

Case # 5-Stage IV NSCLC with Bone Metastases: What is the Role of Bisphosphonates?

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Advanced and Metastatic NSCLC

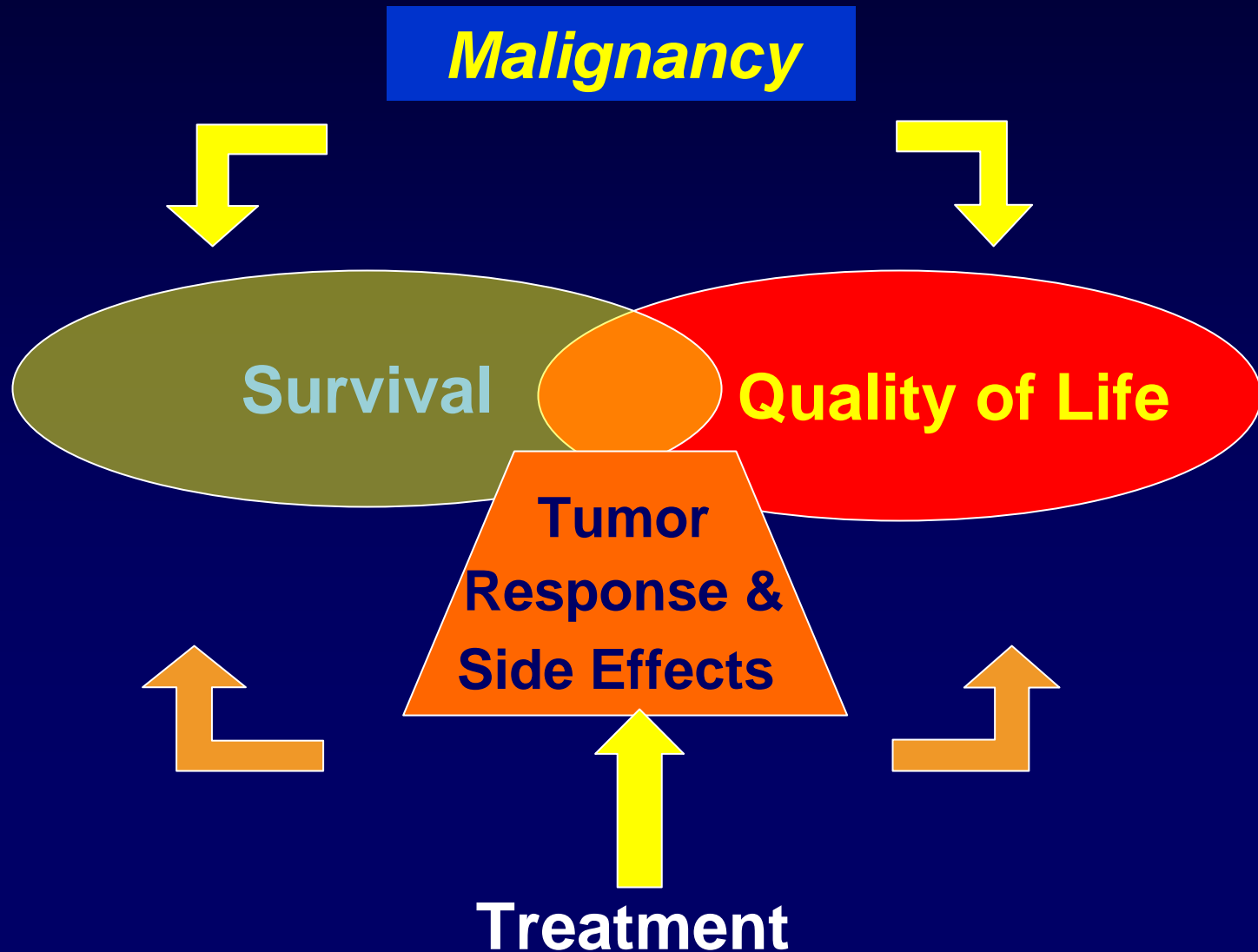
Treatment!

- Some impact on survival but
- Active in any stage of the disease
- Improves symptom control
- Improves Quality of Life
- Active in second line and possibly third line
- Cost-effective

ALL BASED ON A LARGE BODY OF EVIDENCE

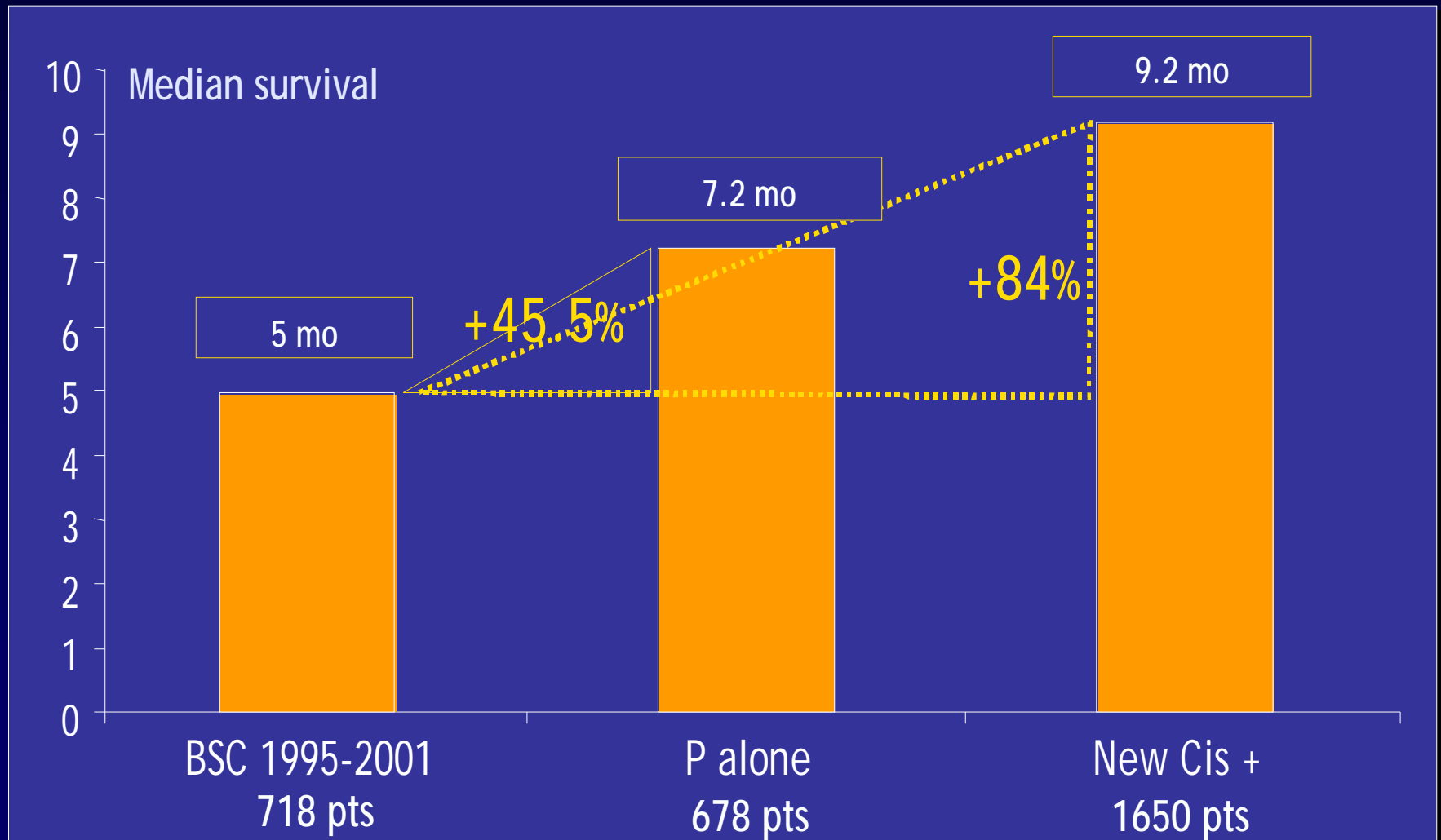
ENDPOINTS AND TREATMENT

Relationships and Role of Patient Reported Outcomes



NSCLC Survival: Supportive Care and Chemotherapy 1991- 2008

(All Stages Advanced N = 10,995 / 9361)

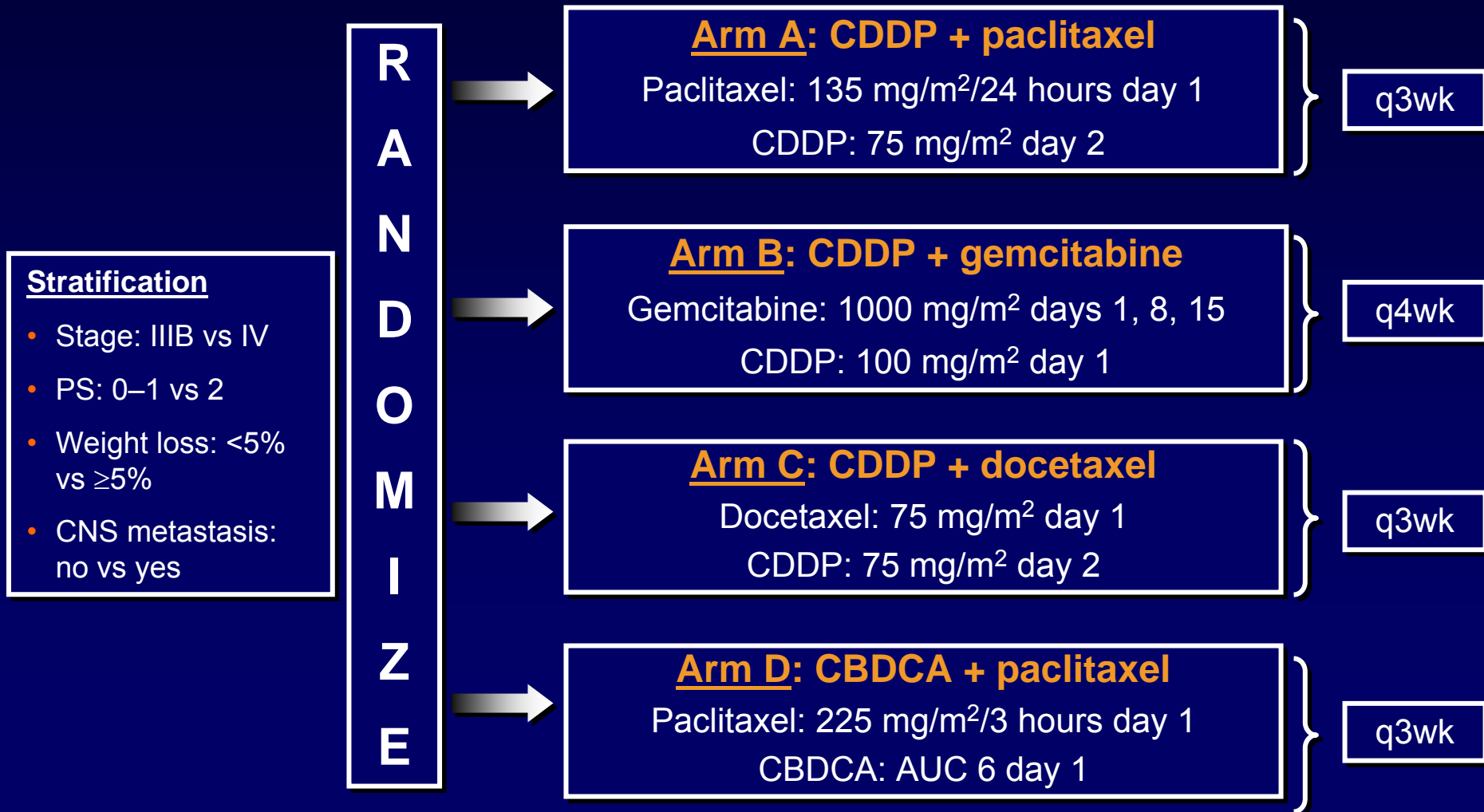


WHAT CHEMOTHERAPY ?

