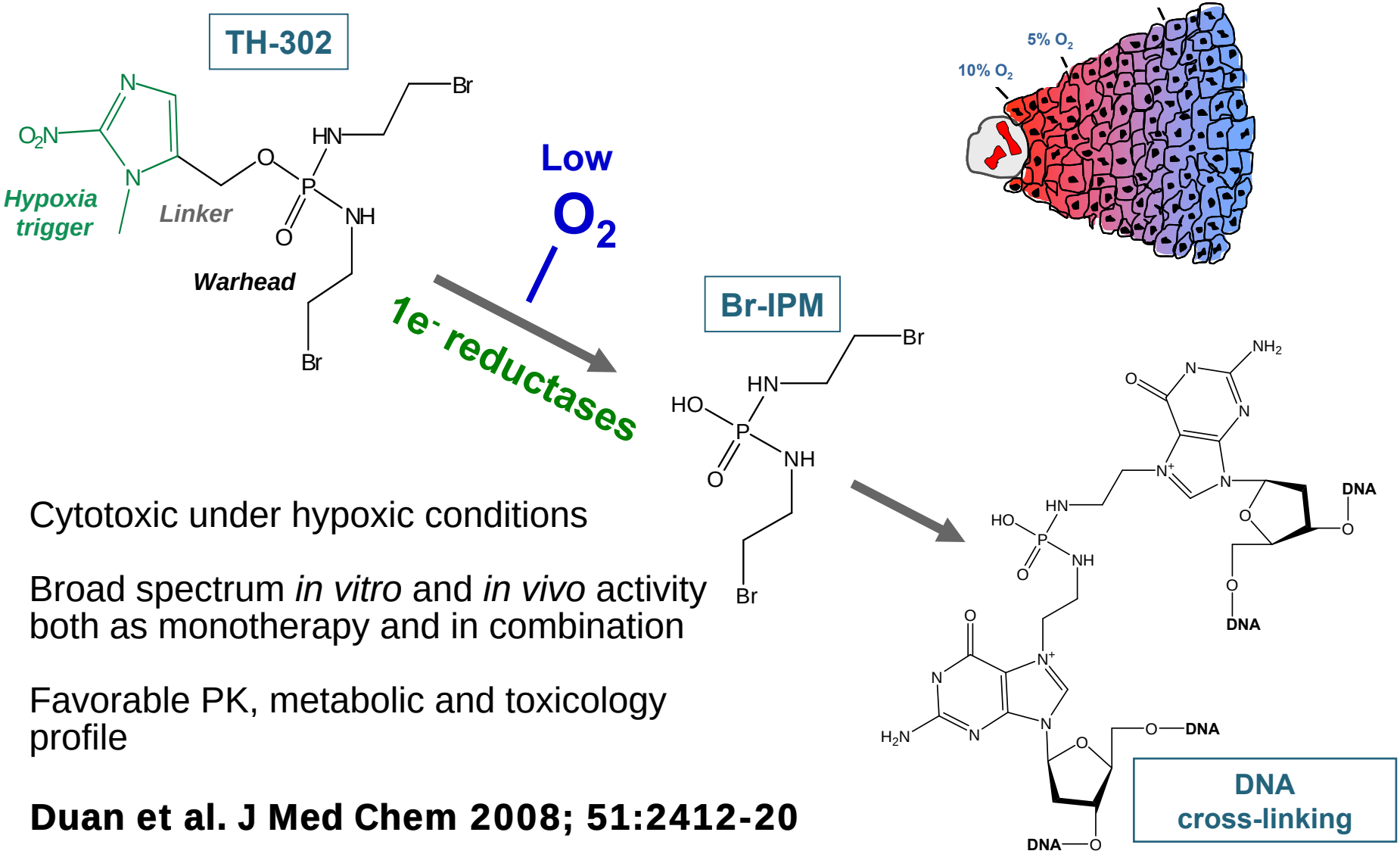


Vessels: Red
Doxorubicin: Blue
Hypoxia: Green

Minchinton and Tannock. Nature Reviews 2006;6:583-92

Hypoxia Activated Pro-Drug (HAP) - TH-302

A tumor-selective hypoxia-activated cytotoxic prodrug

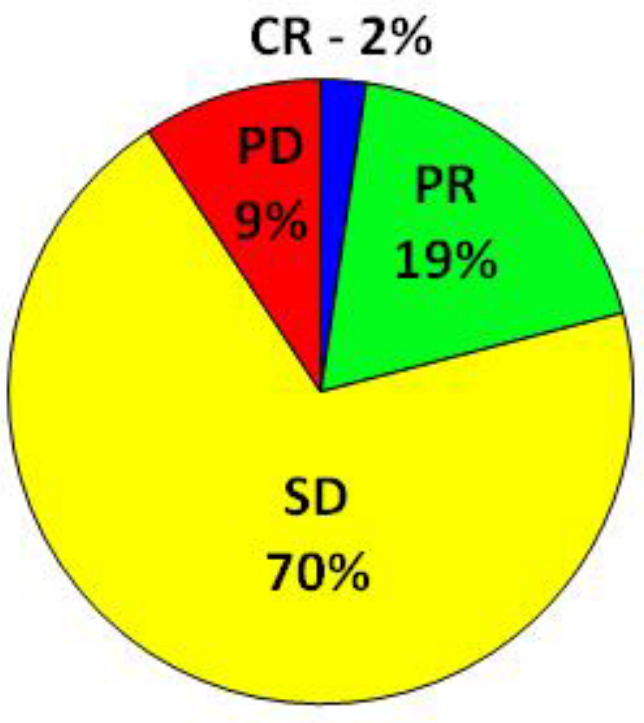


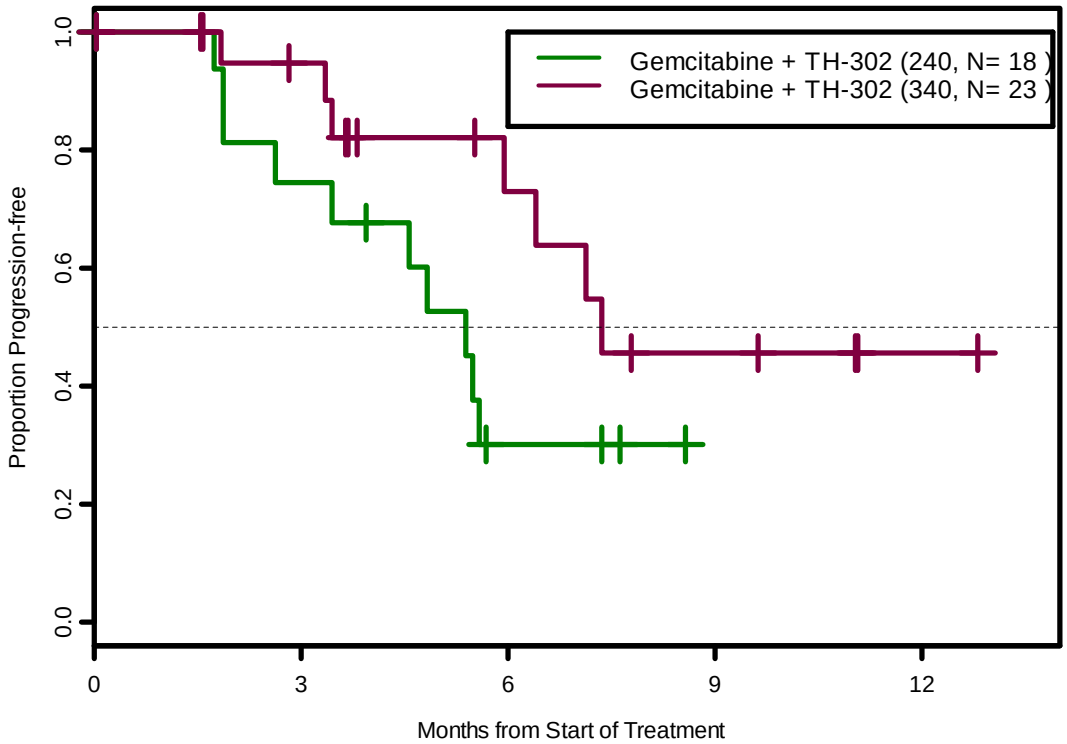
- Cytotoxic under hypoxic conditions
- Broad spectrum *in vitro* and *in vivo* activity both as monotherapy and in combination
- Favorable PK, metabolic and toxicology profile

Duan et al. J Med Chem 2008; 51:2412-20

