# HISTORY OF PLATINUM IN LUNG CANCER

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# PLATINUM:
# AN ONCOLOGIC SUCCESS STORY

# HISTORY OF PLATINUM

- Barnett Rosenberg discovered the effect of Platinum co-ordination complexes on E-coli cell growth in an electrolysis experiment
- Cisdiamminedichloroplatinum demonstrated a wide spectrum of activity against experimental tumors
- First entered human clinical trials in 1972
- Early toxicity outweighed therapeutic advantage
- Germ cell tumors

# CLINICAL UTILITY OF PLATINUM: FIRST-LINE THERAPY

1) Testis cancer
2) Ovarian cancer
3) SCLC
4) NSCLC
5) Bladder cancer
6) Head and neck cancer
7) Cancer of cervix
8) Esophageal cancer
9) Osteosarcoma
10) Thymoma
11) Colorectal cancer (oxaliplatin)

# PLATINUM IN LUNG CANCER

- **SCLC – no current competition from non-cytolytic agents**
- **NSCLC**
  - **Single agent cisplatin first published 1976 (CA Treat Rep 60:1341-1346, 1976)**
  - **Cisplatin combination chemotherapy**
    - **CAP (Mayo Clinic) CA Treat Rep 62:1207-1210, 1978**
    - **Cisplatin + vindesine (MSKCC) Ann Int Med 95:414-420, 1981**
  - **Antiemetics**

# ADJUVANT CHEMOTHERAPY

# IALT RESULTS*

| | Control | Chemotx | p value |
|---|---|---|---|
| No. pts. | 932 | 935 | |
| M.S.T. | 44.4 mos. | 50.8 mos. | |
| DFS (median) | 30.5 mos. | 40.2 mos. | |
| 2 yr. surv. | 67% | 70% | |
| 5 yr. surv. | 40.4% | 44.5% | 0.03 |

*LeChevalier T, et al.: NEJM 350:351-360, 2004

# LUNG ADJUVANT CISPLATIN EVALUATION (LACE)*

- Individual patient data from ALPI, ANITA, BLT, IALT and JBR10
- Median F/U 5.1 years
- Survival benefit 3.9% at 3 years and 5.3% at 5 years

  H.R. 0.89 (0.82 – 0.96; p = 0.03)
- Improved DFS H.R. 0.84 (0.78 – 0.90; p < 0.001)
- Results by surgical stage

| Stage | H.R. (95% C.I.) |
|---|---|
| IA | 1.41 (0.96 – 2.09) |
| IB | 0.92 (0.78 – 1.10) |
| II | 0.83 (0.73 – 0.95) |
| III | 0.83 (0.73 – 0.95) |

*Pignon JP, et al.: JCO 26:3552-3559, 2008

# CHEMOXRT

# CALGB STAGE III NSCLC PHASE III STUDY

RANDOMIZE

XRT (60 Gy over 6 weeks)

Cisplatin 100 mg/m$^2$ day 1 and 29 plus Vinblastine 5 mg/m$^2$ x 5 followed by 60 Gy XRT

1. One hundred fifty-five evaluable patients
2. Stratified according to histology
3. Eligibility: PS 0 or 1, less than 5% wt. loss, no scalene or supraclavicular node

# UPDATE ON CALGB 8433*

| | XRT | chemoXRT |
|---|---|---|
| MST: | 9.6 mos. | 13.7 mos. |
| 1 yr: | 40% | 54% |
| 3 yr: | 10% | 24% |
| 5 yr: | 6% | 17% |
| 6 yr: | 6% | 17% |
| 7 yr: | 6% | 13% |

* Dillman RO, et al.: JNCI 88:1210-1215, 1996

# RTOG 9410: PHASE III STUDY OF CHEMOXRT

RANDOMIZE

- Cisplatin + Vinblastine x 2 followed by XRT (63 Gy)
- Cisplatin + Vinblastine x 2 with concurrent XRT (63 Gy)
- Cisplatin + oral VP-16 + concurrent XRT (69.6 Gy bid)

# SEQUENTIAL VERSUS CONCURRENT CHEMOTX: RTOG 9410*

| | M.S.T. | M.S.T. | 4 yr. surv. | 5 yr. surv. | p value | 3-4 esoph |
|---|---|---|---|---|---|---|
| Sequential | 13.8 mos. | 14.6 | 12% | 10% | | 4% |
| Concurrent | 17.5 mos. | 17 | 21% | 16% | 0.046 | 22% |
| Concurrent bid | 19.7 mos. | 15.6 | 17% | 13% | 0.296 | 45% |

