

## Maintenance Therapy

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## Adjuvant or (maintenance)?

Author, yr	Pts	TX	Outcome
Chandler, 1981	82	CDDP + MTX > S or RT + adjuvant	No difference
H&NCCP, 1987	462	CDDP + BLM > S or RT + adjuvant	No difference < M+
FU, 1987	104	BLM + MTX > RT + adjuvant	No difference

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## Definitions

- **Maintenance:** TX designed to help the original primary treatment succeed. Cancer in remission to prevent relapse. For chemo lower dose
- **Maintenance/consolidation** chemotherapy is the prolongation of chemotherapy duration with the administration of additional drugs at the end of a defined number of initial chemotherapy cycles, after achieving a maximum tumor response in an individual patient. In the absence of significant toxicity, maintenance chemotherapy is continued either for a defined time or until evidence of progressive disease. Maintenance/consolidation chemotherapy consists of either a drug included in the induction regimen or another non-cross-resistant agent, used at a relatively low dose.
- **Intensification** high dose

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### Looking for ....

- TX without toxicity for prolonged (oral) administration
- TX active vs residual tumor cells in a "special" treatment induced microenvironment
- TX able to prevent second primaries

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### EGFRi good candidates...

- Cetuximab first drug approved by FDA in 45 yrs
- LRC and OS significantly improved
- Without adding significant toxicity

#### However

- No control of DM
- No complete control of LR disease

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### About acquired resistance

- CET resistance: VEGF
- Dysregulation of internalisation/degradation: EGFR dependent activation of HER3 (panHERi)

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## Challenges

- Heterogenous expression of targets
- Persistent cross talk
- Mutations

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The Lippincott  
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Rhinological and Otolaryngological Society, Inc.

## Docetaxel Associated Pathways in Cisplatin Resistant Head and Neck Squamous Cell Carcinoma: A Pilot Study

George H. Yoo, MD; Ho-Sheng Lin, MD; Andrew J. Iskander, MD; Marie P. Piechocki, PhD;  
Jeffery Oliver, BS; Danny Kewson, MD; Fulvio Lonardo, MD; Michael A. Tainsky, PhD;  
Hyeon-Reh Kim, PhD; Harold Kim, MD; John F. Euseley, MD

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### Expression of Cell Cycle regulators

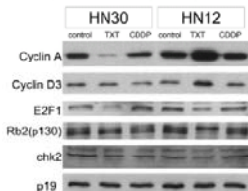


Fig. 3. Alterations in the expression of cell cycle regulators in HN30 and HN12 cells after 48 hours of exposure to docetaxel (TXT, 25 ng/ml), cisplatin (CCDP, 10 uM), or solvent.

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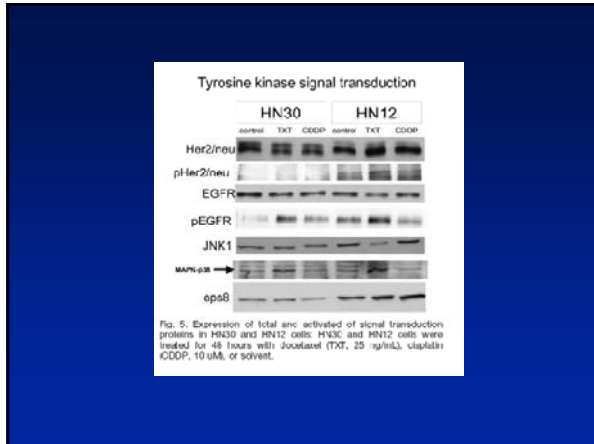
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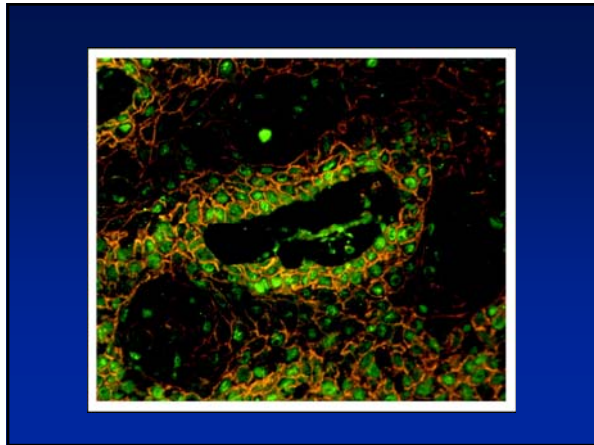
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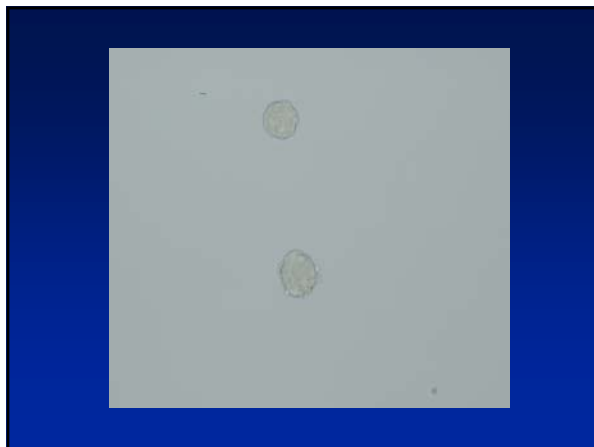
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Seminars in  
**RADIATION  
ONCOLOGY**

