CENTER FOR DRUG EVALUATION AND RESEARCH

ADVISORY COMMITTEE: ONCOLOGIC DRUGS ADVISORY COMMITTEE

DATE OF MEETING: 03/19-20/98

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SLIDES

Taxol ® (paclitaxel)

- Bristol-Myers Squibb Pharmaceutical Research Institute
- sNDA 20-262/SE1-026
- Proposed Indication: First-line therapy for the treatment of advanced ovarian cancer

sNDA 20-262/SE1-026 Taxol®/ Ovarian Cancer Review Team

Discipline	Primary Reviewer	Team Leader
Project Manager	Dianne Spillman	Dotti Pease
Chemistry	Josephine Jee	Rebecca Wood
Pharmacology	Margot Brower	Paul Andrews
Biopharm	Safaa Ibrahim	Atiqur Rahman
Biometrics	Massa Takeuchi	Tony Koutsoukos
		George Chi
Medical	Susan Honig	Grant Williams
DSI	Gurston Turner	David Lepay
DDMAC	Anne Reb	Tracy Acker
Computer/Technical Support	Gary Gensinger	

Pivotal Trial

- GOG 111 submitted as the pivotal trial: Cisplatin-paclitaxel (PT) v. Cisplatin-cyclophosphamide (PC)
- GOG database and CRFs used to create the BMS database
  - BMS used more extensive and detailed AE reporting
  - BMS used all available tumor measurements
  - BMS audited 97 primary patient records at 19 sites to ensure quality of both databases
  - Good concordance; differences did not significantly affect efficacy analyses

Supportive Trials

- Derived from literature review
  - NCI-C/EORTC/Intergroup study: PT v. PC
  - GOG 132: P v. T v. PT
  - ICON3: T + CBDCA v. CBDCA or CAP (no results available)
- Other cited randomized trials of first-line therapy included paclitaxel in both arms; preliminary results only
  - Neijt et al: paclitaxel-cisplatin v. paclitaxel-carboplatin (211 pts)
  - AGO: paclitaxel-cisplatin v. paclitaxel-carboplatin (660 pts)

GOG 111: Objectives

- To determine response rate, response duration, and survival in suboptimal Stage III and Stage IV ovarian cancer treated with PT or PC
  - Amended : Progression-free survival as the primary endpoint, survival the secondary endpoint, response the tertiary endpoint
- To evaluate the relative activity of the 2 regimens
- To evaluate the toxicity of PT in a larger patient population and compare the relative toxicities of PT and PC
- To compare the therapeutic index of PT and PC

GOG 111: Trial Design

- Chemotherapy-naïve suboptimal Stage III and Stage IV ovarian cancer patients
- GOG study; 86 hospitals
- Stratified by measurable v. non-measurable disease; balanced by GOG center
- Randomized to 6 cycles of:
  - Cisplatin 75 mg/m^2 IV Day 1
    Cyclophosphamide 750 mg/ m^2 IV D1 q 21 d
    OR
  - Paclitaxel 135 mg/m^2 over 24 hr D1
    Cisplatin 75 mg/m^2 IV D2 q 21 d

GOG 111: Assessments

- Baseline postoperative CT scan
- Second-look laparotomy required for patients with a clinical CR after chemotherapy and patients with non-measurable disease, unless CA-125 > 100
- Substudy at 9 sites for Neurologic Assessment
- Cardiac monitoring with Taxol administration

GOG 111: Protocol Amendments

- Pts with CA-125 > 100 exempted from second-look lap 5/11/90
- Study endpoints changed 5/11/90
- Sites for Neurologic Assessment added throughout the study; assessment timepoints changed throughout the study
- Cardiac monitoring initially planned for 2 cycles; extended to all cycles

GOG 111: Eligibility Criteria

- Suboptimally debulked (>1 cm) Stage III and IV ovarian cancer patients
- Measurable lesions at least 3 cm in size
- PS 0, 1, 2
- Optimal debulked patients or patients with borderline carcinoma excluded; must have serous, mucinous, clear cell, endometrioid, undifferentiated, or mixed epithelial carcinoma

GOG 111: Enrollment

- 410 patients on study:
  - 196 PT
  - 214 PC
- 240 patients with measurable disease:
  - 113 PT
  - 127 PC
- One patient never treated (died of postoperative PE prior to study therapy; randomized to PC)

GOG 111: Demographics

- 84% of patients had PS 0 or 1; equally distributed between arms
- Similar number of optimally debulked pts (protocol violation) on each arm; all had Stage IV disease
- Only imbalance: serous adenocarcinoma 74% PT and 64% PC (p=0.025)
  - Included in adjusted analyses; not identified as a significant prognostic factor
- Patient and tumor characteristics, extent of disease comparable between the 2 groups

GOG 111: Removal from study

- Cycles completed
  - 85.7% PT received 6 cycles
  - 77.9% PC received 6 cycles
- Reasons off study:

	PT (%)	PC (%)
Drug-related toxicity	6	7
Disease progression	3	9
Death	3	2
Pt Request	2	3
Wrong Primary	1	<1
Never Treated	--	<1
CVA	1	--

GOG 111: Protocol violations

- Major violations

	PT (no.pts)	PC (no. pts)
Wrong primary	8	10
History prior malignancy	--	2 (breast)
Optimally debulked	1	--
Wrong stage	1 (IB)	--

- Minor violations: laboratory abnormalities

GOG 111: On-study therapy

- Dose reductions
  - No dose reductions, only treatment delays, allowed for cisplatin (violations equal on the two arms)
  - 27% incidence of dose-reduction for T
  - 21% incidence of dose-reduction for C
- Treatment delays
  - 21% of courses delayed for PT
  - 55% of courses delayed for PC

GOG 111: Dose Intensity

	Arm A (n=196)		Arm B (n=213)	
	Paclitaxel	Cisplatin	CTX	Cisplatin
Median cumul dose/pt (mg/m^2)	756	448	4212	448
Planned DI ($mg/m^2/wk$)	45	25	250	25
Median delivered DI ($mg/m^2/wk$)	41	24	204	21
Relative DI % scheduled dose (% pts)				
≥ 90%	52	72	33	41
80-90%	33	20	24	31
< 80%	15	7	43	28

GOG 111: Subsequent Therapy

- Most patients received subsequent therapy:
  80% PT, 73% PC
- PC: 38% received paclitaxel (9% as second-line tx)
  Carboplatin, cisplatin, altretamine
- PT: 47% received carboplatin
  Cyclophosphamide, cisplatin, altretamine

GOG 111: Endpoints

- Time to progression
  - Method 1: Date of entry to date of reappearance or increasing parameters of disease or date of last contact
  - Method 2: Date of entry to time to new therapy
  - The sponsor classified patients who died without progression as progressing on the date of death
  - The FDA classified these pts as progressing on the date of last visit
- Survival: Study entry to death

GOG 111: Endpoints

- Response
  - CR, PR: classic definitions with confirmation at 3 weeks
  - PD: $\geq$ 50% increase in the product of any lesion measured from nadir size or new lesion
  - Both BMS and FDA considered second-look surgery as confirmation of a clinical response
- Pathologic response
  - pCR: pathologic confirmation of CR at second-look laparotomy
  - Microscopic residual: absence of gross residual disease but positive blind biopsies

GOG 111: Clinical Response

240 pts with measurable disease: 113 PT, 127 PC

All patients analyzed

	BMS ANALYSIS			FDA ANALYSIS		
Response	**PT**	**PC**	**P-value**	**PT**	**PC**	**P-value**
CR	40/113 (35%)	32/127 (25%)	0.092	40/113 (35%)	30/127 (24%)	0.048
PR	28/113 (25%)	32/127 (25%)		30/113 (27%)	31/127 (24%)	
Overall response	68/113 (60%)	64/127 (50%)	0.153	70/113 (62%)	61/127 (48%)	0.04

GOG 111: Response

- PT:
  - FDA adds 3 patients with "wrong primary"
  - FDA excludes 1 patient for inadequate documentation of response
- PC:
  - FDA adds 1 patient with "wrong primary"
  - FDA excludes 4: BMS agrees that 3 of 4 did not respond; inadequate documentation for the 4th

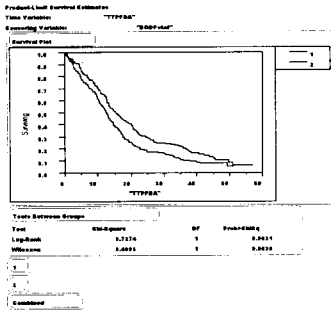
GOG 111: Pathologic Response

RESPONSE	**PT**	**PC**	**P-VALUE**
Pathologic CR	42/196 (21%)	35/214 (16%)	0.196
Clinical CR/Microscopic residual disease	25/196 (13%)	8/214 (4%)	
Total	67/196 (34%)	43/214 (20%)	0.001

GOG 111: Time to Progression

	PT	PC	P-VALUE
BMS Analysis	16.6 months	13.0 months	0.0008
FDA Analysis	15.7 months	12.6 months	0.002

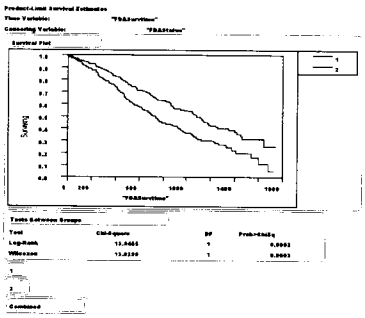
GOG 111: Time to Progression



GOG 111: Survival

	PT	PC	P-VALUE
BMS Analysis	35.5 months	24.2 months	0.0002
FDA Analysis	35.5 months	24.2 months	0.0002

GOG 111: Survival



GOG 111: Myelosuppression

EVENT	PT	PC	P-VALUE
Grade IV neutropenia	81%	58%	Significant
Infections	22%	16%	0.123
Febrile neutropenia	35 courses/1074 courses (3%)	9 courses/1145 courses (<1%)	<0.001

GOG 111: Non-hematologic toxicities

ADVERSE EVENT	PT (%)	PC (%)	P-VALUE
Peripheral neuropathy (gr III-IV)	3	0	0.025
Arthralgia/myalgia:			
Any	10	2	0.002
Grade III (no gr. IV)	1	0	0.479
Hypersensitivity:			
Any	9	2	0.003
Grade III-IV	3	0	0.025
Diarrhea:			
Any	17	8	0.008
Grade III-IV	4	1	0.094
Cardiovascular Events:			
Any	28	7	0.001
Grade III-IV	5	3	0.188
Alopecia	55	37	0.001
Asthenia	17	10	0.041

GOG 111: Mortality

- 10 patients died within 30 days of study treatment
  - PT 6
    - Myocardial infarction (14 days postop)
    - Pulmonary embolus
    - Perforated gastric ulcer
    - Disease progression, 3 patients (1 with AWMI after surgery)
  - PC 4
    - Cardiac arrest (sepsis: staph and Candida)
    - Sepsis
    - Myocardial infarction
    - Disease progression (sepsis: S. aureus)

GOG 111: Study report and Published results

- Published report showed a statistically significantly better response rate with PT (73%) compared with PC (60%) (p=0.01)
- Published report shows a greater absolute difference in median progression-free survival and survival than the study report (5 months compared to 3.6 months and 14 months compared to 11.3 months respectively)
- McGuire and colleagues excluded 24 patients from analysis and did not always require confirmation of response

PT as First-Line Therapy: European-Canadian Intergroup Trial

- 679 evaluable patients randomized to
  - Cyclophosphamide 750 mg/m^2
  - Cisplatin 75 mg/m^2 q 21 days

    OR
  - Paclitaxel 175 mg/m^2 IV over 3 hours
  - Cisplatin 75 mg/m^2 q 21 days
- Differences between GOG 111 and EORTC:
  - Stage IIB - IV eligible (suboptimal St. III and IV for GOG 111)
  - Paclitaxel 175 mg/m^2 over 3 hours; escalation to 200 mg/m^2
  - Up to 9 cycles of chemotherapy
  - Paclitaxel permitted as salvage therapy
  - Second-look laparotomy not required; interval debulking allowed

GOG 111 and EORTC Intergroup Results

EFFICACY PARAMETER	GOG 111			EORTC-CANADA INTERGROUP		
	PT	PC	P-value	PT	PC	P-value
Clinical response rate	60% (68/113)	50% (64/127)	0.153	57% (85/149)	43% (65/151)	0.01
Pathologic CR	21% (42/196)	16% (35/214)	0.196	47% (33/70)	24% (13/55)	
Median progression-free survival	16.6 mo	13.0 mo	0.0008	16.6 mo	12 mo	0.0001
Survival	35.5 mo	24.2 mo	0.0002	35 mo*	25 mo*	0.001*