*Curran WJ, et al.: JNCI 103:1-9, 2011

# TOXICITY OF CONCURRENT CHEMOXRT IN STAGE III NSCLC: RTOG*

- 585 patients from 4 RTOG studies
- Grade 3-4 esophagitis in 37% and grade 2 39%
- Late pulmonary toxicity (grade 3-4) in 19% and 47% grade 2; usually seen between months 3 to 12 but can occur up to 18 months and beyond

* Werner-Wasik M, et al.: Proc ASCO 21:299, 2002 (abstr #1192)

# STAGE IVB NSCLC

# E1594 Schema

**Stratification**

**Performance status 0-1 vs. 2**

**Weight loss in previous 6 months <5% vs. ≥ 5%**

**Disease stage IIIB or IV**

**Presence or absence of brain metastases**

**R A N D O M I Z E**

**Arm A:** Cisplatin + Paclitaxel

Paclitaxel: 135 mg/m$^2$ over 24 hours, day 1

3-week cycle

**Arm B:** Cisplatin + Gemcitabine

Gemcitabine: 1,000 mg/m2 days 1,8,15

Cisplatin: 100 mg/m$^2$ day 1

4-week cycle

**Arm C:** Cisplatin + Docetaxel

Docetaxel: 75 mg/m$^2$ day 1

Cisplatin: 75 mg/m$^2$ day 1

3-week cycle

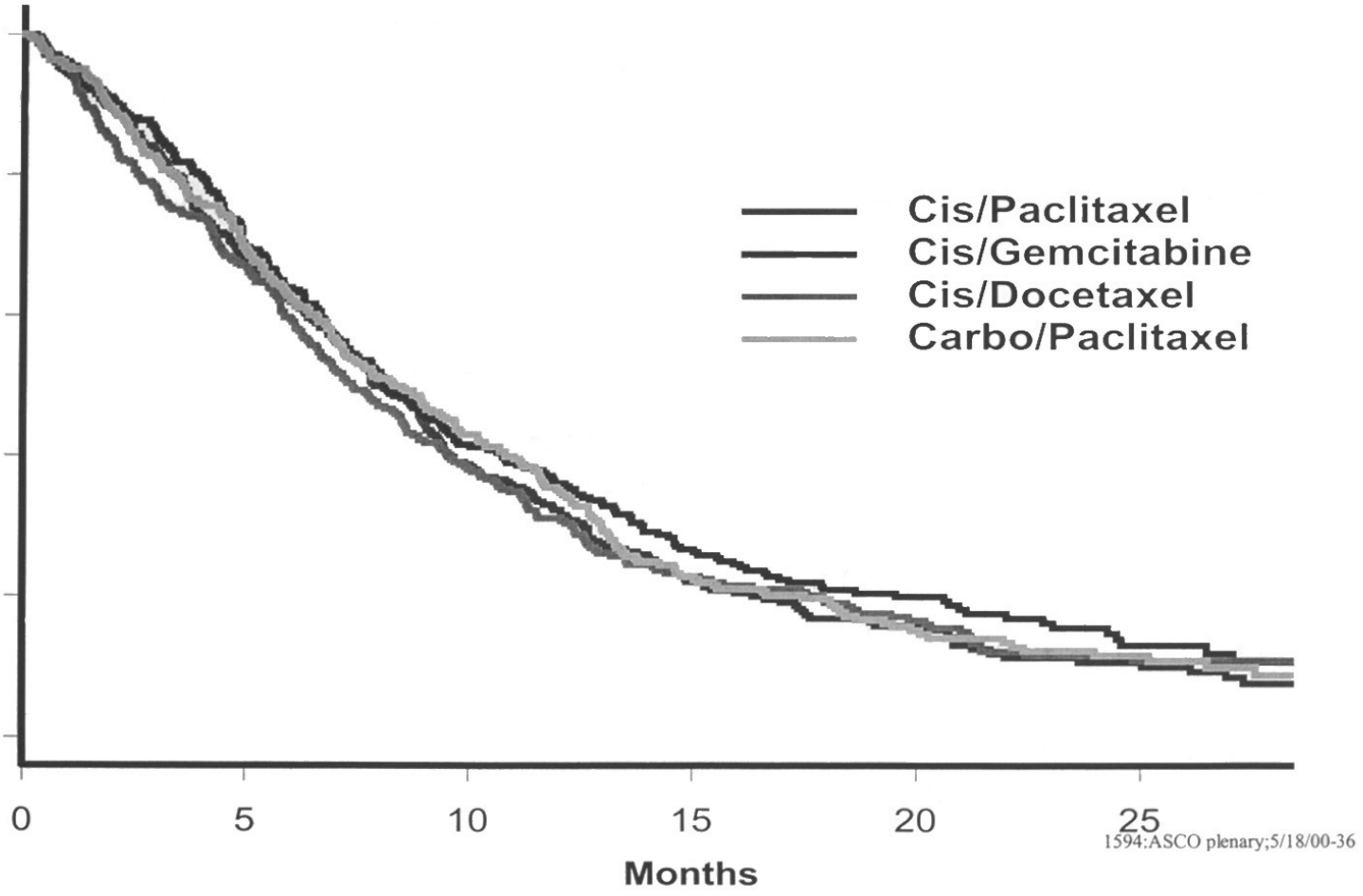
**Arm D:** Carboplatin + Paclitaxel

Paclitaxel: 225 mg/m$^2$ over 3 hours, day 1

Carboplatin: AUC 6.0 day 1

3-week cycle

# Survival by Treatment Group
# All Randomized Cases




1594:ASCO plenary;5/18/00-36

# OTHER PLATINUM DOUBLETS – PHASE III

| Study | Drugs | # Pts. | Resp. Rate | MST (mos.) |
|---|---|---|---|---|