PS1, Symptomatic, Fatigue, Pain

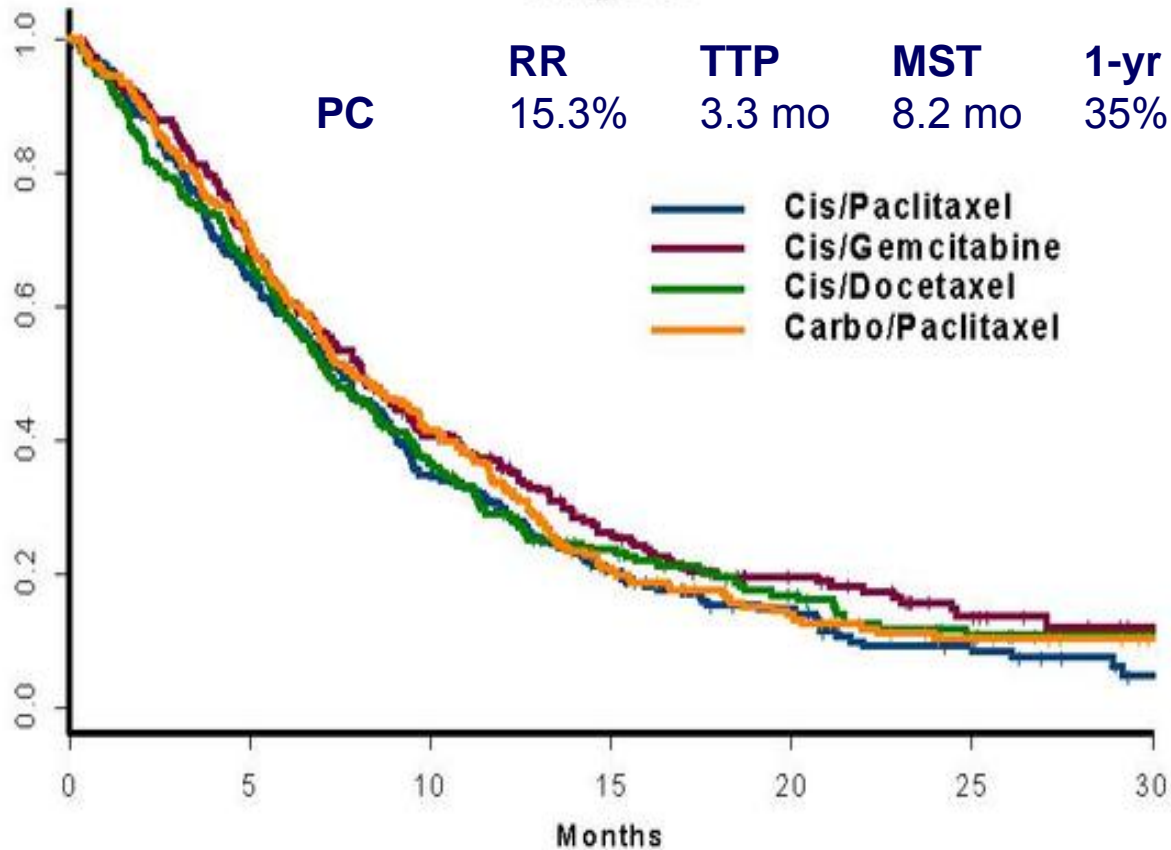
- Pacli + Carbo/Cis
- Pacli + Carbo/Cis +Bev
- Doce + Carbo or Cis
- Gem + Carbo or Cis
- Pemetrexed + Cis
- Bev + anything other than
- Other

ECOG 1594: Study Design



E1594

Survival by Treatment Group
Stage IV



Have we reached the ceiling for improved benefit of cytotoxic chemotherapy in advanced NSCLC?

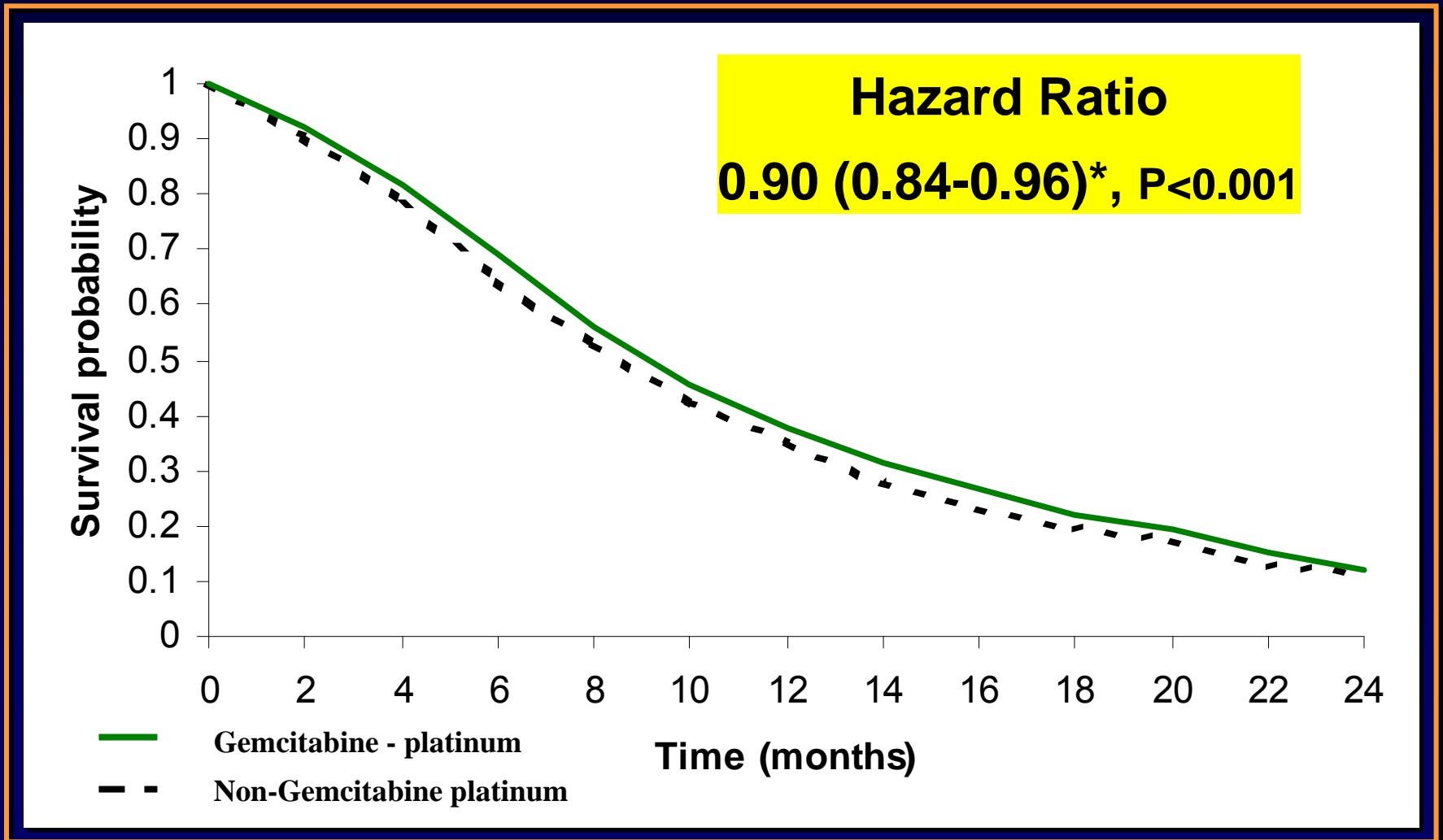
More of Targets Later

WHAT CHEMOTHERAPY ?

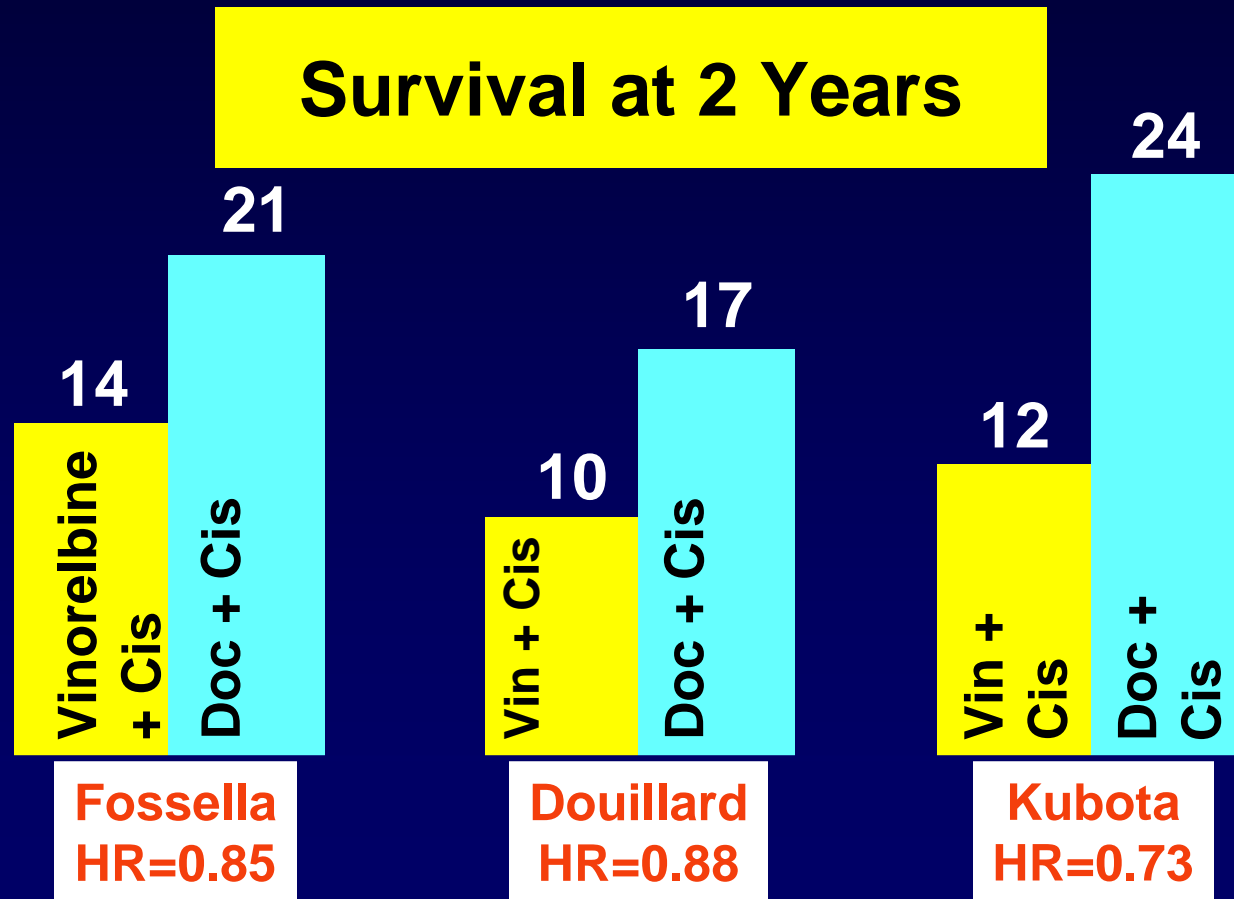
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Gemcitabine Meta-analysis Overall Survival [Le Chevalier & Scagliotti]: Lung Cancer 2005

