Updates in Multidisciplinary Treatment of Head and Neck Cancer

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Outline

• Background
• Curative treatments
• HPV and biomarkers
• Adjuvant chemotherapy
• Chemotherapy for metastatic disease
Changing face of Head and Neck Cancer
Background

• Morphology (95% squamous cell carcinoma)

• Clinical factors
  – Gender (male : female from 2:1 to 4:1)
  – Age (median age late 50’s)
  – Race
    • US rate in African American males x 2 Caucasian population
    • Asian populations and nasopharyngeal carcinoma
Anatomy and Morphology

Nasal Cavity / Paranasal
(Epithelial Malignancy)
- Squamous Cell Carcinoma
- Sinonasal Undifferentiated Carcinoma
- Olfactory Neuroblastoma / Esthesioneuroblastoma

(Non-Epithelial Malignancy)
- Mucosal Melanoma
- Osteosarcomas & Chondrosarcomas

Oral Cavity
- Squamous Cell Carcinoma
- Verrucous Carcinoma

Salivary Gland
- Squamous Cell Carcinoma
- Adenoid Cystic Carcinoma
- Mucoepidermoid Carcinoma
- Acinic Cell Carcinoma
- Adenocarcinoma

Trachea

Thyroid
- Papillary Carcinoma
- Follicular Carcinoma
- Medullary Thyroid Carcinoma
- Anaplastic Thyroid Carcinoma

Nasopharynx
- Squamous Cell Carcinoma
- Nasopharyngeal Carcinoma
  - Keratinizing
  - Non-Keratinizing
  - Undifferentiated
- Lymphomas

Oropharynx
- Squamous Cell Carcinoma
- Lymphoepitheliomas
- Lymphomas

Hypopharynx
- Squamous Cell Carcinoma

Larynx
- Squamous Cell Carcinoma
- Verrucous Carcinoma

Esophagus

Skin
- Squamous Cell Carcinoma
- Basal Cell Carcinoma
- Melanoma
Staging

• Small local tumors (stage I-II)
• Large local disease (Stage III-IVa/b)
  – Amenable to surgery
  – Not amenable to surgery
• Positive lymph nodes (Stage III-IVa/b)
• Metastatic disease (IVc RARE!)
  – Head and Neck Cancer is almost always potentially curable at presentation
  – Late metastatic disease rate? 5-20%
Epidemiology: Head and Neck Cancer is almost always potentially curable.

AJCC Survival – Oropharynx (1985-91)

- Cancer Specific Survival
  - Stage I – 57%
  - Stage II – 53%
  - Stage III – 43%
  - Stage IV - 30%

- Overall Survival
  - Stage I – 50%
  - Stage II – 47%
  - Stage III – 37%
  - Stage IV - 26%

10% of new cases present with metastases
Risk Factors

• Smoking / tobacco / marijuana
  – 80 % attributable risk historically
  – OR 6.5 for smokers
  – Gradual decline over 20 years

• Viral

• Other
GENOMICS OF HEAD AND NECK CARCINOMAS
Detailed characterization of a common and deadly cancer
PAGE 576

EXTREME TECHNICIANS
SUPPORTING ROLES
Quirky jobs that make science possible
PAGE 542

ARCHAEOLOGY
SINKING INTO THE DESERT
Time is running out for Libya’s cultural heritage
PAGE 547

CAREERS
WHO CAN YOU TURN TO?
Careers advice for the mid-term postdoc
PAGE 645
Pathways
Viral: Focus on HPV (type 16)

- Worldwide epidemic
- Oropharynx
- Sexually transmitted disease (Median age mid 40’s?)
- E6 / E7 (bind and inactivate p53 and RB)
- Different disease
  - Prognosis (response to therapy and pattern of spread)
  - Epidemiology
  - Treatment?
Treatment - Multidisciplinary Multimodality

• Surgery - Cornerstone of therapy
  – Diagnosis, staging, definitive, and palliative treatment

• Radiation – Cornerstone of therapy

• Chemotherapy - (cytotoxic chemotherapy, biologic therapy, and targeted agents)

• Curative treatment is USUALLY multimodality

• Disease specific mortality – 50%
The facts....
Chemotherapy added to locoregional treatment for head and neck squamous-cell carcinoma: three meta-analyses of updated individual data

J P Pignon, J Bourhis, C Domenge, L Designé, on behalf of the MACH-NC Collaborative Group*

- Chemo meta analysis
- 1995
- 63 trials
- 1965-1993
- 10,741 patients
- Outcomes
  - Neoadjuvant therapy
  - Adjuvant
  - Concomitant chemoradiation
## Effects of Chemotherapy on Survival at 5 Years: From the Meta-Analysis

<table>
<thead>
<tr>
<th>Trial Category</th>
<th>No. of Trials</th>
<th>No. Patients</th>
<th>Difference(%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All trials</td>
<td>65</td>
<td>10850</td>
<td>+4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Adjuvant</td>
<td>8</td>
<td>1854</td>
<td>+1</td>
<td>0.74</td>
</tr>
<tr>
<td>Induction</td>
<td>31</td>
<td>5269</td>
<td>+2</td>
<td>0.10</td>
</tr>
<tr>
<td>PF</td>
<td>15</td>
<td>2487</td>
<td>+5</td>
<td>0.01</td>
</tr>
<tr>
<td>Other Chemo</td>
<td>16</td>
<td>2782</td>
<td>0</td>
<td>0.91</td>
</tr>
<tr>
<td>Concomitant</td>
<td>26</td>
<td>3727</td>
<td>+8</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Pignon Meta-analysis – multiple citations
Take Home

- **Concomitant therapy improve survival**

- **Adjuvant**
  - complex

- **Induction**
  - Uncertain benefit but high response rates

- **Specific regimens unclear**
  - Drugs
  - Doses
  - Schedules
VA Larynx Trial

• First large trial comparing induction chemotherapy followed by definitive radiation to surgery followed by adjuvant radiation.

