



Princess Margaret Hospital



Molecular targeted approaches to head and neck cancer



Lillian L. Siu

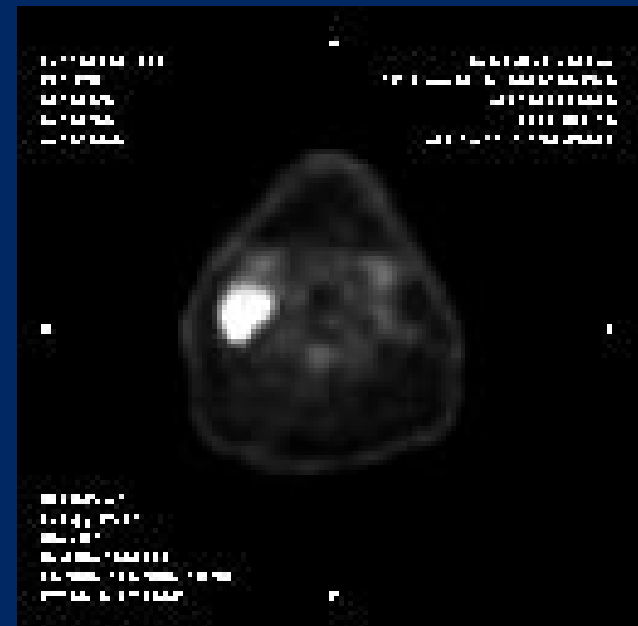
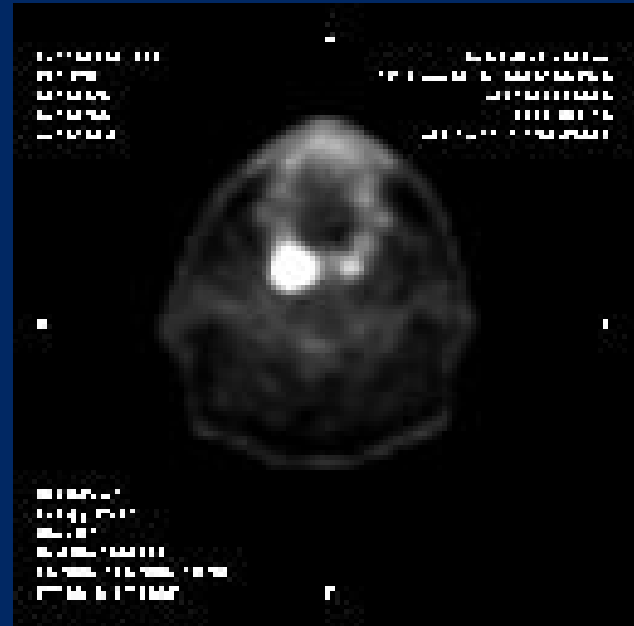
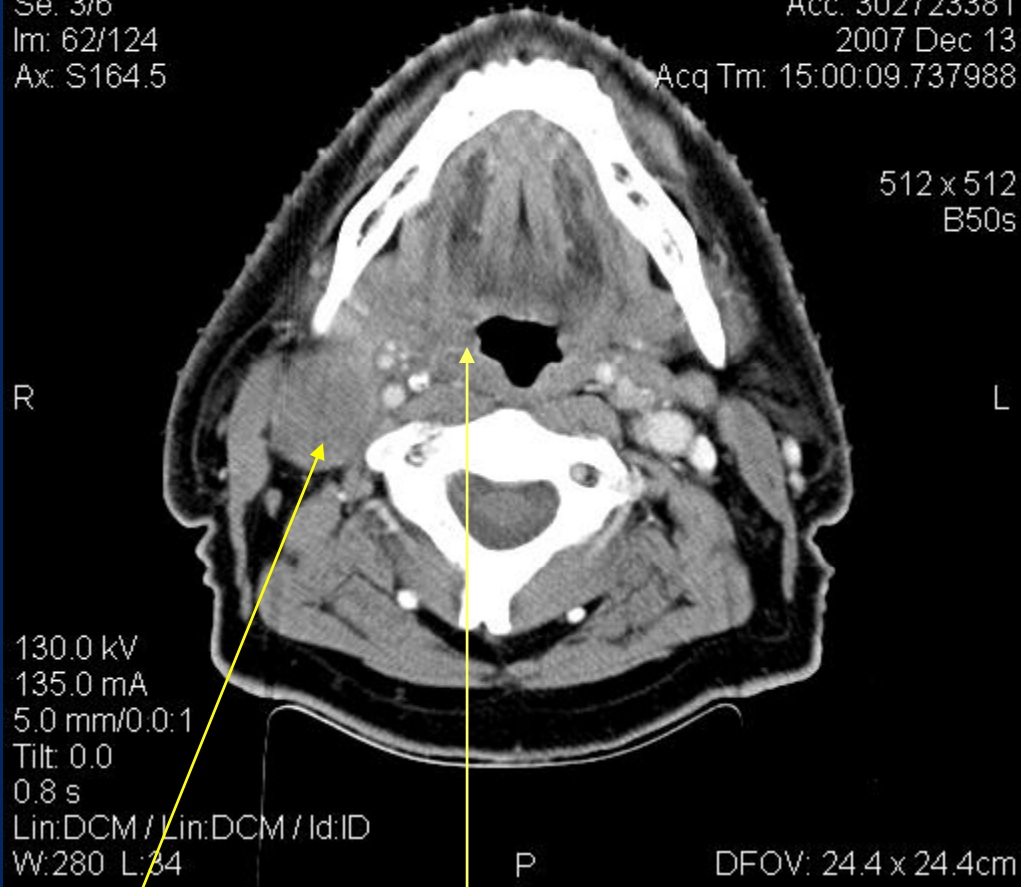
**Department of Medical Oncology &
Hematology**