| SWOG 9503 | Cis-VNR | 202 | 28% | 8 |
| | Carbo-Taxol | 208 | 25% | 8 |
| Scagliotti ILCP | Cis + VNR | 201 | 30% | 9.5 |
| | Cis + Gem | 205 | 30% | 9.8 |
| | Carbo + Taxol | 201 | 32% | 9.9 |
| Tax 326 | Cis + VNR | 404 | 25% | 10.1 |
| | Cis + TXT | 408 | 32% | 11.3 |
| | Carbo + TXT | 402 | 24% | 9.4 |

# META-ANALYSIS OF CISPLATIN VERSUS CARBOPLATIN*

- Eight trials (2,948) were identified, five of which investigated drug regimens containing a new agent plus cisplatin versus carboplatin
- Higher objective response rate with cisplatin ($p = 0.001$)
- For all eight trials, 5% improvement in overall survival with cisplatin ($p = 0.52$); however, for the five trials (2,141 randomized patients) with a new agent, 11% superior survival with cisplatin ($p = 0.039$; HR 1.106; 95% C.I. 1.005 to 1.218)

- *Hotta K, et al.: JCO 22:3852-3859, 2004

# 22 YEARS OF PHASE III TRIALS FOR PATIENTS WITH NSCLC: SOBERING RESULTS*

- Co-authors include Mark Green, David Johnson, David Gandara, Michael O'Connell, Francis Shepherd and Bruce Johnson for co-op groups
- Review of phase III trials in North America from 1973-1994
- 33 trials in 8,434 patients; 23 included a platinum compound
- Five of 33 trials demonstrated a statistically significant difference in survival with median increase 2 months (range 0.7 to 2.7 months)