• 332 patients with glottic or supraglottic tumors.
VA Larynx Study

PF: Cisplatin $100_{D1} + 5$-FU $1000_{CI-D1-5} \quad Q 3 \ weeks = \text{STANDARD}$
VA Larynx Trial

- 85% PR to PF in the induction arm.
- 31% CR in the induction arm at the primary site after 2 cycles of chemo.
- 49% CR after 3 cycles.
- 15% failed to obtain at least a PR to 2 cycles of PF and thus required a laryngectomy.
VA Larynx Trial

• 64% of the patients in the chemotherapy and radiation arm were able to preserve their larynx.

• Overall survival was equivalent between the surgery arm and the larynx preserving arm.
Intergroup 91-11

• Is chemotherapy plus radiation better than radiation alone for organ preservation?

• Is concurrent chemoradiation superior to sequential therapy?
Intergroup 91-11

PF: Cisplatin 100_d1_ + 5-FU 1000_CI-D1-5_ Q 3 weeks
Intergroup 91-11

• Distant metastasis similar between the induction group and the concurrent chemoradiotherapy group.

• Overall Survival was exactly the same between the 3 groups approximately 55% at 5 years.

• This trial made concurrent chemoradiotherapy the standard of care for larynx preserving therapy.
However...

Induction Chemotherapy
Induction Chemotherapy – Continued Interest

• To select patients more likely to respond to definitive chemoradiation.

• Improve the induction chemotherapy regimen.

• In combination with concurrent chemoradiation.
TAX 324: **Sequential Combined Modality Therapy**
TPF vs PF Followed by Chemoradiotherapy

**TPF:** Docetaxel 75\textsubscript{D1} + Cisplatin 100\textsubscript{D1} + 5-FU 1000\textsubscript{CI-D1-4} Q 3 weeks x3

**PF:** Cisplatin 100\textsubscript{D1} + 5-FU 1000\textsubscript{CI-D1-5} Q 3 weeks x3

Carboplatinum - AUC 1.5 Weekly
Daily Radiotherapy
Surgery as Needed

M. Posner ASCO 2006
Inclusion / Exclusion

• Inclusion
  – Stage III or IV SCC
  – Unresectable or of low surgical curability on the basis of advanced tumor stage (3 or 4) or regional-node stage (2 or 3, except T1N2)
  – Or candidate for organ preservation
  – PS 0-1

• Exclusion
  – Severe weight loss
  – COPD
TAX324: Survival

Log-Rank P = 0.0058
Hazard Ratio = 0.70

Number of patients at risk
TPF: 255 234 196 176 163 136 105 72 52 45 37 20 11
PF: 246 223 169 146 130 107 85 57 36 32 28 10 7

Slide obtained from M. Posner presentation at ASCO 2006
However…

Is sequential therapy superior to concurrent?
Negative Induction Trials

**DeCIDE Trial**

**Paradigm Trial**

**Recurrence-Free Survival by Treatment Arm**

**PARADIGM: Progression Free Survival**

<table>
<thead>
<tr>
<th></th>
<th>Arm A (ST)</th>
<th>Arm B (CRT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>#PFS Events</td>
<td>23</td>
<td>22</td>
</tr>
<tr>
<td>3 Year PFS</td>
<td>67%</td>
<td>69%</td>
</tr>
<tr>
<td>HR (95CI) p-value</td>
<td>1.07^ (0.59-1.92) 0.82</td>
<td></td>
</tr>
<tr>
<td>3 Year PFS - Non Oropharynx</td>
<td>66%</td>
<td>55%</td>
</tr>
<tr>
<td>3 Year PFS - Oropharynx</td>
<td>67%</td>
<td>83%</td>
</tr>
</tbody>
</table>

*Sequential vs. Concurrent*
HPV story

- HPV generally associated with:
  - lower risk profile
  - younger age and fewer comorbidities
  - Higher stage (node positive)!
- HPV may be associated with higher response rates
- Higher local control rates but distant metastasis rate may be similar to non-HPV tumors
- No consensus diagnostic (p16, ISH, IHC, PCR)
- No prospective trials data
743 patients from RTOG 0129 randomized between receive accelerated-fractionation radiotherapy or standard-fractionation
Survival by Stage in Oropharyngeal SCCHN:

1995-2004 UNC Chapel Hill (n=482)

1998-1999 (SEER) from AJCC 7th Edition
“De-intensification” Strategies

70 Gy + Cisplatin 300mg/m²
7 weeks

“Standard of Care”

70 Gy + Cetuximab
6 weeks

“Gentler Chemo & No decrease in Radiotherapy”
➢ RTOG 1016 (phase III)

Neoadjuvant Chemo
9 weeks

50 to 60 Gy + Chemo
5 to 6 weeks

“Tougher Chemo ➔ Less Radiotherapy”
➢ ECOG 1308 (Phase II)
➢ Outback trial (Phase III)