TH-302 + Gemcitabine in First-Line Pancreatic Cancer

Single Arm Dose Expansion Formed Basis for Randomized Design



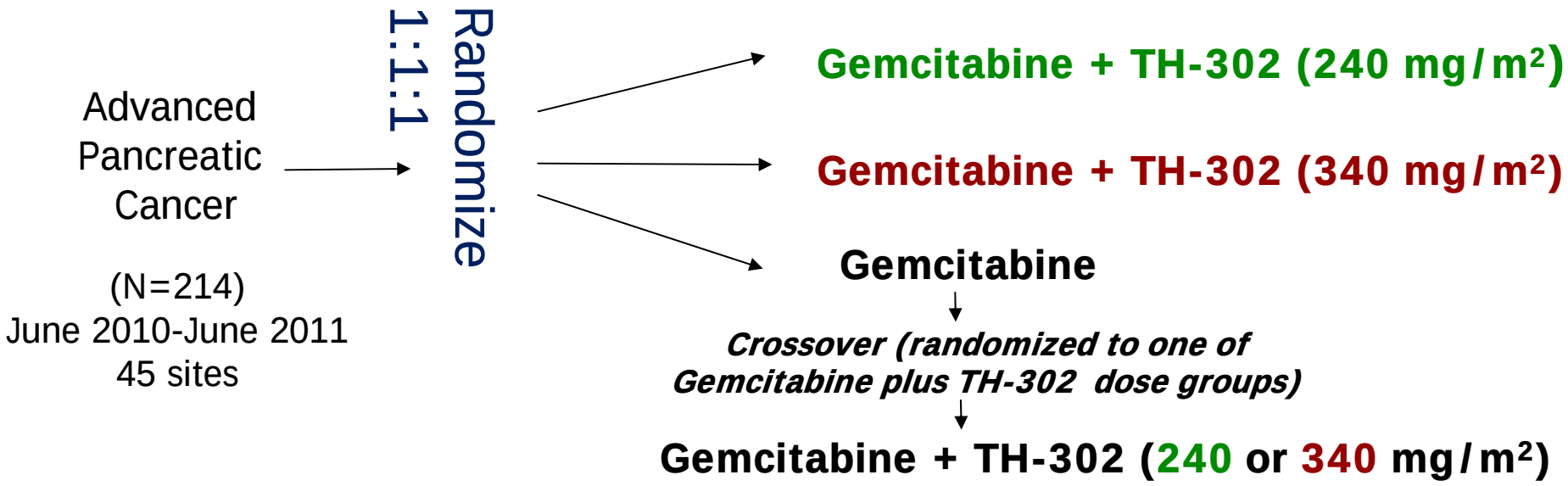


- **47 patients** with advanced first-line pancreatic cancer
- Response rate of **21%** and median PFS of 5.9 months
- Greater efficacy at higher doses 240 mg/m^2: 0% Response, **5.4 mo median PFS**
- 340 mg/m^2 : **33% Response**, **7.4 mo median PFS**
- Skin and mucosal toxicity not dose limiting at these doses; single agent MTD = 575 mg/m2
- Better dose intensity at lower doses

