2024 Summer Institute In Statistics for Clinical & Epidemiological Research

Module 3:

Design, Conduct, and Analysis of Randomized Clinical Trials with Time to Event Primary Endpoints

Lecture 26:

Noninferiority

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Outline

- 2004 Case Study: Anti-folate therapy in NSCLC
  - Prior History
  - Design of Trial
  - Trial Results
- Regulatory Setting
  - Scientific Issues
  - Statistical Issues
- My Conclusions
  - Scientific
  - Statistical
  - Logistical

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Case Study

Prior History

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Second Line Therapy in NSCLC

- Non-Small Cell Lung Cancer
- 1997 Standard of treatment
  - ASCO: No proof of effective second line treatment
  - Best supportive care (BSC)
    - Median survival time: 4 – 5 months
    - One-year survival probability: 12 – 18%
- Clinical trials: TAX 317 and TAX 320
  - Docetaxel 100 mg/m2 (later 75 mg/m2) vs BSC
  - Docetaxel 75 and 100 mg/m2 vs Vinorelbine or Ifosfamide

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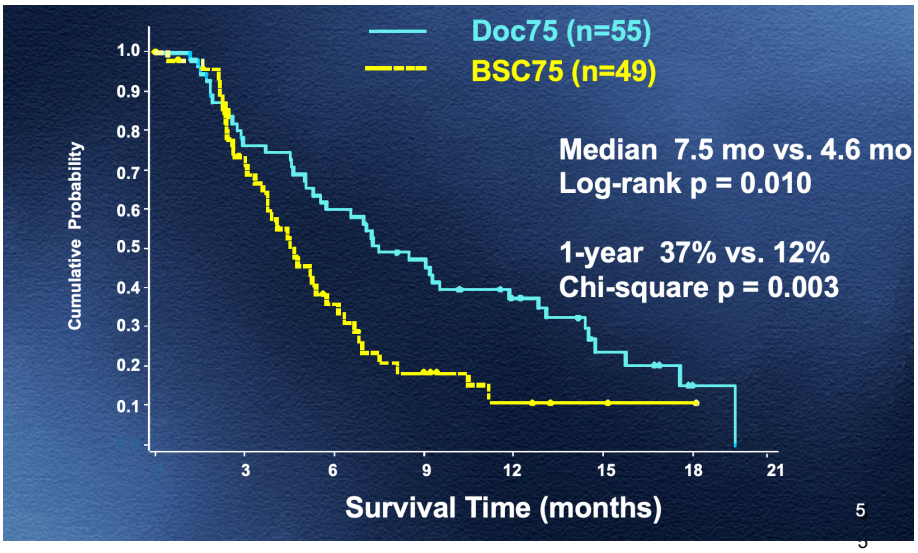
Overall Survival - TAX 317B



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Efficacy Results – TAX 317

	Doc100 (n=49)	Doc75 (n=55)	BSC (n=49)
Partial Response	6%	6%	—
TTPD	—	12.3 wk	7.0 wk
Median Survival	5.9 mo	7.5 mo	4.6 mo
Log-rank p-value	0.780	0.010*	—
One-Year Survival	19%	37%	12%

* **44% reduction in risk of death compared to BSC**

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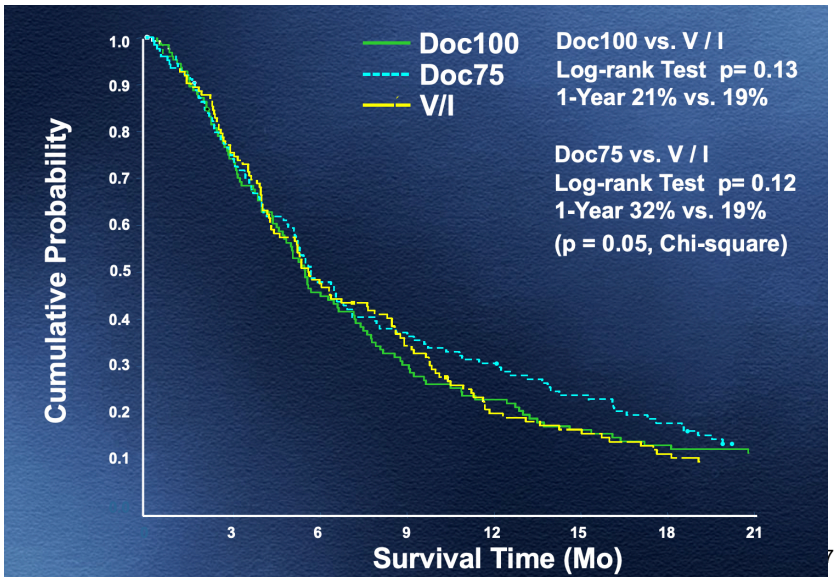
Overall Survival - TAX 320