Transoral Surgery

Risk Adapted Radiation/Chemotherapy
5 to 6 weeks

“Surgery ➔ Less Radiotherapy/Chemotherapy”
➢ ECOG 3311 (Phase II)

60 Gy + Cisplatin 180mg/m²
6 weeks

UNC De-intensification Regimen

UNC Phase II De-Intensification Study

- **Eligibility**
  - T0-3, N0 to N2c, M0
  - Oropharyngeal or Unknown primary
  - Squamous cell carcinoma, HPV and/or p16 positive
  - Minimal smoking history

- **De-intensified Chemoradiotherapy**
  - 60 Gy at 2 Gy/fx, daily, 6 weeks (IMRT)
  - Cisplatin 30mg/m², 6 weekly doses

- **Primary endpoint is path CR rate** \( \Rightarrow H_0 \) is pCR 87%
  - 6 to 14 weeks after CRT all patients get biopsy of primary site and resection of initially positive nodes

- **Secondary endpoints**:
  - Toxicity, Quality of Life
  - Clinical outcomes: LRC, DMFS, OS

**10 Gy reduction**
**40% chemo reduction**
## Results

<table>
<thead>
<tr>
<th></th>
<th>Complete Pathological Response</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total (N=43)</strong></td>
<td>37/43 (86%)</td>
</tr>
<tr>
<td><strong>Primary</strong></td>
<td>40/41 (98%)</td>
</tr>
<tr>
<td>(2 were T0)</td>
<td></td>
</tr>
<tr>
<td><strong>Neck</strong></td>
<td>33/39 (84%)</td>
</tr>
<tr>
<td>(4 were N0)</td>
<td>(all microscopic foci)</td>
</tr>
</tbody>
</table>

All patients alive with no evidence of disease
(median f/u 20 months, 4-37 months)
<table>
<thead>
<tr>
<th>Acute Toxicities (up to 6 weeks post CRT)</th>
<th>CTCAE version 4.0 (Grade 3 or 4)</th>
<th>Patient Reported Outcomes-CTCAE (Severe/Very severe)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Hematologic</td>
<td>10</td>
<td>n/a</td>
</tr>
<tr>
<td>Nonhematologic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Xerostomia</td>
<td>2%</td>
<td>75%</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>39%</td>
<td>55%</td>
</tr>
<tr>
<td>Mucositis</td>
<td>34%</td>
<td>45%</td>
</tr>
<tr>
<td>Nausea/Vomiting</td>
<td>18%</td>
<td>34%</td>
</tr>
<tr>
<td>Dermatitis</td>
<td>5%</td>
<td>34%</td>
</tr>
<tr>
<td>Pain</td>
<td>5%</td>
<td>48%</td>
</tr>
<tr>
<td>Osteonecrosis of jaw</td>
<td>3%</td>
<td>n/a</td>
</tr>
<tr>
<td>Surgical</td>
<td>16%</td>
<td>n/a</td>
</tr>
</tbody>
</table>

- 39% required a feeding tube, for a median of 15 weeks (7 - 22 weeks)
- No permanent feeding tubes
Conclusion on HPV

Early in understanding of predictive versus prognostic significance

BE CAREFUL: Undertreatment carries a bigger risk because treatment mortality is low
Future?
Induction Chemotherapy and Cetuximab for Locally Advanced Squamous Cell Carcinoma of the Head and Neck: Results From a Phase II Prospective Trial


- **Diagnostic biopsy, staging, and functional awareness assay** (N = 47)
  - Weekly chemotherapy
    - Cetuximab 400 mg/m² wk 1
    - 250 mg/m² wks 2-6
    - Paclitaxel 135 mg/m² wks 1-6
    - Carboplatin (AUC 2) wks 1-6

- **Assessment of response**
- **Assignment based on site/staging at diagnosis**
  - Radiation (n = 23)
  - Chemo RT (n = 23)
  - Surgery (n = 1)

Radiation as a single modality if T1-2
Concomitant chemotherapy radiation if T3-4 or
Surgery if an oral cavity was the primary site
Table 3. Responses to Induction Chemotherapy

<table>
<thead>
<tr>
<th>Clinoradiographic Assessment After PCC</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
</tr>
<tr>
<td>Primary tumor</td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>30</td>
</tr>
<tr>
<td>PR</td>
<td>13</td>
</tr>
<tr>
<td>Stable disease</td>
<td>0</td>
</tr>
<tr>
<td>Neck</td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>10</td>
</tr>
<tr>
<td>PR</td>
<td>34</td>
</tr>
<tr>
<td>Stable disease</td>
<td>2</td>
</tr>
<tr>
<td>Overall response (primary tumor and neck)</td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>9</td>
</tr>
<tr>
<td>PR</td>
<td>36</td>
</tr>
<tr>
<td>Stable disease</td>
<td>2</td>
</tr>
</tbody>
</table>

Abbreviations: PCC, paclitaxel, carboplatin, and cetuximab; CR, complete response; PR, partial response.
Concurrent Chemoradiation
Intergroup 91-11

PF: Cisplatin 100$_{D1}$ + 5-FU 1000$_{CI-D1-5}$ Q 3 weeks
Optimal Radiation

- Tolerability - IMRT
- Efficacy – Altered fractionation (RTOG 0219)
- Convenience