* ASCO 1998 abstract submitted by sponsor; primary data not reviewed

PT as First-Line Therapy: GOG 132

- 615 eligible patients (suboptimal St. III and IV) randomized to:
  - Cisplatin 100 mg/m^2 q 21 days x 6
    OR
  - Paclitaxel 200 mg/m^2 IV over 24 hours q 21 days x 6
    OR
  - Cisplatin 75 mg/m^2
    Paclitaxel 135 mg/m^2 IV over 24 hours q 21 days x 6

PT as First-Line Therapy: GOG 132 (continued)

- 83% of patients completed PT compared to 69% P, 71% T
- 18% of patients refused to continue or were removed for toxicity on P, compared to 4% T and 5% PT
- 19% of patients had early PD on T, compared to 8% P and 6% PT

GOG 132: Efficacy Results*

EFFICACY PARAMETER	P	T	PT	P-VALUE (T v. OTHER ARMS)
Clinical response	75%	46%	72%	P< 0.05
Pathologic CR	15% (29/200)	6% (12/213)	22% (44/201)	Significant
Median progression-free survival	16.4 mo	11.4 mo	14.1 mo	Significant
Median survival	30.2 mo	26.0 mo	26.6 mo	NS

*Unreviewed data submitted in abstract form by the sponsor

GOG 132: Efficacy

- Unreviewed data suggest that single-agent paclitaxel may be inferior to single-agent "high-dose" cisplatin or PT in terms of clinical response, pathologic CR, and TTP
- No survival difference between the 3 arms
- PT appears comparable to single-agent "high-dose" cisplatin for efficacy, but higher completion rate and better patient acceptance

Summary of GOG 111 Efficacy

Efficacy Parameter	BMS Analysis			FDA Analysis		
	PT	PC	P-value	PT	PC	P-value
Response rate	60%	50%	0.153	62%	48%	0.04
Pathologic CR	21%	16%	0.196	21%	16%	0.196
Median progression-free survival	16.6 mo	13.0 mo	0.0008	15.7 mo	12.6 mo	0.002
Overall survival	35.5 mo	24.2 mo	0.0002	35.5 mo	24.2 mo	0.0002

Reviewer Summary

- GOG 111 demonstrates clinically and statistically significantly improved progression-free survival and overall survival with PT compared to PC
- These findings are supported by the published literature
- Toxicity profile is consistent with prior experience with paclitaxel
- Toxicity profile was acceptable to patients

sNDA 20-262/024

PACLITAXEL IN NON-SMALL CELL LUNG CANCER

REVIEW TEAM (sNDA 20-262)

	PRIMARY REVIEWER	SECONDARY REVIEWER
MEDICAL	Isagani Chico, MD	Grant Williams, MD
STATISTICS	David Smith, Ph.D.	Tony Koutoukos, Ph.D.
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BIOPHARM	Safaa Ibrahim, Ph.D.	Atiqur Rahman, Ph.D.
CHEMISTRY	Josephine Jee, PhD.	Rebecca Wood, Ph.D.
DSI	Gurston Turner, Ph.D.	
PROJECT MANAGER	Dianne Spillman	Dotti Pease

PROPOSED INDICATION

"Taxol is indicated for the treatment of NSCLC in patients who are not candidates for potentially curative surgery and/or radiation therapy."

ODAC RECOMMENDATIONS (1990)

- Randomized, controlled studies
- Establish contribution of the "new" drug
- Superiority of the "new" drug
- Response rate, response duration and time to tumor progression were not recommended as surrogate endpoints
- Improvement in symptoms is a valuable endpoint and may be sufficient for drug approval

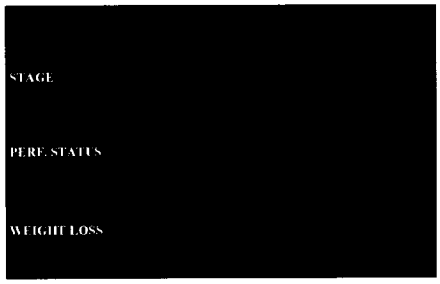
BRIEF HISTORY

November 1994	**24-hour infusion**
	Study 129 (Phase II)
	Study 165 (Phase III)
June 1997	**24-hour infusion**
	Study 165 (Phase III)
	3-hour infusion
	Study 103 (Phase III)
	Study 208 (Phase III)
	Single Agent Phase II trials

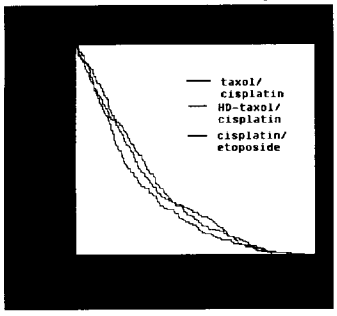
PHASE III TRIALS

T= Taxol, **C**= Cisplatin, **E**= Etoposide, **Ten**= Teniposide

PATIENT POPULATION

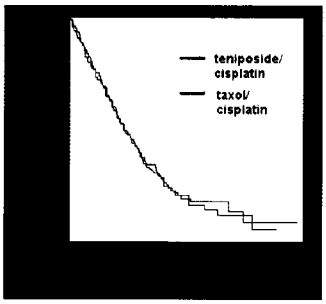


SURVIVAL (Study 165)



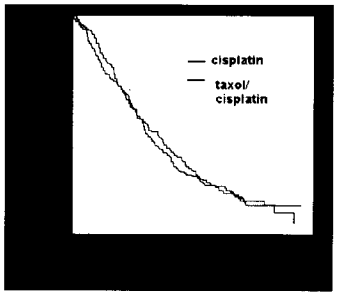
- 541/599 (90%) dead
- median survival:
  - T/C- 9.3 months
  - HD-T/C- 10 months
  - C/E- 7.4 months
- C/E versus:
  - T/C-
    - p-value: 0.12 (α = .0125)
    - hazard ratio: 1.18
    - (95%CI 0.9-1.55)
  - HD-T/C-
    - p-value: 0.08 (α = .0125)
    - hazard ratio: 1.21
    - (95%CI 0.92-1.58)

SURVIVAL (Study 103)



- 248/313 (75%) dead
- median survival:
  Ten/C- 9.9 months
  T/C- 9.5 months
- Ten/C vs. T/C-
  p-value: 0.80 (α =0.05)
  hazard ratio: 1.03
  (95%CI 0.8-1.33)

SURVIVAL (Study 208)

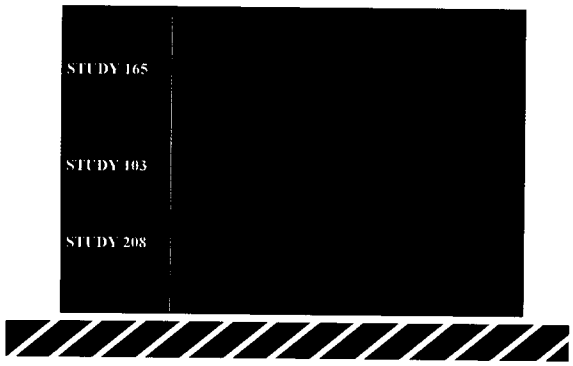


- 335/414 (81%) dead
- median survival:
  C- 8.6 months
  T/C- 8.1 months
- C vs. T/C-
  p-value: 0.86 (α= 0.05)
  hazard ratio: .98
  (95%CI=0.79-1.22)

SURVIVAL (PIVOTAL TRIALS)

- No statistically significant differences between Taxol arms and control

TIME TO TUMOR PROGRESSION



TIME TO TUMOR PROGRESSION (PIVOTAL TRIALS)

- Significant difference favoring the HD-Taxol arm in study 165 (not a proposed regimen)
- No statistically significant differences between taxol arms and control for the treatment regimens proposed by the applicant

RESPONSE RATES

SUMMARY OF EFFICACY RESULTS

- **No statistically significant differences in survival and time to tumor progression**
- **Tumor response rates favored the taxol combination arms**

QUALITY OF LIFE ANALYSIS

STUDY 165 (T/C vs. HD-T/C vs. C/E)

- No statistically significant difference between treatment arms

STUDY 103 (T/C vs. Ten/C)

- Insufficient data (50 patients per arm)
- Physical Functioning better with taxol/cisplatin (?)

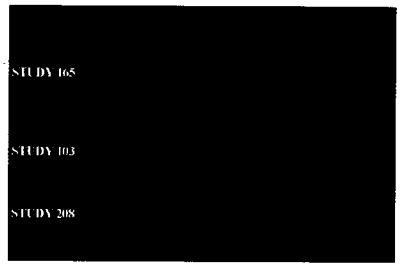
STUDY 208 (T/C vs. HD-C)

- Physical Functioning, nausea and vomiting, loss of appetite and constipation in favor of taxol/cisplatin
- Hair loss and peripheral neuropathy in favor of cisplatin

SAFETY ANALYSIS

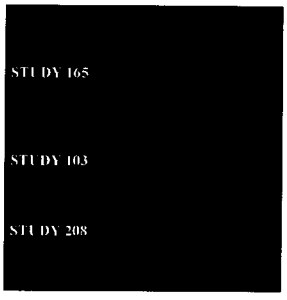
- **Deaths**
- **Dose Reduction**
- **Dose Delays**
- **Hematologic Toxicity**
- **Non-Hematologic Toxicity**

DEATHS WITHIN 30 DAYS



DOSE REDUCTION

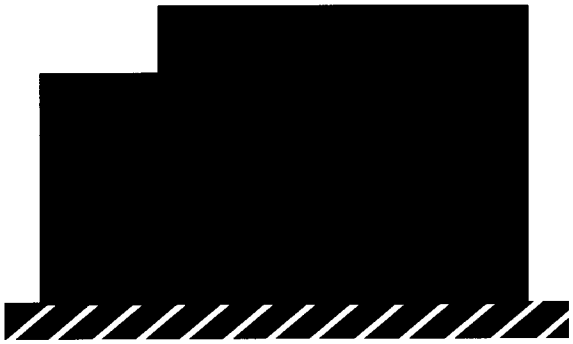
DOSE DELAY



HEMATOLOGIC TOXICITY

GRADE III/IV
NON-HEMATOLOGIC TOXICITY

GRADE III/IV
NON-HEMATOLOGIC TOXICITY



TAXOL IN NON-SMALL CELL LUNG CANCER

- Data provided by three large, randomized studies
- 1300+ patients
- Efficacy and safety data using two dosing schedules

SUMMARY (STUDY 165)

STRENGTHS	WEAKNESSES
• Randomized, controlled	• No survival advantage
• Control arm with known safety profile	• No Quality of Life advantage
• Higher response rate	• More severe neutropenia
	• More arthralgia, myalgia, diarrhea

SUMMARY (STUDY 103)

STRENGTHS	WEAKNESSES
• Randomized, controlled	• Efficacy and safety of control arm not well established
• Higher response rate	• No survival advantage
• Better hematologic profile	• Missing QOL data
• Better Physical functioning (?)	• More neurosensory adverse events, arthralgia, myalgia

SUMMARY (STUDY 208)

STRENGTHS	WEAKNESSES
• Randomized, controlled	• Unequal doses of cisplatin
• Higher response rate	• Equivalent efficacy results
• Physical functioning, nausea, vomiting, loss of appetite and constipation	• No survival advantage
• Less ototoxicity	• Hair loss, peripheral neuropathy
	• More severe neutropenia, fever and neutropenia
	• More hypersensitivity, alopecia, arthralgia, myalgia, diarrhea

SUMMARY OF EFFICACY RESULTS

- No statistically significant differences in survival and time to tumor progression
- Tumor response rates favored the taxol combination arms
- Better Physical Functioning in favor of taxol/cisplatin :Studies 103(?) and 208

SUMMARY OF SAFETY RESULTS

STUDY 165

STUDY 103

STUDY 208

SUMMARY OF ISSUES

- **CONSIDERATIONS FOR APPROVAL**
  - Significant improvement in survival and/or,
  - Significant response rates, time to progression, and QOL; and
  - Tolerable toxicity profile
- **PERTINENT NDA FINDINGS**
  - No significant improvement in survival
  - Higher response rates, no prolongation of TTP for arms proposed
  - Improvement in some QOL subscales, problem with missing data
  - More toxicity in study 165 and 208

Xeloda™

(Capecitabine)
New Drug Application (NDA) #: 20-896

Alison Martin, M.D.
Medical Reviewer, F.D.A.