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Efficacy Results – TAX 320

	Doc100 (n=124)	**Doc75 (n=124)**	V/I (n=122)
Partial Response	11%	**7%**	1%
TTPD	8.4 wk	**8.5 wk**	7.9 wk
Median Survival	5.5 mo	**5.7 mo***	5.6 mo
One-Year Survival	21%	**32%***	19%

*** Log-rank p=0.13, Chi square p=0.05**

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Docetaxel Toxicities (75 mg/m^2)

Toxicity	Any	Grade 3/4
Neutropenia	84.1	65.3
Infection	33.5	10.2
Diarrhea	22.7	2.8
Febrile Neutropenia	-	6.3 *
Neurosensory	23.3	1.7
Alopecia	56.3	-

*** Grade 4 neutropenia with fever >38°C with iv antibiotics or hospitalization**

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Second Line Therapy in NSCLC

- Non-Small Cell Lung Cancer
- 2004 standard of treatment
  - ASCO: Docetaxel for second line treatment
  - (Increasing use of docetaxel as first line)

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Case Study

Pivotal Trial Design

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Intervention

- Pemetrexed
  - Anti-folate
  - Administered with folic acid supplementation

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Pilot Studies

- Single arm studies of pemetrexed with or without other chemotherapy
- First line NSCLC
- Second line NSCLC
- (Also studied in mesothelioma; FDA approval Feb 04)

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2000: On To Phase III

- Ideal
  - Randomized, double blind RCT of new treatment against placebo to show efficacy
- Real world
  - Clinical trials that simultaneously ensure
    - Scientific / statistical credibility
    - Individual ethics of patients on trial
    - Group ethics of patient population

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Design of Pivotal Study

- Randomized with docetaxel active control
- BSC considered not feasible in US
- Combination chemotherapy not feasible due to toxicity
- Docetaxel only approved agent for second line NSCLC

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Potential Hypotheses

- Survival as a primary endpoint
  - Secondary ORR, PFS, TTP, DoR
- Hazard ratio compares survival distributions
- Superiority not necessary for efficacy
  - Efficacy = superior to placebo
- Equivalence study
  - Establish HR approximately 1 with high precision
- Noninferiority study
  - Establish HR not too much greater than 1

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Prespecified Hypotheses

- Superiority or Noninferiority
- Superior if CI excludes HR $\geq$ 1
- Noninferior if CI excludes HR $\geq$??
  - European agency suggested 1.1
    - Power calculation assumed true HR 0.83
    - 400 events (520 subjects) to have 80% power
    - Observe estimated HR < 0.90 to rule out true HR > 1.1
  - Consistent with retaining > 50% docetaxel effect

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Percent Retention Method

- Rothmann, et al. (Jan, 2003)
- Historical trial (TAX 317)
  - Docetaxel : BSC HR 0.56 (95% CI 0.35, 0.88)
- Hypothetically "significant results" from planned trial
  - Pemetrexed : Docetaxel HR 0.90 (95% CI 0.74, 1.10)
- "Induced" Pemetrexed : BSC comparison
  - Use estimates AND standard errors to estimate
    - Pemetrexed : BSC HR and 95% CI
    - Express that ratio as a proportion of Docetaxel : BSC HR
      - Also provide 95% CI for the "percent retention"