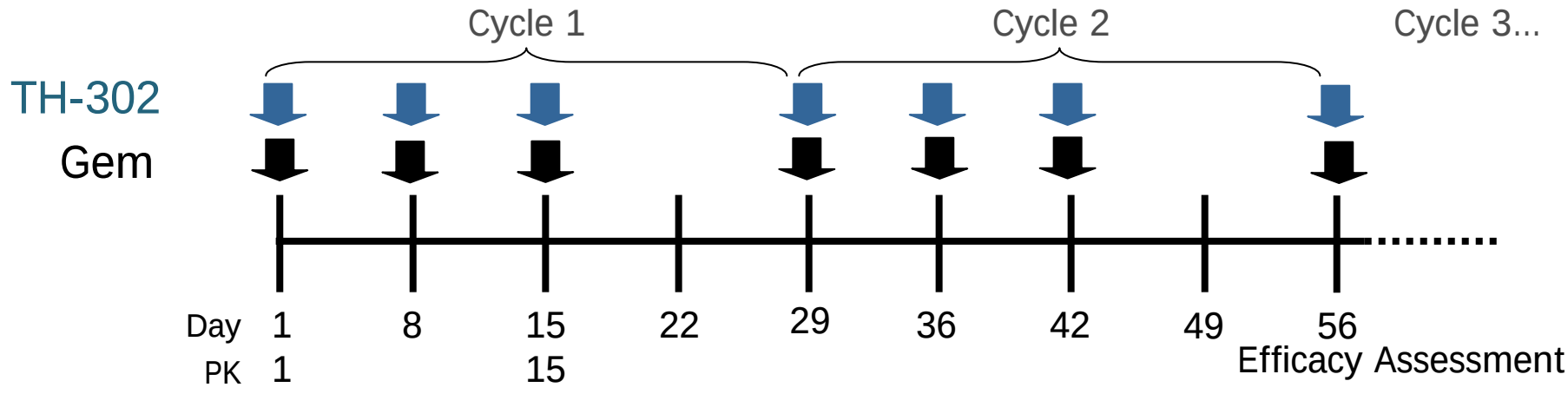
Borad et al. ASCO GI 2011

Study TH-CR-404

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



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



Study TH-CR-404
Key Eligibility Criteria

- Locally advanced or metastatic pancreatic ductal adenocarcinoma confirmed by histology or cytology

- No prior systemic therapy other than:
  - Radiosensitizing doses of 5-fluorouracil/gemcitabine - if relapse after gemcitabine occurred at least 6 months after completion of gemcitabine
  - Neoadjuvant/Adjuvant chemotherapy if relapse occurred at least 6 months after therapy

- Measurable disease by RECIST 1.1 criteria

- Documentation of disease progression if prior adjuvant or neoadjuvant therapy

- ECOG performance status of 0 or 1

Study TH-CR-404
Endpoints

- Primary:
  - Progression-free Survival (PFS)
  - Safety
- Secondary:
  - Response rate (RECIST 1.1)
  - Change in CA19-9 including CA19-9 response (>50% decrease)
  - Similar endpoints following crossover
- Secondary (*not included in today's presentation*)
  - Overall survival
  - Change in performance status
  - Change in VAS (Visual Analog Pain Scale)
  - Pharmacokinetics

Study TH-CR-404
Statistical Considerations

- Primary Efficacy Analysis of PFS:
  - **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
  - **200** patients required to obtain the **144** events for primary PFS efficacy analysis
  - Phase 2b **one-sided alpha = 10% (two-sided 20%)**
  - Test statistic: **stratified logrank test comparing the pooled data from the two combination arms** to the gemcitabine alone arm
  - Additional analyses comparing each of the combination arms with the gemcitabine control arm

- No interim analyses

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/Female**	**58%/42%**	**62%/38%**	**57%/43%**
Locally Advanced Unresectable **N (%)**	**14 (20%)**	**16 (23%)**	**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	**20 (30%)**	**31 (45%)**	**28 (39%)**
1	**47 (70%)**	**38 (55%)**	**43 (61%)**
Site of primary pancreatic tumor involves Head N (%)	**41 (59%)**	**40 (56%)**	**44 (59%)**
Baseline CA19-9[1]	**(N=53)**	**(N=53)**	**(N=58)**
Median	**1291**	**2575**	**2391**
IQR	**427 – 4337**	**266 – 26751**	**204 – 13775**
Metastatic Sites			
Liver N (%)	**46 (67%)**	**45 (63%)**	**42 (57%)**
Lung[2] N (%)	**10 (14%)**	**11 (15%)**	**15 (20%)**

[1] Elevated CA19-9 at baseline (>35 U/mL); upper limit of quantification = 42,500 U/mL

[2] Five patients had metastases detected only in the lungs

Study TH-CR-404

Prior Therapy

	Gemcitabine (N=69)	**Gemcitabine + TH-302 (240 mg/m²)** (N=71)	**Gemcitabine + TH-302 (340 mg/m²)** (N=74)
Prior Systemic Therapy (Adjuvant/Neoadjuvant/ Radiosensitizing)	**9 (13%)**	**6 (8%)**	**8 (11%)**
Prior Radiotherapy	**6 (9%)**	**5 (7%)**	**5 (7%)**
Prior Surgery (with curative intent)	**9 (13%)**	**10 (14%)**	**9 (12%)**

Study TH-CR-404

Enrollment and Subject Distribution

	Gemcitabine	Gemcitabine + TH-302 (240 mg/m^2)	Gemcitabine + TH-302 (340 mg/m^2)
Patients Treated (6/30/10 – 6/30/11)	69	71	74
Cycles Completed			
Median	4	5	6
Mean	4.4	5.2	6.1
Range	1 - 14	1 - 17	1 - 16
Follow-up (months)			
Median	6.9	7.7	8.1
Mean	7.4	7.4	8.1
Range	0.5 – 18.4	0.4 – 16.1	0.6 – 16.4
Ongoing	2 (3%)	7 (10%)	6 (8%)
Discontinued	67 (97%)	64 (90%)	68 (92%)