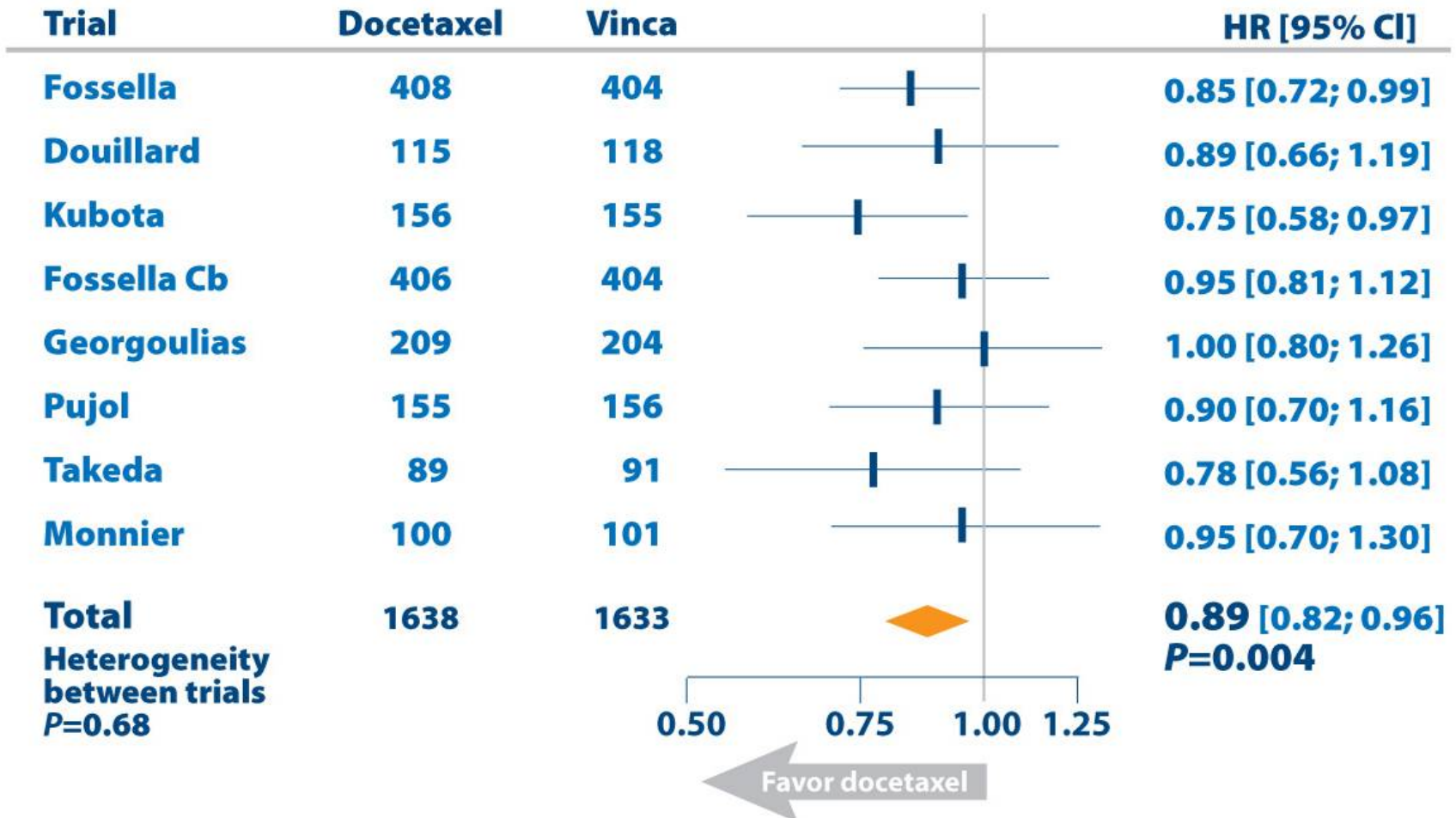


First-Line Docetaxel



FOSELA et al. *J Clin.Oncol.* 2003;21:3016-3024; **DOUILLARD** et al. *Ann Oncol.* 2005;16:81-89;
KUBOTA et al. *J Clin Oncol.* 2004;22:254-261.

Docetaxel Overview: Overall Survival



Cisplatin vs Carboplatin NSCLC

- 5 Randomized studies:

authors

- Klastersky
- Jelic
- Gatzemeier
- Schiller
- Belani

outcome

- similar
- carbo superior
- ?carbo inferior
- similar
- similar

European Guidelines: First-Line Therapy

- PS 0-1:

- Platinum-based chemotherapy with vinorelbine, gemcitabine, or a taxane prolongs survival, improves QOL, and controls symptoms for patients with good PS

ESMO (Ann Oncol. 2005; 16 (Suppl 1): 128 – 9)

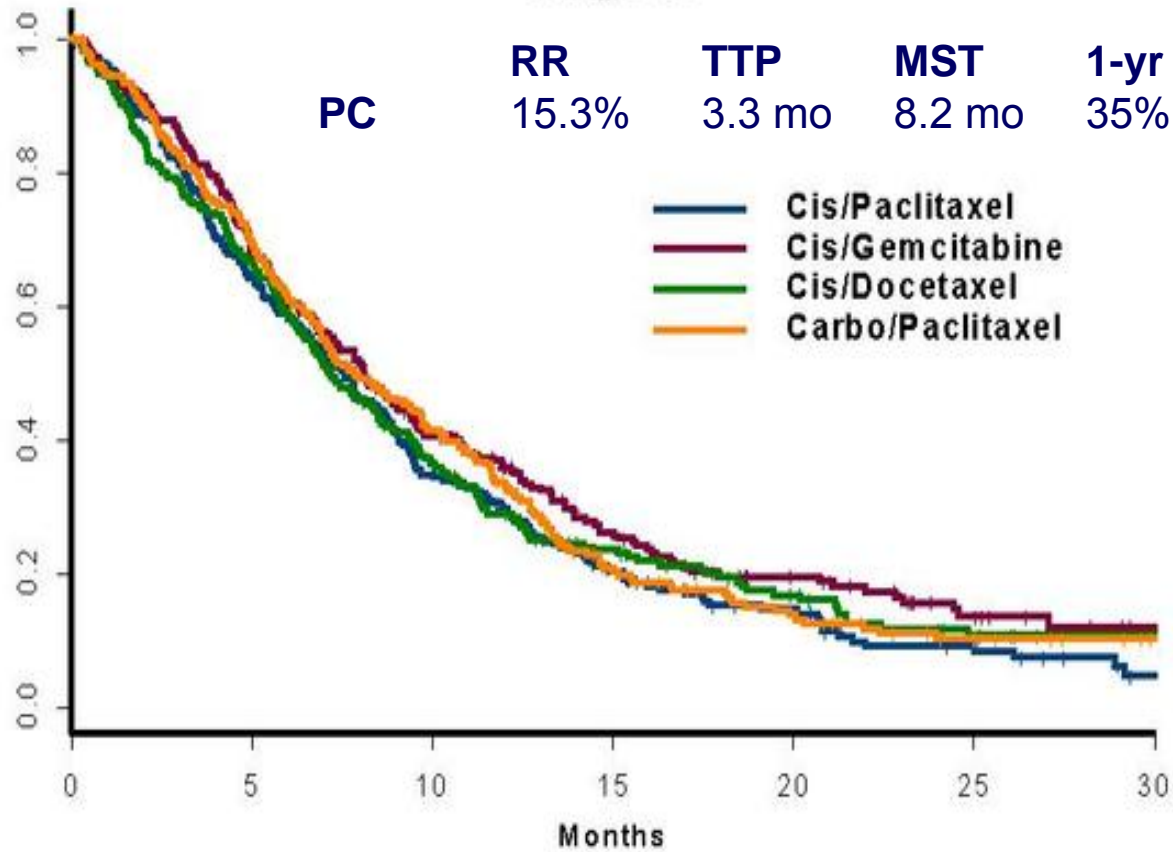
- PS 2:

- Single-agent chemotherapy with third-generation drug or carboplatin-/low-dose cisplatin-based chemotherapy for PS2 patients

European Expert Panels (Ann Oncol 2004;15:419-26.)

E1594

Survival by Treatment Group
Stage IV



More of Targets Later

Phase III Trial of Bevacizumab in 855pts Non-Squamous NSCLC: ECOG 4599

Eligibility:

- Non-squamous NSCLC
- No Hx of hemoptysis
- No CNS metastases

Stratification Variables:

- RT vs no RT
- Stage IIIB or IV vs recurrent
- Wt loss <5% vs \geq 5%
- Measurable vs non-measurable

(PC)

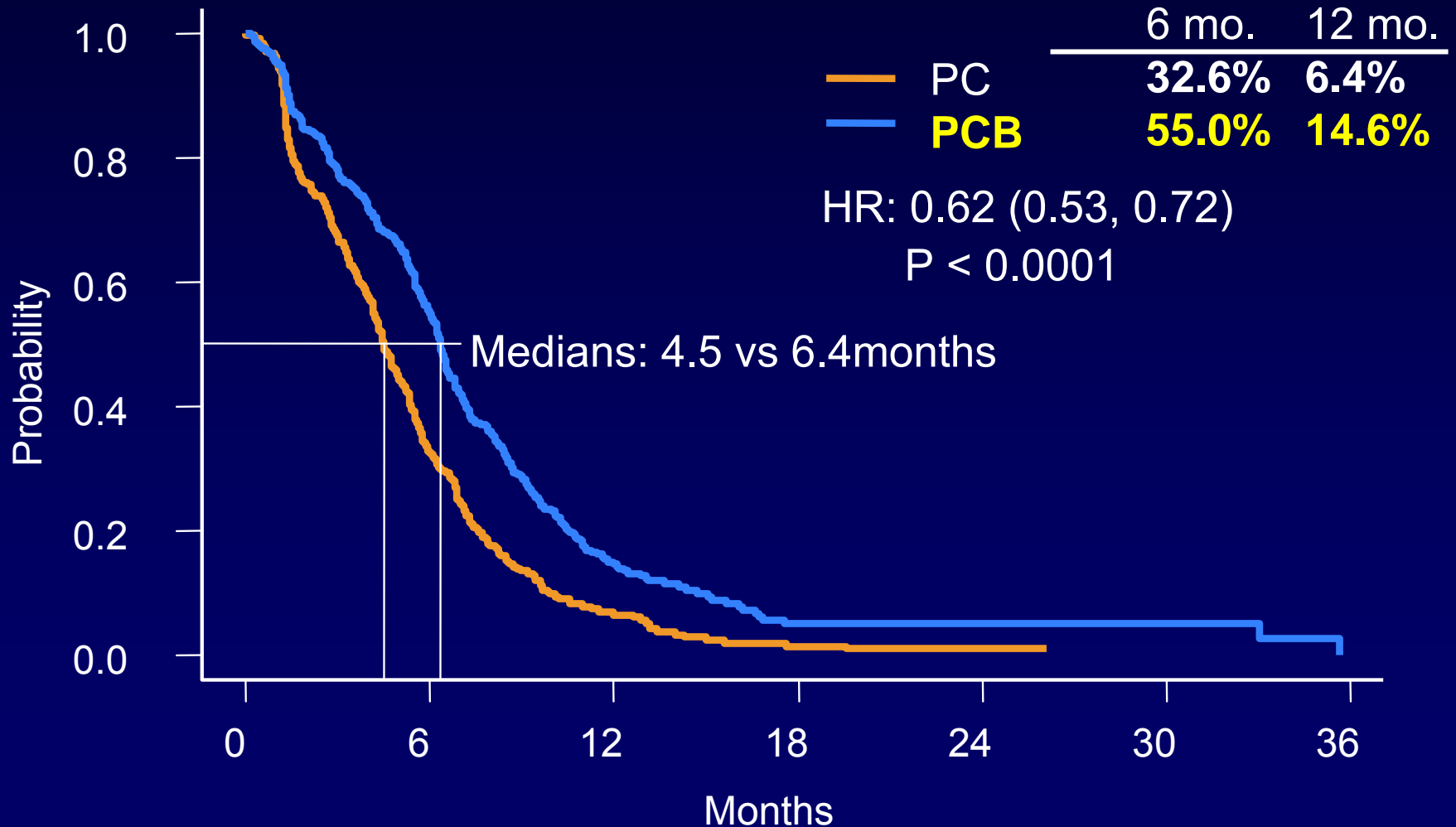
Paclitaxel 200 mg/m²
Carboplatin AUC = 6
(q 3 weeks) x 6 cycles