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Case Study

2003 Trial Results

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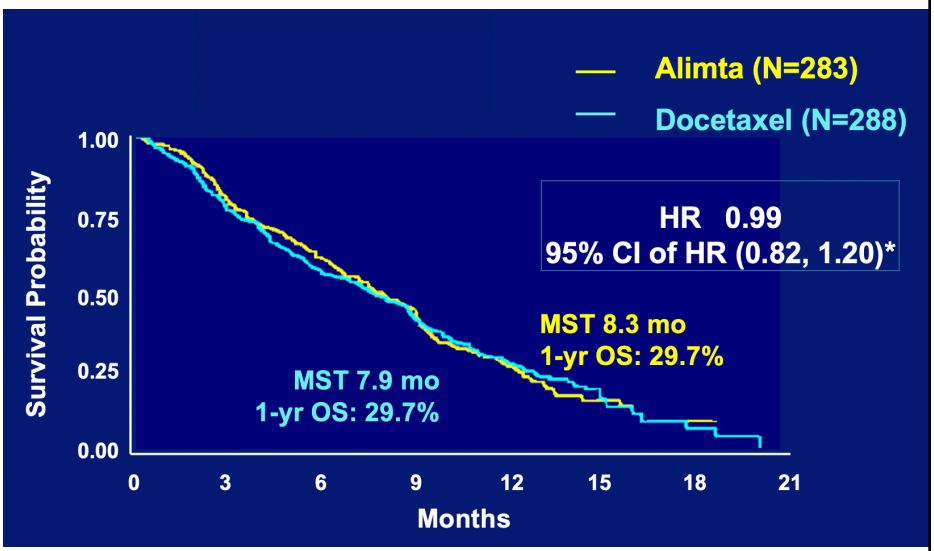
Survival (ITT)