ODAC Presentation
March 19, 1998

FDA Review Team

Chemistry:	Cheng Yi Liang, Ph.D.
	Liang Zhou, Ph.D.
Pharmacology:	David McGuinn, Ph.D.
	Paul Andrews, Ph.D.
Biopharmaceutics:	Saafa Ibrahim, Ph.D.
	Atiqur Rahman, Ph.D.
Biometrics:	Masahiro Takeuchi, Sc.D.
	Tony Koutsoukos, Ph.D.
Medical:	Alison Martin, M.D.
	Julie Beitz, M.D.
Project Manager:	Maureen Pelosi, R.Ph.

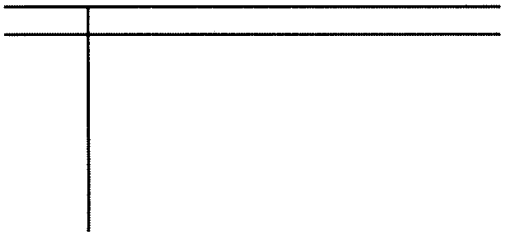
Xeloda™: Proposed Indication

"Treatment of patients with metastatic breast cancer after failure of paclitaxel and an anthracycline-containing chemotherapy regimen"

Outline of Presentation

- Regulatory History
- Phase 2 Trial: SO 14697
  - Patient Population
  - Results
    - Efficacy
    - Safety
- Summary

Regulatory History: Timeline



Regulatory History: Issues

- Single Phase 2 trial
- Phase 2 Endpoint: response rate
  - appropriate for accelerated, not traditional, approval
  - QOL data difficult to interpret without a comparator arm
- Appropriate patient population

Patient Population for Accelerated Approval

- No adequate therapeutic alternative
- Meaningful therapeutic benefit over the alternatives

Outline of Presentation

- ☑ Regulatory History
- Phase 2 Trial: SO 14697
  - Patient Population
  - Results
    - Efficacy
    - Safety
- Summary

SO 14697: Primary Objective

- "To determine that the overall response rate of patients with measurable metastatic breast cancer who have failed previous paclitaxel chemotherapy is in the range of 20% ..."

SO 14697: Secondary Endpoints

- Efficacy
  - Duration of Response
  - Time to Progression
  - Time to Treatment Failure
  - Overall Survival
  - QOL: Clinical Benefit Response Score
    - Pain intensity, analgesic consumption, PS
- Safety

SO 14697: Eligibility Criteria

- Bi-dimensionally measurable or evaluable disease;
- At least 2, but not more than 3, prior regimens;
- Resistance to paclitaxel:
  - progression on therapy
  - response followed by progression while on rx
  - ~~relapse < 12 months after paclitaxel containing adjuvant regimen~~

Patient Enrollment by Center

- 163 patients; 1 patient not dosed
  - 155 patients from 21 centers in the U.S.
  - 8 patients from 4 centers in Canada
- 135 patients with measurable disease
- Enrollment/center ranged from 1-37
- Center #17150 accrued 37 patients; 35 with measurable disease

Baseline Demographics

	100%	100%
	84%	86%
	90	90

NDA 20-896

13

Baseline Clinical Characteristics

	46%	42%
	75%	68%

NDA 20-896

14

NDA Definitions: Resistance vs Failure

Resistance	*Failure*
■ Relapse ≤ 6 mo. of adjuvant regimen	■ Relapse ≤6-12 mo. of adjuvant regimen
■ PD on rx	■ Response followed by PD within 12 mo.
	■ SD on rx for 4 mo.

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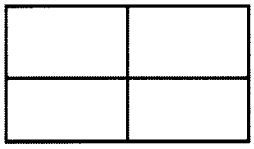
Prior Chemotherapy: Paclitaxel or Anthracycline Failure or Resistance

	103 (77%)	124 (77%)
	55 (41%)	67 (41%)

Patients with Measurable Disease Composite Drug Resistant Profile (N = 91)



FDA: Alternative Approach to Composite Drug Resistance

- Retain definition of resistance
- Replace "failure" with "exposure"
  - definition is weakened by lack of a minimum dose
  - captures 26 of the 32 patients considered neither resistant nor failed

Patients with Measurable Disease
Composite Drug Resistant Profile
(N = 117)

43	

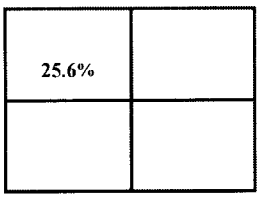
Response Rate
(N = 135)

RESPONSE	*SPONSOR*	*IRC REVIEW*	*FDA JUDGEMENT*
	27		25

Differences in Assessments of RR:
Sponsor, IRC and FDA

PT. ID SPONSOR IRC FDA

Response Rate by Resistance or Exposure to Two Drugs



Consistency in Results

- Responses in all subgroups
- 24 centers: 4 accrued > 10 pts; RR in 4 vs 20 centers was similar (about 20%)
- Lower bound of 95% CI for either group, large vs small, is >10%
- Center #17150 accrued 35 patients with measurable disease; 17% RR

Secondary Efficacy Endpoints: N = 162 or N = 135

- **Duration of Response*** (n = 25)
  - starting at time of 1st response
  - 154 days (range 63 to 233)
- TTP
  - all patients: 94 days (95% CI 84-117)
  - measurable disease: 90 days (95% CI 68-100)
- Survival
  - all patients (70 died): 384 days (95% CI 258 - *)
  - measurable disease (62 died): 306 days (95% CI 243 - 420)

Secondary Efficacy Endpoints in Patients Resistant to Two Drugs N = 43

- Duration of Response (n = 11)
  - 154 days (range 63 to 233)
- TTP:
  - 102 days (95% CI 61 - 129))
- Survival
  - 255 days (95% CI 213 - 306)

Outline of Presentation

- ☑ Regulatory History
- ☑ Phase 2 Trial: SO 14697
  - ☑ Patient Population
  - ☑ Results
    - ☑ Efficacy
    - Safety
- Summary

Frequent Adverse Events: Gastrointestinal

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Frequent Adverse Events: "Other"

NDA 20-896

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NDA 20-896: Xeloda™

Weaknesses	*Strengths*
■ Single Phase 2 Trial	■ Large, multicenter
■ Endpoint = RR	■ 75% confirmed by IRC; Consistency across centers
■ Heterogeneous Population	■ 43 patients doubly resistant ; Responses in all subgroups
■ Short-term safety data	■ Safety data commensurate with other cytotoxics
	■ Oral

NDA 20-896

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Xeloda (capecitabine) Tablets
NDA 20-896
ODAC Meeting
March 19, 1998

-1-

Indication Sponsor Seeks Approval For:

Capecitabine is indicated for the treatment of patients with metastatic breast cancer after failure of paclitaxel and an anthracycline-containing regimen

-2-

Regulatory History for Breast Cancer Program

May 1994	Filed US IND
Dec. 1995	End of Phase I meeting (ODAC consultant Dr. J. Ingle) *Agreement on large Phase II study design* *Patient population (failed paclitaxel and anthracycline)* *Endpoints (RR as primary; CBR, TTP, survival as secondary)* *Need replication across centers*
Aug. 1997	Pre-NDA meeting (ODAC consultant Dr. S. Swain) *Acceptable to file based on the Phase II trial* *Need to confirm RR in the refractory patient population* *Need to submit plan for Phase IV study*
Oct. 1997	Filed original NDA 20-896
Dec. 1997	Submitted Phase III breast cancer study (SO14999)
Feb. 1998	Submitted 4-month safety update
March 1998	FDA Advisory Committee

-3-

Basis for Approval from a Single Study

- Patient population with no standard alternative therapy
- Large, multicenter study with clinically significant RR
- RR is replicated across centers and across subpopulations
- Response rate and time to progression confirmed by blinded independent panel review
- Multiple endpoints show consistent therapeutic benefit (RR, TTP, CBR, survival)
- Predictable and manageable toxicity for an outpatient therapy

Roche Presentation Agenda

Introduction	Dr. Cynthia Dinella *Regulatory Affairs*
Expert Review of Treatment Options	Dr. Joyce O'Shaughnessy *Texas Oncology, PA* *Physician Reliance Network*
Development Program Preclinical Rationale Efficacy/Safety Overall Clinical Benefit	Dr. Tom Griffin *Clinical Science Leader*

Experts Available for Q & A

Joanne Blum, MD	*Physician Reliance Network*
Uli Burger, PhD	*Roche Statistician*
Celine Eliahou	*Roche Toxicologist*
Priscilla Kromelis, RN	*Physician Reliance Network*
Patricia LoRusso, MD	*Harper Hospital, Detroit*
Bruno Osterwalder, MD	*Quintiles Oncologist*
Bruno Reigner, PhD	*Roche Pharmacokineticist*
Alain Thibault, MD	*Roche Oncologist*

Xeloda (capecitabine) Tablets
NDA 20-896
ODAC Meeting
March 19, 1998

Treatment of Refractory, Advanced Metastatic Breast Cancer

Joyce A. O'Shaughnessy, M.D.

Texas Oncology, P.A.

Physician Reliance Network

Metastatic Breast Cancer

- Major public health problem
- Median survival of about 2 years
- Very heterogeneous disease
- Approximately one-third of patients receive second and third line chemotherapy (Gregory et al, *Br J Ca*, 1993)

Chemotherapy for Metastatic Breast Cancer

- Modestly improves survival
- Goal of treatment is disease palliation
- Disease response generally reduces tumor-related symptoms
- Anthracyclines and taxanes are the most active agents

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Salvage Chemotherapy for Pretreated Metastatic Breast Cancer

- No standard definition describes disease refractory to both anthracyclines and taxanes
- Clinical definition: "third-line" treatment for patients previously treated with an anthracycline and a taxane who are not expected to benefit from additional treatment with same
- Patients receiving "third-line" chemotherapy often have significant disease-related symptoms
- Single agent chemotherapy is often chosen as "third-line" treatment

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"Third-Line" Chemotherapy for Metastatic Breast Cancer

- No standard "third-line" chemotherapy
- Few data on "third-line" agents/regimens in patients who have been pretreated with doxorubicin and a taxane

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"Third-Line" Chemotherapy for Metastatic Breast Cancer

- Interpretation of tumor response rates for salvage chemotherapy is complicated by:
  - heterogeneous patient populations
  - single institution studies
  - variable criteria for response
  - response rates reported as "intent-to-treat" versus selected subpopulations
  - publication bias

Agents Used as "Third-Line" Chemotherapy Following Anthracyclines and Taxanes

Single Agents

Vinorelbine
5FU/Leucovorin or CIV 5FU
Gemcitabine
Mitoxantrone
Phase I/II Agents

Combinations

Mitomycin/Vinblastine
Cyclophosphamide, Methotrexate, Fluorouracil
Mitoxantrone/5FU, Leucovorin
Mitomycin, Methotrexate, Mitoxantrone
Others

Treatment After Anthracycline and Paclitaxel

Drug	Population	N	RR	Reference
Docetaxel	paclitaxel resistant anthra exposed	36	(3/26) 11.5%	Valero (Proc. ASCO '96)
Vinorelbine	paclitaxel failures 71% exposed to anthra	14	0%	Fazeny (Ca Chemo Pharm '96)
Vinorelbine + G-CSF	95% paclitaxel refractory, 100% anthra exposed	40	25% (ITT)	Livingston (JCO '97)
Paclitaxel (96h)	PD on taxanes 33% anthra exposed	28	(7/26) 27%	Seidman (JCO '96)
5-FU (CI)	prior anthracycline and/or paclitaxel	35	12% (ITT)	Ragaz (San Antonio '97)

Emerging Paradigm for Treatment of Metastatic Breast Cancer

- "Chronic Disease" Model

  Maximize duration and quality of patients' lives by controlling disease, maintaining performance status, and minimizing toxicity and inconvenience.