### Table 1. Optimal Schedules of RT As Single Modality for Advanced HNC

<table>
<thead>
<tr>
<th>Phase III Trial</th>
<th>RT Control</th>
<th>RT Experimental</th>
<th>Outcome</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>EORTC 22791(^{85})  (n = 356)</td>
<td>2 Gy daily; 70 Gy/7 weeks</td>
<td>1.15 Gy bid; 80 Gy/7 weeks</td>
<td>19% improvement; LC</td>
<td>Hyperfractionation</td>
</tr>
<tr>
<td>RTOG 90-03(^{86}) (n = 1,073)</td>
<td>2 Gy daily; 70 Gy/7 weeks</td>
<td>1.8/1.5 Gy bid; 72 Gy/6 weeks</td>
<td>8.5% improvement; LC</td>
<td>Accelerated fractionation</td>
</tr>
<tr>
<td>RTOG 90-03(^{86}) (n = 1,073)</td>
<td>2 Gy daily; 70 Gy/7 weeks</td>
<td>1.2 Gy bid; 79 Gy/7 weeks</td>
<td>8.5% improvement; LC</td>
<td>Hyperfractionation</td>
</tr>
<tr>
<td>DAHANCA(^{67})  (n = 1,476)</td>
<td>2 Gy daily; 70 Gy/7 weeks</td>
<td>2 Gy qd (6 x/week); 70 Gy/6 weeks</td>
<td>10% improvement; LC and DSS</td>
<td>Accelerated fractionation</td>
</tr>
</tbody>
</table>

Abbreviations: RT, radiotherapy; HNC, nonmetastatic squamous carcinoma of the head and neck; EORTC, European Organisation for the Research and Treatment of Cancer; LC, local control; RTOG, Radiation Therapy Oncology Group; DAHANCA, Danish Head and Neck Cancer; hyperfractionation, increased total dose during standard 7 week treatment course; accelerated fractionation, same total dose but reduced overall treatment time; DSS, disease-specific survival.
Optimal Chemotherapy

- Tolerability
- Efficacy
- Convenience

<table>
<thead>
<tr>
<th>Phase III Trial</th>
<th>RT</th>
<th>CRT</th>
<th>CT</th>
<th>Cisplatin Dosing</th>
<th>Survival (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duke University²² (n = 122)</td>
<td>75</td>
<td>70</td>
<td>Cisplatin, FU</td>
<td>12 mg/m²²/d, two 5-day cycles</td>
<td>40 v 29</td>
<td>.05</td>
</tr>
<tr>
<td>Yugoslavian Cooperative Group³⁴ (n = 130)</td>
<td>77</td>
<td>77</td>
<td>Cisplatin</td>
<td>6 mg/m²²/d daily</td>
<td>46 v 25</td>
<td>.008</td>
</tr>
<tr>
<td>FNLCC/GORTEC³⁷ (n = 171)</td>
<td>80</td>
<td>80</td>
<td>Cisplatin, FU</td>
<td>100 mg/m²²/d, three cycles</td>
<td>48 v 36</td>
<td>.05</td>
</tr>
<tr>
<td>Charité University³⁸,³⁹ (n = 284)</td>
<td>78</td>
<td>70</td>
<td>Mitomycin, FU</td>
<td>—</td>
<td>29 v 24</td>
<td>.008</td>
</tr>
<tr>
<td>Swiss Cooperative Group⁷⁰ (n = 224)</td>
<td>74</td>
<td>74</td>
<td>Cisplatin</td>
<td>20 mg/m²²/d, two 5-day cycles</td>
<td>46 v 32</td>
<td>.15</td>
</tr>
</tbody>
</table>

NOTE: RT-only control arms all deliver > 70 Gy in ≤ 7 weeks.
Abbreviations: CRT, chemoradiotherapy; RT, radiotherapy; CT, chemotherapy; FNLCC, Fédération Nationale des Centres de Lutte Contre le Cancer; GORTEC, Groupe Oncologie Radiothérapie Tête et Cou; FU, fluorouracil.
Arm 1: cisplatin, 10 mg/m² daily and FU 400 mg/m² continuous infusion daily for the final 10 days of radiation treatment.

Arm 2: consisted of hydroxyurea 1 gram every 12 hours (given orally, 11 doses per cycle) and FU 800 mg/m²/d continuous infusion delivered concurrently with each daily fraction of radiation.

Arm 3: received paclitaxel 30 mg/m² every Monday and cisplatin 20 mg/m² every Tuesday.

Fig 2. Disease-free survival. NED, no evidence of disease; RT, radiation therapy; FU, fluorouracil.
EGF-induced Signal Transduction and Tumorigenesis

- EGFR is a large tyrosine kinase growth factor receptor
- Activated by binding of endogenous ligands
  - EGF
  - Transforming growth factor alpha (TGF-α)
- Activated EGFR signals through Ras, MAPK, PI3K/akt, and STAT
- Results in cell-cycle progression and proliferation
- Blockade of EGFR can prevent
  - Proliferation
  - Survival
  - Angiogenesis
  - Invasion/metastasis
Phase III Trial: Cetuximab + RT vs RT Alone in Locally or Regionally Advanced SCCHN

Treatment Schema

Untreated Patients

Eligibility
- Stage III/IV disease
- Measurable disease: squamous cell carcinoma of the oropharynx, hypopharynx, or larynx
- No distant metastases
- No prior systemic therapy within last 3 years, surgery, or radiation therapy

Stratification
- T1-3 vs T4
- N0 vs N+
- RT fractionation
- KPS (60%-80% vs 90%-100%)

