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# Head and Neck Cancer

**Locally Advanced Disease: Treatment Choice Based  
on Risk Factors**

## Optimizing Drug Prescription

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# Financial Disclosures

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# Outline of Talk

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- **Discuss risk stratifications in the multi-modality treatment of localized or locoregionally advanced SCCHN**
- **Highlight selected recently completed or currently ongoing phase III trials in locoregionally advanced SCCHN**

# Glossary

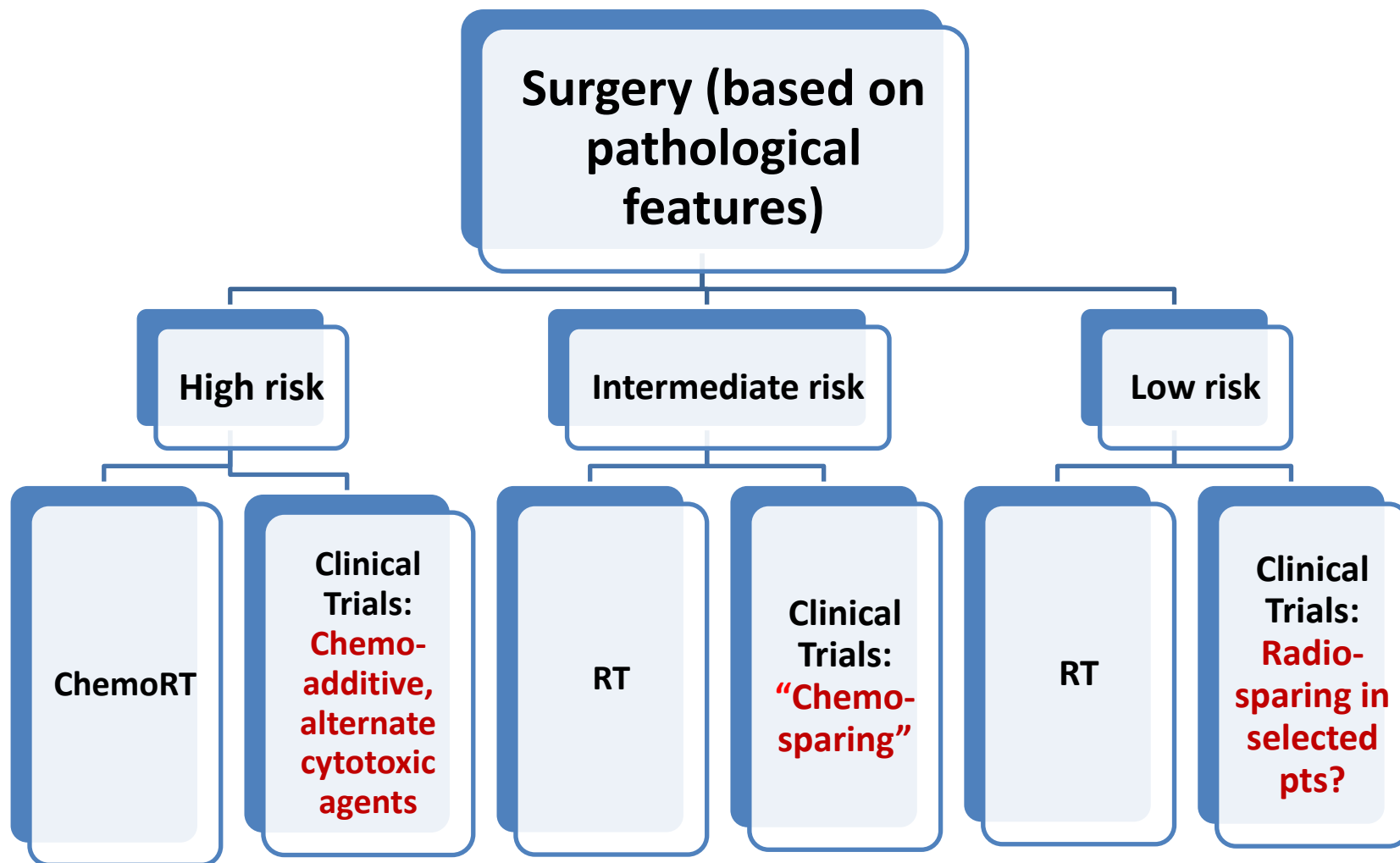
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- **Sequential therapy:** Induction chemotherapy + concurrent chemo-radiotherapy/bio-radiotherapy
- **Chemo-additive:** Adding another agent (e.g. targeted agent) to a standard chemo-containing regimen
- **Chemo-sparing:** Using another agent (e.g. targeted agent) to replace or reduce chemotherapy in a chemo-containing regimen
- **Radio-sparing:** Using an alternate treatment (e.g. TORS, or systemic agent) to reduce RT dose/intensity