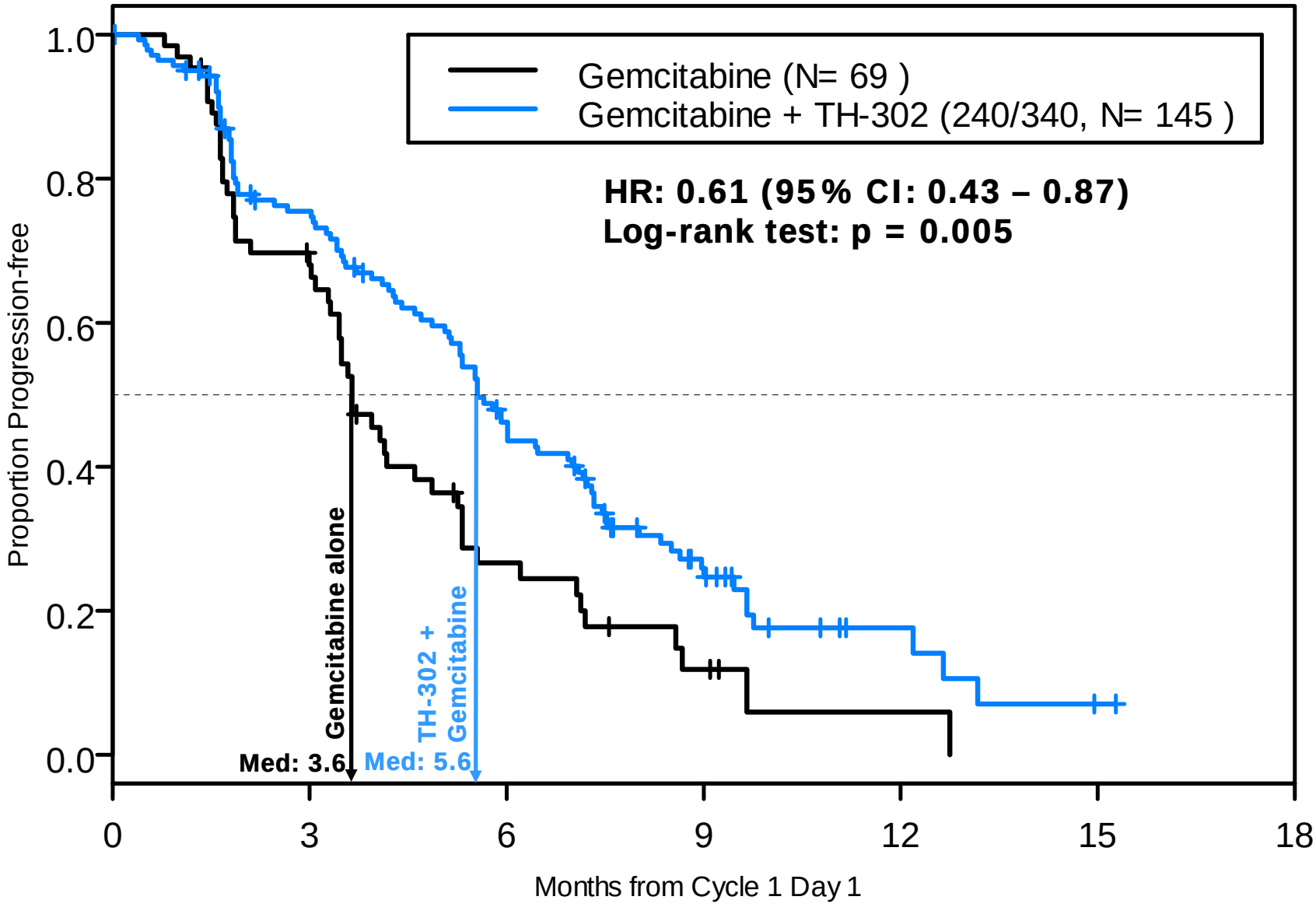
Study TH-CR-404

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	**6 (9%)**	**11 (15%)**	**20 (27%)**
Mean Cumulative Gemcitabine Dose Intensity			
End of Cycle 2	**92%**	**86%**	**82%**
End of Cycle 4	**91%**	**83%**	**76%**
End of Cycle 6	**88%**	**81%**	**72%**