RANDOMIZATION
No testing for EGFR required

Cetuximab + RT (n = 211)
- RT (daily, twice daily, or Concomitant Boost)
  - plus
  - Cetuximab loading dose 400 mg/m² starting 1 wk before RT followed by 250 mg/m² weekly
  (completed 1 hr prior to RT for duration of RT [6-7 wk])

RT Alone (n = 213)
- QD 70.0 Gy in 35 fractions/7 wk
  - or
- Twice daily 72.0-76.8 Gy in 60-64 fractions/6-6.5 wk
  - or
- Concomitant boost 72.0 Gy in 42 fractions/6 wk

RT = radiation therapy; SCCHN = squamous cell carcinoma of the head and neck; KPS = Karnofsky performance status; IHC = immunohistochemistry; EGFR = epidermal growth factor receptor.
Cetuximab + RT in Loco-regionally Advanced SCCHN: Overall Survival


<table>
<thead>
<tr>
<th></th>
<th>Cetuximab w/ RT</th>
<th>RT Alone</th>
<th>HR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median survival (mo)</td>
<td>49.0</td>
<td>29.3</td>
<td>0.74</td>
<td>0.03</td>
</tr>
<tr>
<td>(95% CI)</td>
<td></td>
<td></td>
<td>(0.57-0.95)</td>
<td></td>
</tr>
</tbody>
</table>

Overall survival (%) over time:
- Radiotherapy plus cetuximab
- Radiotherapy alone

Months

0 10 20 30 40 50 60 70

Radiotherapy plus cetuximab
Radiotherapy
Cetuximab + RT in Loco-regionally Advanced SCCHN: Adverse Events

<table>
<thead>
<tr>
<th>Toxicity (All Grades)</th>
<th>RT Alone (N=212)</th>
<th>Cetuximab +RT (N=208)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mucositis (%)</td>
<td>94</td>
<td>93</td>
</tr>
<tr>
<td>Acneform rash (%)</td>
<td>10</td>
<td>87*</td>
</tr>
<tr>
<td>Radiation dermatitis (%)</td>
<td>90</td>
<td>86</td>
</tr>
<tr>
<td>Weight loss (%)</td>
<td>72</td>
<td>84†</td>
</tr>
<tr>
<td>Xerostomia (%)</td>
<td>71</td>
<td>72</td>
</tr>
<tr>
<td>Infusion reaction (%)§</td>
<td>2</td>
<td>15*</td>
</tr>
</tbody>
</table>

*P<0.001; †P=0.005, Fisher’s exact test.
§Listed for its relationship to cetuximab.

Increased Efficacy

Adding agent with non-overlapping and low toxicity
RTOG 0522: Phase III Trial of Cisplatin Chemoradiation +/- Cetuximab in Advanced SCCHN (Accrual Achieved!)

Postoperative Stage III or IV SCCHN

Stratify
- Nodal disease
- ECOG status
- Prior radiation
- PET/CT
- Primary site

RANDOMIZE

n=720

Cetuximab 400 mg/m² d1, then 250 mg/m² weeks 2-8
+ Radiotherapy weeks 2-7
+ Cisplatin 100 mg/m² d8, 20

No cetuximab only arm

Radiotherapy weeks 1-6
+ Cisplatin 100 mg/m² d1, 22

Following chemoradiotherapy, patients with poor response are to proceed to surgery.

RTOG 0522
Progression-Free Survival & Overall Survival

### Progression-Free Survival (%)

- **Hazard Ratio (95% CI):** 1.05 (0.84, 1.29)
- **P-value:** 0.66 (log-rank, 1-sided)
- **2-Year Rate (95% CI):**
  - Cisplatin: 64.3% (59.7, 68.8)
  - Cisplatin+Cet: 63.4% (58.7, 68.0)

### Overall Survival (%)

- **Hazard Ratio (95% CI):** 0.87 (0.66, 1.15)
- **P-value:** 0.17 (log-rank, 1-sided)
- **2-Year Rate (95% CI):**
  - Cisplatin: 79.7% (75.9, 83.6)
  - Cisplatin+Cet: 82.6% (78.9, 86.3)

---

# Patients at Risk

- **Years after Randomization:**
  - Cisplatin: 448, 316, 217, 78
  - Cisplatin+Cet: 447, 302, 197, 80

---

# Patients at Risk (Overall Survival)

- **Years after Randomization:**
  - Cisplatin: 448, 385, 266, 96
  - Cisplatin+Cet: 447, 378, 251, 94
Adjuvant
## Risk of Recurrence

<table>
<thead>
<tr>
<th>Risk Level</th>
<th>RTOG 85-03</th>
<th>M.D. Anderson Cancer Center</th>
<th>University of Pennsylvania</th>
<th>UZ Amsterdam</th>
<th>EORTC/RTOG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Highest risk</td>
<td>Margin s</td>
<td>ECS; 2+ factors</td>
<td>ECS; margins; 2+ LNs</td>
<td>ECS in 2+ LNs; T3 (with margins); pN3</td>
<td>ECS; margins</td>
</tr>
<tr>
<td>Intermediate or high risk</td>
<td>2+ LNs; ECS</td>
<td>1 risk factor</td>
<td>1 risk factor</td>
<td>ECS in 1 LN; T1-2,T4; with margins</td>
<td>Perineural invasion; LN+ at levels 4-5 in oropharynx and oral cavity cancer patients; vascular embolisms; and stage III-IV</td>
</tr>
</tbody>
</table>
Table 2. Main Prospective Trials on Adjuvant Treatments Comparing Chemoradiotherapy With Radiotherapy Alone After Primary Surgery