**Princess Margaret Hospital,
University of Toronto**

Locally Advanced HNSCC

Emotion Duo
Ex: 1502624009
Neck 5mm 5.0 B50s
Se: 3/6
Im: 62/124
Ax: S164.5

Princess Margaret Hospital PET/CT
Acc: 302723381
2007 Dec 13
Acq Tm: 15:00:09.737988



Locally Advanced HNSCC

RT +/-
Surgery

Concurrent
ChemoRT
+/- Surgery

??

2000: MACH-NC meta-analysis

2006: MARCH meta-analysis

2000+:

- Molecular targeting
- Renewed interest in induction chemotherapy
- Intensity modulated radiation therapy
- Image-guided radiation therapy

Concurrent Chemotherapy



Concurrent

↓ LRR

↓ Distant mets

↑ Survival

**Compared to
RT alone**

**Standard
of Care**



Meta-Analysis of Chemotherapy
in Head & Neck Cancer

Overall survival

(63 trials, 10741 pts: 1965-1993)

Chemotherapy timing	Risk reduction	p-value	Absolute benefit at 5 years *
Adjuvant	2 %	NS	1 %
Neoadjuvant	5 %	NS	2 %
Concomitant	19 %	< 0.0001	8 %
Total	10 %	< 0.0001	4 %

* 5-year survival rate in control group : 32 %



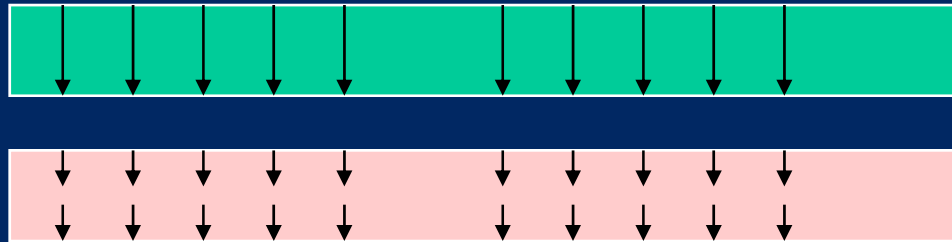
Meta-Analysis of Chemotherapy
in Head & Neck Cancer

Update: Overall survival **(87 trials, 16665 pts: 1965-2000)**

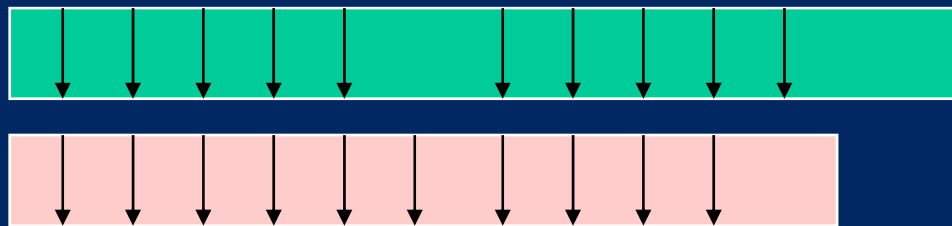
Chemotherapy timing or type	Hazard ratio	Absolute benefit at 5 yr
Concomitant CT+ RT	0.81 (0.78-0.86)	8% (Stewart's) 6.5% (Peto's)
conventional RT	0.83	
altered fractionation RT	0.73	
platin monotherapy	0.74	
platin + 5-FU	0.77	