Goals of "Third-Line" Treatment: Maximize Duration and Quality of Life

- Reduction of Tumor-Related Symptoms
- Maximize Progression-Free and Overall Survival
- Maintain Performance Status
- Minimize Toxicity
- Enhance Convenience/Control for Patient

Potential Advantages of Oral Chemotherapy as Treatment for Advanced, Refractory Metastatic Breast Cancer

- Ability to titrate daily dose to minimize toxicity
- Maintain patients' performance status by avoiding toxicity
- Enhanced patient control
- Holiday from IV access
- Less time in oncology clinic

Metastatic Breast Cancer Patients' Preference for Oral Therapy

Preference	N	Rationale	Reference
89% Oral 10% IV	103	Convenience No IV Outside of Clinic	Liu (JCO '97)

*Patients were generally not willing to sacrifice efficacy for their preference

Conclusions

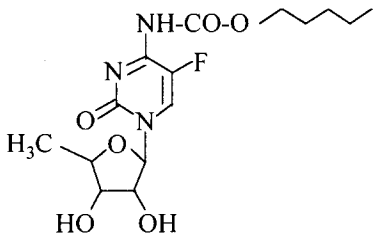
- "Third-line" chemotherapy can palliate tumor-related symptoms
- No standard chemotherapy for patients previously treated with an anthracycline and a taxane
- Few data assess response rates of the agents currently in use

Conclusions

- Data do not identify a therapy with proven clinical utility
- New agents with defined effectiveness are needed
- Goals of "third-line" treatment:
  - Diminish tumor-related symptoms
  - Minimize toxicity
  - Maintain quality of life

Xeloda (capecitabine) Tablets
NDA 20-896
ODAC Meeting
March 19, 1998

Capecitabine



Capecitabine

- Tumor-selective
- Orally active
- Antitumor activity in difficult patient population

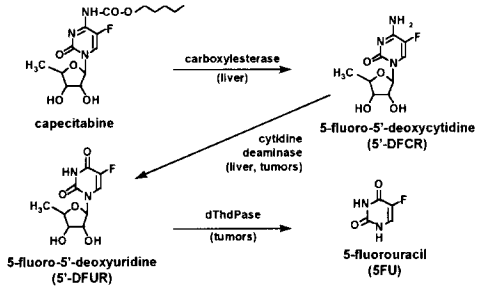
Outline

- Preclinical results
- Clinical pharmacology studies
- Efficacy in pivotal trial
- Safety
- Clinical benefit response
- Conclusions

Preclinical Results

- Bioenzymatic activation
- Antitumor activity in xenograft models
- Tumor-selective activation

Tumor Selective Metabolic Pathway

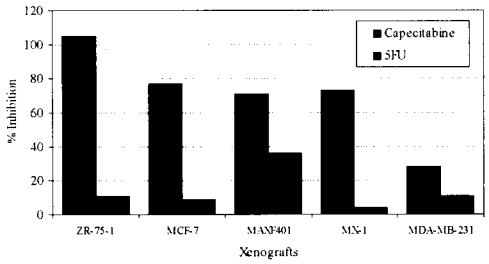


Thymidine Phosphorylase in Breast Cancer

Anti-Thymidine Phosphorylase

Control IgG

Tumor Growth Inhibition (%) of Human Breast Cancer Xenografts in Nude Mice



Capecitabine: Tumor-Selective Generation of 5FU

		Capecitabine Administration		5FU Administration	
Cancer Xenograft		5FU C_{MAX}	5FU AUC_t	5FU C_{MAX}	5FU AUC_t
CXF 280	Tumor	58.6	289	11.5	13.1
	Plasma	9.23	1.38	16.4	4.77
Ratio Tumor/Plasma		207		2.7	
Ratio AUC_{cape}/AUC_{5FU}		22			
Tumor Volume Change, mm^3		-25		228	

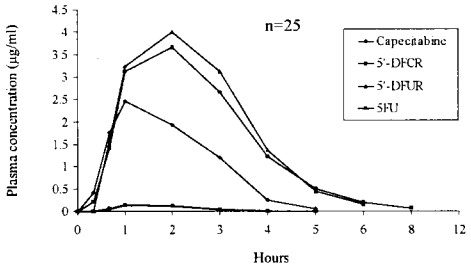
qd x 7/wk for 3 weeks

Ishikawa et al, Biochemical Pharmacology, in press

Clinical Pharmacology

- Pharmacokinetics
- Oral absorption
- Tumor selectivity in patients

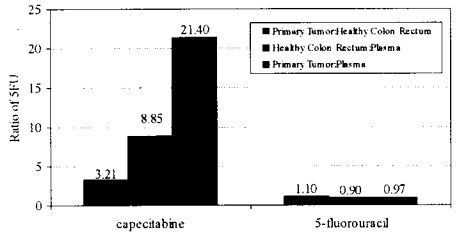
Plasma Concentration of Capecitabine and Metabolites After Oral Administration



Consistency of GI Absorption

Extensive gastrointestinal absorption (≥70% of dose) with limited variability among patients

5FU Ratios with Capecitabine/5FU Administration



Kovach JS and Beart RW, Investigational New Drugs (1989)

34

Capecitabine Clinical Development Program US/EU

[redacted]

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Pivotal Trial Protocol Objectives

Primary Objective

- Overall response rate ≈ 20%

Secondary Objective

- Duration of response
- Time to progressive disease
- Survival
- Safety
- Clinical benefit response

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Summary of Demographic Characteristics

ITT population	162 patients
No. of centers	25 US/Canada
Age (mean)	55.8 (26-78)
Karnofsky Performance Status (mean)	86.2 (70-100)
Time from diagnosis to recurrence (median)	2.5 years
Pre/postmenopausal	62/100
Measurable disease	135
Evaluable disease	27

Pivotal Trial
Sites of Metastatic Disease

Median Number of Metastatic Organ/Tissue Sites: 3 (range 1-11)

	No.	%
Lung/Pleura	94	(58)
Liver	69	(43)
Bone	87	(54)
Soft Tissue	38	(23)

(n=163)

Pivotal Trial
Patient Population: Prior Hormonal Therapies

	No.	%
tamoxifen	109	(67)
megesterol acetate	52	(32)
aromatase inhibitors	21	(13)
androgens	17	(10)
others (including oophorectomy)	20	(12)

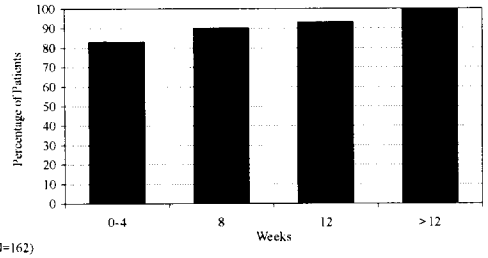
(n=163)

Pivotal Trial
Prior Chemotherapeutic Drugs

Chemotherapeutic Drug	No.	%
paclitaxel	163	(100)
doxorubicin	137	(84)
cyclophosphamide	150	(93)
5-fluorouracil	133	(82)
methotrexate	57	(35)
vinorelbine	27	(17)
carboplatinum	15	(9)
mitoxantrone	12	(7)
thiotepa	11	(7)
cisplatin	9	(6)
vincristine	9	(6)
etoposide	8	(5)
mitomycin C	3	(2)
epirubicin	2	(1)
others/investigational	17	(10)

(n=163)

Pivotal Trial
Time to Disease Progression After Last Paclitaxel Dose



(N=162)

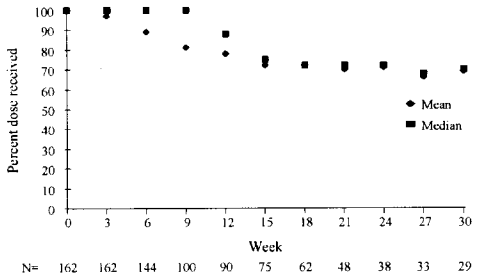
Pivotal Trial
Dose and Schedule

- 2500 mg/m2 PO bid 14 days on, 7 days off
- Dose determined by standard phase I dose-escalation trial
- Dose adjustment based on grade 2/ grade 3 toxicity

Dose Modification Schema

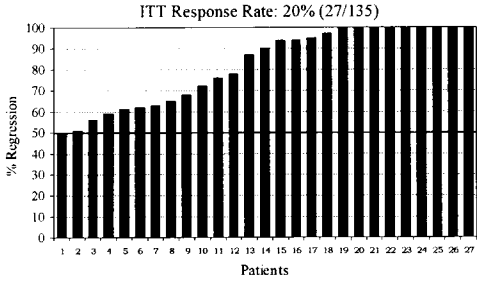
	Grade 2	Grade 3	Grade 4
1st appearance	Interrupt treatment until resolved to grade 0-1; **same dose**	Interrupt treament until resolved to grade 0-1; **75%**	Discontinue treatment or if in the best interest of the patient; **50%** once toxicity has resolved to grade 0-1
2nd appearance	Interrupt treament until resolved to grade 0-1: **75%**	Interrupt treatment until resolved to grade 0-1: **50%**	
3rd appearance of same toxicity	Interrupt treament until resolved to grade 0-1: **50%**	Discontinue treatment	
4th appearance of same toxicity	Discontinue treatment		

Median/Mean Dose Received Over Time



Pivotal Trial
Tumor Response

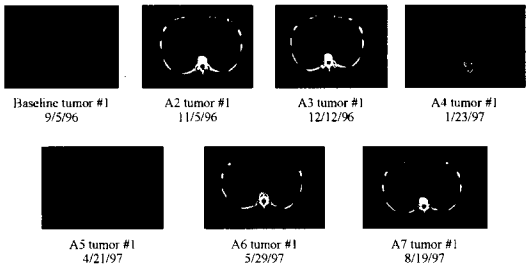
ITT Response Rate: 20% (27/135)



Pivotal Trial
Responses by Metastatic Site

Site	Number of Responses
Liver	12
Lung	4
Breast	4
Lymph	5
Skin	5

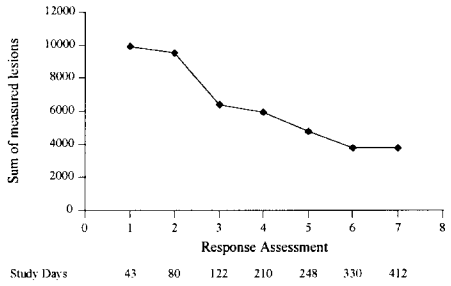
Patient #2401



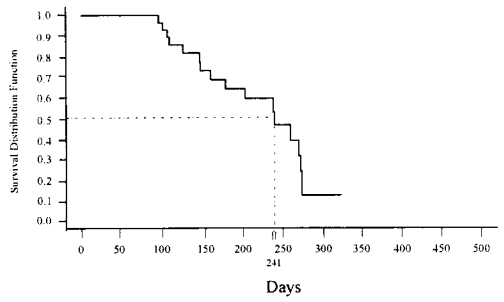
Baseline tumor #1 9/5/96 | A2 tumor #1 11/5/96 | A3 tumor #1 12/12/96 | A4 tumor #1 1/23/97

A5 tumor #1 4/21/97 | A6 tumor #1 5/29/97 | A7 tumor #1 8/19/97

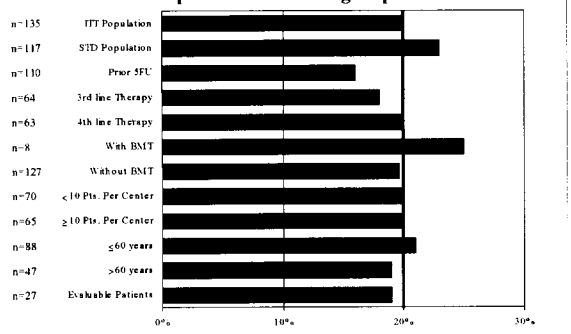
Patient 2401
Tumor Assessments



Pivotal Trial
Duration of Response



Response Rates of Subgroups



Definition of Drug Resistance

- **R1**: Disease relapse within 6 months of completing adjuvant therapy
- **R2**: Objective response to therapy followed by disease progression while on therapy
- **R3**: Disease progression on therapy without improvement

Definition of Drug Failure

- **F1**: Disease relapse within 6 -12 months of completing adjuvant therapy
- **F2**: Objective response to therapy followed by disease progression within 12 months of last dose
- **F3**: Stable disease while on therapy for a minimum of 4 cycles

Pivotal Trial Response Rate by Subgroup (Refractory Category)

Paclitaxel	Anthracycline	n	RR
R	R	42	29%
R	F	25	20%
F	R	13	31%
F	F	10	20%
		90	25%

Independent Review Objectives

- Blinded review of all patients with radiographic disease
- Determination of response rate and time to progression
- No reconciliation/interactions with investigator

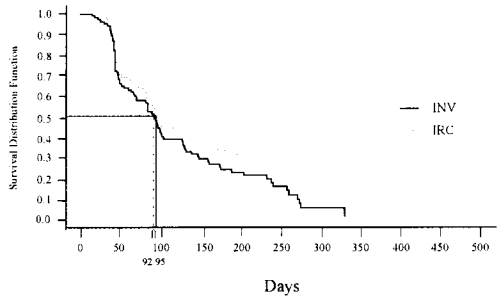
Independent Review Process

- Anatomic locations of indicator lesions provided
- X-rays digitized and stored electronically
- Tumor size determined with magnification, contrast adjustment and computer measurement