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>No. of Patients</th>
<th>Sites</th>
<th>Type of CT</th>
<th>P</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weissberg et al</td>
<td>1989</td>
<td>120</td>
<td>*</td>
<td>Mitomycin</td>
<td>&lt; .01</td>
<td>NS</td>
</tr>
<tr>
<td>Bachaud et al</td>
<td>1991</td>
<td>88</td>
<td>†</td>
<td>Cisplatin</td>
<td>&lt; .01</td>
<td>NS</td>
</tr>
<tr>
<td>Weissler et al</td>
<td>1992</td>
<td>26</td>
<td>†</td>
<td>Cisplatin, fluorouracil</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Haffty et al</td>
<td>1993</td>
<td>120</td>
<td>†</td>
<td>Mitomycin</td>
<td>&lt; .01</td>
<td>NS</td>
</tr>
<tr>
<td>Smid et al</td>
<td>2003</td>
<td>114</td>
<td>†</td>
<td>Mitomycin, bleomycin</td>
<td>.037</td>
<td>.036</td>
</tr>
<tr>
<td>Bernier et al</td>
<td>2004</td>
<td>334</td>
<td>†</td>
<td>Cisplatin</td>
<td>.007</td>
<td>.02</td>
</tr>
<tr>
<td>Cooper et al</td>
<td>2004</td>
<td>459</td>
<td>†</td>
<td>Cisplatin</td>
<td>.01</td>
<td>.19</td>
</tr>
</tbody>
</table>

Abbreviations: CT, chemotherapy; LRC, local-regional control.
*Oral cavity; naso-, oro-, and hypopharynx; larynx.
†Oral cavity; oro-, and hypoparynx; larynx.

Postoperative Irradiation with or without Concomitant Chemotherapy for Locally Advanced Head and Neck Cancer

Jacques Bernier, M.D., Ph.D., Christian Domenge, M.D., Mahmut Ozsahin, M.D., Ph.D., Katarzyna Matuszewska, M.D., Jean-Louis Lefèvre, M.D., Richard H. Greiner, M.D., Jordi Giralt, M.D., Philippe Maingon, M.D., Frédéric Rolland, M.D., Michel Bolla, M.D., Francesco Cognetti, M.D., Jean Bourhis, M.D., Anne Kirkpatrick, M.Sc., and Martine van Glabbeke, M.D., M.Sc., for the European Organization for Research and Treatment of Cancer Trial 22931

The NEW ENGLAND JOURNAL of MEDICINE

Postoperative Concurrent Radiotherapy and Chemotherapy for High-Risk Squamous-Cell Carcinoma of the Head and Neck

Recurrent Disease
<table>
<thead>
<tr>
<th>Agent</th>
<th>No. of Patients Assessable</th>
<th>Response Rate (%)</th>
<th>Median Survival (months)</th>
<th>Year of Publication</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methotrexate</td>
<td>8-37 (average 31)</td>
<td></td>
<td></td>
<td>1984</td>
<td>9, 8</td>
</tr>
<tr>
<td>Bleomycin</td>
<td>6-45 (average 21)</td>
<td></td>
<td></td>
<td>1977-84</td>
<td>9, 89</td>
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<tr>
<td>Cisplatin</td>
<td>14-41 (average 28)</td>
<td></td>
<td></td>
<td>1983-94</td>
<td>9, 34, 35, 90</td>
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<tr>
<td>Carboplatin</td>
<td>25</td>
<td></td>
<td></td>
<td>1986</td>
<td>91</td>
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<tr>
<td>Oxaliplatin</td>
<td>10</td>
<td></td>
<td></td>
<td>1996</td>
<td>71</td>
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<tr>
<td>Cyclophosphamide</td>
<td>36</td>
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<td>1980</td>
<td>92</td>
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<tr>
<td>Doxorubicin</td>
<td>24</td>
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<td>1980</td>
<td>92</td>
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<tr>
<td>Hydroxyurea</td>
<td>18</td>
<td></td>
<td>39</td>
<td>1990</td>
<td>10</td>
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<tr>
<td>Vinblastine</td>
<td>29</td>
<td></td>
<td></td>
<td>1980</td>
<td>10</td>
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<tr>
<td>Vinorelbine</td>
<td>6</td>
<td></td>
<td></td>
<td>1994</td>
<td>74</td>
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<tr>
<td>Fluorouracil</td>
<td>15</td>
<td></td>
<td></td>
<td>1984</td>
<td>9</td>
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<tr>
<td>Gemcitabine</td>
<td>61</td>
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<td>13</td>
<td>1994</td>
<td>93</td>
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<tr>
<td>Capecitabine</td>
<td>14</td>
<td></td>
<td>8</td>
<td>2003</td>
<td>94</td>
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<tr>
<td>Orzel</td>
<td>42</td>
<td></td>
<td>21</td>
<td>2001</td>
<td>95</td>
</tr>
<tr>
<td>Irinotecan</td>
<td>0-14</td>
<td></td>
<td></td>
<td>2005</td>
<td>72</td>
</tr>
<tr>
<td>Paclitaxel 24-hour infusion</td>
<td>34</td>
<td></td>
<td>40 (4 CRs)</td>
<td>1998</td>
<td>39</td>
</tr>
<tr>
<td>Paclitaxel 96-hour infusion</td>
<td>Chemotherapy naïve/paclitaxel naïve/paclitaxel exposed</td>
<td>13/1/0</td>
<td>5.5</td>
<td>2004</td>
<td>41</td>
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<tr>
<td>Docetaxel</td>
<td>21-42</td>
<td></td>
<td></td>
<td>1994-2005</td>
<td>36-38, 96</td>
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<td>Pemetrexed</td>
<td>35</td>
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<td>26</td>
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<td>Ifosfamide</td>
<td>26</td>
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<td>Cetuximab</td>
<td>103</td>
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<td>Erlotinib</td>
<td>115</td>
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<td>73</td>
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<td>Gefitinib</td>
<td>47</td>
<td></td>
<td>11</td>
<td>2003</td>
<td>70</td>
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<tr>
<td>Sorafenib (BAY 43-9006)</td>
<td>10</td>
<td></td>
<td>6 SD (60%); 4 SCCHN + 2 NPC; range. 3-6 cycles</td>
<td>2005</td>
<td>87</td>
</tr>
</tbody>
</table>