No crossover to
Bevacizumab
permitted

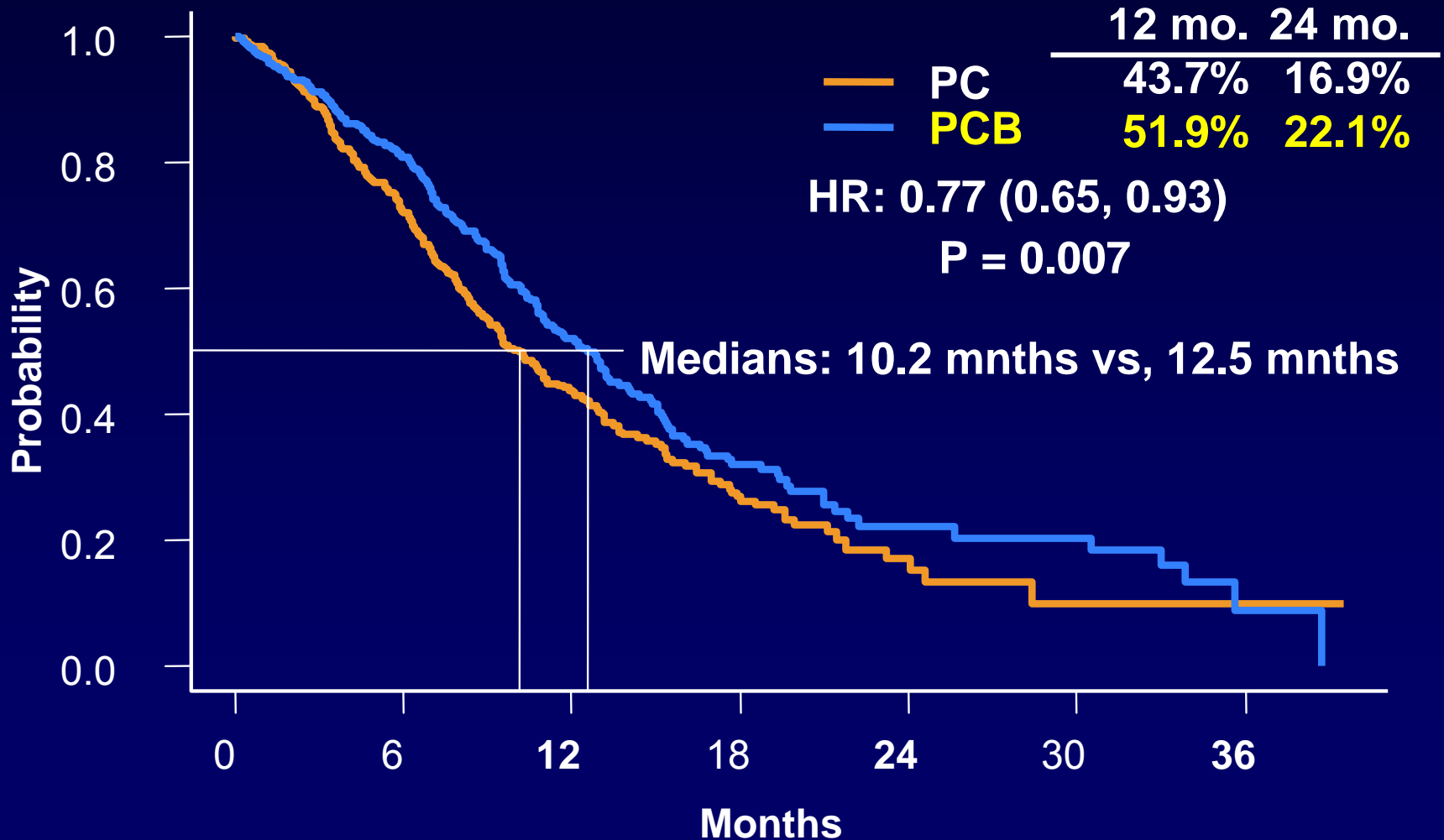
(PCB)

PC x 6 cycles
+
Bevacizumab
(15mg/kg q 3 wks) to PD

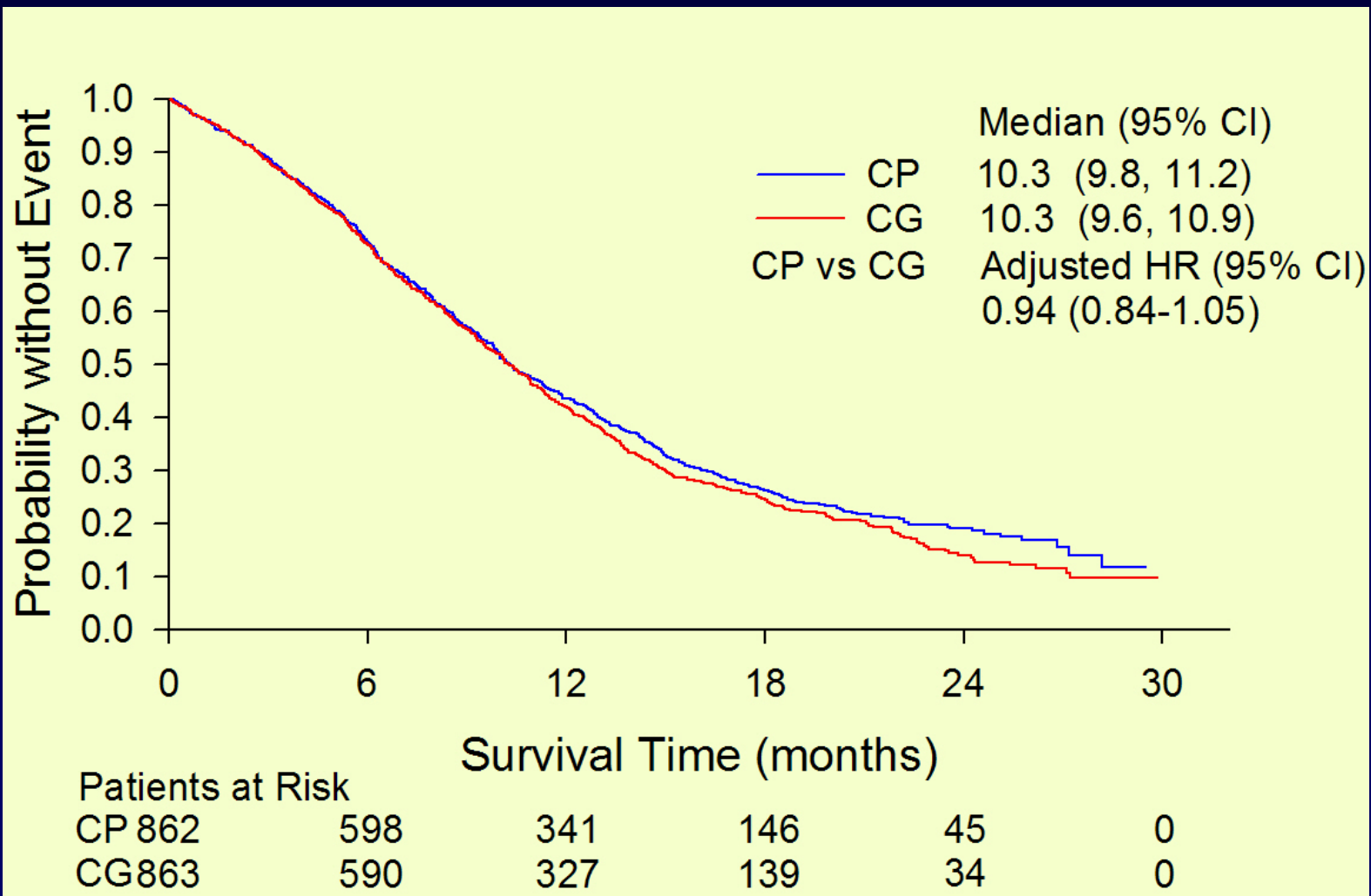
Progression-Free Survival by Treatment



ECOG 4599: Overall Survival by Treatment

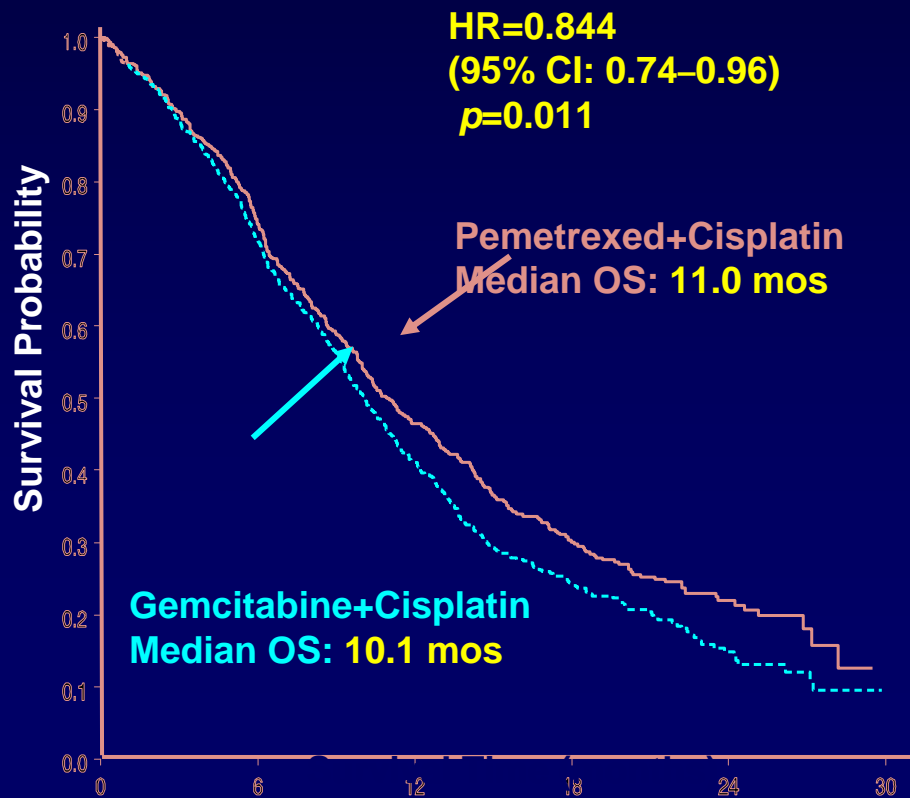


Pem/Cis vs Gem/Cis in NSCLC

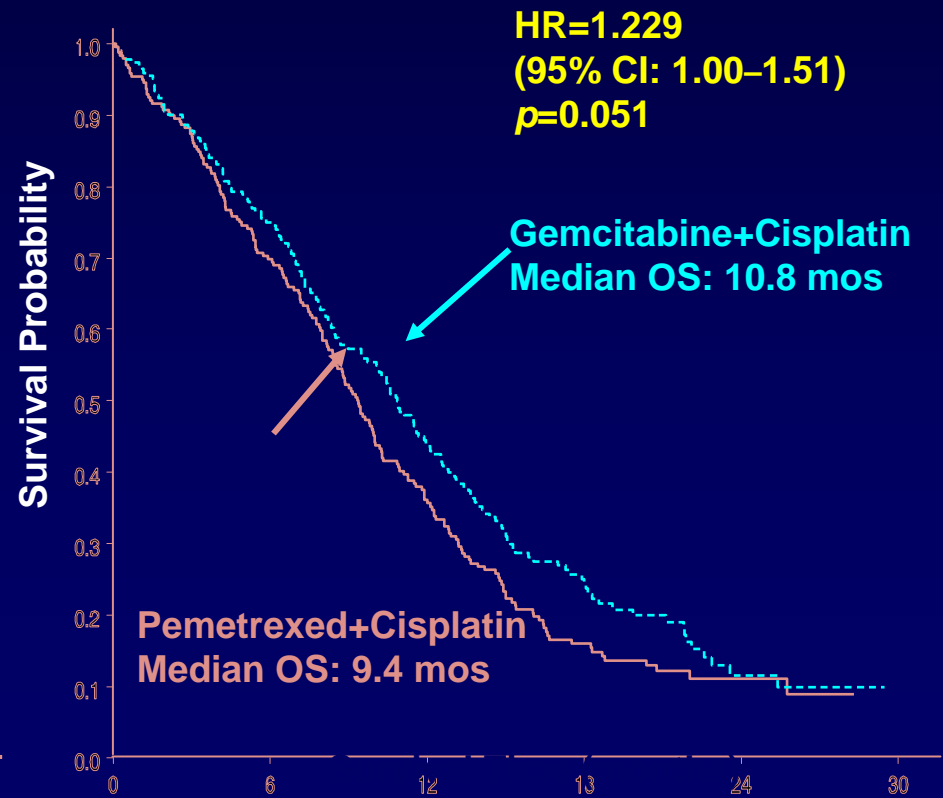


Pem/Cis vs Gem/Cis in NSCLC: Prospective Analysis

Nonsquamous* (n=1252)



Squamous (n=473)



* Nonsquamous=adenocarcinoma, large cell carcinoma, and other/indeterminate NSCLC histology

HOW MANY CYCLES?