ITT = intent to treat
MST = median survival time

** Does not rule out a margin greater than 1.11*

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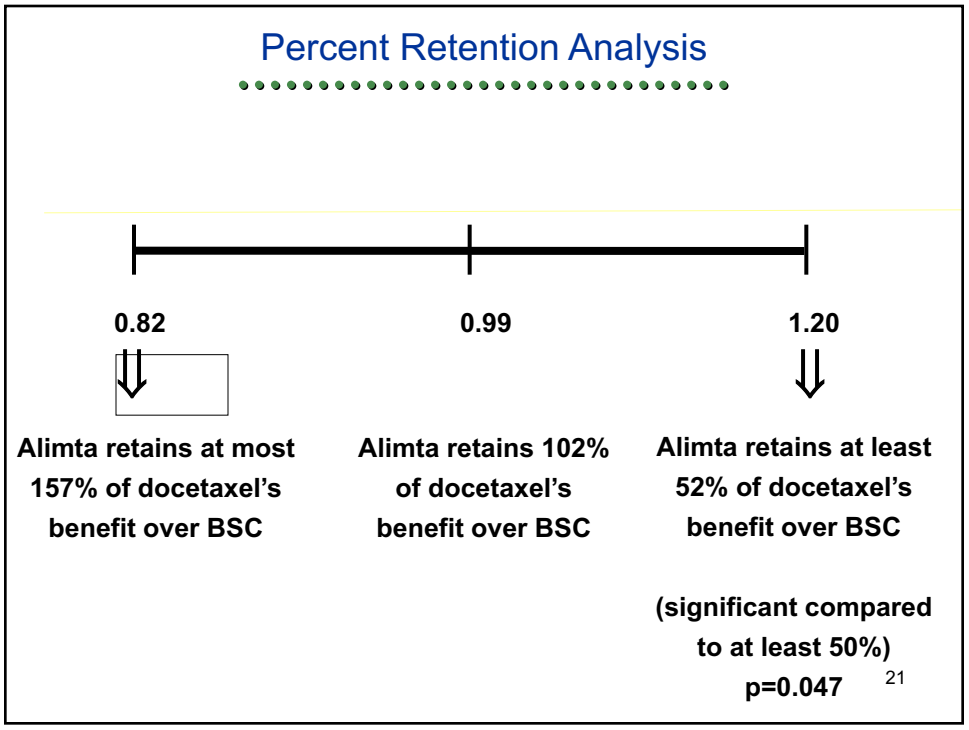
Percent Retention Analysis
0.82
0.99
1.20
Alimta retains at most 157% of docetaxel's benefit over BSC
Alimta retains 102% of docetaxel's benefit over BSC
Alimta retains at least 52% of docetaxel's benefit over BSC
(significant compared to at least 50%)
p=0.047
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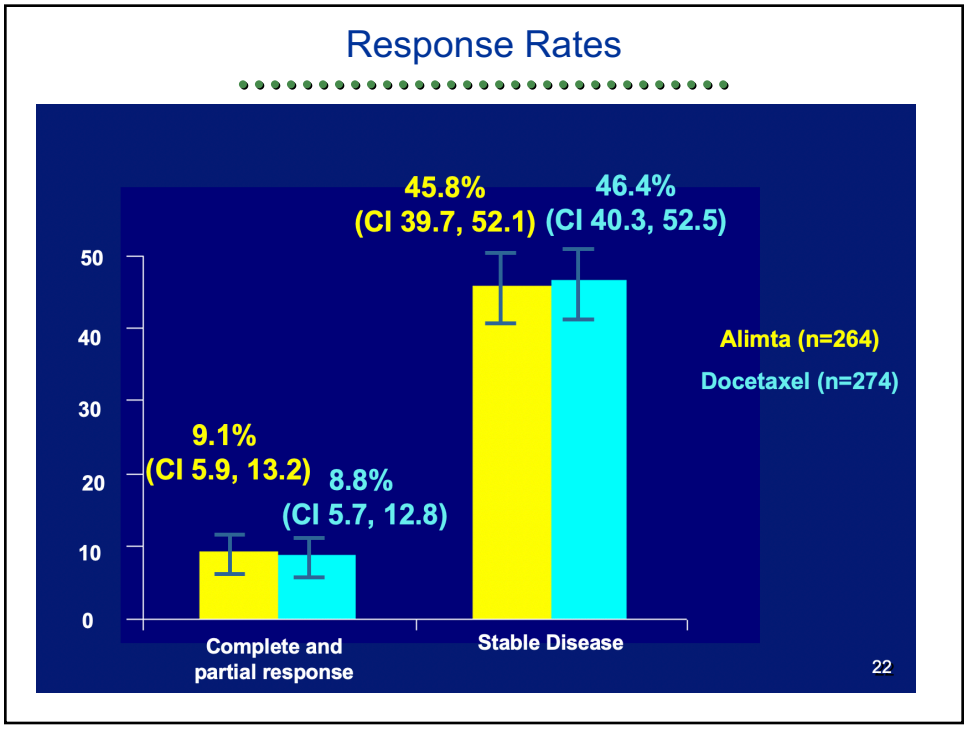
Response Rates
45.8%
(CI 39.7, 52.1)
46.4%
(CI 40.3, 52.5)
50
40
30
20
10
0
9.1%
(CI 5.9, 13.2)
8.8%
(CI 5.7, 12.8)
Alimta (n=264)
Docetaxel (n=274)
Complete and partial response