Abbreviations: SCCHN, squamous cell carcinoma of the head and neck; CR, complete response; SD, stable disease; NPC, nasopharyngeal carcinoma.
<table>
<thead>
<tr>
<th>Agent</th>
<th>No. of Patients Assessable</th>
<th>Response Rate (%)</th>
<th>Survival (months)</th>
<th>Year of Publication</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatin + fluorouracil</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Locally recurrent post-XRT</td>
<td>19</td>
<td>89</td>
<td>8</td>
<td>1984</td>
<td>32</td>
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<tr>
<td>Metastatic</td>
<td>11</td>
<td>36</td>
<td>6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>30</td>
<td>70 (27% CR)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Cisplatin + fluorouracil</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>No prior treatment</td>
<td>31</td>
<td>84 (23% CR)</td>
<td></td>
<td>1985</td>
<td>31</td>
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<tr>
<td>Recurrent post-XRT</td>
<td>30</td>
<td>50 (1% CR)</td>
<td>9</td>
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<tr>
<td>Docetaxel + fluorouracil</td>
<td>17</td>
<td>24</td>
<td></td>
<td>2000</td>
<td>63</td>
</tr>
<tr>
<td>Prior chemotherapy</td>
<td>20</td>
<td>25</td>
<td></td>
<td>2004</td>
<td>62</td>
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<tr>
<td>No prior chemotherapy</td>
<td>43</td>
<td>19</td>
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<tr>
<td>Paclitaxel + cisplatin</td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>3-hour IV</td>
<td>36</td>
<td>41 (6 CR)</td>
<td>11</td>
<td>2004</td>
<td>47</td>
</tr>
<tr>
<td>No prior chemotherapy; 3-hour IV</td>
<td>50</td>
<td>22 (10% CR)</td>
<td>10</td>
<td>2002</td>
<td>61</td>
</tr>
<tr>
<td>Paclitaxel + carboplatin</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Paclitaxel 3-hour IV</td>
<td>37</td>
<td>27 (3% CR)</td>
<td>4.9</td>
<td>2001</td>
<td>59</td>
</tr>
<tr>
<td>Paclitaxel 1-hour IV weekly</td>
<td>31</td>
<td>52 (3 CR)</td>
<td>12.8</td>
<td>2003</td>
<td>57</td>
</tr>
<tr>
<td>Docetaxel + cisplatin</td>
<td>40</td>
<td>53 (18% CR)</td>
<td>11</td>
<td>2002</td>
<td>58</td>
</tr>
<tr>
<td>No prior chemotherapy</td>
<td>34</td>
<td>53 (17% CR)</td>
<td></td>
<td>2002</td>
<td>60</td>
</tr>
<tr>
<td>Cisplatin + vinorelbine</td>
<td>42</td>
<td>33 (10% CR)</td>
<td>6</td>
<td>2002</td>
<td>98</td>
</tr>
<tr>
<td>TIP</td>
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<td></td>
<td></td>
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<tr>
<td>Paclitaxel 3-hour IV</td>
<td>53</td>
<td>58 (17% CR)</td>
<td>8.8</td>
<td>1998</td>
<td>66</td>
</tr>
<tr>
<td>TIC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paclitaxel 3-hour IV</td>
<td>56</td>
<td>59 (17% CR)</td>
<td>9.1</td>
<td>2001</td>
<td>67</td>
</tr>
<tr>
<td>TPF</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Chemotherapy naive</td>
<td>19</td>
<td>44 (12.5% CR)</td>
<td>11</td>
<td>2000</td>
<td>68</td>
</tr>
<tr>
<td>Docetaxel + irinotecan</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemotherapy naive</td>
<td>17</td>
<td>18</td>
<td>9.8</td>
<td>2005</td>
<td>99</td>
</tr>
<tr>
<td>Prior chemotherapy</td>
<td>34</td>
<td>3</td>
<td>4.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cetuximab + cisplatin</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Prior PD to cisplatin</td>
<td>96</td>
<td>10</td>
<td>6.5</td>
<td>2005</td>
<td>81</td>
</tr>
<tr>
<td>Gefitinib, docetaxel, and cisplatin</td>
<td>24</td>
<td>50 (30% CR)</td>
<td></td>
<td>2005</td>
<td>82</td>
</tr>
<tr>
<td>Cetuximab + cisplatin or carboplatin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No response to prior platinum</td>
<td>132</td>
<td>13</td>
<td>6.5</td>
<td>2005</td>
<td>83</td>
</tr>
<tr>
<td>Erlotinib + bevacizumab</td>
<td>48</td>
<td>15</td>
<td>8.8</td>
<td>2005</td>
<td>80</td>
</tr>
<tr>
<td>Gefitinib + celecoxib</td>
<td>19</td>
<td>22</td>
<td></td>
<td>2005</td>
<td>79</td>
</tr>
</tbody>
</table>