Modified Fractionated Radiotherapy in HNSCC

- XRT hyperfractionation (same treatment duration, smaller dose per fraction) - to ↓ injury on normal tissues



- XRT acceleration (shorter treatment duration, same fraction size) - to ↓ clonogenic tumor cell proliferation



MARCH (15 trials, 6515 pts)

Altered Fractionation vs Standard Fractionation

Regimens	Absolute benefit at 5 years	Risk reduction	p
Overall survival			
Hyperfractionation	8.2 %	22 %	
AFX (\cong Total Dose)	2 %	3 %	
(\downarrow Total Dose)	1.7 %	6 %	
.....			
All group	3.4 %	8 %	0.003

Concurrent Chemotherapy + RT: Toxicity

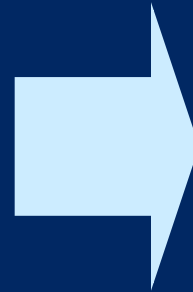
Trial	Concurrent Arm	Acute Tox Gr 3-4	Late Tox
Adelstein (2003)	Standard RT + Cis x 3	42% leucopenia 45% mucositis 52% feeding tube	Not reported
Jeremic (2004)	Standard RT + daily Cis Hyperfr. RT + daily Cis	16% stomatitis 49% stomatitis	↑ xerostomia and ↑ skin toxicity with hyperfr. RT
Denis + Calais (2004)	Standard RT + 5FU + Carbo	71% mucositis 36% feeding tube	Similar between arms
Budach (2005)	Hyperfr. Acc. RT + 5FU + MMC	9% leucopenia 2% platelets 66% mucositis Prophylactic feeding tube in most	Similar between arms

RTOG 0129 Ph III:
SFX + Cisplatin vs AFX-CB + Cisplatin

**Stage III or IV
SCCHN**

N = 743

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**Standard
fractionation (SFX)
+ Cis (D1, 22, 43)**

**Accelerated
fractionation by
concomitant boost
(AFX-CB)
+ Cis (D1+22)**

1^o endpoint = OS

RTOG 0129: Feeding Tube

	SFX + CDDP	AFX-C + CDDP
➤ Before therapy	89/361 (25%)	79/361 (22%)
➤ End of therapy	247/361 (68%)	239/357 (67%)
➤ At 1 year	98/328* (30%)	88/325** (27%)

*39 (40%) and **31 (35%) had feeding tube at baseline

Radiation +/- vs Cetuximab in Locally Advanced HNSCC

N = 424 pts

Median F/U = 38 m

Stage III (32%)
Stage IV (68%)

Oropharynx
Hypopharynx
Larynx

KFS:
90-100 vs 60-80

Node:
+ (20%)
vs - (80%)

T stage:
T1-3 (72%)
vs T4 (28%)