Stable Disease
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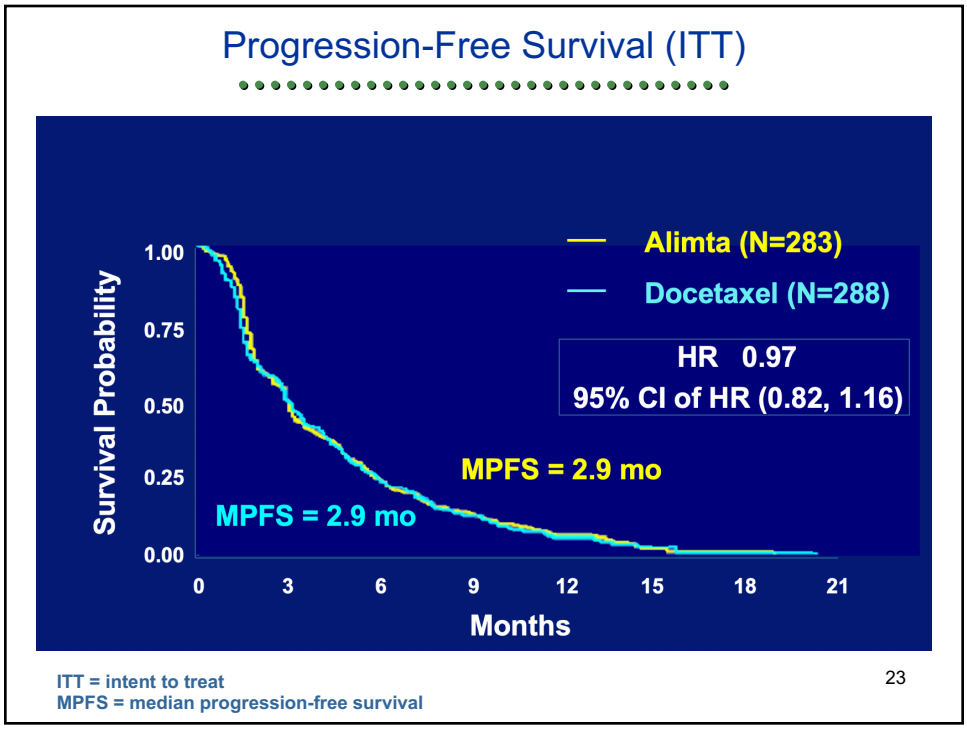
Progression-Free Survival (ITT)
Survival Probability
1.00
0.75
0.50
0.25
0.00
0
3
6
9
12
15
18
21
Months
Alimta (N=283)
Docetaxel (N=288)
HR 0.97
95% CI of HR (0.82, 1.16)
MPFS = 2.9 mo
MPFS = 2.9 mo
ITT = intent to treat
MPFS = median progression-free survival
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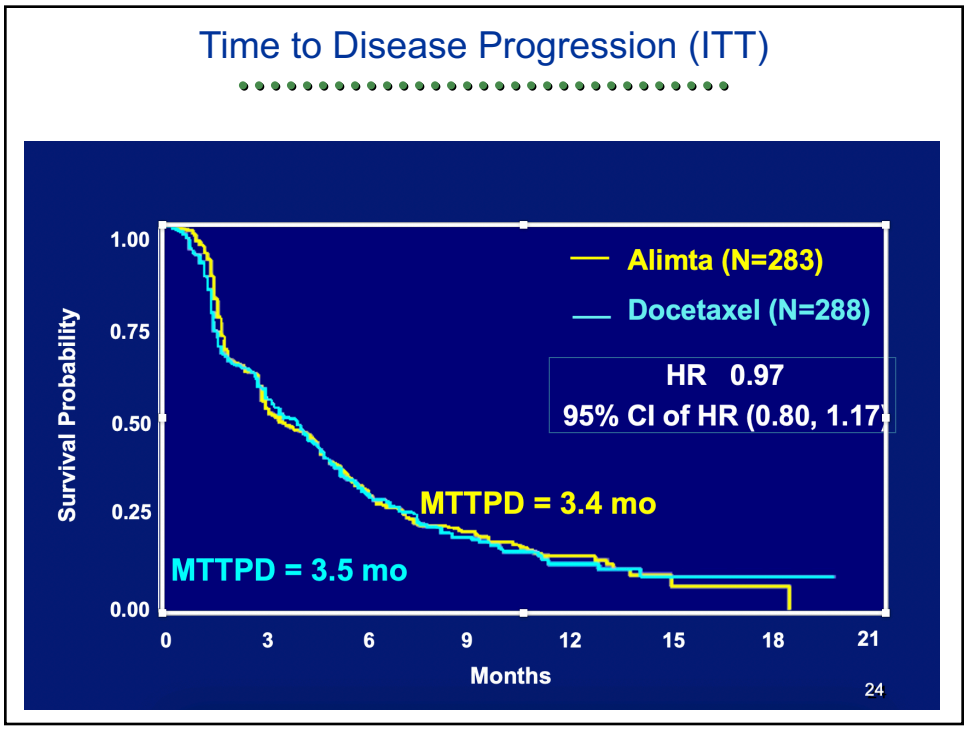
Time to Disease Progression (ITT)
Survival Probability
1.00
0.75
0.50
0.25
0.00
0
3
6
9
12
15
18
21
Months
Alimta (N=283)
Docetaxel (N=288)
HR 0.97
95% CI of HR (0.80, 1.17)
MTTPD = 3.4 mo
MTTPD = 3.5 mo
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Toxicities