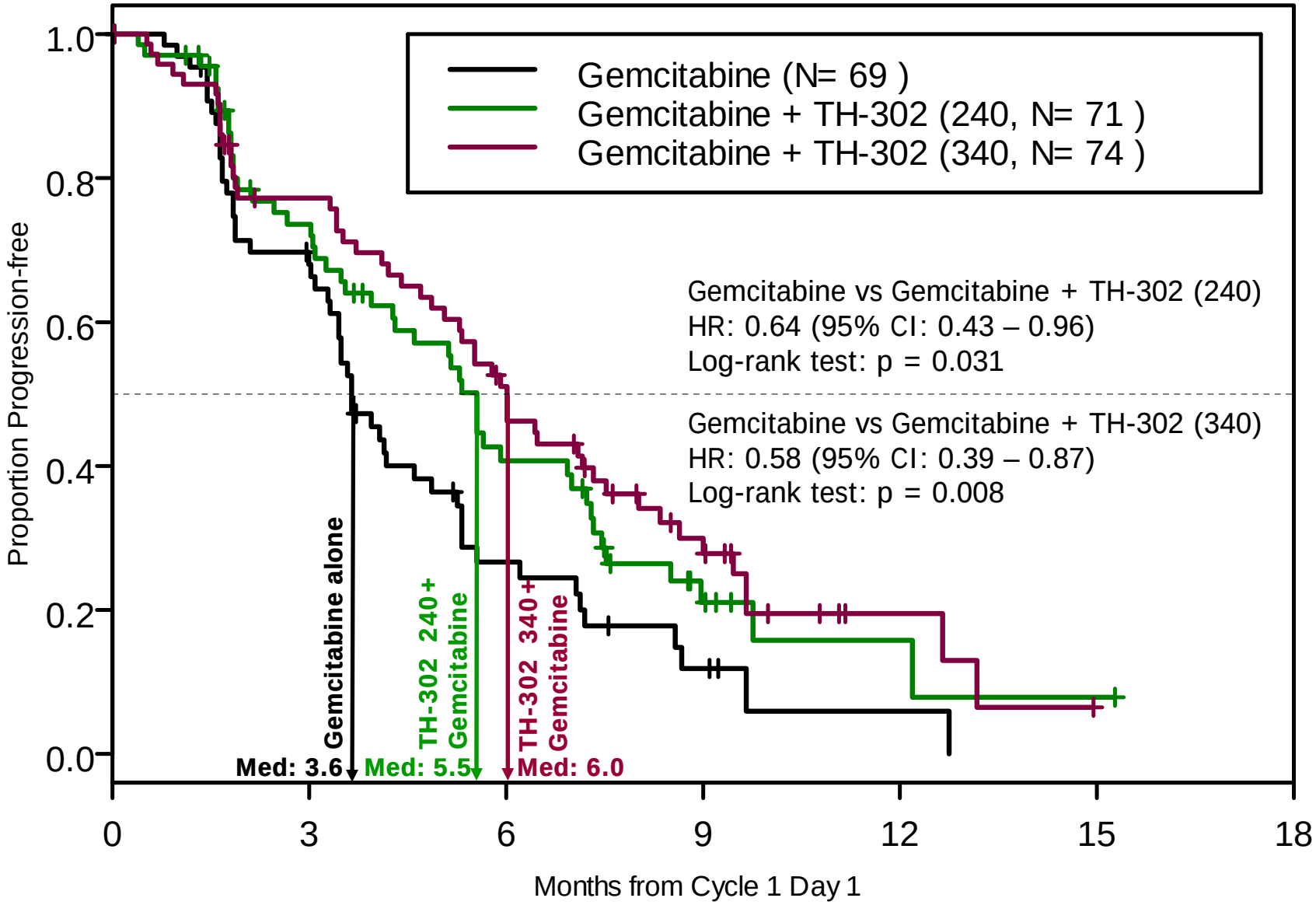
Study TH-CR-404

Progression-free Survival – Primary Efficacy Endpoint Analysis



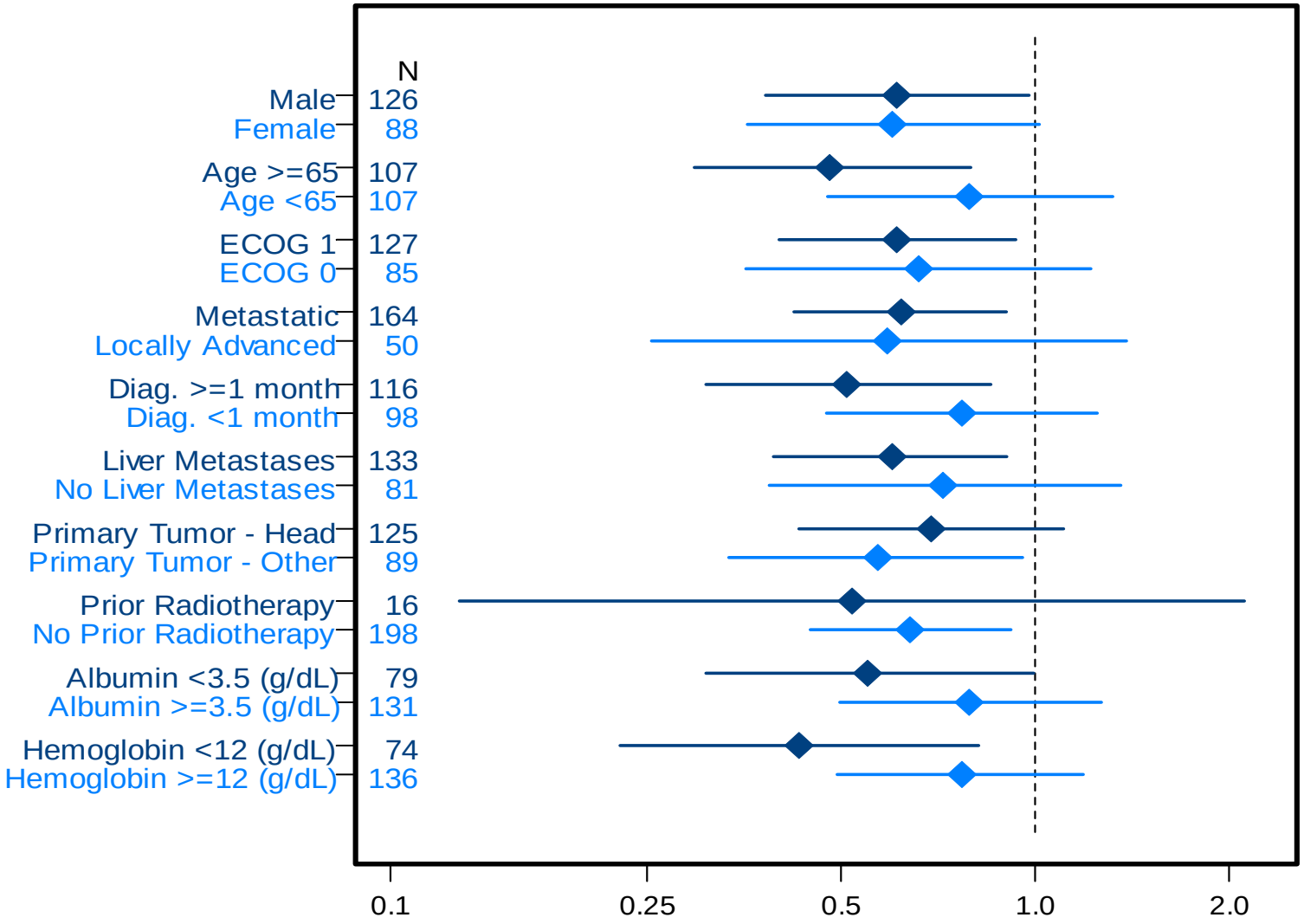
Study TH-CR-404

Progression-free Survival by Treatment Arm



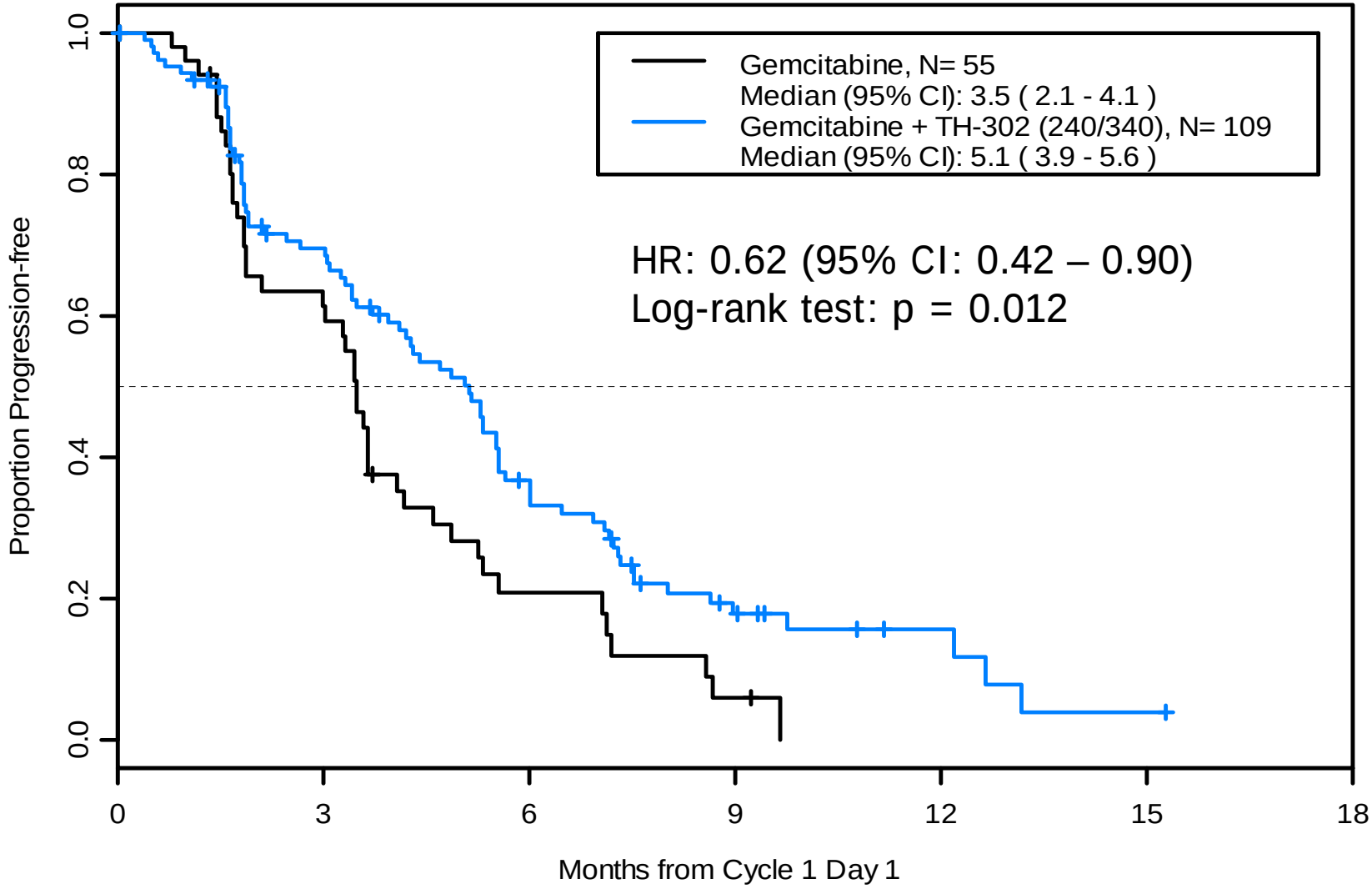
Study TH-CR-404

Progression-free Survival by Subgroups: Forest Plot



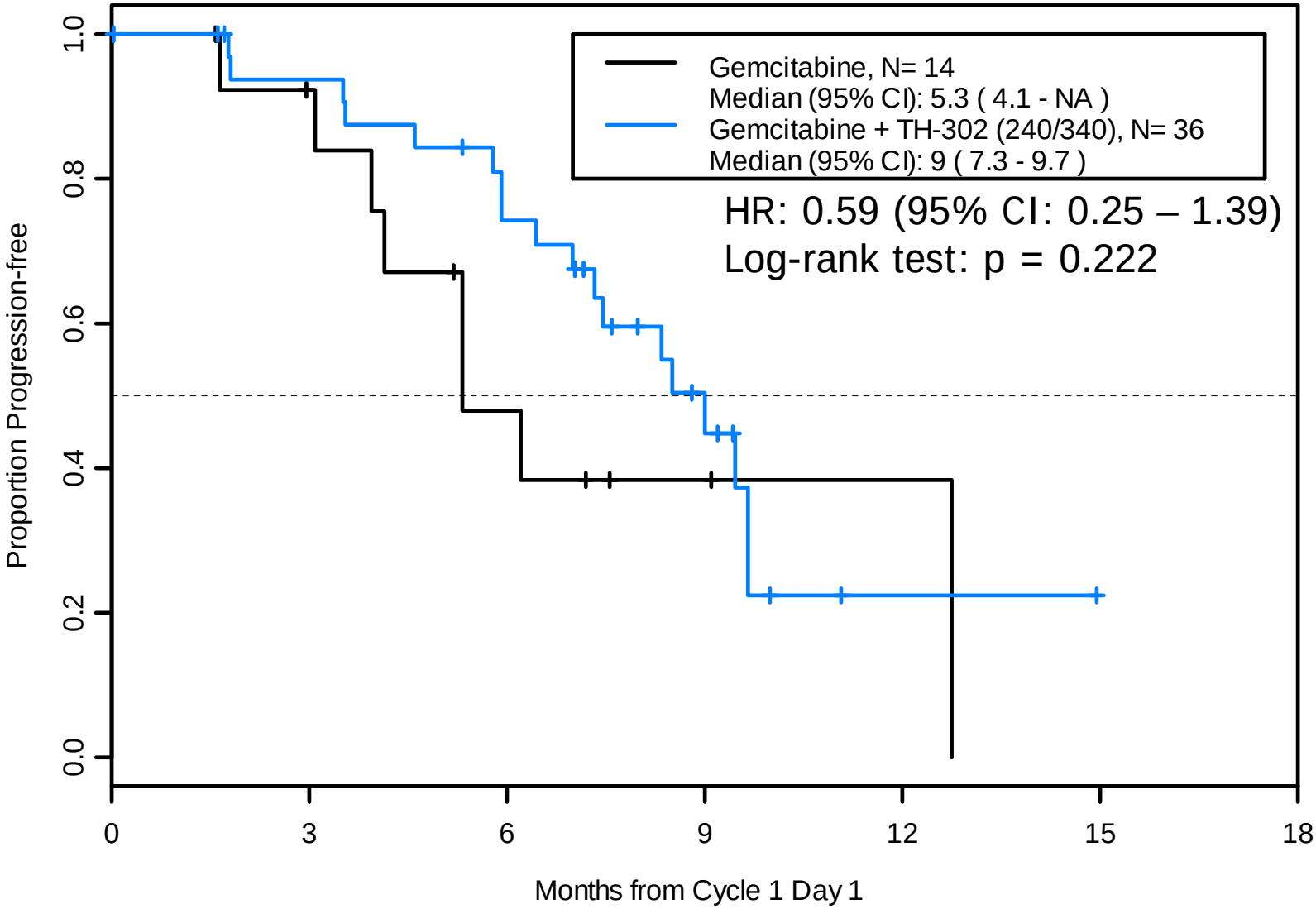
Study TH-CR-404

Progression-free Survival : Metastatic Disease



Study TH-CR-404

Progression-free Survival : Locally Advanced Disease



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%)	1 (1%)
PR	8 (12%)	12 (17%)	19 (26%)
SD	38 (55%)	41 (58%)	36 (49%)
PD	12 (17%)	13 (18%)	12 (16%)
NA[1]	11 (16%)	5 (7%)	6 (8%)
Overall Response Rate (RR)			
Rate (PR + CR)	**8 (12%)**	**12 (17%)**	**20 (27%)**
Distant Mets RR	**6 (11%)**	**12 (22%)**	**13 (24%)**
Locally Advanced RR	**2 (14%)**	**0 (0%)**	**7 (35%)**
SD or Better	46 (67%)	53 (75%)	56 (76%)