# Treatment Algorithm:

## Surgery as 1° Modality

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# Post-Operative Adjuvant Therapy

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**Low Risk:** No intermediate or high risk features

**Intermediate Risk:** LVI, PNI, 1 lymph node >3 cm,  $\geq 2$  lymph nodes (all <6 cm), close margins, T3/T4a

**High Risk:** Extracapsular extension, positive margins

# Adjuvant Therapy: **High Risk**

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- **Strategy 1: Addition of targeted agents to CRT (chemo-additive)**
  - **Anti-EGFR agents:**
    - Lapatinib – **NCT004244255** (concurrent + 1 year maintenance)
    - Nimotuzumab – **NCT00957086** (concurrent)
    - Afatinib – **NCT01427478** (1 year maintenance)

# Adjuvant Therapy: **High Risk**

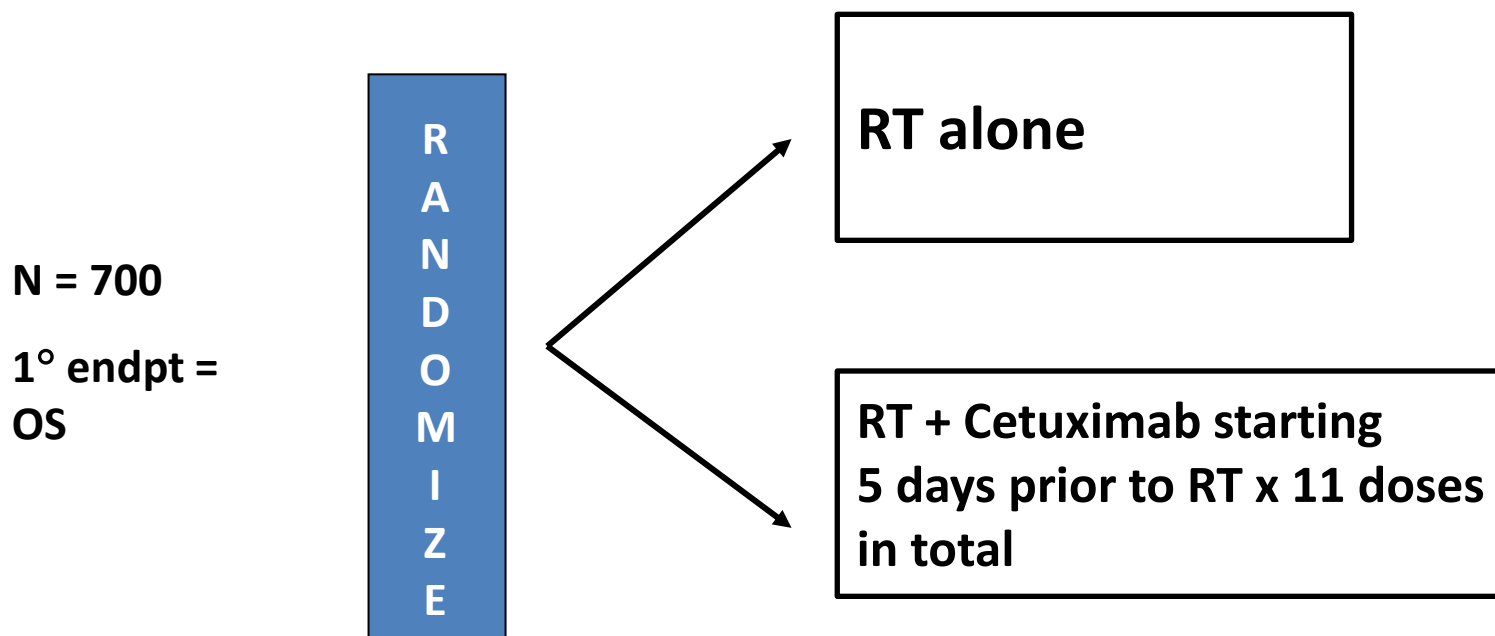
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- **Strategy 2: Use of non-platinum cytotoxic chemotherapy**
  - **RTOG 0234 (randomized phase II trial):**
    - N = 238, median follow-up = 2.5 years
    - Compared (A) RT + weekly CDDP (30 mg/m<sup>2</sup>) + Cetuximab vs (B) RT + weekly Docetaxel (15 mg/m<sup>2</sup>) + Cetuximab
    - 2-year OS: 69% vs 79%, 2-year DFS: 57% vs 66%
    - Compared to RTOG 9501, absolute improvement in 2-yr DFS = 2% for Arm A and 11% for Arm B, due to improvement in distant control
  - **RTOG 1216 being planned (randomized phase II/III trial):**
    - (A) RT + weekly CDDP (40 mg/m<sup>2</sup>) vs (B) RT + weekly Docetaxel (15 mg/m<sup>2</sup>) vs (C) RT + weekly Docetaxel (15 mg/m<sup>2</sup>) + Cetuximab