	Percent of Patients		
Toxicity	Alimta (N=265)	Docetaxel (N=276)	p-value
Infect w Gr 3/4 Neutropenia	**0**	**5.8**	**<0.001**
Fatigue	15.8	16.7	0.817
Nausea	3.8	2.5	0.466
Vomiting	1.5	1.4	1.0
Stomatitis	1.1	1.1	1.0
Diarrhea	**0.4**	**4.0**	**0.006**
Pulmonary Toxicity	6.8	9.8	0.217
Neurosensory (Gr 2-4)	**0.8**	**4.3**	**0.012**
Alopecia (all grades)	**6.7**	**37.7**	**<0.001**

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Regulatory Setting

Scientific Issues

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Noninferiority Trials

- ICH E-10 Guidelines
  - Active control treatment must truly be active in the study population
- Possible differences from historical trial
  - Patient population
  - (Ancillary) treatments
  - Clinical endpoints
    - Measure summarizing distribution

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Clinically Important Effects

- Therapeutic index
  - New treatment is better than placebo
  - New treatment is safe
- But: Need to be able to mount ethical clinical trial
  - New treatment cannot be too much worse than existing treatment in serious disease

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Clinically Important Effects: ODAC

- Pemetrexed has a more favorable toxicity profile than docetaxel?
  - Unanimous yes
- Supporting efficacy data on tumor response and progression-free survival outweigh the uncertainly about loss of docetaxel survival effect by using post-study pemetrexed?
  - Unanimous yes
- Given the potential confounding effect of crossover and the problem of estimating control effect, is there sufficient evidence to warrant regular approval?
  - 8 No; 5 Yes
- Recommended accelerated but not full approval

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Clinically Important Effects

- Richard Pazdur, MD (FDA, Oncology Drugs):

"The active control in a clinical trial, in this case docetaxel, should have a pronounced and measurable effect, and we should have multiple trials so we could perform meta-analysis. In this case, there is neither. In addition, the primary objective—survival—was not achieved, and the significant crossover from pemetrexed to docetaxel obscures the differences between the two drugs."

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Regulatory Setting

Statistical Issues

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General Issues

- Multiple comparisons
  - Can we simultaneously consider superiority and noninferiority?
    - Science vs Statistics vs Game theory
- Pivotal results
  - Usual Phase III standards:
    - Two independent level 0.025 trials
  - Pivotal study:
    - Level .000625?
    - Level .004?

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Noninferiority Trials

- Issues in setting the "margin"
  - What measure compares distributions?
  - Is the treatment effect random?
  - How much of a decrease in effect is acceptable?
  - Need to avoid "cherry picking" worst historical results
  - How to account for variability in the estimate(s) from historical trials?

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Precedence

- Is the treatment effect random?
  - Ideally use meta-analysis of multiple trials
- How much of a decrease in effect is acceptable?
  - 10%, 20%, retain 50% of active control effect?
- How to account for variability in the estimate(s) from historical trials?
  - Use worst case from historical 95% CI?
    - 95-95 rule
  - Explicitly account for variability in historical trial

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My Conclusions

Scientific Issues

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Active Control Trials

- Rationale for decisions about efficacy when using active controls
- Control treatment is truly active in study population
  - Superiority
  - Noninferiority if a margin can be established
- Control treatment is standard of care
  - Superiority
  - Noninferiority if superior on secondary endpoints

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Noninferiority Trials

- Assessing possible differences from historical trial
- Patient population
  - Baseline risk factors
- (Ancillary) treatments
  - Post randomization factors
- Clinical endpoints
  - Similarity of response under active treatment for new and historical trials
  - Measure summarizing distribution
    - Transitivity

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Baseline Comparison

	TAX 317 Data (N=204)	JMEI (N=571)
Median Age	61	58
Female	33%	28%
Performance status (2)	15%	12%
Stage IV	79%	75%
Number of prior chemo (2)	25%	6%
Prior platinum	100%	91%
Prior taxane	0%	27%
Best response to prior chemo (other than CR/PR)	65%	64%

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Post Study Chemotherapy

Type	No. of Patients in Each Arm (%)	
	Alimta (N=265)	Docetaxel (N=276)
≥ 1 Chemotherapy	126 (47.5)	107 (38.8)
Platinum	9 (3.4)	15 (5.4)
Docetaxel	85 (32.1)	11 (4.0)
Paclitaxel	4 (1.5)	3 (1.1)
Vinorelbine	6 (2.3)	25 (9.1)
Gemcitabine	17 (6.4)	32 (11.6)
Other chemo	22 (8.4)	34 (12.3)
Gefitinib	5 (1.9)	21 (7.6)

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Survival by Post Study Chemotherapy

Patient Population	Alimta (N=265)	MS	Docetaxel (N=276)	MS
No post-study chemo	139	6.2 mo	169	5.0 mo
Any post-study chemo	126	9.8 mo	107	10.8 mo
Post-study docetaxel therapy	85	9.6 mo	11	10.1 mo
Other chemotherapy	41	10.6 mo	96	11.2 mo