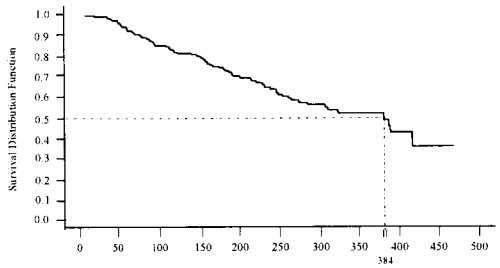
IRC Review Comparison with Investigator Assessment (N=100)

- Total response rate
  - INV: 18%
  - IRC: 20%
- Median regression in responding patients
  - INV: 73%
  - IRC: 69%
- Median regression in stable patients
  - INV: 21%
  - IRC: 24%

Pivotal Trial
Time to Progression Comparison Investigator/IRC



Pivotal Trial
Survival Time



Summary of Antitumor Effects of Capecitabine in Pivotal Breast Cancer Trial

- Strong response rate in heavily pretreated patients
- Excellent duration of response
- Long survival

Outline of Safety Results

- Total patients treated
- Adverse events in pivotal trial
- Safety in pooled population

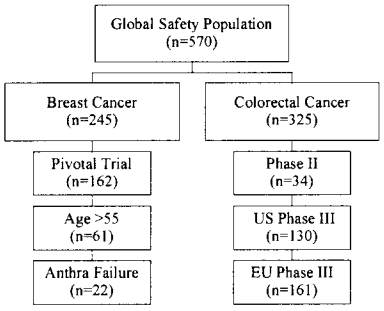
Patients Treated with Capecitabine

Phase I	222
Phase II/III	627
Ongoing	406
Total	1275

Pivotal Trial
Patients with Adverse Events

- Most frequent grade 3/4 related adverse events:
  - Diarrhea 11% (Gr. 3), 3% (Gr. 4)
  - HFS 10% (Gr. 3)
  - Stomatitis 7% (Gr. 3), 0% (Gr. 4)
- 4% grade 4 adverse events
- 7% withdrew due to treatment-related events
- 10% hospitalizations due to treatment-related events

Overview of the Global Safety Population



Safety Endpoints in Capecitabine Clinical Trials

Events - Probably, Possibly, Remotely Related to Capecitabine	Pivotal Study (N=162)		4 Month Safety Update (N=570)	
Deaths	0	(0.0)	7	(1.2)
Serious Adverse Events	18	(11.1)	73	(12.8)
Hospitalizations	17	(10.5)	72	(12.6)
Withdrawals due to Adverse Events	11	(6.8)	50	(9.0)
Withdrawals due to Laboratory Abnormalities	0	(0.0)	1	(0.2)
Grade 4 Adverse Events	6	(3.7)	20	(3.5)

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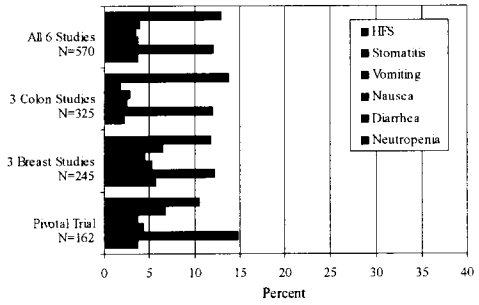
Hand-Foot Syndrome Grading Scale

Grade	Clinical Domain	Functional Domain
1	Numbness, dysesthesia parasthesia, painless swelling or erythema	Discomfort which does not disrupt normal activities
2	Painful erythema with swelling	Discomfort which affects activities of daily living
3	Moist desquamation, ulceration, blistering, severe pain	Severe discomfort, unable to work or perform activities of daily living

65

% Patients with Related Grade 3/4 Adverse Events Comparisons of Treatment Populations



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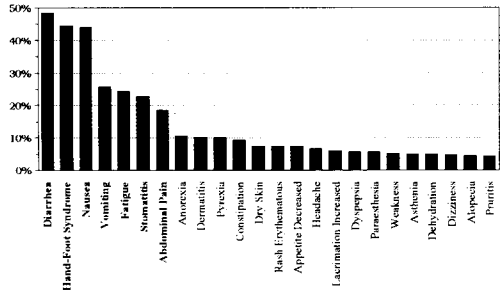
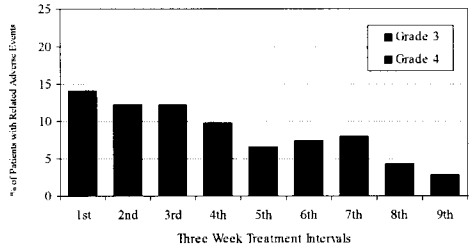
Related Adverse Events

Four Month Safety Update (N=570)



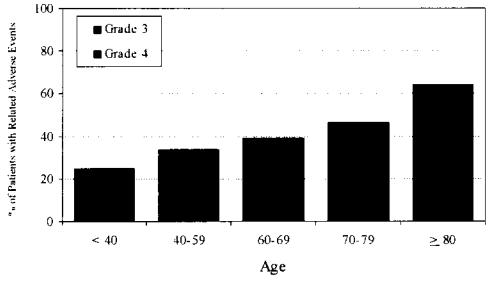
Incidence of Adverse Events by Cycle

Four Month Safety Update
N=570



Impact of Age

Four Month Safety Update
N=570



Hyperbilirubinemia
Incidence of Grade 3/4 Events

Pivotal Trial:	9.3% (15/162)
4 Month Safety Update:	16.8% (96/570)

Hyperbilirubinemia

Grade 3/4 events

Patients with liver metastases at baseline:	72
Patients with medical condition or new liver metastases:	4
No known liver disease:	20
4 month safety update (N=570):	96

Hyperbilirubinemia

Average bilirubin concentrations in patients experiencing isolated hyperbilirubinemia

	(n)	Baseline (mg/dl)	Peak (mg/dl)	Median Time to Peak (d)
Breast	8	1.0	2.4	74
Colon	12	0.8	2.1	87

Clinical Benefit Response

- Definition
- Response rate
- Longitudinal analysis

Parameters of Clinical Benefit Response

- Daily pain assessment
- Daily record of consumption of analgesics
- Weekly self assessment of Karnofsky Performance Score

Clinical Benefit Response
Definition of Response

Pain Score

- ≥ 20 mm pain at baseline
- 50% improvement compared to baseline
- Sustained for 4 weeks

Clinical Benefit Response
Definition of Response

Analgesic Consumption

- ≥ 70 mg morphine equivalents per week at baseline
- 50% reduction
- Sustained for 4 weeks

Clinical Benefit Response
Definition of Response

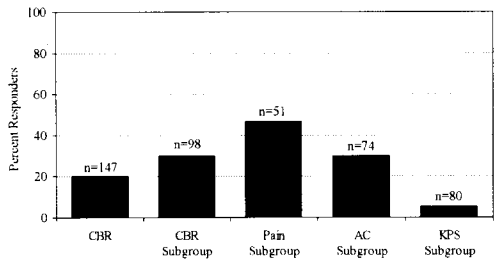
Karnofsky Performance Status

- Improvement by ≥ 20 points compared to baseline
- Sustained for 4 weeks

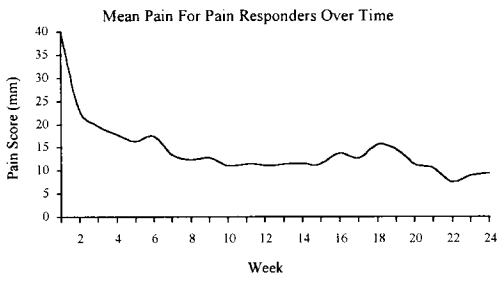
Clinical Benefit Response
Algorithm for Response

- Clinical benefit responder:
  - At least one parameter is positive and no parameters are negative
- Clinical benefit non responder:
  - Negative for at least one parameter
- Stable:
  - Stable in all 3 parameters

Clinical Benefit Responders



Clinical Benefit Response



Risk/Benefit Assessment Comparison with Other Agents

Drug	Reference	(n)	RR (%)	DR (mo)	TTP (mo)	Survival (mo)	12 mo Survival (%)
capecitabine 3rd/4th Line	Pivotal Trial	162	20%	8.1	3.2	12.8	52%
paclitaxel 2nd/3rd Line	USPI						
175 mg/m^2		235	28%	8.1	4.2	11.7	NR
135mg/m^2		236	22%	8.1	3.0	10.5	NR
docetaxel 2nd Line	USPI	134	41%	6.0	4.0	11.8	43%
vinorelbine 2nd/3rd Line	Jones (JCO 95)	115	16%	NR	3.0	8.8	36%

NR = not reported

Conclusions
Benefit/Risk Assessment

- Refractory patient population
- Response rate 20%, 40% stable disease
- Duration of response 241 days
- Median survival of 12.8 months
- 1 year survival 52%

Conclusions
Benefit/Risk Assessment

- Predictable adverse events: diarrhea, HFS
- Manageable adverse events: dose modifications at grade 2
- Overall clinical benefit response in 20% of patients, with 47% of symptomatic patients had significant durable pain response
- Patient preference for oral outpatient therapy

Gemzar®
Gemcitabine HCl

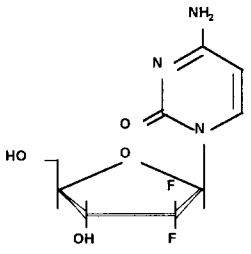
Anders Pedersen, M.D.

Medical Director
Gemzar Product Team
Lilly Research Laboratories

Gemzar®
Gemcitabine HCl

- Gemcitabine HCl is approved for the treatment of patients with locally advanced or metastatic adenocarcinoma of the pancreas.
- Eli Lilly and Company is seeking approval for gemcitabine as a single agent and in combination with cisplatin for the treatment of patients with locally advanced or metastatic NSCLC.

Gemzar®
Gemcitabine HCl



Difluorodeoxycytidine

Gemcitabine Mechanisms of Action

- **Inhibition of DNA synthesis**
  - » dFdCTP competes with dCTP for incorporation into DNA resulting in inhibition of DNA synthesis.
- **Masked DNA chain termination**
  - » DNA chain elongation is terminated following gemcitabine incorporation.
  - » The repair function of DNA polymerase is impaired.
- **Self-potentiation**
  - » Depletion of nucleotide pools by direct inhibition of ribonucleotide reductase.
  - » Decreased intracellular catabolism secondary to inhibition of intracellular deamination.

Agenda of Presentation

Introduction

Anders Pedersen, M.D. — Medical Director, Gemzar Product Team, Lilly Research Laboratories

Overview of Chemotherapy in NSCLC

Lawrence Einhorn, M.D. — Distinguished Professor of Medicine, Indiana University Medical Center

Agenda of Presentation

Gemcitabine / Cisplatin vs. Cisplatin (JHEX)

Alan Sandler, M.D. — Assistant Professor of Medicine, Indiana University Medical Center

Gemcitabine / Cisplatin vs. Cisplatin / Etoposide (JHBR)
Gemcitabine vs. Cisplatin / Etoposide (JHEZ)

Rafael Rosell, M.D., Ph.D. — Chief, Medical Oncology Service, Hospital Germans Trias i Pujol, Spain

Summary of Phase 2 Studies and Conclusions

Lawrence Einhorn, M.D. — Distinguished Professor of Medicine, Indiana University Medical Center

Consultants

Paul Bunn Jr., M.D.	Professor of Medicine University of Colorado Cancer Center
Claude Denham, M.D.	Medical Oncologist Texas Oncology Professional Assoc.
Dewey Conces Jr., M.D.	Professor of Radiology Indiana University Medical Center

Gemzar®
Gemcitabine HCl

Lawrence Einhorn, M.D.