- Until Progression
- 4
- 4, 5, --- 6 +
- 4 or 6

**Would You Give Zoledronic Acid
as Part of Initial Treatment?**

Zoledronic Acid as Part Of Initial Treatment?

YES

Bisphosphonate Indications

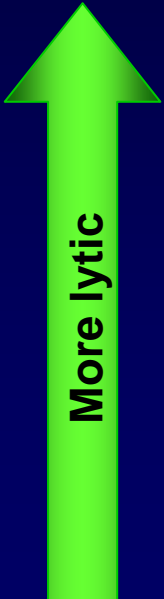
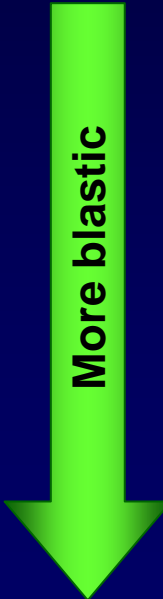
	Indication				
	HCM	Breast cancer	Multiple myeloma	Prostate cancer	LC / OST
Clodronate (oral or IV)	✓	✓	✓		
Pamidronate (IV only)	✓	✓	✓		
Zoledronic acid (IV only)	✓	✓	✓	✓	✓
Ibandronate (oral or IV)	✓	✓			

✓ = European registration

✓ = World wide registration

Metastatic Bone Disease is Prevalent

	5-year world prevalence, thousands ¹	Incidence of bone metastases in cancers ²	Median survival, Months ²⁻⁴
Myeloma	144	70 - 95	6 - 54
Renal	480	20 - 25	12
Melanoma	533	14 - 45	6
Bladder	1,000	40	6 - 9
Thyroid	475	60	48
Lung	1,394	30 - 40	6 - 7
Breast	3,860	65 - 75	19 - 25
Prostate	1,555	65 - 75	12 - 53


More lytic

More blastic

1. Ferlay J, et al. IARC Globocan 2000. Cancer Incidence, Mortality, and Prevalence. 2. Coleman RE. *Cancer Treat Rev.* 2001;27:165-176. 3. Coleman RE. *Cancer.* 1997;80:1588-1594. 4. Zekri J et al. *Int J Oncol.* 2001;19:379-382.

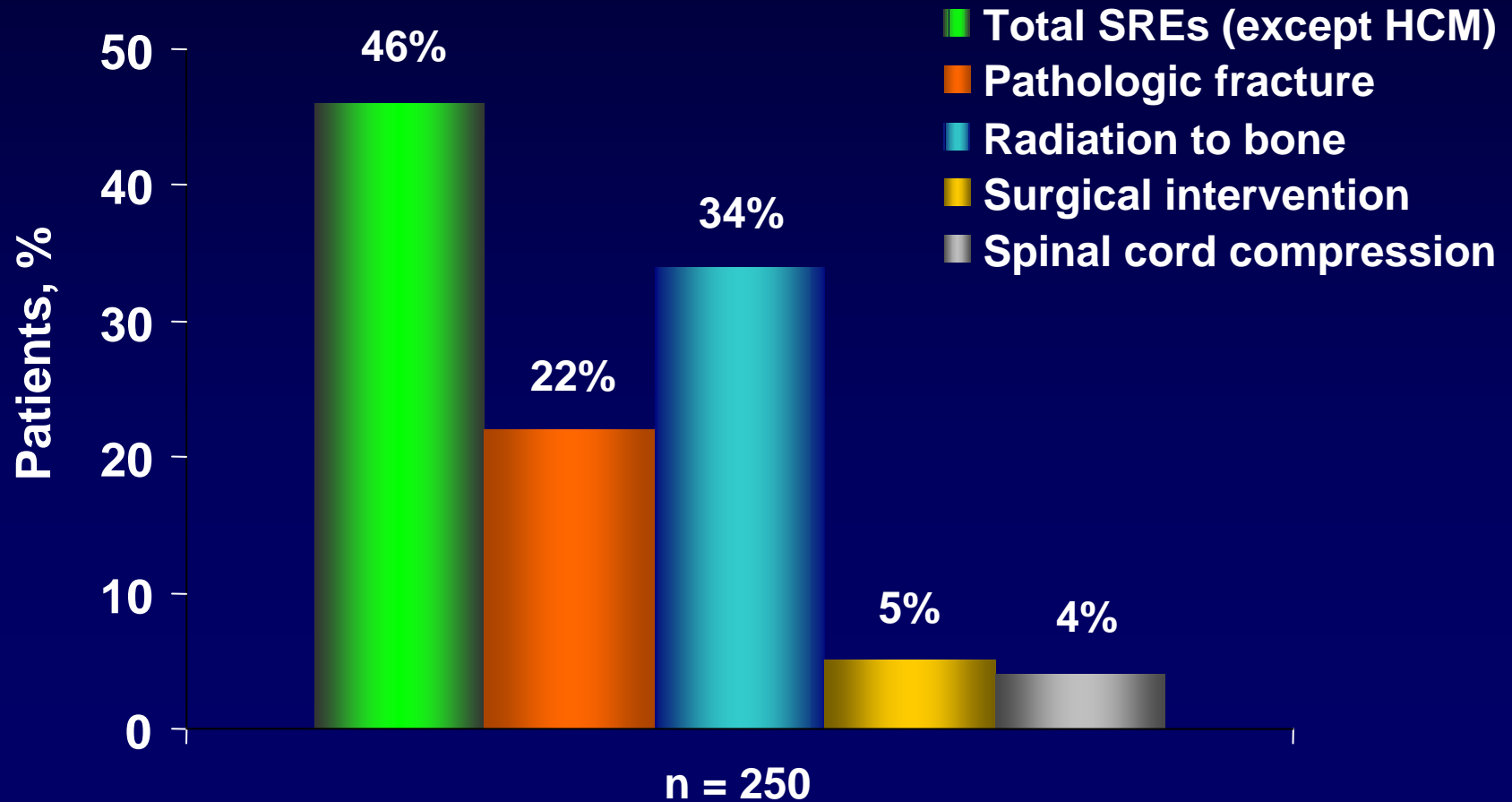
Bone metastases in NSCLC

Are they an issue?

- Median survival of advanced stage NSCLC is **12.3 months**
- Maintenance of QOL must be a priority of treatment
- There is significant morbidity and expense associated with bone metastases

SREs Are a Serious Threat to Patients With NSCLC or Other Solid Tumors if Bone Metastases Are Untreated

21-month data from PLACBO arm of randomized study



SRE = Skeletal-related event; NSCLC = Non-small cell lung cancer; HCM = Hypercalcemia of malignancy.

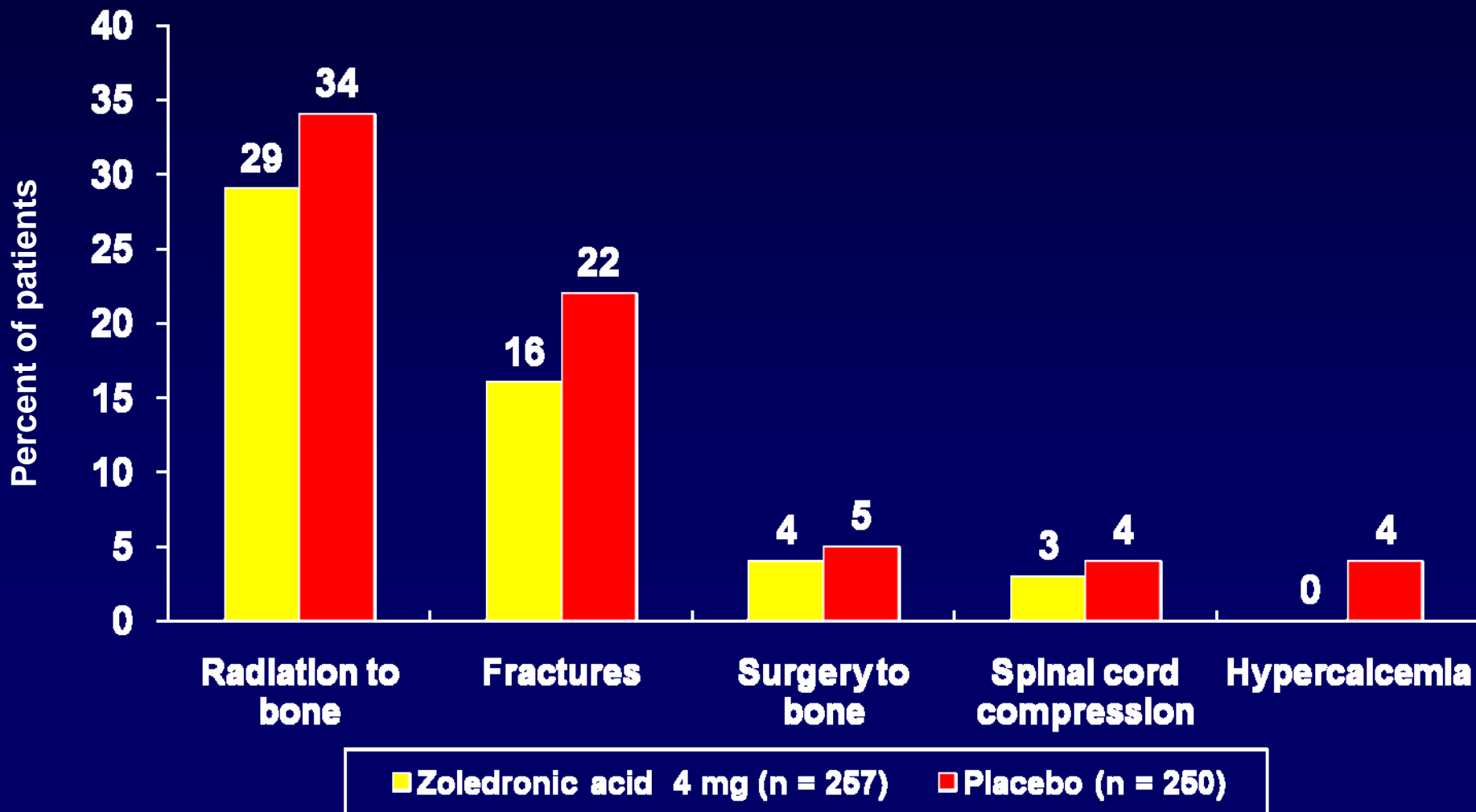
Rosen LS et al. *Cancer*. 2004;100:2613-2621.