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Major Issue

- Did apparent similarity of survival arise solely from the cross-over to the current Standard of Care (docetaxel)?
  - Were we in effect just testing immediate vs delayed docetaxel?
- What to make of
  - More Alimta patients receiving post study chemotx: 48% vs 39%
  - 32% of Alimta patients receiving post docetaxel (vs 4%)
  - Longer median survival estimate for
    - Chemotx following docetaxel (10.8 mo) vs Alimta (9.8 mo)
    - Docetaxel following docetaxel (10.1 mo) vs Alimta (9.6 mo)
    - Other chemotx following docetaxel (11.2 mo) vs Alimta (10.6 mo)

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Time Varying Covariate Analysis

- Adjust for post-study chemo as time varying covariate
- Better (but still not perfect) approach
- Prior to post-study chemo
  - Alimta : Docetaxel HR 0.84 (95%CI 0.65, 1.08)
- Post-study chemo to No post-study chemo
  - Docetaxel arm: HR 1.12 (95%CI 0.81, 1.53)
  - Alimta arm: HR 1.58 (95%CI 1.17, 2.12)
- Clearly no strong benefit of docetaxel after Alimta
  - Did use of Alimta make docetaxel ineffective?
  - Does higher use of docetaxel explain worse survival?

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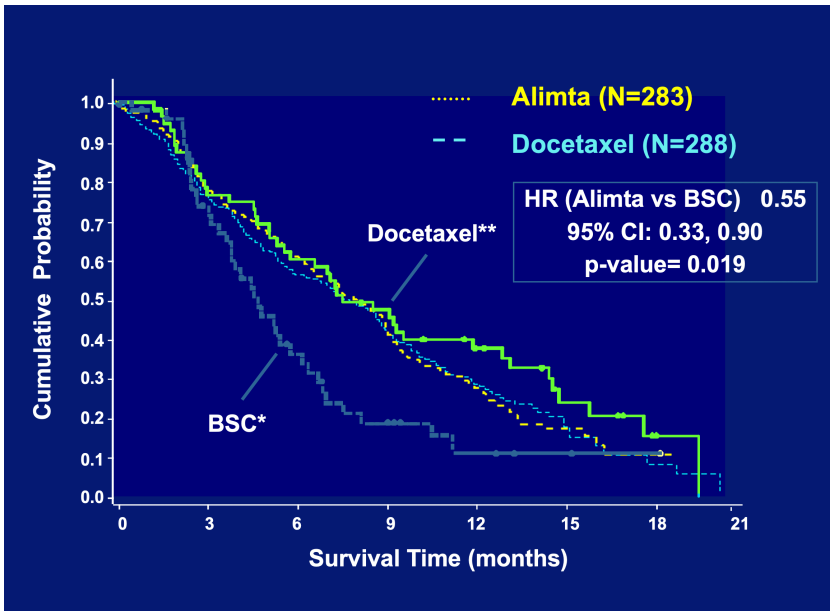
Consistency Across Studies



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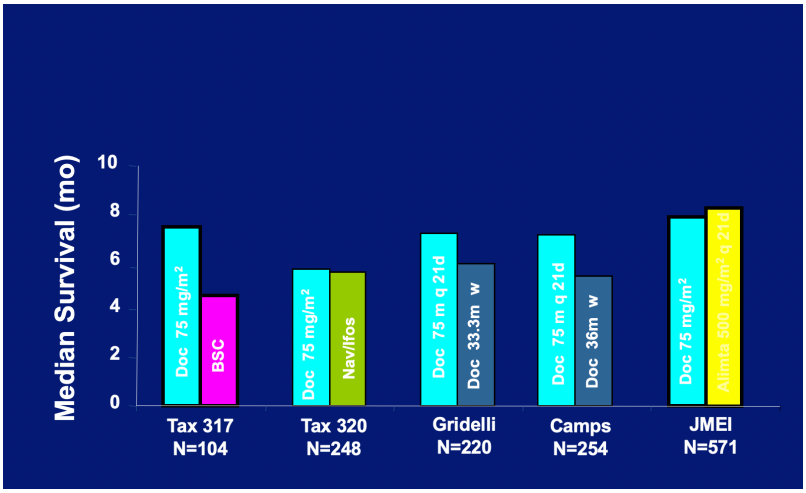
Consistency Across Studies