RT:
Conc. Boost
Daily
BID



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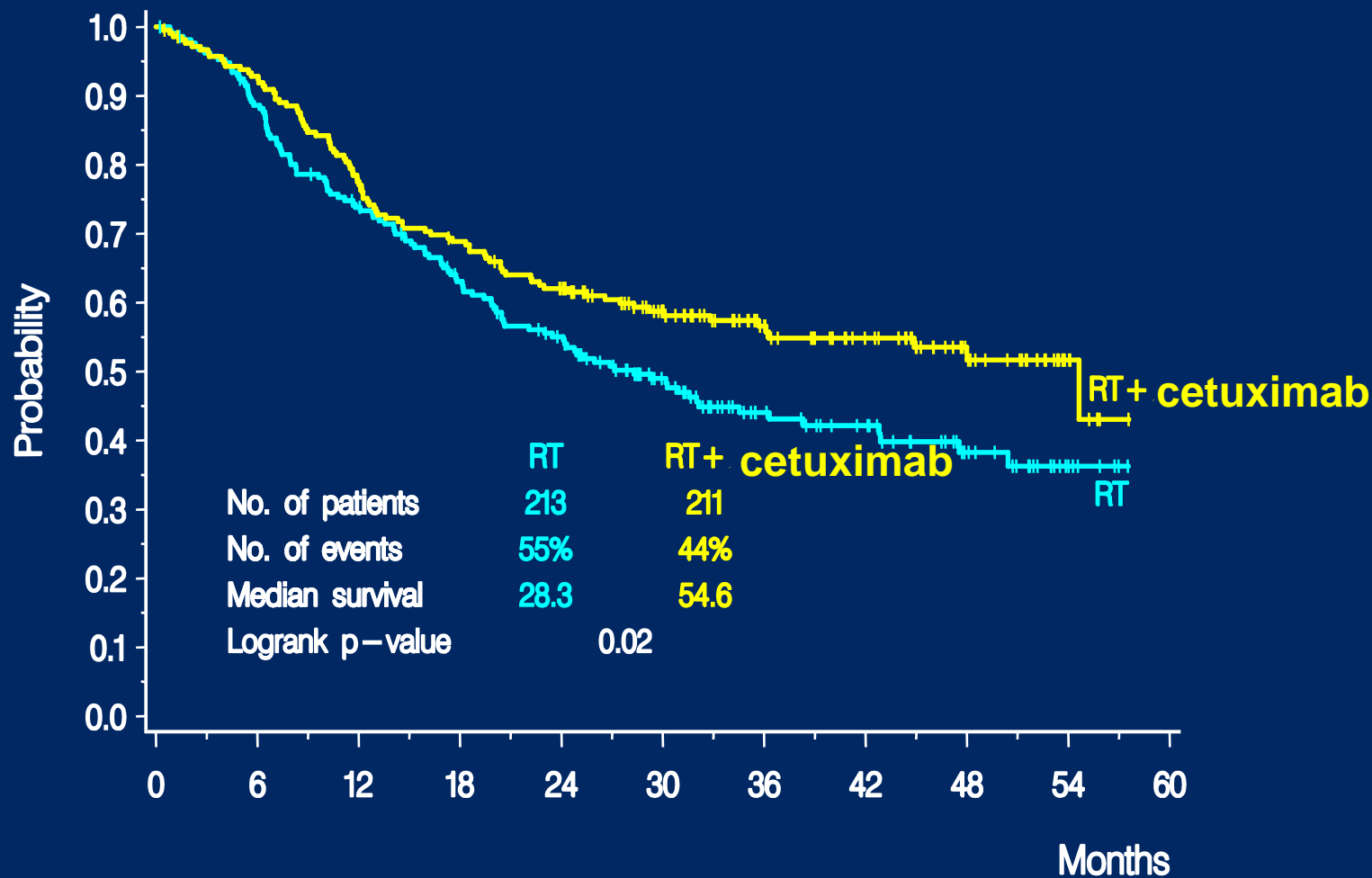
RT

RT

+

Cetuximab

Radiation +/- Cetuximab: Overall Survival



	Cetuximab + RT (n = 211)	RT Alone (n = 213)	Hazard Ratio (95% CI)	Stratified Log- Rank P Value
Median overall survival, mo	49.0	29.3	0.74 (0.57-0.97)	0.03
3-y survival rate, %	55	45	—	0.05

Incidence of Selected Toxicities

	Cetuximab + RT % (n = 208)		RT % (n = 212)	
	All Grades	Grade 3-5	All Grades	Grade 3-5
Mucositis	93	56	94	52
Dysphagia	65	26	63	30
Xerostomia	72	5	71	3
Radiation dermatitis	86	23	90	18
Weight Loss	84	11	72	7

- **Cetuximab did not exacerbate the common toxic effects associated with radiotherapy of the head and neck, including mucositis, xerostomia, dysphagia, pain, weight loss , and performance-status deterioration.**

Late Radiation Toxicity by Site

	Cetuximab + RT % (n = 208) Any Grade	RT % (n = 212) Any Grade
Salivary glands	65	56
Larynx	52	36
Subcutaneous tissue	49	45
Mucous membranes	48	39
Esophagus	44	35
Skin	42	33

- **Higher overall incidence of late radiation toxicities (any grade) in Cetuximab + RT group**
- **Similar incidence of Grade 3 or 4 late RT toxicities between both groups**

“Chemoadditive”