Consequences of SREs in Patients With Lung Cancer

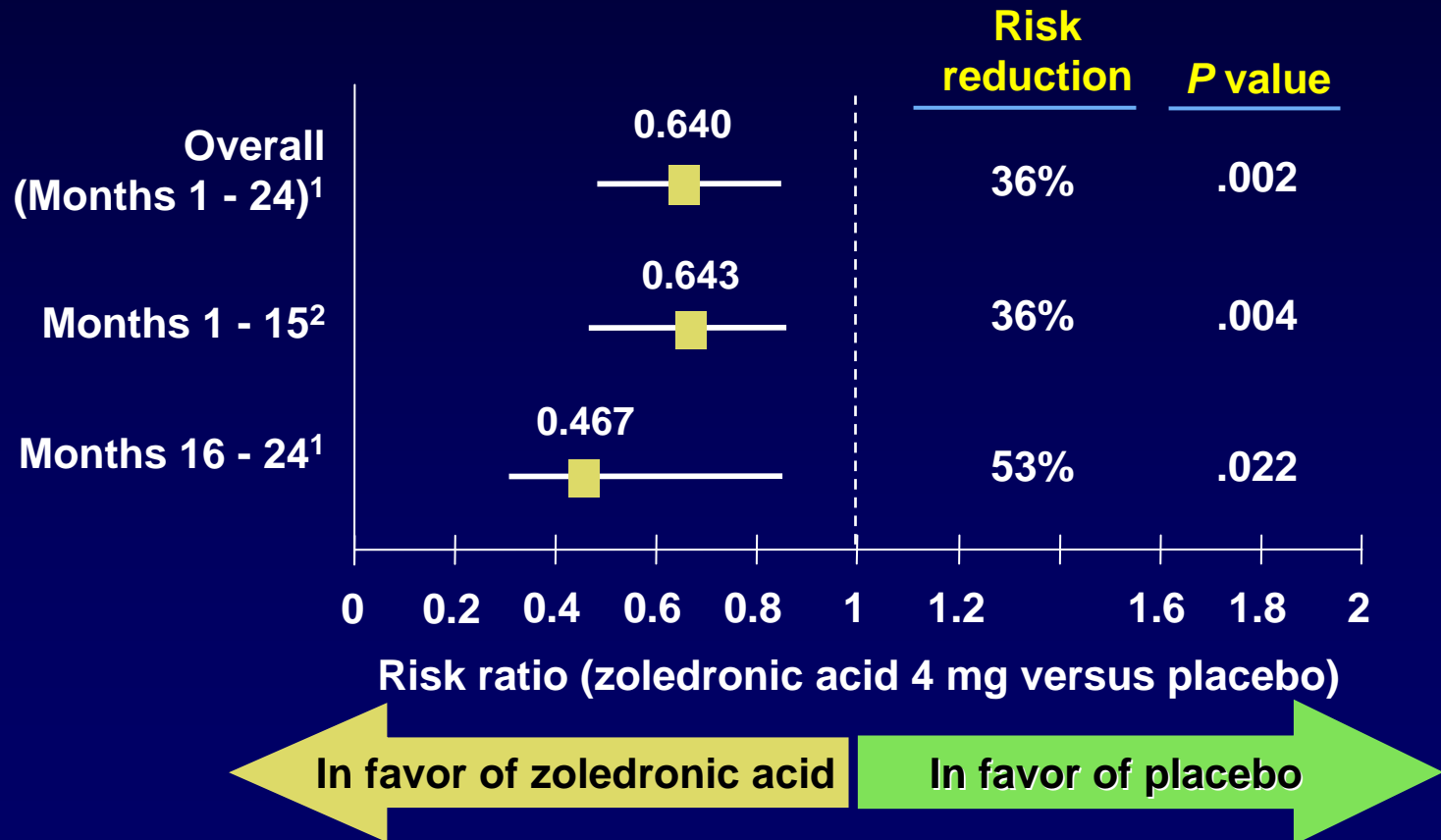
- 50% of patients with bone metastases experience ≥ 1 SRE each year¹
- In patients with an SRE, median survival = **4 months**²
- In a recent chart review of patients with bone metastases from lung cancer (N = 70), patients with SREs had **~50% shorter survival** versus patients without SREs³
- A history of SREs is associated with a significant **41% increased risk** of experiencing **additional SREs** compared with patients with no prior SRE ($P = .036$)⁴

Proportion (%) of Patients With Each SRE Zoledronic Acid vs Placebo

Zoledronic acid consistently reduced all types of SREs

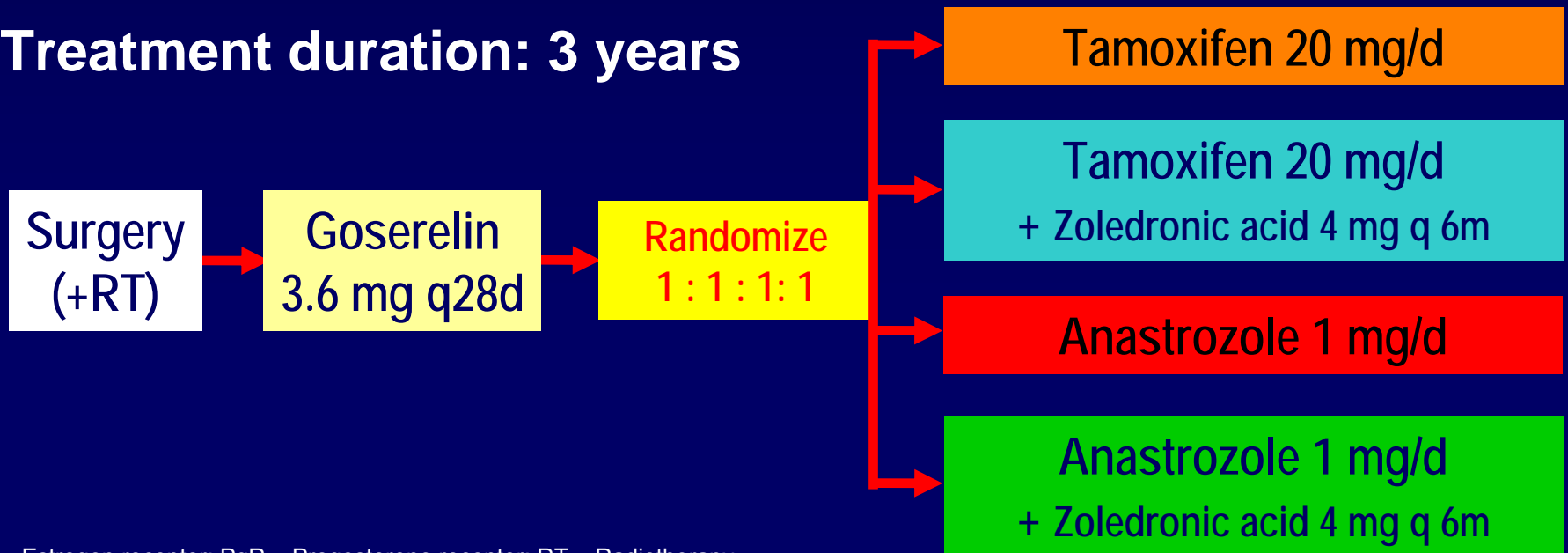


Long term benefit of zoledronic acid in prostate cancer

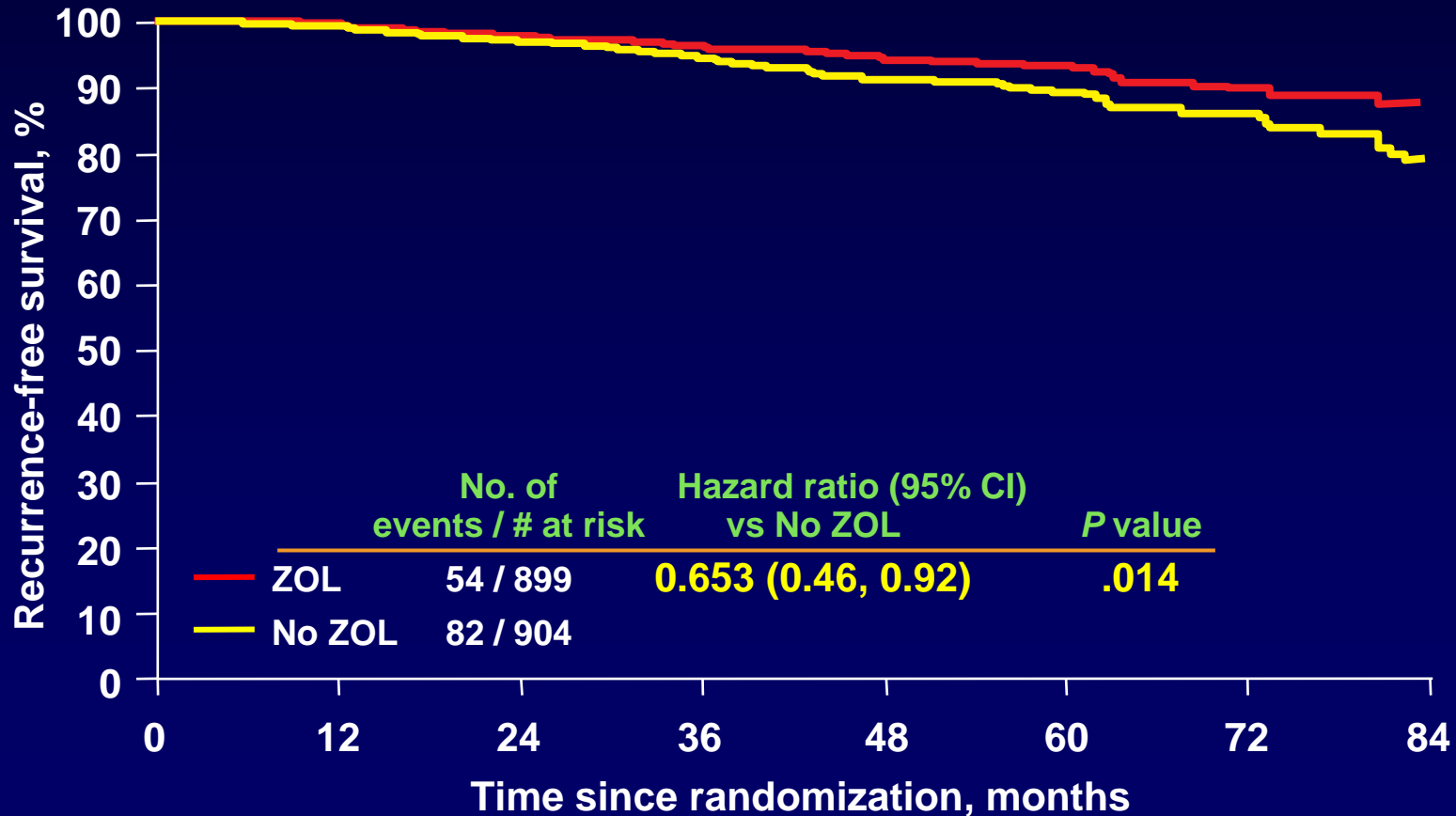


ABCSG-12 Trial Design

- Accrual 1999-2006
- 1,803 premenopausal breast cancer patients
- Endocrine-responsive (ER and/or PgR positive)
- Stage I & II, < 10 positive nodes
- No chemotherapy except neoadjuvant
- Treatment duration: 3 years