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Scientific Comparability

- Some issues with comparability are inevitable, however
  - Baseline variables largely similar
    - And adjustment for disparities preserves effect
  - Post randomization treatments differ
    - But no real evidence that conferred advantage
  - Similar response to Docetaxel across studies
    - Suggests no large random treatment effect
  - (Sensitivity analysis)

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My Conclusions

Statistical Issues

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Noninferiority Trials

- Issues with induced hazard ratio estimates
- Transitivity of hazard ratio estimate
  - Proportional hazards or same survival and censoring distribution
- Setting the margin
  - Science versus statistics
  - Game theory
- Multiple comparisons
  - Only a single estimate and CI is used
- Sensitivity analysis

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Transitivity

- The weighting scheme used in the weighted logrank statistics also introduces intransitivity to studies
- The weights are stochastically determined from
  - Each group's survivor function
  - The censoring distribution

$$T = \sum_t \frac{(O_t - E_t)^2}{E_t}$$

$$W = \sqrt{\frac{N_0 + N_1}{N_0 N_1}} \sum_t \frac{n_0 n_1}{n_0 + n_1} \left(\hat{\lambda}_1(t) - \hat{\lambda}_0(t) \right)$$

- Hence we can obtain A > B > C > A
  - Very distressing to regulatory agencies, if not all scientists

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Setting the Margin

- Scientific issues should govern how we would react to particular hazard ratios if we knew the truth
- Statistical issues should govern whether we have discriminated between hypotheses that would cause us to act differently

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Sensitivity Analysis

- We can consider the possibility that the new trial only has P% of the study participants similar to the historical trial
- Assume that neither the active control nor the new treatment are effective in the (100-P)%
- How large can P be and have the new study suggest a statistically significant beneficial effect of Alimta over BSC?
  - Turns out to be related to the percent retention analysis:
    - So long as P = 48%

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My Conclusions

Logistical Issues

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Pivotal Trial

- Clearly there are several unresolved issues
- Comparability of patient population
- Effect of ancillary treatments
- Consistency of treatment effects across studies
- Strength of evidence
  - Induced Alimta : BSC HR 0.55 (95% CI 0.33-0.90)
  - Does not exclude 1 with p-value < .004

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Nevertheless

- There are also mitigating factors
- Alimta did show evidence of anti-cancer effect in mesothelioma
- There is a promising estimate of therapeutic index in NSCLC
  - Best estimate: equal efficacy, better toxicity
- This trial is as large as any reported trial in 2nd line NSCLC
  - Unlikely to do a replication of this trial exactly
  - Could a second trial be done in other settings?
    - First line
    - Combinations?

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Time Marched On: 2008

- First line NSCLC trial Alimta + cisplatin vs gemcitabine + cisplatin
  - HR: 0.94 (95% CI 0.84 – 1. 05)
  - Prespecified subgroups
    - Non squamous cell HR: 0.84 (95% CI 0.74 – 0.96)
    - Squamous cell HR: 1.23 (95% CI 1.00 – 1. 51)
- Retrospective (*post hoc)* analysis of 2nd line Alimta vs docetaxel
  - Adjusted for ECOG PS, time since prior tx, stage, sex
  - HR: 0.93 (95% CI 0.76 – 1. 13) (2004 ODAC, no adj for sex)
  - Subgroups motivated by 1st line results
    - Non squamous cell HR: 0.78 (95% CI 0.61 – 1.00)
    - Squamous cell HR: 1.56 (95% CI 1.08 – 2.26)
- FDA approval for non squamous NSCLC
  - 1st line: Alimta (+ folate) + cisplatin
  - 2nd line: monotherapy (+ folate)

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What About Censoring at Change of Therapy

- This case provides data about possible impact of the approach based on censoring subjects when they change therapies
  - Overall survival was primary endpoint pre specified in protocol
- Censoring at change of therapy suggested clear noninferiority
  - Prior to post-study chemo
    - Alimta : Docetaxel HR 0.84 (95%CI 0.65, 1.08)
- But on the full analysis, there were suggestions of differential behavior of chemotherapy in general and docetaxel in particular
- The per randomization analysis can be trusted, even if still leaving a dilemma re standards for noninferiority
  - Alimta : Docetaxel HR 0.99 (95%CI 0.82, 1.20)

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