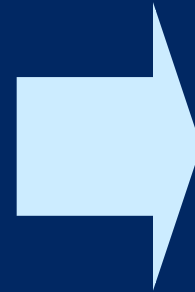
RTOG 0522 Ph III:

AFX-CB + Cis vs AFX-CB + Cis + Cetuximab

Stage III or IV
SCCHN

N \approx 900

R
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Accelerated
fractionation by
concomitant boost
(AFX-CB) + Cis
(D1+22)

Accelerated
fractionation by
concomitant boost
(AFX-CB) + Cis
(D1+22) + **Cetuximab**

1^o endpoint = DFS

“Chemosparing”

NCIC CTG HN.6:

SFX + Cis vs AFX + Panitumumab

N = 320 pts

Anatomic:

Hypopharynx vs
oral cavity vs
oropharynx vs
larynx

Node:

N0-1 vs N2-3

T stage:

T1-3 vs T4

RT:

IMRT vs 3DCRT

1^o endpoint = DFS



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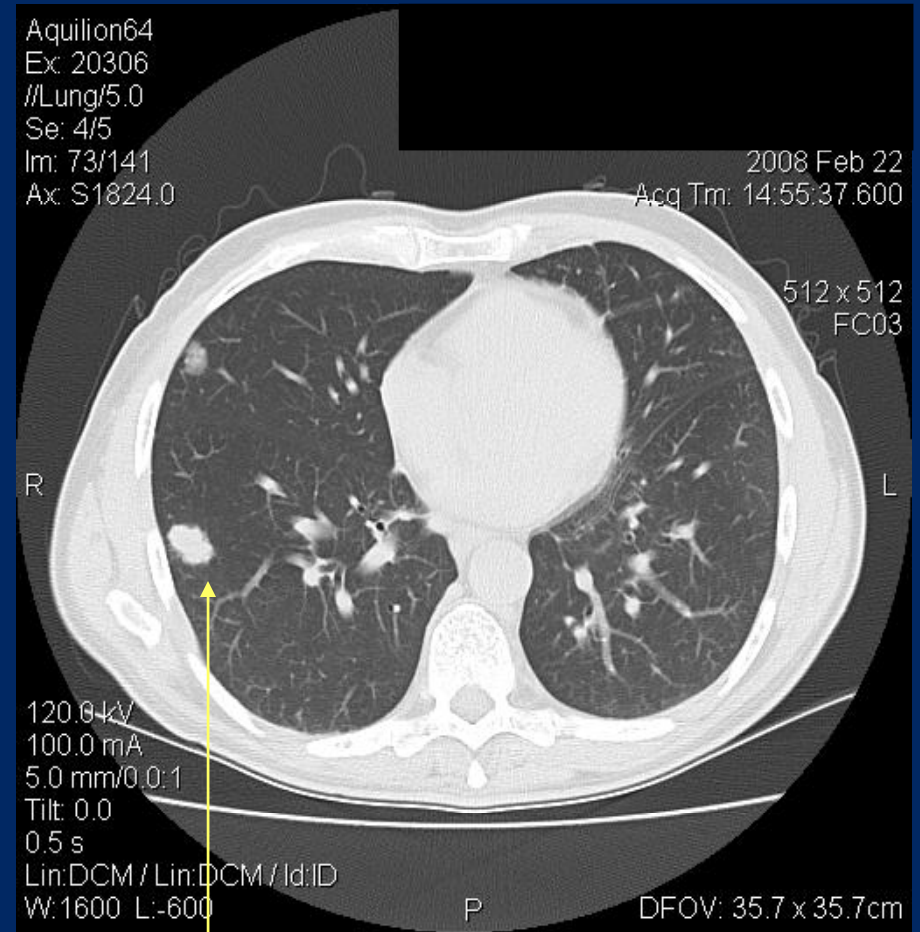
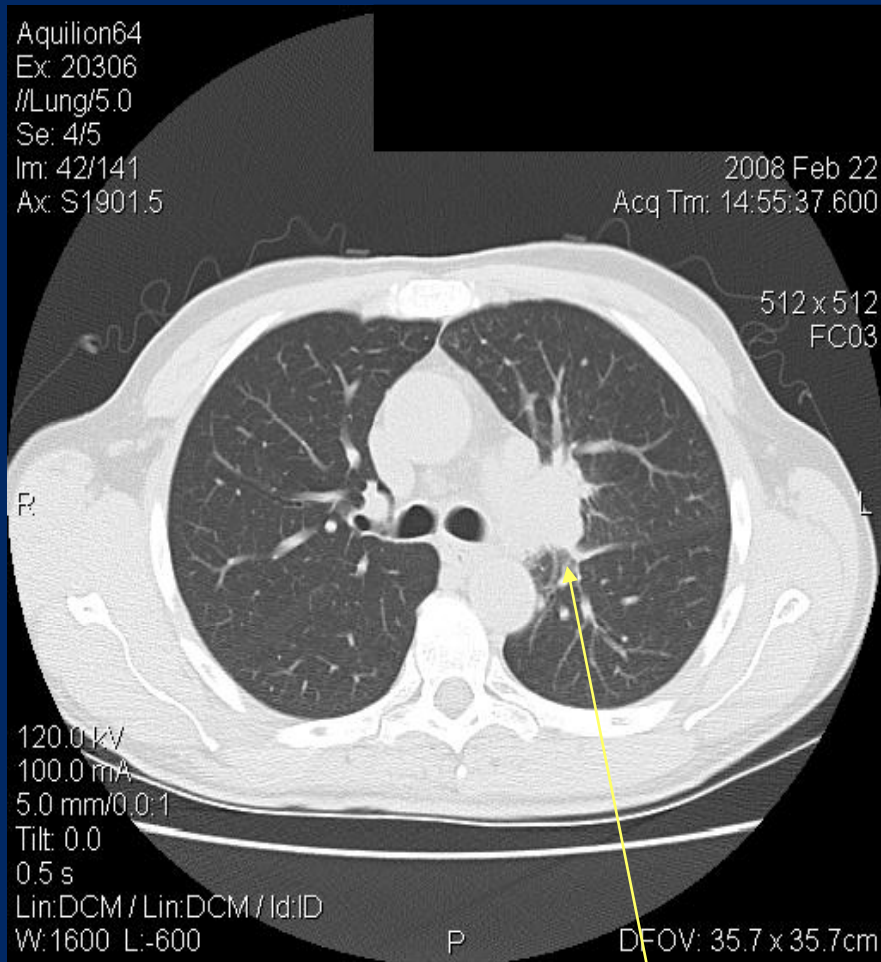
Arm 1