**Cancer Stem Cells and Tumor Response to  
Therapy: Current Problems and Future Prospects**

Luka Milas, MD, PhD<sup>1</sup>, and Walter N. Hittelman, PhD<sup>1</sup>

April 2009

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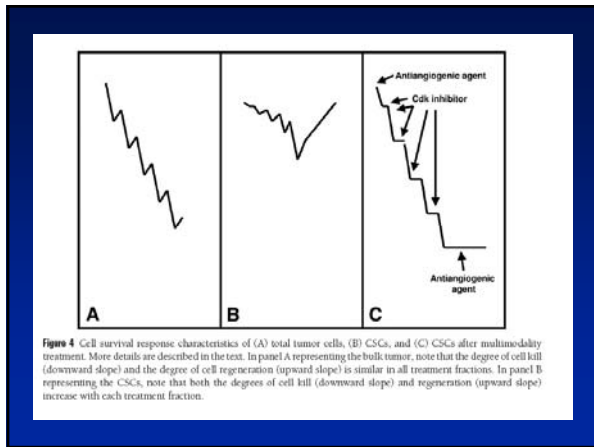
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**C**

Timing critical (4-6 days):  
Transient vascular normalisation, ↓ extracascular pressure, ↑ tumor oxygenation

EGFR expression important  
CDK inhibitors (flavopiridol)

Microenvironment:  
C225 tumor delay > in preRT areas  
EGFRi > in preRT areas  
Antiangiogenic agents: ↓ vasculature > CSCs dormancy  
Inflammatory CK > CSCs survival and expansion

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### Statistical methods: efficacy endpoints

		Maintenance treatment		
		Placebo	Gefitinib 250 mg	Gefitinib 500 mg
Concomitant treatment	Placebo	A	F	G
	Gefitinib 250 mg	B	D	X
	Gefitinib 500 mg	C	X	E

**Principal statistical questions for primary endpoint:**

F1: Maintenance gefitinib (250 + 500 mg) improves I DCR at 2 years?  
(D+E+F+G vs A+B+C)

F2: Concomitant gefitinib (250 + 500 mg) improves LDCR at 2 years?  
(B+G+D+E vs A+F+G)

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### Gefitinib / placebo exposure: maintenance phase

	Placebo (A,B,C)	Gefitinib 250 mg (F,G)	Gefitinib 500 mg (C,F)
	N=94	N=57	N=41
Median time on treatment (range), days*	580.0 (2, 700)	332.0 (2, 715)	263.0 (2, 758)
Dose reduction due to toxicity or AEs and / or dose interruption, %	25.6	24.6	24.4
Gefitinib / placebo discontinuation, %	61.1	63.2	61.0

\*Including interruptions  
\*Duration of treatment = [date of last dose] - [date of first dose] + 1

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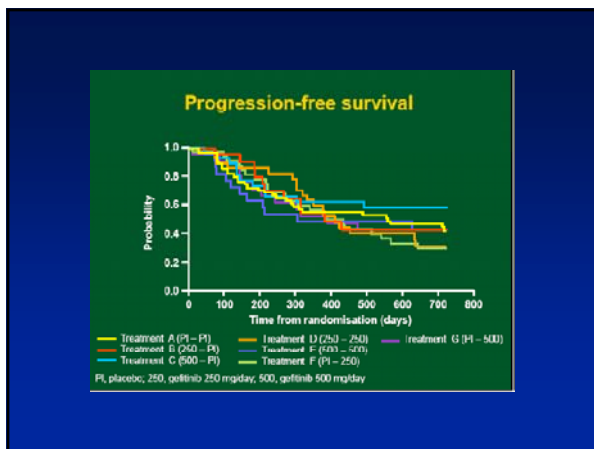
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### Conclusions...

- HNC represents a biological model for designing better strategies to improve cancer cure
- Time for revisiting the Skipper-Schabel hypothesis
- Targeted therapies ideal agents that can be strategically exploited within the tumor response profile including the maintenance phase
- Convergent development of such drugs will help in rationalise their use

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