*Breathnach O, et al.: J Clin Oncol 19:1734-1742, 2001

# Study Design*

**Randomization Factors**

- Stage
- PS
- Gender
- Histo vs cyto dx
- Brain mets hx

R

Cisplatin 75 mg/m$^2$ ,day 1 plus
Pemetrexed 500 mg/m$^2$, day 1

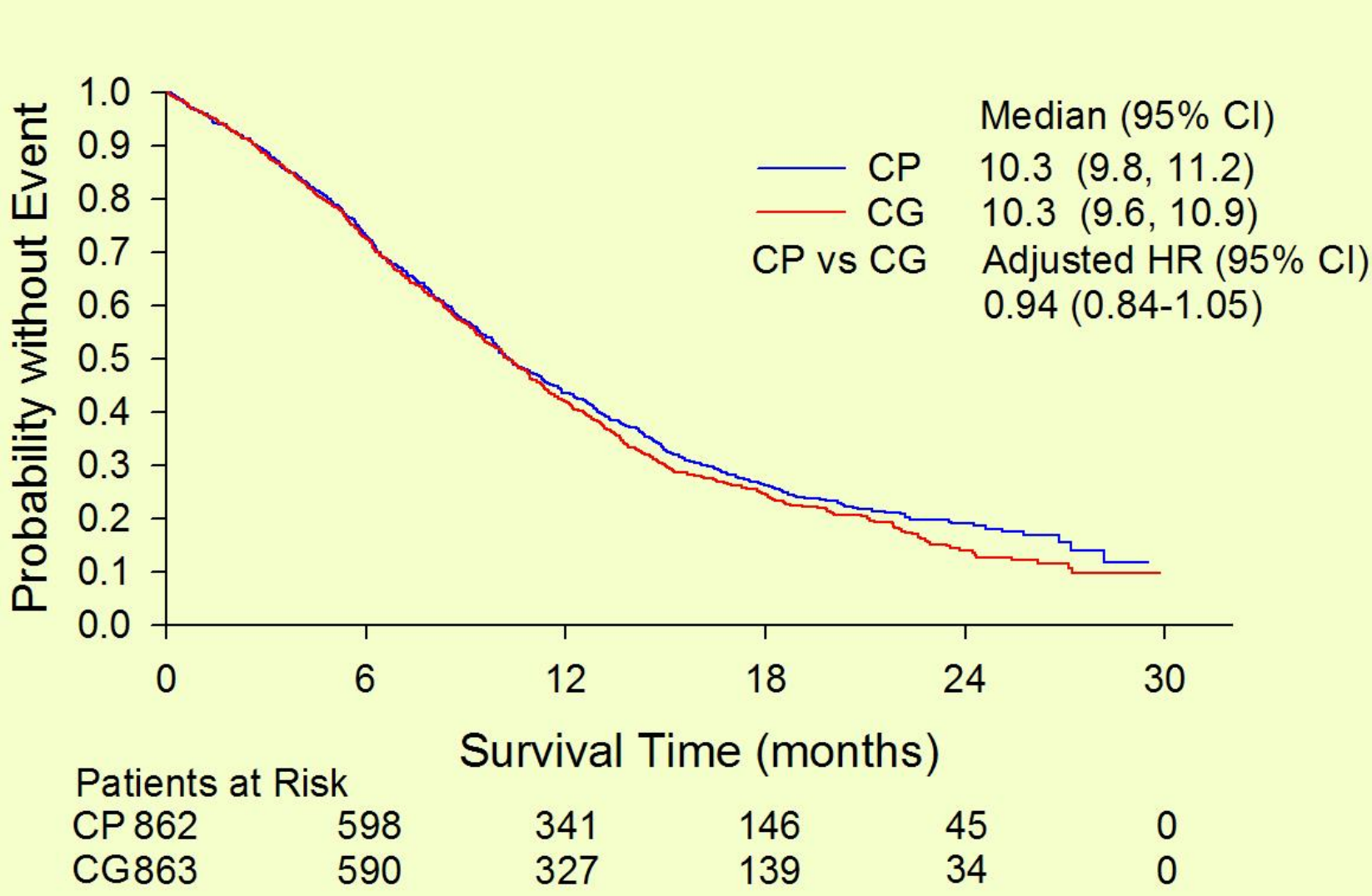
Each cycle repeated
q3weeks up to 6 cycles