Standard RT: 70 Gy/35
over 7 weeks
Cisplatin 100 mg/m²
days 1, 22, 43

Arm 2

Accelerated RT: 70 Gy/35
over 6 weeks
Panitumumab 9 mg/kg
Q3w x 3 (starts 1
week before RT)

Metastatic/Recurrent HNSCC



EXTREME Study design

Randomized

Group A

Cetuximab 400 mg/m² initial dose
then 250 mg/m² weekly +
EITHER carboplatin (AUC 5, d1)
OR cisplatin (100 mg/m² IV, d1)
+ 5-FU (1000 mg/m² IV, d1-4):
3-week cycles

Group B

EITHER carboplatin (AUC 5, d1)
OR cisplatin (100 mg/m² IV, d1)
+ 5-FU (1000 mg/m² IV, d1-4):
3-week cycles

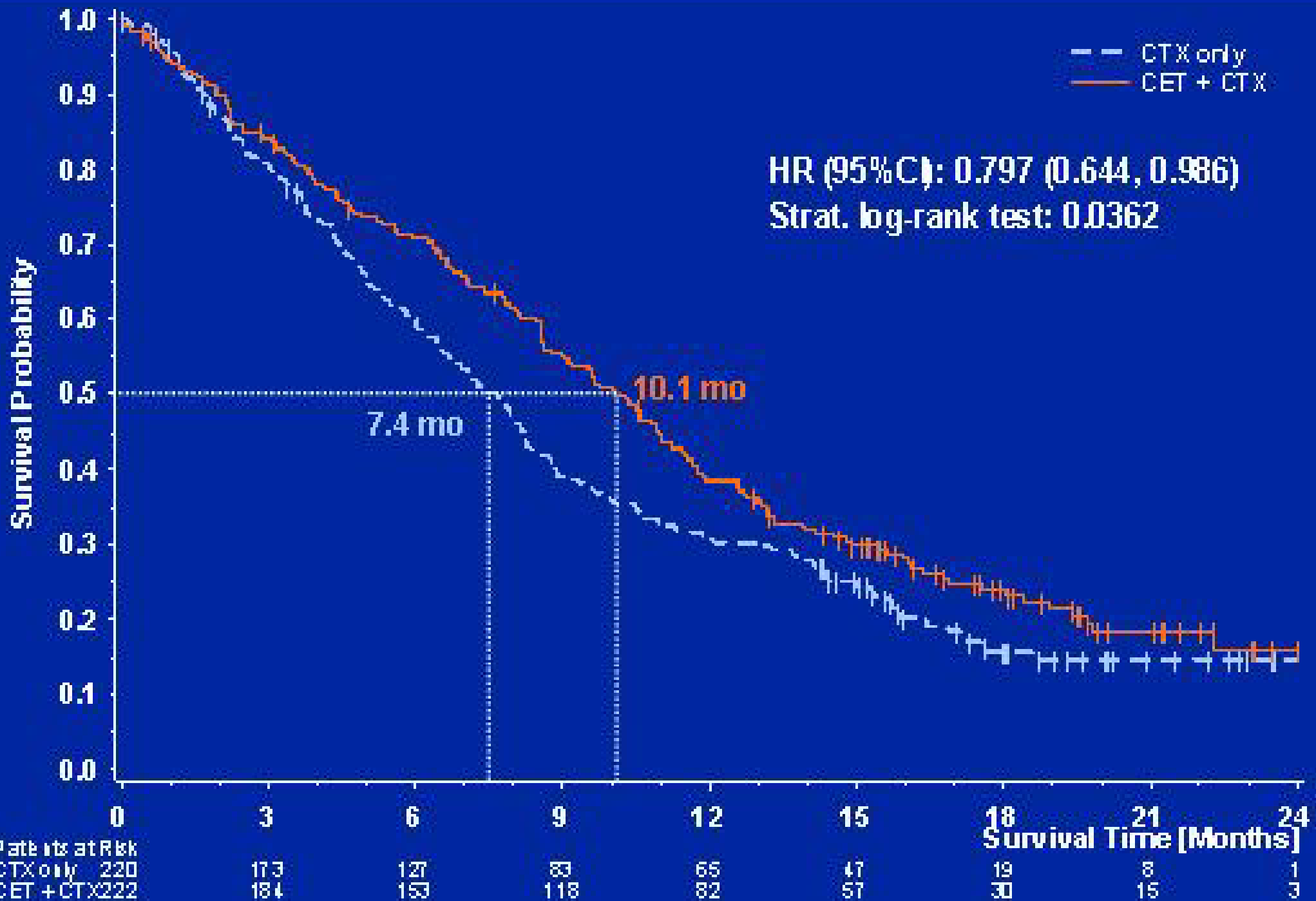
6 chemotherapy cycles maximum

Cetuximab

No treatment

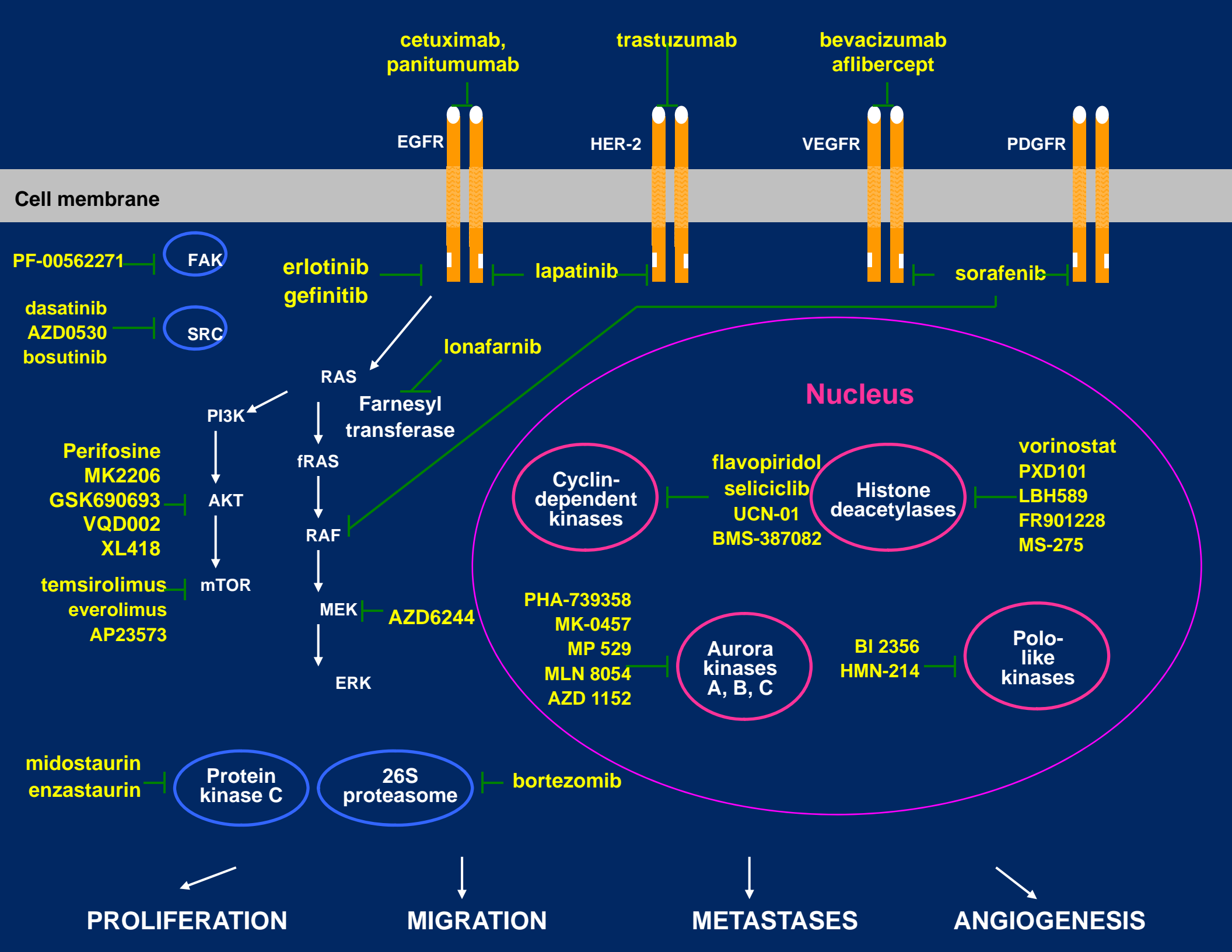
Progressive disease or unacceptable toxicity

Overall Survival



Activity of EGFR TK and other kinase inhibitors in recurrent/metastatic HNSCC

Drug	Setting	CR (%)	PR (%)	SD (%)	TTP or PFS (m)	OS (m)
Gefitinib 500 mg	1 st or 2 nd line	0-2.1	9	28-43	3-3.4	6-8
	2 nd or 3 rd line	0	2-7.6	26	2.6	4.3-6.7
Gefitinib 250 mg	2 nd or 3 rd line	0	1.4-2.7	32	1.8	5.5
Erlotinib	1 st or 2 nd line	0	4.3	34	2.3	6
Lapatinib	Without prior EGFRi	0	0	20	1.7	-
	With prior EGFRi	0	0	37	1.6	-