ZOL Significantly Improves RFS Compared With Endocrine Therapy Alone

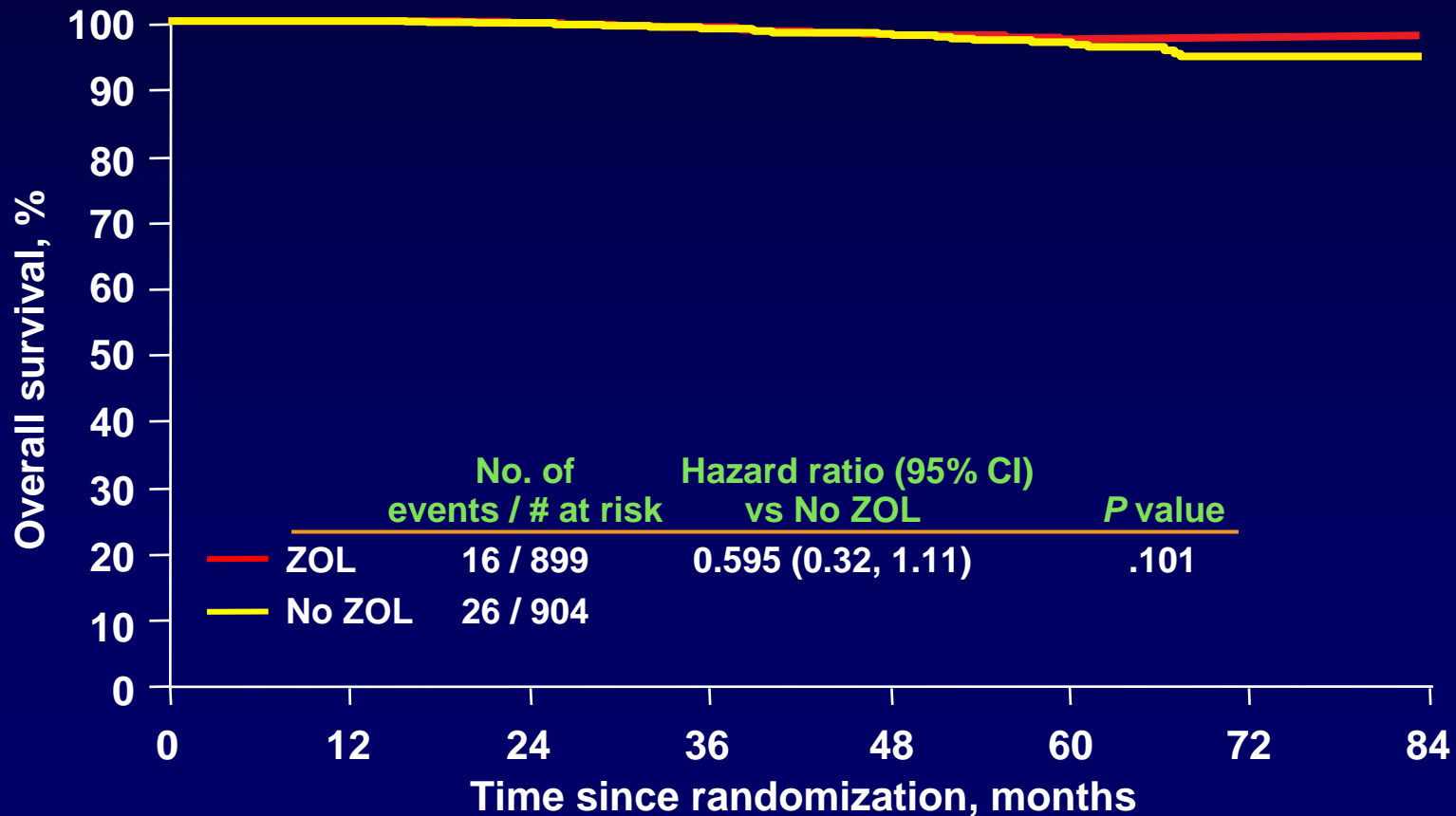


Median follow-up = 60 months.

ZOL = Zoledronic acid; RFS = Recurrence-free survival; CI = Confidence interval.

Gnant M, et al. Presented at: ASCO 2008. Chicago, IL. Abstract LBA4.

ZOL-Treated Patients Showed a Trend Toward Improved OS vs No ZOL



Median follow-up = 60 months.

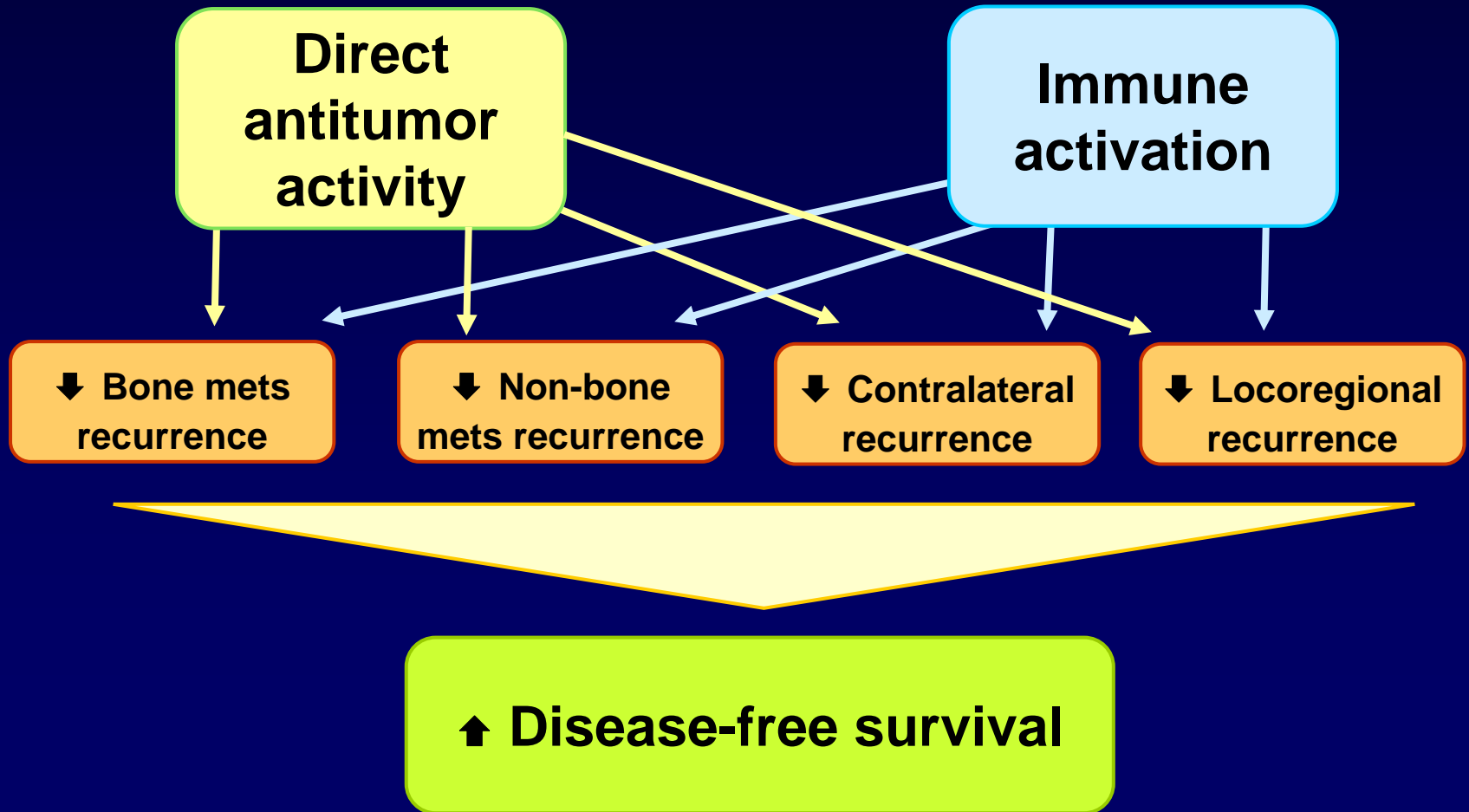
ZOL = Zoledronic acid; OS = Overall survival; CI = Confidence interval.

Gnant M, et al. Presented at: ASCO 2008. Chicago, IL. Abstract LBA4.

Efficacy: ZOL vs No ZOL

- Zoledronic acid significantly prolonged DFS and RFS vs endocrine therapy alone
 - ↓ risk of DFS events by 36% (HR = 0.64; $P = .01$)
 - ↓ risk of RFS events by 35% (HR = 0.65; $P = .015$)
- Zoledronic acid produced a trend toward improved OS (HR = 0.60; $P = .10$)
- Nonsignificant reduction in bone metastases with zoledronic acid
 - 16 ZOL vs 23 No ZOL (HR = 0.68; $P = .224$)

Zoledronic Acid-Mediated Mechanisms Contributing to Improved Disease-Free Survival



Potential Uses for Bone Markers

- Early diagnosis of bone metastasis
- To monitor /predict response to Tx
- Prediction of SREs and prognosis
- Tx decisions should be based on efficacy

Biochemical Markers of Bone Remodeling

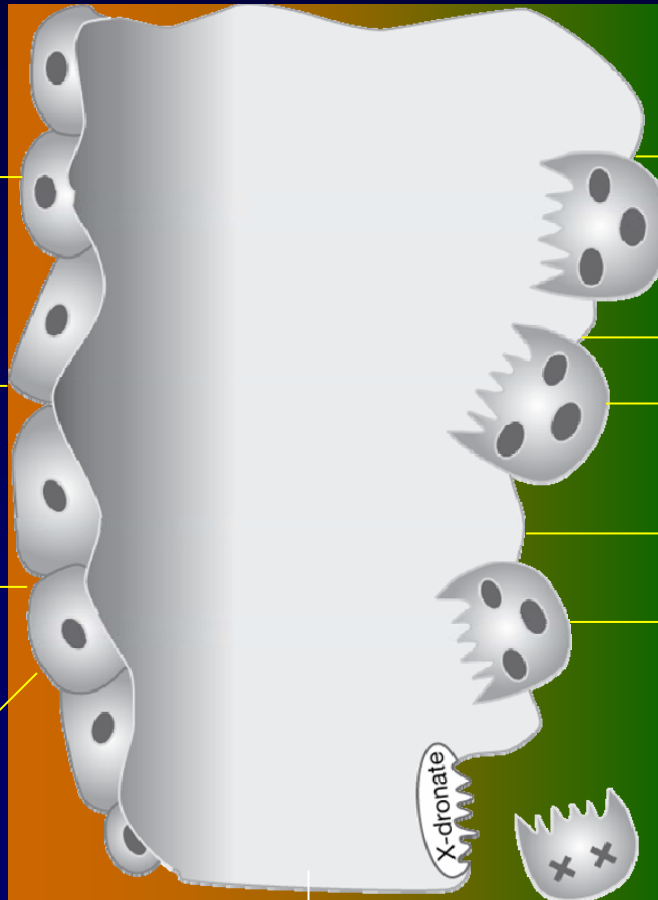
Bone formation

BALP

Collagen type I
propeptides

Osteocalcin

Osteoblasts



Bone matrix

Osteoclasts

Bone resorption

Calcium

TRAcP

Bone sialoprotein

OH-proline
OH-lysine-glycosides

Pyridinium crosslinks

Collagen type I degradation
products:

N- and C-terminal crosslinking
telopeptides of collagen type I
(NTX and CTX)

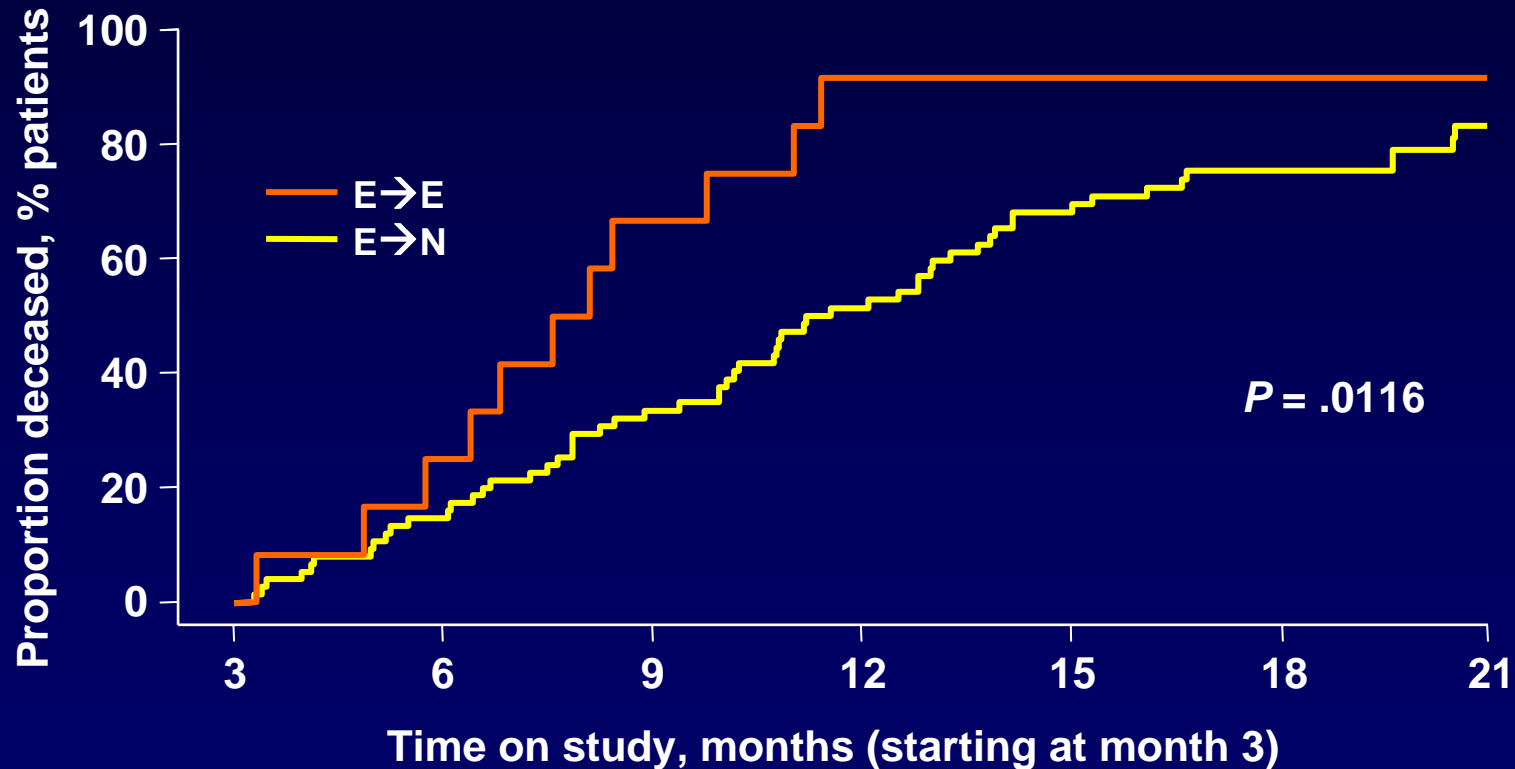
C-terminal crosslinking
telopeptide of type I collagen
generated by MMPs (ICTP)