Cisplatin 75 mg/m$^2$ day 1 plus
Gemcitabine 1250 mg/m$^2$ day 1 & 8

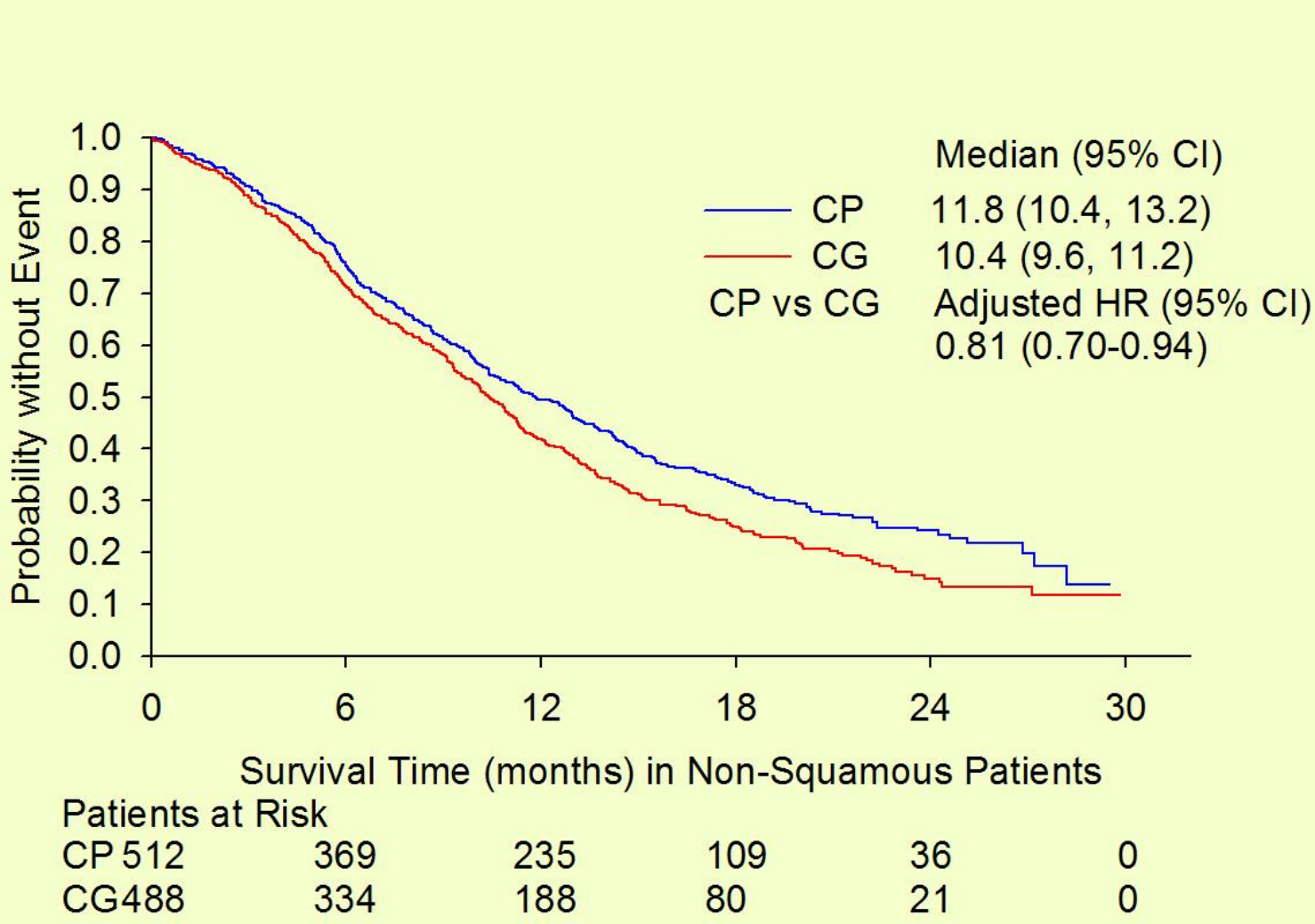
Vitamin B12, folate, and dexamethasone given in both arms