Distinguished Professor of Medicine
Indiana University Medical Center
Indianapolis, Indiana

Lung Cancer Statistics

- **Projected 171,500 newly diagnosed cases and 160,000 deaths in 1998**
- **Number 1 cause of cancer deaths in both American men and women; exceeds the number 2, 3, and 4 causes of cancer death combined**
- **NSCLC comprises 75% of cases**

Surgical Stages of NSCLC

Stage		5-year survival
IA	T1 N0	67%
IB	T2 N0	57%
IIA	T1 N1	55%
IIB	T2 N1 or T3 N0	39%
IIIA	Tx N2 or T3 N1	23%

NSCLC: Combination Chemotherapy

Regimen	Institution	RR	MST	Group	RR	MST
CAP	Mayo	42%	6 mo	SECSG	10%	6 mo
CAMP	Chicago	36%	9 mo	ECOG	17%	5 mo
MACC	Mt. Sinai	44%	8 mo	ECOG	12%	4 mo

Meta-Analysis of Chemotherapy in NSCLC*

- Meta-analysis of all published Phase 3 combination chemotherapy vs. supportive care trials.
- Seven studies involving 706 patients; 3 individual studies demonstrated survival benefits and 4 did not, but all 7 studies had improved median survival with chemotherapy.
- Modest but statistically significant reductions in the mortality rate with chemotherapy at 3 and 6 months; reduction not significant at 9, 12, or 18 months.
- "Although the risk reduction is low, we believe that combination chemotherapy should be given to patients with NSCLC."

*Souquet PJ, et al.: *Lancet* 342:19-21, 1993.

Phase 3 Trials of Combination Chemotherapy in NSCLC*

- Review of 3,937 patients in 27 published studies.
- Response rates varied from 0 to 53%.
- Twenty-six of 27 Phase 3 trials failed to demonstrate improved survival for one combination compared to another.

*Splinter TAW: *Eur J Cancer* 26:1093-1099, 1990.

SWOG Phase 3 Trial (1982-1984)*

Regimen	N	RR %	MST (months)
PE	135	16	5.3
PE + MeGAG	136	33	4.9
P + VIb	142	24	5.9
MVP	134	17	5.0
FOMI/CAP	133	10	5.0

*Welck, et al.: *J Clin Oncol* 9:1157-1162, 1991.

ECOG Phase 3 Study NSCLC

Regimen	N	RR %	MST (months)
CAMP	115	17	5.8
MVP	121	31	5.3
P + Vindesine	126	25	6.0
EP	124	20	6.2
TOTAL	486	23	5.8

ECOG 1583 Phase 3 NSCLC

Regimen	Response Rate %	MST (months)
MVP	20	5.3
P + VIb	13	5.8
MVP + CAMP	13	5.8
CBDCA	9	7.4
CHIP	6	6.0

699 patients entered 1/84 to 1/86

New Agents in NSCLC

- Taxanes (paclitaxel and docetaxel)
- Irinotecan (CPT-11)
- Vinorelbine (Navelbine®)
- Gemcitabine (Gemzar®)

Vinorelbine in NSCLC*

- Review of trials using single-agent vinorelbine (20 to 35 mg/m^2/week)
- Total of 1,146 patients in 15 studies
- Overall response rate 24% (+/-10%) and MST 32 weeks (+/- 4 weeks)

*LeChevalier T: *Lung Cancer* 18:587, 1997.

Vinorelbine vs. 5-FU plus Leucovorin

- 2:1 randomization of vinorelbine (30 mg/m^2/week) vs. 5-FU (425 mg/m^2 weekly x 5) plus leucovorin (20 mg/m^2 x 5) every 4 weeks
- KPS 70-100, Stage IV disease, and no prior chemotherapy

Vinorelbine vs. 5-FU plus Leucovorin: Results*

	Vinorelbine (N=143)	5-FU + Leucovorin (N=68)	
Response rate	12%	3%	NS
MST (months)	6.7	4.8	p=0.03
1-yr survival	25%	16%	

*Crawford J, et al.: *J Clin Oncol* 14:2774-2784, 1996.

Phase 3 Study of Vinorelbine in NSCLC

R
A
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- Vinorelbine (30 mg/m^2 weekly)
- Vinorelbine + Cisplatin (120 mg/m^2)
- Vindesine + Cisplatin (120 mg/m^2)

Phase 3 Vinorelbine Study

- European multicenter study
- 612 patients entered from 6/89 to 5/91
- 44% Stage III, including 14% Stage IIIA
- 80% performance status 0-1; 20% PS 2

Phase 3 Vinorelbine Results*

	Vinorelbine (N=206)	VNR + CDDP (N=206)	Vindesine + CDDP (N=200)	p-value
RR	14%	30%	19%	p=0.02
MST (mo)	7.1	9.2	7.4	p=0.04

* Le Chevalier T, et al.: *J Clin Oncol* 12:360-367, 1994.

SWOG Phase 3 Cisplatin vs. Cisplatin + Vinorelbine

- Between 10/93 and 4/95, 432 patients randomized to cisplatin (100 mg/m^2) every 4 weeks with or without vinorelbine (25 mg/m^2) weekly
- All patients performance status, 0-1
- Response rates 12% vs. 26%

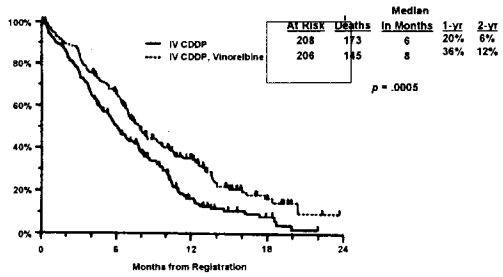
SWOG Phase 3 Cisplatin vs. Cisplatin + Vinorelbine* (Continued)

- 5% vs. 81% Grade 3-4 granulocytopenia
- Progression free survival: 2 vs. 4 months (p=0.0001)
- Overall survival 6 vs. 8 months (p=0.0018), with 20% vs. 36% 1-year survival

*Wozniak AJ, et al.: *Proc ASCO* 15:374, 1996.

Southwest Oncology Group Study 9306

Survival by Treatment Arm



Gemzar®

Gemcitabine HCl

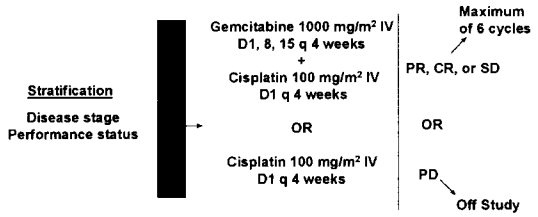
Alan Sandler, M.D.

Assistant Professor of Medicine
Indiana University Medical Center
Indianapolis, Indiana

Study JHEX

- This was a randomized, multinational, multicenter trial conducted in 5 countries at 55 sites by 70 investigators
- From 8/95 - 2/97, 522 eligible patients were entered on study
  - » Interim analysis - 8/95 - 8/96 (309 patients)
- This study was based on a phase II trial conducted by the Hoosier Oncology Group involving 28 eligible patients with advanced NSCLC revealing a RR of 31% with a median survival of 8.4 months

Gemcitabine / Cisplatin vs. Cisplatin in Patients with Advanced or Metastatic NSCLC
Study JHEX



Endpoints for Complete Study
Gemcitabine / Cisplatin vs. Cisplatin
Study JHEX

<u>Primary</u>:

- Survival

<u>Statistical Design:</u>

- N= 520; 1-year accrual and 1-year follow-up
- H_a = 33% difference in median survival
  H_o = no survival difference
  Alpha = 0.05, power ≥80%

Endpoints for Complete Study
Gemcitabine / Cisplatin vs. Cisplatin
Study JHEX

Secondary:

- Objective tumor response
- Time-to-event efficacy measures such as:
  - » time to progressive disease
  - » time to treatment failure
  - » time to objective tumor response
  - » duration of response for responding patients
- Relative toxicities
- Changes in QOL

Endpoints for Interim Analysis
Gemcitabine / Cisplatin vs. Cisplatin
Study JHEX

Primary:

- Objective tumor response
- Time to progressive disease

Statistical Design:

- N = 309; 1-year accrual and 6 month follow-up
- H_a = 2 month difference in time to PD
  H_o = no difference in time to PD
  Alpha = 0.02, power ≥80%

Inclusion Criteria
Gemcitabine / Cisplatin vs. Cisplatin
Study JHEX

- Histologic or cytologic confirmed diagnosis of NSCLC: unresectable Stage IIIA or IIIB or Stage IV; lesions not amenable to surgery or radiation of curative intent
- No prior chemotherapy
- Prior radiation allowed if not only source of measurable disease
- KPS 70 - 100
- Adequate bone marrow reserve

Summary of Baseline Disease Characteristics
Study JHEX: Interim Analysis

Variable	N=309	Gemcitabine/Cisplatin N=155	Cisplatin N=154
Median Age:	63	62	64
Gender:			
Female	31%	33%	29%
Male	69%	67%	71%
Diagnosis:			
NSCLC	16%	18%	14%
Squamous	26%	29%	23%
Large Cell	13%	14%	12%
Adeno	43%	38%	49%
Adeno-Squamous	2%	1%	3%

Summary of Baseline Disease Characteristics
Study JHEX: Interim Analysis

Variable	N=309	Gemcitabine/Cisplatin N=155	Cisplatin N=154
Stage:			
IIIA	7%	7%	8%
IIIB	25%	26%	23%
IV	68%	68%	69%
Performance Status:			
70	15%	18%	12%
80	27%	21%	32%
90	44%	49%	40%
100	12%	10%	14%

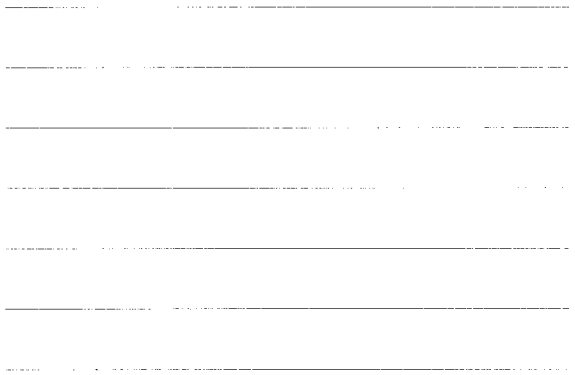
Efficacy Results
Study JHEX: Interim Analysis

	Gemcitabine/ Cisplatin	Cisplatin	
Patients Entered	155	154	
Tumor Response (95% C.I.)	32% (24 to 39%) (2 CR, 46 PR, 1 PRNM)	10% (6 to 15%) (15 PR, 1 PRNM)	p<0.0001[a]
Median Duration of Response (months, 95% C.I.)	6.9 (5.0 to 9.2)	4.2 (3.2 to 7.9)	p = 0.2122[b] p = 0.1434[c]

[a]Fisher's Exact [b]Log-Rank [c]Wilcoxon

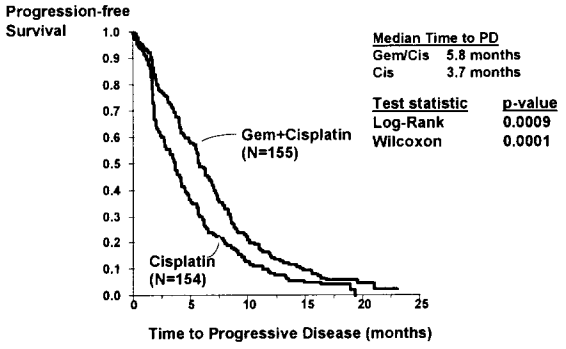
Patient Scan--Patient #4077

Patient Scan--Patient #4077



Patient Scan--Patient #4077

Time to Progressive Disease
Study JHEX: Interim Analysis

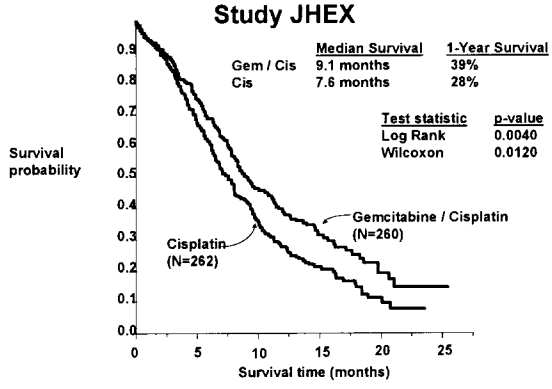


Efficacy Results Continued
Study JHEX: Final Analysis

	Gemcitabine/ Cisplatin	Cisplatin	
Patients Entered	262	260	
Median Survival	9.1	7.6	p = 0.0040[a]
(months, 95% C.I.)	(8.3 to 10.6)	(6.5 to 8.2)	p = 0.0120[b]
1-year Survival Probability	39%	28%	
Censoring	33%	24%	