Influence of Accelerated Bone Resorption on Outcome in Solid Tumors Including Lung Cancer (n =238)

NTX > 100 v < 100 nmol/mmol creatinine	Relative Risk*	95% C.I.	P value
All SREs	3.25	2.26 - 4.68	<.001
First SRE	3.05	1.96 - 4.72	<.001
Prog Disease	2.02	1.48 - 2.74	<.001
Death	4.59	2.82 - 7.46	<.001

Survival by 3-Month NTX Status on zoledronic acid

NSCLC and OST



NTX = N-telopeptide of type I collagen; E→E = Patients whose NTX levels remained elevated at 3 months; E→N = Patients whose NTX levels normalized at 3 months from elevated baseline levels; NSCLC = Non-small cell lung cancer; OST = Other solid tumors.

Zoledronic Acid Improved Survival Due to Normalized NTX in Lung Cancer

- High NTX levels on-study correlated with poor survival in all patients
- Reduction of high NTX or maintenance of normal NTX in zoledronic acid-treated patients may have contributed to improved survival
- Provide further insight into the basis of the potential zoledronic acid-mediated survival benefit in the high-NTX NSCLC patient subset

Clinical Reports Suggest Antitumor Activity in Several Clinical Settings

- **Renal cell carcinoma**
- **Prostate cancer**
- **Multiple myeloma**
- **Breast cancer**
- **Anti-angiogenic properties**

Pre-clinical Antitumor Effects of Zoledronic Acid



Proliferation and viability



Tumor cell apoptosis



Efficacy of other anticancer therapies
(cytostatics, steroids, radiation)



Cell adhesion and matrix invasion



Tumor angiogenesis

NSCLC: ECOG Study

Key endpoints:

- Primary: Time to bone metastases
- Secondary: Time to disease progression, Overall survival at 12 & 24 mo

n=584

NSCLC Stage IIIB with pleural effusion, Stage IV or recurrent disease

- No prior 1st line treatment
- No bone metastases

R

Chemotherapy +/- targeted therapy + zoledronic acid 4 mg q 3-4 weeks

Chemotherapy +/- targeted therapy (control group)

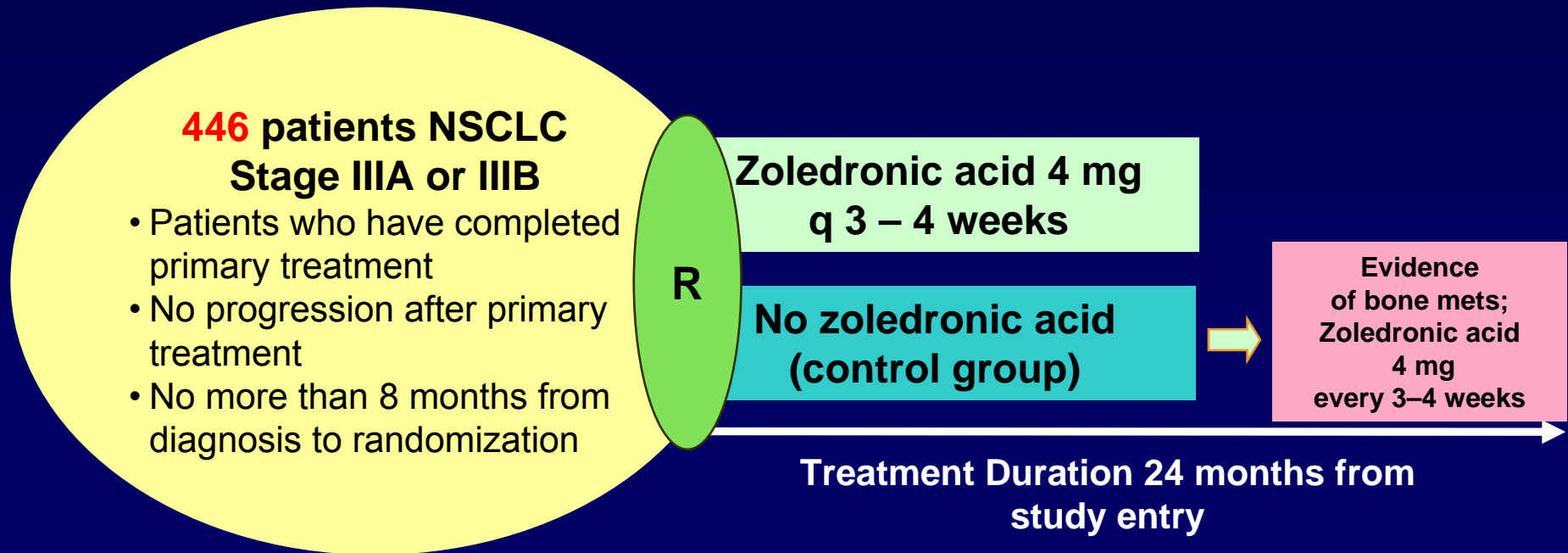
24 months Follow-up for disease progression and survival

Until development of bone metastases

Trial 2419: Zoledronic Acid in the Prevention of Bone Metastasis in NSCLC

Key Endpoints:

- Primary endpoint: Time to bone metastases
- Secondary endpoints: SREs, overall survival, adverse events



500 mg calcium and 400-500 IU of vit D in both groups

NSCLC = Non-small cell lung cancer; SREs = Skeletal-related events.

Efficacy & Safety:

- ~55% of lung cancer patients with bone metastases experienced one or more SREs over mean follow-up of 7.4 months
 - 20% had 2 or more events
- QOL and economic burden of SREs is very large
- Potent IV bisphosphonates, such as Zoledronic Acid can reduce risk of SREs in lung cancer patients
- Safety:
 - Common adverse events: Flu-like symptoms
 - Uncommon adverse events: Renal-function effects and ONJ (frequency ~ 0.7%)¹
 - Maintain good oral hygiene to reduce the risk of possible ONJ

Prevention and Management of ONJ: Guidance

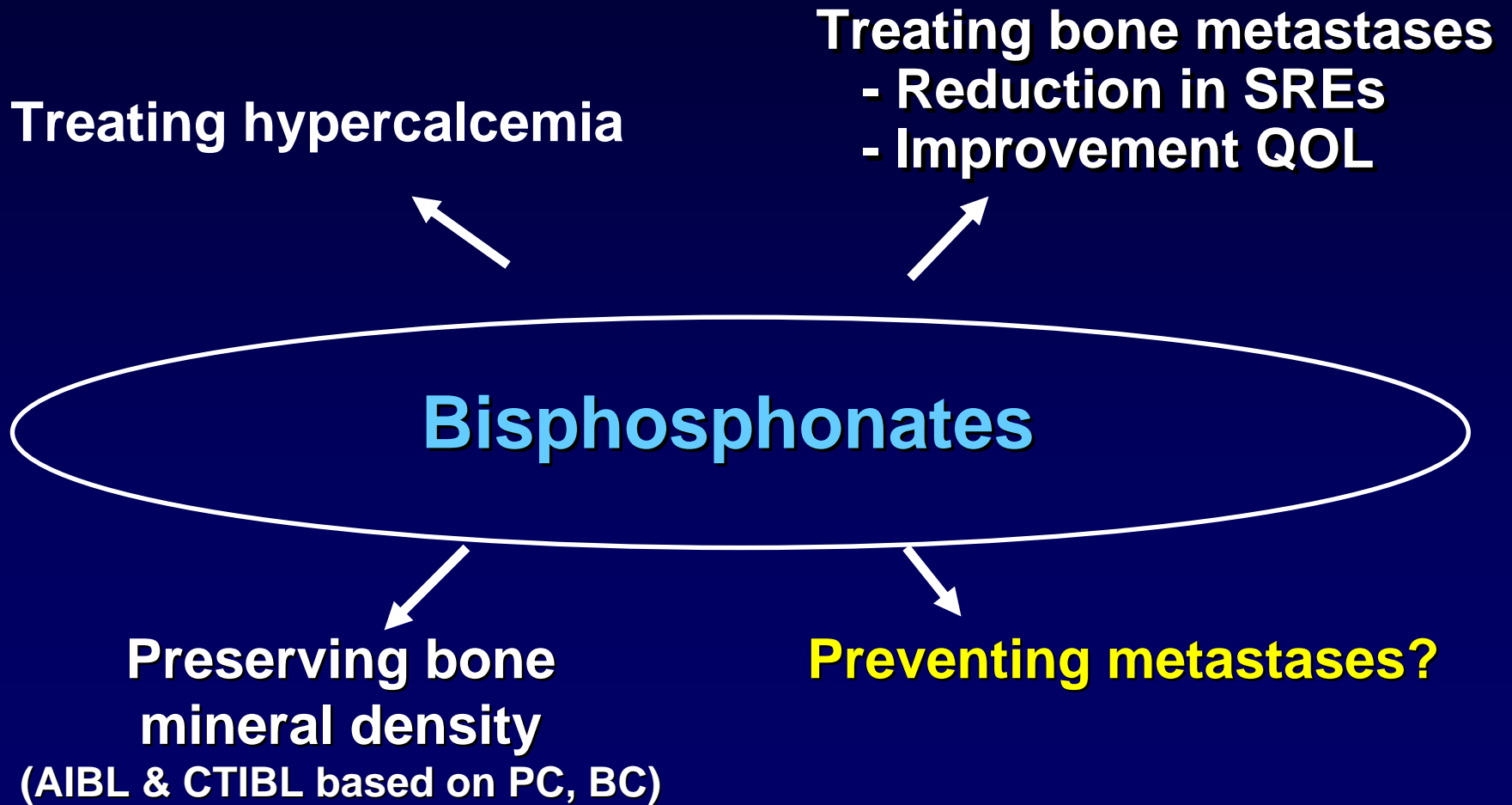
- Dental exam with appropriate preventive dentistry
- Remove abscessed and non-restorable teeth, teeth with severe periodontal disease, and teeth with poor long-term prognosis
- Avoid invasive dental procedure
- Functionally rehabilitate salvageable dentition
- Educate patients on oral hygiene and signs and symptoms of ONJ

Renal Precautions and Dose Modifications

- Serial monitoring of renal function—prior to each dose
- Maintain hydration status
- Adjust dose for reduced creatinine clearance at baseline
- If serum creatinine increases, resume therapy only when creatinine returns to within 10% of baseline.

Baseline CrCl, mL/min	Recommended ZOL dose (mg)
> 60	4.0
50 - 60	3.5
40 - 49	3.3
30 - 39	3.0

Bisphosphonates and Cancer



Conclusions

- Proven efficacy of zoledronic acid up 2 years of treatment in lung cancer, solid tumors, and multiple myeloma
 - Treatment can be continued for as long as tolerated
- Benefits of zoledronic acid treatment outweigh the risks
- Ongoing clinical trials:
 - Zoledronic acid therapy based on baseline bone marker levels
 - Zoledronic acid treatment regimen beyond 2 years