*Scagliotti G, et al.: JCO 26:3543-3551, 2008

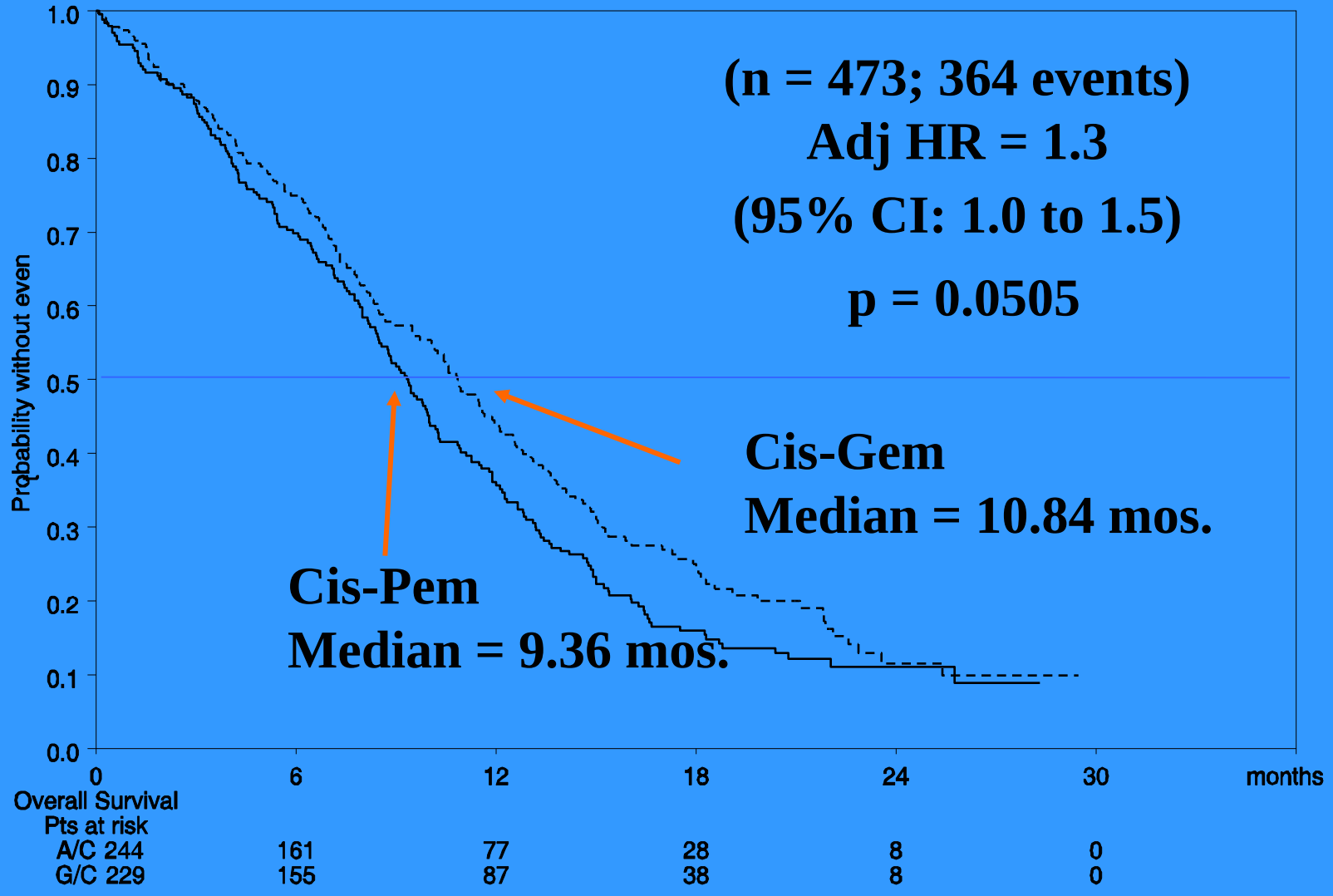
# Overall Survival



# Overall Survival in Patients with Adenocarcinoma or Large Cell Ca

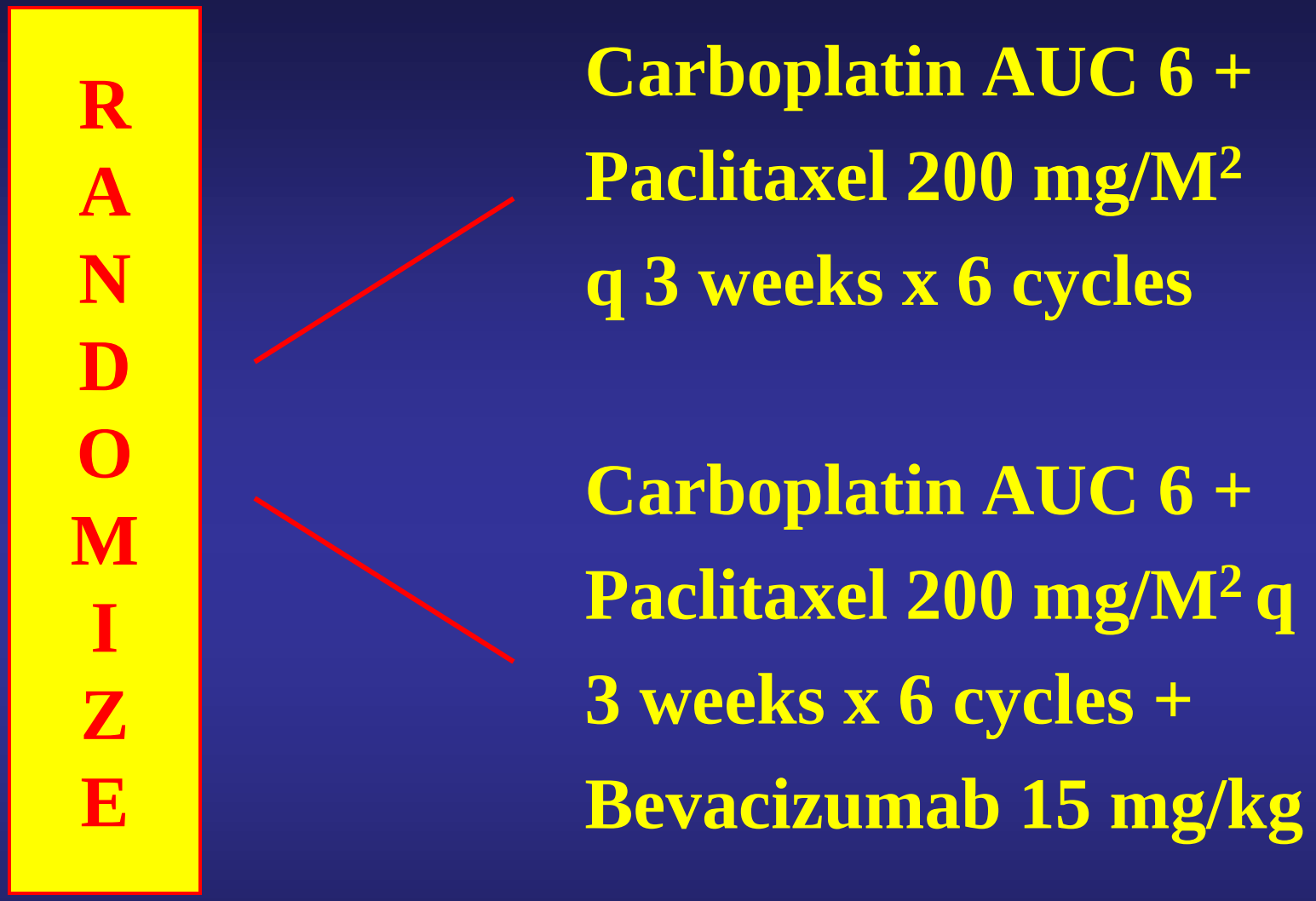


# OVERALL SURVIVAL IN PATIENTS WITH SQUAMOUS CELL CARCINOMA



# RELATIONSHIP OF SMOKING AND SURVIVAL

- M.S.T. for never smokers 15.9 months versus 10.0 months for former or current smokers on pemetrexed arm ($p < 0.001$; HR 1.74)
- Similar results on gemcitabine arm 15.3 versus 10.3 months