[a]Log-Rank [b]Wilcoxon

Survival on All Patients (N=522)
Study JHEX

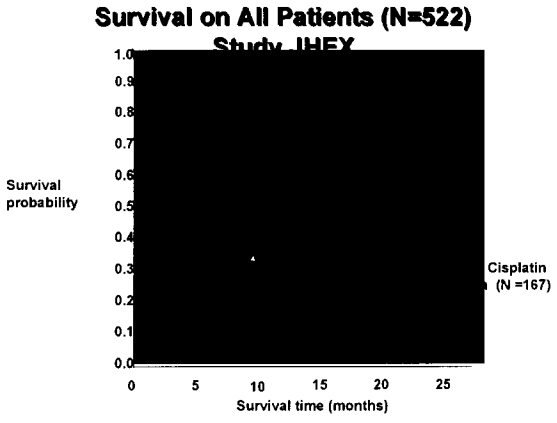


Cox Proportional Hazard Model for Survival (FDA)--Study JHEX

Factors Considered	p-value
Treatment	0.0010
Region (Europe vs. North America)	0.9067
Treatment x Region	0.0880

Cox Proportional Hazard Model for Survival (Sponsor)--Study JHEX

Factors Considered	p-value
Treatment	0.0013
Region (North America vs. Europe)	0.9026
Treatment x Region	0.1381
Disease Stage	0.0013
Age (≤65 vs. >65)	0.7700
Performance Status	<0.0001
Gender	0.6175
Prior Radiation	0.1245
Time Since Diagnosis	0.0352



Hematologic Toxicity
Study JHEX: Interim Analysis

CTC Grade %	Gemcitabine / Cisplatin 3	Gemcitabine / Cisplatin 4	Cisplatin 3	Cisplatin 4
Anemia*	21%	5%	4%	1%
Neutropenia*	23%	35%	4%	1%
Thrombocytopenia*	23%	28%	2%	1%
Total % Patients				
Febrile Neutropenia	4%		1%	
PRBC Transfusion*	34%		10%	
Platelet Transfusion*	22%		0%	
Toxic Deaths	0%		0%	

*Statistically significant

Renal and Hepatic Toxicity
Study JHEX: Interim Analysis

CTC Grade %	Gemcitabine / Cisplatin 3	Gemcitabine / Cisplatin 4	Cisplatin 3	Cisplatin 4
Creatinine	5%	0%	2%	0%
Transaminase	1%	1%	1%	0%

Nonlaboratory Toxicity
Study JHEX: Interim Analysis

CTC Grade %	Gemcitabine / Cisplatin 3	Gemcitabine / Cisplatin 4	Cisplatin 3	Cisplatin 4
Nausea	28%	3%	23%	1%
Vomiting	9%	15%	10%	11%
Alopecia	0%	0%	0%	0%
Neuro Hearing	7%	0%	6%	0%
Neuro Sensory	1%	0%	0%	0%

Nonlaboratory Toxicity Continued

Study JHEX: Interim Analysis

CTC Grade %	Gemcitabine/ Cisplatin 3	Gemcitabine/ Cisplatin 4	Cisplatin 3	Cisplatin 4
Fever	0%	0%	0%	0%
Infection	2%	1%	1%	0%
Dyspnea	5%	5%	4%	2%
Hemorrhage	0%	0%	0%	0%

Conclusions

Gemcitabine / Cisplatin vs. Cisplatin

Study JHEX: Interim Analysis

- **Gemcitabine / cisplatin has a statistically significantly greater response rate than single-agent cisplatin (32% vs. 10%; $p < 0.0001$).**
- **Time to PD is substantially longer for gemcitabine / cisplatin compared to cisplatin (median of 5.8 months vs. 3.7 months; Wilcoxon $p = 0.0001$, Log Rank $p = 0.0009$).**

Conclusions

Gemcitabine / Cisplatin vs. Cisplatin

Study JHEX: Interim Analysis

- **Bone marrow suppression is more pronounced with gemcitabine / cisplatin than with cisplatin.**
- **Nonhematologic toxicities occur at approximately the same frequency in both treatment arms.**

Conclusions

Gemcitabine / Cisplatin vs. Cisplatin

Study JHEX
Survival: Final Analysis

- **Survival is significantly longer for gemcitabine / cisplatin patients compared to single-agent cisplatin patients (Median of 9.1 months vs. 7.6 months; Wilcoxon p = 0.0120, Log-Rank p = 0.0040).**
- **1-year survival for gemcitabine / cisplatin patients compared to cisplatin patients is 39% vs. 28% respectively.**

Gemzar®

Gemcitabine HCl

Rafael Rosell, M.D., Ph.D.

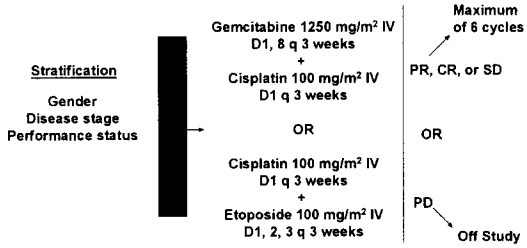
Chief, Medical Oncology Service
Hospital Germans Trias i Pujol
Spain

Gemcitabine / Cisplatin vs. Cisplatin / Etoposide in the Treatment of Locally Advanced or Metastatic NSCLC

Study JHBR

- **Number of Sites: 14**
- **Number of Patients Accrued: 135**
- **Accrual Dates: July 1995 - June 1996**
- **Last Data Cut-off Date:**
  - **» Safety: April 1997**
  - **» Efficacy: January 1998**

Gemcitabine / Cisplatin vs. Cisplatin / Etoposide in the Treatment of Locally Advanced or Metastatic NSCLC Study JHBR



Endpoints

Gemcitabine / Cisplatin vs. Cisplatin / Etoposide Study JHBR

Primary:

- Objective tumor response

Secondary:

- Time to progressive disease
- Survival
- Relative toxicities
- Changes in QOL

Summary of Inclusion Criteria

Gemcitabine / Cisplatin vs. Cisplatin / Etoposide Study JHBR

- Histologic or cytologic diagnosis of Stage IIIB or IV NSCLC; lesions not amenable to surgery or radiation of curative intent
- No prior chemotherapy
- Prior radiation allowed if not only site of measurable disease
- KPS $\geq$ 60
- Adequate bone marrow reserve

Summary of Baseline Disease Characteristics
Study JHBR

Variable	All N=135	Gemcitabine/ Cisplatin N=69	Cisplatin/ Etoposide N=66
Median Age:	59	58	60
Gender:			
Female	7%	7%	8%
Male	93%	93%	92%
Diagnosis:			
Squamous	45%	41%	50%
Adeno	34%	36%	32%
Large Cell	10%	12%	9%
NSCLC	10%	10%	9%
Adeno-Squamous	1%	1%	0%

Summary of Baseline Disease Characteristics
Study JHBR

Variable	All N=135	Gemcitabine/ Cisplatin N=69	Cisplatin/ Etoposide N=66
Stage:			
IIIB	50%	48%	52%
IV	50%	52%	49%
Performance Status:			
70	15%	17%	12%
80	33%	28%	39%
90	34%	35%	33%
100	18%	20%	15%

Efficacy Results
Study JHBR

	Gemcitabine/ Cisplatin	Cisplatin/ Etoposide	
Patients Entered / Qualified	69 / 69	66 / 64	
Tumor Response (95% C.I.)	41% (29 to 53%) 28 PR	22% (13 to 34%) 14 PR	p = 0.0253[a]
Median Duration of Response (months, 95% C.I.)	8.4 (6.9 to 9.5)	6.1 (4.5 to 10.0)	p = 0.9791[b] p = 0.6632[c]

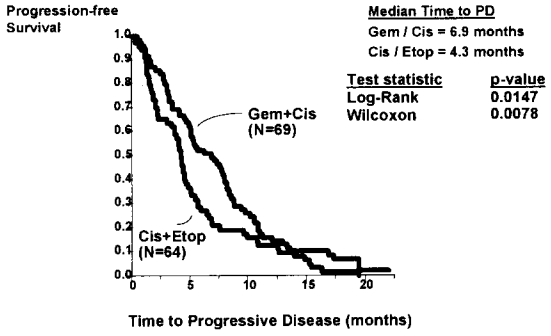
[a]Fisher's Exact [b]Log-Rank [c]Wilcoxon

Efficacy Results Continued
Study JHBR

	Gemcitabine/ Cisplatin	Cisplatin/ Etoposide	
Median Time to PD	6.9	4.3	p =0.0147[a]
(months, 95% C.I.)	(5.0 to 8.1)	(3.5 to 4.7)	p =0.0078[b]
Median Survival	8.7	7.2	p =0.1885[a]
(months, 95% C.I.)	(7.7 to 10.2)	(6.1 to 9.8)	p =0.2186[b]
1-year Survival Probability	32%	26%	
Censoring	16%	11%	

[a]Log-Rank [b]Wilcoxon

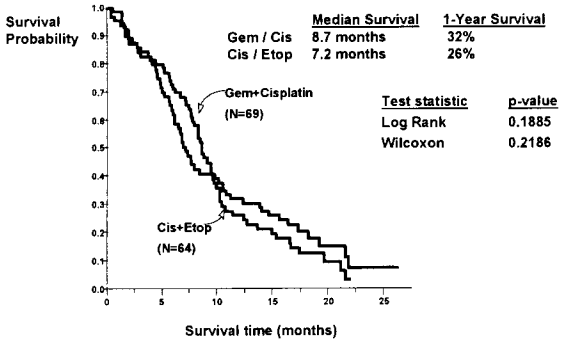
Time to Progressive Disease
Study JHBR



Median Time to PD
Gem / Cis = 6.9 months
Cis / Etop = 4.3 months

Test statistic	p-value
Log-Rank	0.0147
Wilcoxon	0.0078

Survival
Study JHBR



	Median Survival	1-Year Survival
Gem / Cis	8.7 months	32%
Cis / Etop	7.2 months	26%

Test statistic	p-value
Log Rank	0.1885
Wilcoxon	0.2186

Hematologic Toxicity
Study JHBR

WHO Grade %	Gemcitabine / Cisplatin 3	Gemcitabine / Cisplatin 4	Cisplatin / Etoposide 3	Cisplatin / Etoposide 4
Anemia	22%	0%	13%	2%
Neutropenia*	36%	28%	20%	56%
Thrombocytopenia*	39%	16%	8%	5%
Total % Patients				
Febrile Neutropenia	7%		12%	
PRBC Transfusion	29%		21%	
Platelet Transfusion	3%		8%	
Toxic Deaths	1%		0%	

* Statistically significant

Nonlaboratory Toxicity
Study JHBR

WHO Grade %	Gemcitabine / Cisplatin 3	Gemcitabine / Cisplatin 4	Cisplatin / Etoposide 3	Cisplatin / Etoposide 4
Nausea / Vomiting	35%	4%	19%	7%
Hemorrhage	0%	3%	0%	3%
Fever	0%	0%	0%	0%
Infection	3%	1%	8%	0%
Dyspnea	0%	1%	0%	0%
Alopecia*	13%	0%	51%	0%
Paresthesias	0%	0%	2%	0%

* Statistically significant

Conclusions
Gemcitabine / Cisplatin vs. Cisplatin / Etoposide
Study JHBR

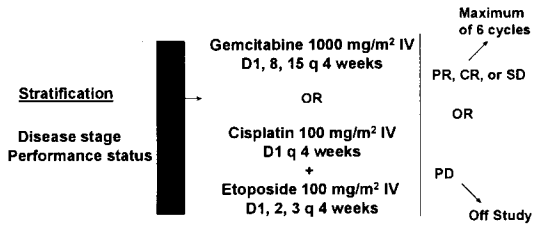
In chemonaive patients with NSCLC:

- Gemcitabine / cisplatin has a statistically significant advantage in response rate compared to cisplatin / etoposide (41% vs. 22%; p= 0.0253).
- Time to PD is longer in the gemcitabine / cisplatin arm compared to cisplatin / etoposide (median of 6.9 months vs. 4.3 months; Wilcoxon p= 0.0078, Log-Rank 0.0147).
- The toxicity profile of gemcitabine / cisplatin is similar to cisplatin / etoposide.