Abbreviations: XRT, radiotherapy; CR, complete response; IV, intravenous infusion; TIP, paclitaxel + ifosfamide + cisplatin; TIC, paclitaxel + ifosfamide + carboplatin; TPF, docetaxel + cisplatin + fluorouracil; PD, progressive disease.
Phase II Trial: Cetuximab in Platinum-Refractory Recurrent/Metastatic Head & Neck Cancer

Results

<table>
<thead>
<tr>
<th></th>
<th>Single-Agent cetuximab</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(N = 103)</td>
</tr>
<tr>
<td>Objective response rate, % (95% CI)</td>
<td>13 (7-21)</td>
</tr>
<tr>
<td>Median duration of response, mo (range)</td>
<td>5.8 (1.2-5.8)</td>
</tr>
</tbody>
</table>

CI = confidence interval.

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

Randomized
Overall Survival

HR (95%CI): 0.797 (0.644, 0.986)
Strat. log-rank test: 0.0362

Patients at Risk Survival Time [Months]
CTX only
CET + CTX
220 173 127 83 65 47 19 8 1
222 184 153 118 82 57 30 15 3

Survival Probability

0.0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1.0
0 3 6 9 12 15 18 21 24

Survival Time [Months]

Patients at Risk
CTX only 220
CET + CTX 222

Survival Time

0 3 6 9 12 15 18 21 24

0.5
10.1 mo
10.1 mo

Survival Probability

0.5

7.4 mo

64
The EXTREME Trial: A Phase III Trial of PF vs PF Plus Cetuximab – Vermorken et al

- First Line PFC Improves Survival Compared to PF
- However
  - Choice of chemotherapy?
  - Multi-agent versus sequential therapy
  - Toxicity?
Pembrolizumab (MK-3475)

- High-Affinity, IgG4, Humanized Monoclonal Antibody Against PD-1
- Exerts dual ligand blockade of PD-L1 and PD-L2
- No cytotoxic (ADCC/CDC) activity
- Low occurrence of anti-drug antibodies and no impact on pharmacokinetics
- Demonstrated antitumor activity in multiple tumor types\(^1\)-\(^7\)

HNSCC expansion cohort of the KEYNOTE-012 Nonrandomized, Phase 1b Multi-cohort trial*

Patients:
• Recurrent or metastatic HNSCC, regardless of PD-L1 or HPV status
• Have measurable disease based on RECIST 1.1
• ECOG performance status of 0 or 1

Treatment:
- Pembrolizumab 200 mg Q3W

Primary and secondary end points:

Response assessment: Every 8 weeks
Primary end points: ORR per modified RECIST v1.1 by investigator review; safety
Secondary end points: PFS, OS, duration of response

*Additional cohorts included bladder cancer, TN breast cancer, and gastric cancer.
†Treatment beyond progression was allowed.
‡Re-treatment was permitted.
## Overall Response Rate [Site Radiology Review]*

<table>
<thead>
<tr>
<th>Best overall response</th>
<th>Total N = 117†</th>
<th>HPV+ n = 34</th>
<th>HPV− n = 81</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%) 95% CI</td>
<td>n (%) 95% CI</td>
<td>n (%) 95% CI</td>
</tr>
<tr>
<td><strong>ORR</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete Response</td>
<td>1 (0.9) 0.0-4.7</td>
<td>1 (2.9) 0.1-15.3</td>
<td>0 (0) 0-4.5</td>
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<tr>
<td>Partial Response</td>
<td>28 (23.9) 16.5-32.7</td>
<td>6 (17.6) 6.8-34.5</td>
<td>22 (27.2) 17.9-38.2</td>
</tr>
<tr>
<td>Stable Disease</td>
<td>29 (24.8) 17.3-33.6</td>
<td>9 (26.5) 12.9-44.4</td>
<td>19 (23.5) 14.8-34.2</td>
</tr>
<tr>
<td>Progressive Disease</td>
<td>48 (41.0) 32.0-50.5</td>
<td>13 (38.2) 22.2-56.4</td>
<td>34 (42.0) 31.1-53.5</td>
</tr>
<tr>
<td>No Assessment#</td>
<td>9 (7.7) 3.6-14.1</td>
<td>4 (11.8) 3.3-27.5</td>
<td>5 (6.2) 2.0-13.8</td>
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<tr>
<td>Non-evaluable‡</td>
<td>2 (1.7) 0.2-6.0</td>
<td>1 (2.9) 0.1-15.3</td>
<td>1 (1.2) 0.0-6.7</td>
</tr>
</tbody>
</table>
Conclusions: SCCHN

- Concurrent therapy saves lives

- There are a lot of good ideas for an individual patient with much less data
  - Induction / sequential chemotherapy
  - Weekly regimens

- Take care with HPV recommendations

- Many patients with head and neck cancer will die from their tumor

- Toxicity is important, but recurrences is almost always usually worse

- Key issue is biology and biomarkers
Thanks