Sorafenib	1 st or 2 nd or 3 rd line	0	3.7	37	1.8	4.2
Sunitinib	1 st or 2 nd line: ECOG 0/1	0	8	25	2.2	5.3
	1 st or 2 nd line: ECOG 2	0	0	29	2.8	4.8



Preclinical

Early clinical trial

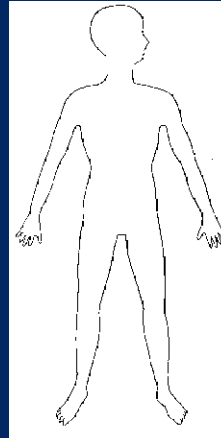
Confirmation and registration strategy

Drug discovery

- Target identification in head and neck cancer
- Proof of mechanism
- Proof of principle
- Development of potential biomarkers
- Toxicity
- Pharmacokinetics

Phase I trials

- Toxicity
- Pharmacokinetics
- Proof of concept
- Optimization of dose
- Optimisation of schedule
- Search for biological active dose



Phase II trials

Initial biopsy

Baseline evaluation e.g. (pre-operative, or first-line recurrent or metastatic disease):

- Tumor tissues, serum biomarker, functional imaging

Final biopsy

Post-treatment evaluation:

- Tumor tissues, serum biomarker, functional imaging
- Clinical outcome (e.g. Progression-free survival, objective response)
- Correlation between biomarkers and clinical outcome
- Identification of molecular biomarkers of resistance

Phase III trials

- Combination strategy
- Benchmarking for competitors