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

Study TH-CR-404

CA19-9 Maximum Decrease and Response

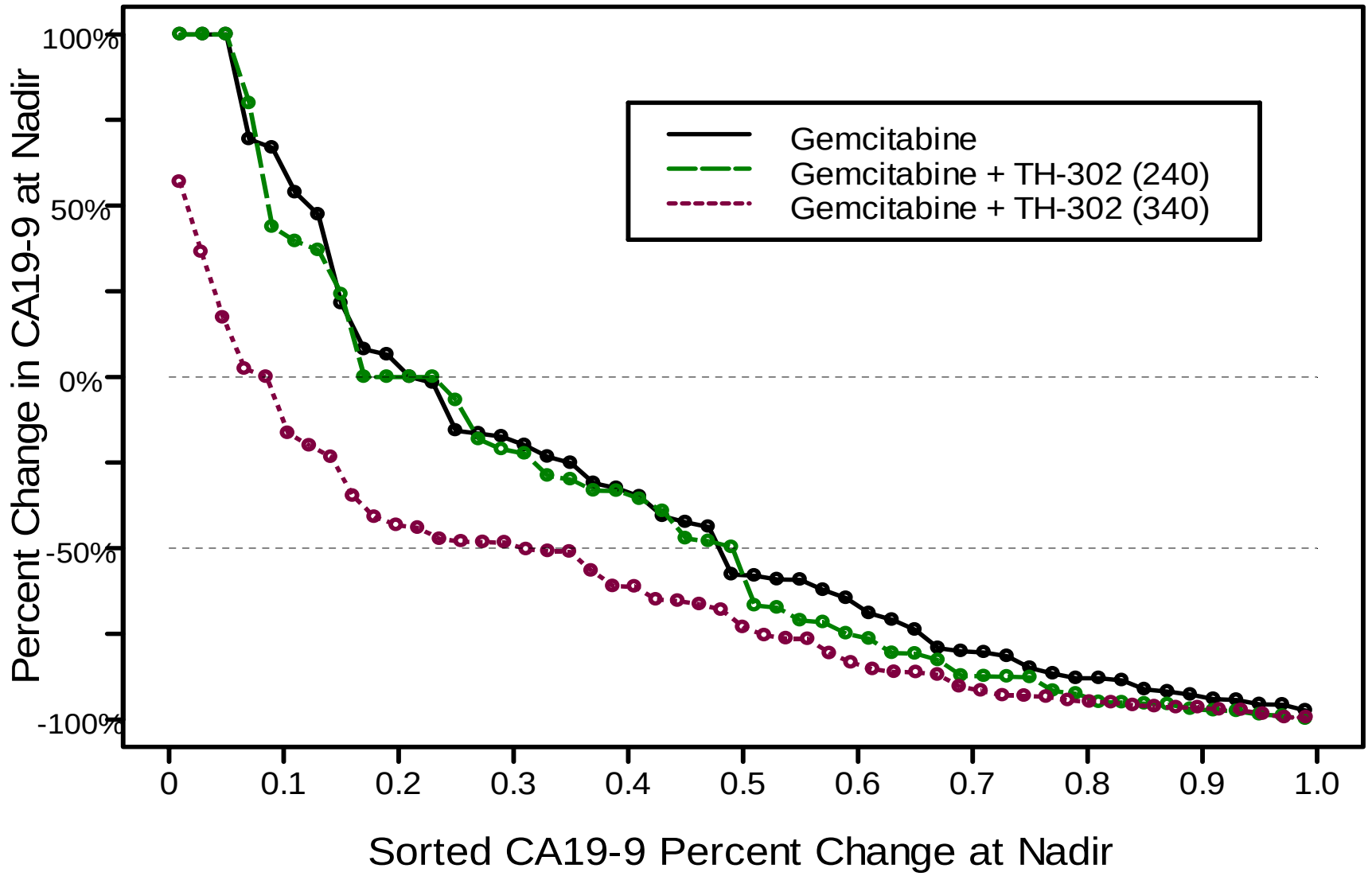
	Gemcitabine	Gemcitabine + TH-302 (240 mg/m²)	Gemcitabine + TH-302 (340 mg/m²)
Elevated CA19-9 and Follow-up (N)[1]	50	50	53
Nadir Change in CA19-9 Mean Median Range	 -523 -295 -17870 – 8490	 -3909 -284 -42051 - 18866	 -5385[2] -1208 -40108 - 13968
CA 19-9 Decrease >20% >50% >90%	 34 (68%) 26 (52%) 8 (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)

[1] Subjects with baseline assessment > ULN and at least one post-baseline CA19-9 assessment.

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

Study TH-CR-404

Percent Change in CA19-9 Waterfall Plot – Baseline Elevated CA19-9



Study TH-CR-404

Crossover Efficacy Summary

	Gemcitabine + TH-302 (240 mg/m²) (N=13)	Gemcitabine + TH-302 (340 mg/m²) (N=12)
Median Progression-free Survival (mo)	**1.8 (95% CI: 1.6-1.9)**	**2.9 (95% CI: 1.8-NR)**
Best Response	**0%**	**0%**
CA19-9 Response	**0% (0/11)**	**25% (2/8)**

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)	
	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4
Fatigue	28 (41%)	3 (4%)	40 (56%)	6 (8%)	37 (50%)	3 (4%)
Nausea	27 (39%)	4 (6%)	27 (38%)	7 (10%)	37 (50%)	4 (5%)
Constipation	25 (36%)	1 (1%)	25 (35%)	1 (1%)	23 (31%)	0 (0%)
Peripheral edema	26 (38%)	3 (4%)	21 (30%)	0 (0%)	26 (35%)	0 (0%)
Any Rash	10 (14%)	0 (0%)	28 (39%)	1 (1%)	33 (45%)	3 (4%)
Vomiting	17 (25%)	2 (3%)	15 (21%)	4 (6%)	25 (34%)	6 (8%)
Diarrhea	16 (23%)	1 (1%)	17 (24%)	2 (3%)	23 (31%)	3 (4%)
Abdominal pain	19 (28%)	3 (4%)	25 (35%)	6 (8%)	25 (34%)	9 (12%)
Pyrexia	14 (20%)	0 (0%)	17 (24%)	1 (1%)	22 (28%)	2 (3%)
Decreased Appetite	13 (19%)	1 (1%)	18 (25%)	4 (6%)	19 (26%)	3 (4%)
Stomatitis	4 (6%)	0 (0%)	12 (17%)	0 (0%)	27 (36%)	0 (0%)