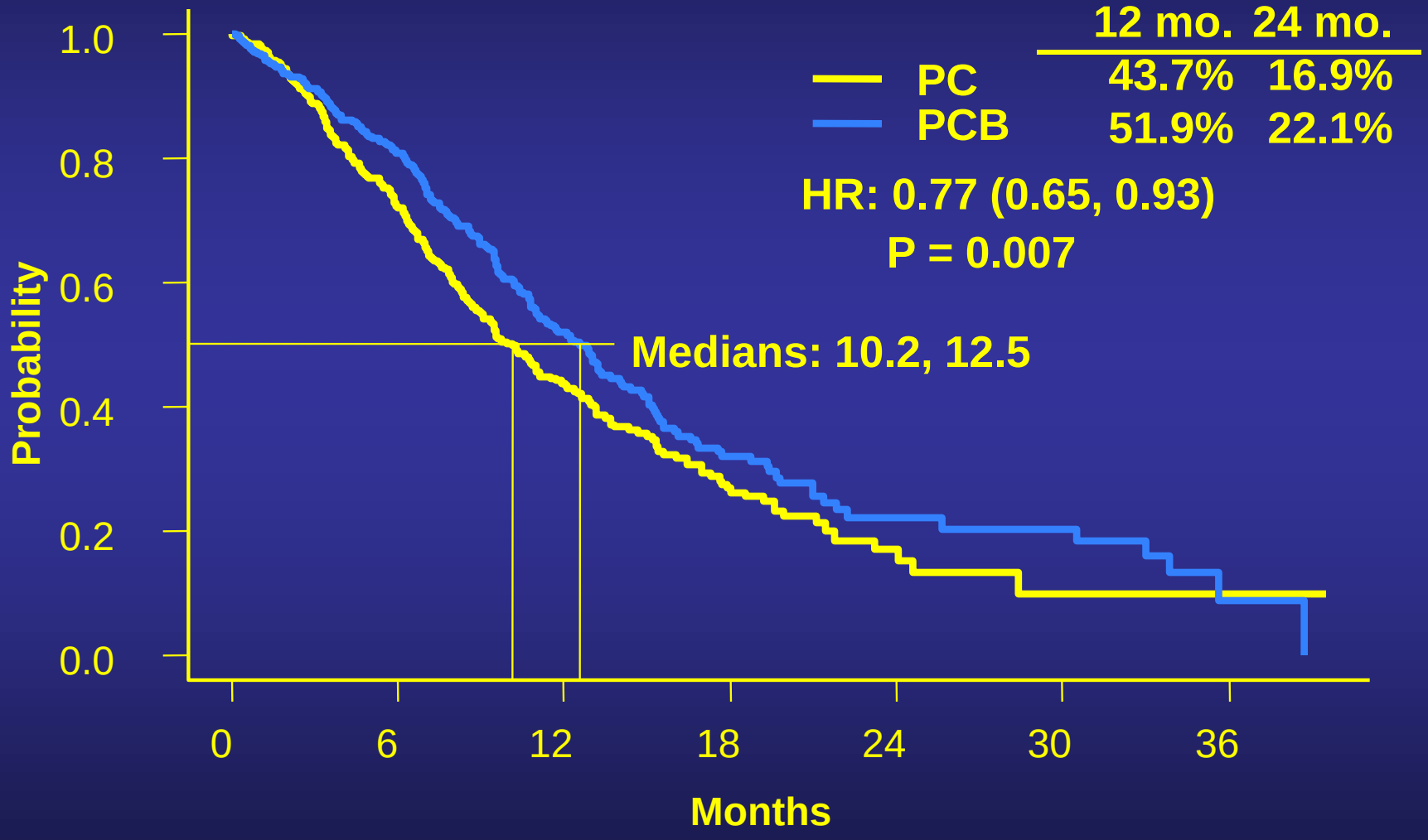



* Excludes squamous cell, ECOG PS > 1, CNS mets, history of thrombosis or active hemoptysis

# E4599 RESULTS*

| | Carbo + Pac | Carbo + Pac + Bev | p value |
|---|---|---|---|
| No. pts. | 444 | 434 | |
| Resp. rate | 15% | 35% | < 0.0001 |
| PFS (mos.) | 4.5 | 6.2 | < 0.001 |
| M.S.T. (mos.) | 10.3 | 12.3 | 0.003 |
| 1 yr. surv. | 44% | 51% | |
| 2 yr. surv. | 15% | 23% | |

# E4599: Overall Survival



# PHASE III TARGETED THERAPY

| AGENT | NO. PTS. | RESULTS |
|---|---|---|
| Bexarotene | 1,200 | Neg |
| MMPI | 2,000 | Neg |
| Erlotinib | 2,000 | Neg |
| Gefitinib | 2,000 | Neg |
| PKC inhibitor | 1,000 | Neg |
| Lonafarnib (FTI) | 700 | Neg |
| Motesanib | 1,090 | Neg |

# PHASE III TARGETED THERAPY (cont'd)

| AGENT | NO. PTS. | RESULTS |
|---|---|---|
| Thalidomide | 700 | Neg |
| Sorafenib | 1,800 | Neg |
| PF-3512676 | 1,667 | Neg |
| NOV-002 | 902 | Neg |
| ASA-404 | 1,299 | Neg |
| Figitumumab (IGF-IR) | 820 | Neg |
| Celecoxib | 561 | Neg |
| TOTAL | 17,744 | |


CIGARETTES

# DAVID LETTERMAN TOP TEN LIST

# TOP TEN WAYS THE TOBACCO INDUSTRYCAN IMPROVE THEIR IMAGE

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10. Sponsor inspirational youth singing group: The Nic-O-Teens

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9. Suggest new strategy for financially strapped social security: free cigarettes for everyone over age 65

# TOP TEN WAYS THE TOBACCO INDUSTRY CAN IMPROVE THEIR IMAGE

8. New Philip Morris advertisement: Lung cancer – perhaps. Great taste – you betcha!

# TOP TEN WAYS THE TOBACCO INDUSTRY CAN IMPROVE THEIR IMAGE

7. **Remind smokers that because of their high mutational load, they will be more likely to respond to an immune checkpoint inhibitor when they get lung cancer**

# TOP TEN WAYS THE TOBACCO INDUSTRY CAN IMPROVE THEIR IMAGE

6. Have Marlboro man come out of the closet

# TOP TEN WAYS THE TOBACCO INDUSTRY CAN IMPROVE THEIR IMAGE

5. **Replace Surgeon General's warning with "Smoke up, you crazy bastards"**

# TOP TEN WAYS THE TOBACCO INDUSTRY CAN IMPROVE THEIR IMAGE

4. Start selling something a little less dangerous – like crack cocaine

# TOP TEN WAYS THE TOBACCO INDUSTRY CAN IMPROVE THEIR IMAGE

3. New series of ads inwhich Joe Camel wears “the patch”

# TOP TEN WAYS THE TOBACCO INDUSTRY CAN IMPROVE THEIR IMAGE

2. President Clinton pondering about Monica: "Should a gentleman offer a lady a Tiparillo?"

# TOP TEN WAYS THE TOBACCO INDUSTRY CAN IMPROVE THEIR IMAGE

1. Re-run Sharon Stone's police interrogation scene from Basic Instinct