Gemcitabine vs. Cisplatin / Etoposide in the Treatment of Locally Advanced or Metastatic NSCLC Study JHEZ

- Number of Sites: 33
- Number of Patients Accrued: 147
- Accrual Dates: July 1995 - January 1996
- Last Data Cut-off Dates:
  - » Safety: June 1996
  - » Efficacy: January 1998

Gemcitabine vs. Cisplatin / Etoposide in the Treatment of Locally Advanced or Metastatic NSCLC Study JHEZ



Endpoints Gemcitabine vs. Cisplatin / Etoposide Study JHEZ

Primary:
- Objective tumor response

Secondary:
- Time-to-event efficacy measures such as:
  - » duration of response for responding patients
  - » time to progressive disease
  - » survival
- Relative toxicities
- Changes in QOL

Summary of Inclusion Criteria

Gemcitabine vs. Cisplatin / Etoposide
Study JHEZ

- Histologic or cytologic diagnosis of NSCLC: Stage IIIA (if inoperable), IIIB, or IV; lesions not amenable to surgery or radiation of curative intent
- No prior chemotherapy
- Zubrod ≤2
- Prior radiation allowed if not only site of measurable disease
- Adequate bone marrow reserve

Summary of Baseline Disease Characteristics

Study JHEZ

Variable	All N=147	Gemcitabine N=72	Cisplatin/ Etoposide N=75
Median Age:	59	59	59
Gender:			
Female	22%	26%	19%
Male	78%	74%	81%
Diagnosis:			
Adeno	47%	53%	41%
Squamous	32%	31%	32%
NSCLC	12%	8%	16%
Large Cell	9%	8%	9%
Large/Adeno	1%	0%	1%

Summary of Baseline Disease Characteristics

Study JHEZ

Variable	All N=147	Gemcitabine N=72	Cisplatin/ Etoposide N=75
Stage:			
IIIA	7%	6%	8%
IIIB	18%	18%	17%
IV	75%	76%	75%
Performance Status:			
0	22%	21%	23%
1	64%	61%	68%
2	13%	17%	9%

Efficacy Results
Study JHEZ

	Gemcitabine	Cisplatin / Etoposide	
Patients Entered / Qualified	72 / 67	75 / 72	
Tumor Response (95% C.I.)	18% (10 to 29%) 12 PR	15% (8 to 26%) 11 PR	p = 0.8199[a]
Median Duration of Response (months, 95% C.I.)	6.5 (3.8 to 9.8)	5.8 (4.8 to 7.2)	p = 0.8624[b] p = 0.8281[c]

[a]Fisher's Exact [b]Log-Rank [c]Wilcoxon

Patient X-Ray--Patient #4168

Patient X-Ray--Patient #4168

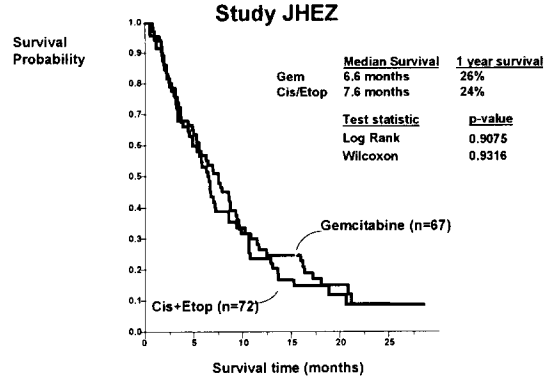
Patient X-Ray--Patient #4168

Efficacy Results
Study JHEZ Continued

	Gemcitabine	Cisplatin/ Etoposide	
Median Time to PD	3.0	3.2	p =0.86[a]
(months, 95% C.I.)	(2.2 to 3.9)	(2.1 to 4.8)	p =0.86[b]
Median Survival	6.6	7.6	p =0.91[a]
(months, 95% C.I.)	(4.9 to 7.3)	(5.4 to 9.3)	p =0.93[b]
1-Year Survival Probability	26%	24%	
Censoring	19%	17%	

[a]Log-Rank [b]Wilcoxon

Survival
Study JHEZ



Hematologic Toxicity
Study JHEZ

WHO Grade %	Gemcitabine 3	Gemcitabine 4	Cisplatin / Etoposide 3	Cisplatin / Etoposide 4
Anemia	6%	0%	3%	0%
Neutropenia	7%	1%	3%	11%
Thrombocytopenia	1%	0%	0%	0%
Total % Patients				
Neutropenic Sepsis*	0%		7%	
PRBC Transfusion	14%		23%	
Platelet Transfusion	0%		4%	
Toxic Death	0%		0%	

*Fisher's Exact Test, p = 0.0585

Nonlaboratory Toxicity
Study JHEZ

WHO Grade %	Gemcitabine 3	Gemcitabine 4	Cisplatin / Etoposide 3	Cisplatin / Etoposide 4
Nausea / Vomiting*	11%	0%	26%	4%
Hemorrhage	0%	0%	1%	0%
Fever	3%	0%	1%	0%
Infection	4%	0%	4%	4%
Dyspnea	4%	6%	4%	0%
Alopecia*	0%	0%	61%	1%
Paresthesias	0%	0%	1%	0%

*Statistically significant

Number of Drug-Related Hospitalizations
Study JHEZ

Reason	*Gemcitabine*	*Cisplatin / Etoposide*
Fever	*6*	*7*
Nausea and Vomiting	*0*	*2*
Anemia	*2*	*4*
Neutropenia	*0*	*3*
Sepsis	*1*	*4*
Dyspnea	*1*	*1*
Other	*8*	*16*
Total	*18*	*37*
Average Duration of Stay (days)	*7*	*5*

Antiemetic and Growth Factor Usage

Study JHEZ

	Gemcitabine (N = 72)	*Cisplatin / Etoposide (N = 75)*
Antiemetics		
5-HT_3 Antagonists	*24%*	*100%*
Dexamethasone	*2.8%*	*66.6%*
Metoclopramide	*43%*	*56%*
Growth Factors	*0%*	*1%*

Conclusions
Gemcitabine vs. Cisplatin / Etoposide
Study JHEZ

In chemonaive patients with NSCLC:

- **Gemcitabine is as effective as cisplatin / etoposide.**
- **Gemcitabine is less toxic than cisplatin / etoposide.**
- **Gemcitabine requires less supportive care than cisplatin / etoposide.**

Gemzar®
Gemcitabine HCl

Lawrence Einhorn, M.D.

Distinguished Professor of Medicine
Indiana University Medical Center
Indianapolis, Indiana

Single Agent Gemcitabine in NSCLC

Study	# Pts	RR%	MST (months)	1-yr Survival (%)
Europe (E004)	71	23	8.8	34%
Canada/Europe (E018)	151	22	9.5	43%
South Africa (JHAX)	76	20	10.7	40%
Japan	136	23	9.6	----
U.S.	32	25	11.3	44%
Total	466	23	10.2	40%

Hematology Toxicities for Single Agent Gemcitabine Studies
Studies E004, JHAX, and E018

	E004 N=82		JHAX N=84		E018 N=161	
WHO Grade %	3	4	3	4	3	4
Granulocytes	18	5	25	4	21	6
Hemoglobin	5	0	7	0	5	1
Platelets	0	1	0	2	1	1
Fever	1	0	1	0	0	0
Hemorrhage	NR	NR	1	4	0	0
Infection	0	0	2	0	0	0

NR= Not Reported

Non-Hematologic Toxicities for Single Agent Gemcitabine Studies
Study E004, JHAX, and E018

	E004 N=82		JHAX N=84		E018 N=161	
WHO Grade %	3	4	3	4	3	4
Nausea / Vomiting	38	0	5	0	10	1
Peripheral Neuropathy	0	0	0	0	0	0
Creatinine	1	0	0	0	0	0

Gemcitabine + Cisplatin in NSCLC

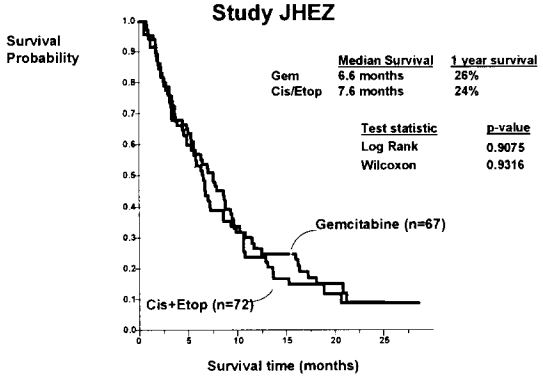
Study	# Pts	RR%	MST (months)	1-yr Survival (%)
H.O.G. (JHBD)	27	33	8.4	37%
Italy (JHBM)	48	54	15.4	59%
South Africa (JHBI)	50	52	13.0	55%
Europe-Canada (P0020)	51	37	10.2	40%
Canada (JHBJ)	46	24	8.4	30%
Total	222	40	11.1	44%

Gemcitabine vs. Cisplatin + Etoposide
Study JHEZ

	Gemcitabine (N=67)	Cisplatin + Etoposide (N=72)	
Response Rate	18%	15%	p=0.819[a]
MST (months)	6.6	7.6	p=0.91[b]
			p=0.93[c]
1-yr Survival	26%	24%	

[a]Fisher's exact [b]Log-Rank [c]Wilcoxon

Survival
Study JHEZ



Gemcitabine vs. Cisplatin + Etoposide: Grade 3-4 Toxicity
Study JHEZ

	Gemcitabine	Cisplatin + Etoposide
Anemia	6%	3%
Granulocytopenia	8% (1% Gr 4)	14% (11% Gr 4)
Thrombocytopenia	1%	0%
Nausea & Vomiting	11%	30%
Alopecia	0%	62%

Gemcitabine + Cisplatin versus Cisplatin + Etoposide
Study JHBR

	Gemcitabine + Cisplatin (N=69)	Cisplatin + Etoposide (N=64)	p-value
Response Rate	41%	22%	p=0.0253[a]
TTP (months)	6.9	4.3	p=0.0147[b] p=0.0078[c]
MST (months)	8.7	7.2	p=0.1885[b] p=0.2186[c]

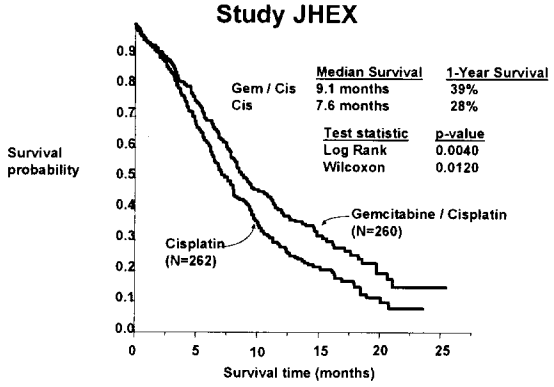
[a]Fisher's Exact [b]Log Rank [c]Wilcoxon

Gemcitabine + Cisplatin vs. Cisplatin
Study JHEX: Interim Analysis

	Gemcitabine + Cisplatin (N=155)	Cisplatin (N=154)	p-value
Response rate	32%	10%	p<0.0001[a]
MDR (months)	6.9	4.2	p=0.2122[b]
			p=0.1434[c]
TTP (months)	5.8	3.7	p=0.0009[b]
			p=0.0001[c]
MST (months)	8.7	7.3	p=0.0766[b]
			p=0.1153[c]

[a]Fisher's Exact [b]Log Rank [c]Wilcoxon

Survival on All Patients (N=522)
Study JHEX



Single Agent Gemcitabine Conclusions

- Single agent gemcitabine is one of the most widely studied agents in NSCLC
- Toxicities such as myelosuppression, nausea, vomiting, alopecia, mucositis, and organ toxicity are minimal, making this an attractive drug for patients who are not candidates for cisplatin combination chemotherapy

Single Agent Gemcitabine Conclusions (Continued)

- Response rates are remarkably reproducible within a narrow range (20 - 25%) worldwide
- Single agent gemcitabine is as effective as cisplatin + etoposide, and associated with less Grade 3-4 granulocytopenia (8% vs. 14%), nausea and vomiting (11% vs. 30%), and alopecia (0% vs. 62%) in a randomized study (JHEZ)

Gemcitabine + Cisplatin Conclusions

- Randomized study of gemcitabine plus cisplatin (N=69) vs. cisplatin plus etoposide (N=64) demonstrates improved response rates (41% vs. 22%; p=0.025[a]) and time to progression (6.9 vs. 4.3 months; p=0.0147[b], p=0.0078[c]) favoring the gemcitabine regimen.

[a]Fisher's Exact [b]Log Rank [c]Wilcoxon

Gemcitabine + Cisplatin Conclusions (Continued)

- Randomized study (JHEX) compared gemcitabine plus cisplatin to cisplatin
- Interim analysis of 309 patients revealed response rates of 32% vs. 10% (p<0.0001[a]) and time to progressive disease 5.8 vs. 3.7 months (p=0.0009[b], p=0.0001[c])
- Analysis of survival for all 522 patients demonstrated MST 9.1 vs. 7.6 months with 1-year survival 39% vs. 28% (p=0.004[b], p=0.012[c])

[a]Fisher's Exact [b]Log Rank [c]Wilcoxon