Study TH-CR-404

Laboratory Adverse Events

	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%)**	**16/11 (39%)**	**22/21 (59%)**
ANC Grade 3/4	**16/3 (28%)**	**31/8 (56%)**	**27/16 (59%)**
Hemoglobin Grade 3/4	**4/0 (6%)**	**12/2 (20%)**	**20/0 (27%)**
Bilirubin Grade 3/4 (increase)	**3/1 (6%)**	**9/1 (13%)**	**5/0 (7%)**
Creatinine Grade 3/4 (increase)	**0/0 (0%)**	**0/0 (0%)**	**0/0 (0%)**

*Note: Percents based on evaluable subjects (subjects with post-baseline assessment);
Number of Grade 3 / Number of Grade 4 (% Grade 3/4)

Study TH-CR-404

SAEs and SAE/AEs Resulting in Discontinuation

	Gemcitabine (N=69)	**Gemcitabine + TH-302 (240 mg/m²)** (N=71)	**Gemcitabine + TH-302 (340 mg/m²)** (N=74)
Any SAE	36 (52%)	32 (45%)	41 (55%)
AE leading to study discontinuation	11 (15.9%)	11 (15.5%)	8 (10.8%)
	• Fever • Biliary Obstruction • Dehydration • Purpara • Pneumonia • Cardiac Pain • Pneumonitis (2) • Anasarca • Pain • CVA	• GI Bleed • COPD • Biliary Obstruction • Pneumonitis • Thrombocytopenia • Hyperbilirubinemia (3) • Duodenal Hemorrhage • Rash • Rash/elevated bilirubin	• Thrombocytopenia (3) • Biliary tract infection • Elevated Alk Phos • Hypersensitivity reaction • Pneumonitis • Embolic stroke

Study TH-CR-404
Summary

- TH-302 adds to the efficacy of gemcitabine in first-line pancreatic cancer with statistically significant improvements
  - Median PFS increased from **3.6** to **5.6 months** (p=0.005)
  - Response rate increased from **12%** to **22%** (p=0.066)
  - Mean CA19-9 decreased from **-523** to **-4669** (p=0.038)
- Dose response with greatest efficacy at TH-302 dose of 340 mg/m^2
  - Median PFS of **6.0 months** (p=0.008)
  - Response rate of **27%** (p=0.025)
  - Greater CA19-9 declines (p=0.008)
- The combination was well tolerated
  - No increase in discontinuations for adverse events
  - Skin and mucosal toxicities were TH-302 dose dependent but not dose limiting
  - Myelosuppression was dose dependent and dose limiting but reduction in gemcitabine dose intensity was not associated with loss of efficacy
  - There was no apparent TH-302 related renal or hepatic toxicity

Study TH-CR-404
Acknowledgments

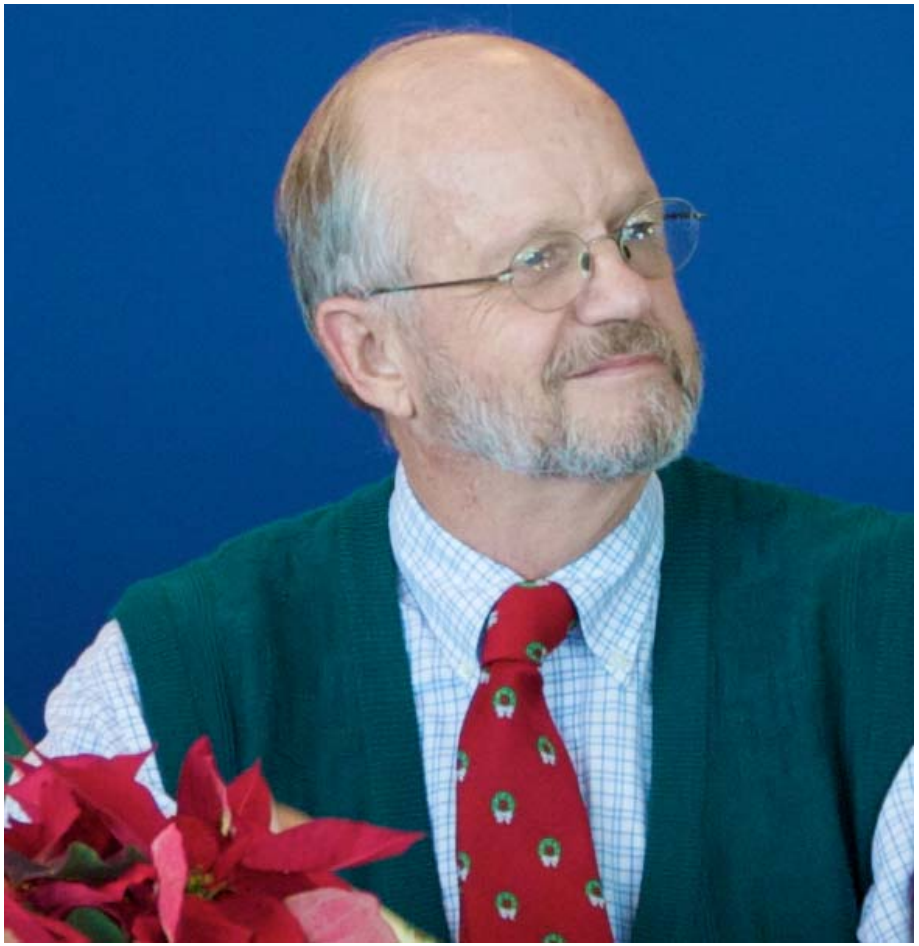
- **We would like to acknowledge and thank all of the patients that participated in the study and their families**
- **Investigators and their teams**

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

Study TH-CR-404
In Memoriam

"The progress in cancer research gives me hope and optimism that many new therapies and treatments are on the horizon for patients living with cancer. We need more treatments which are effective and affordable … it's clear to me that the progress continues and the final chapters are not yet written."

John Curd on April 5, 2011 following the 2011 AACR Annual Meeting



John Gary Curd, M.D.
July 2, 1945 – April 20, 2011