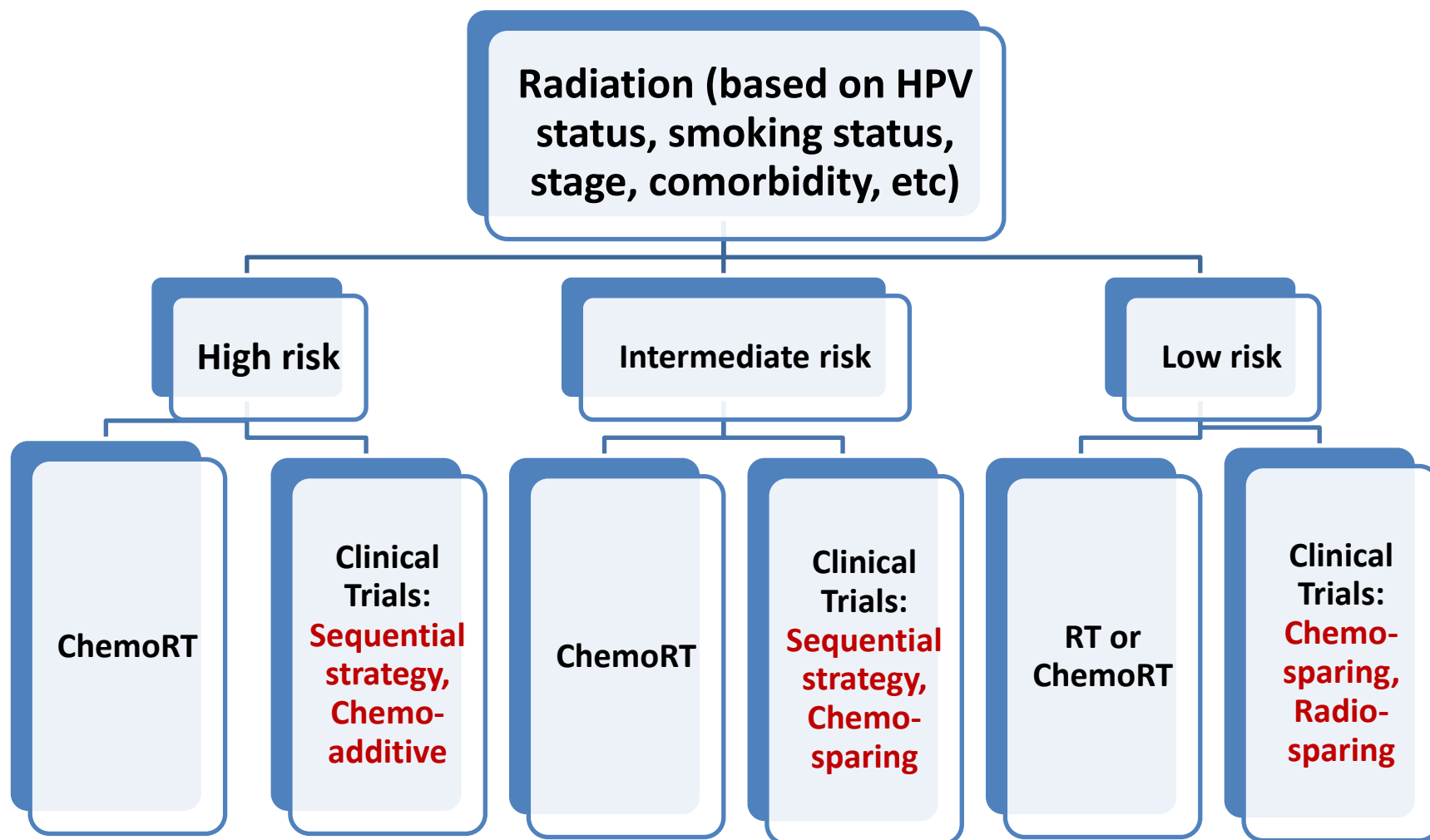
# Adjuvant Therapy: **Intermediate Risk**

- **Strategy: Addition of targeted agents to RT**
  - Anti-EGFR agents (Cetuximab):
    - RTOG 0920 – NCT00956007

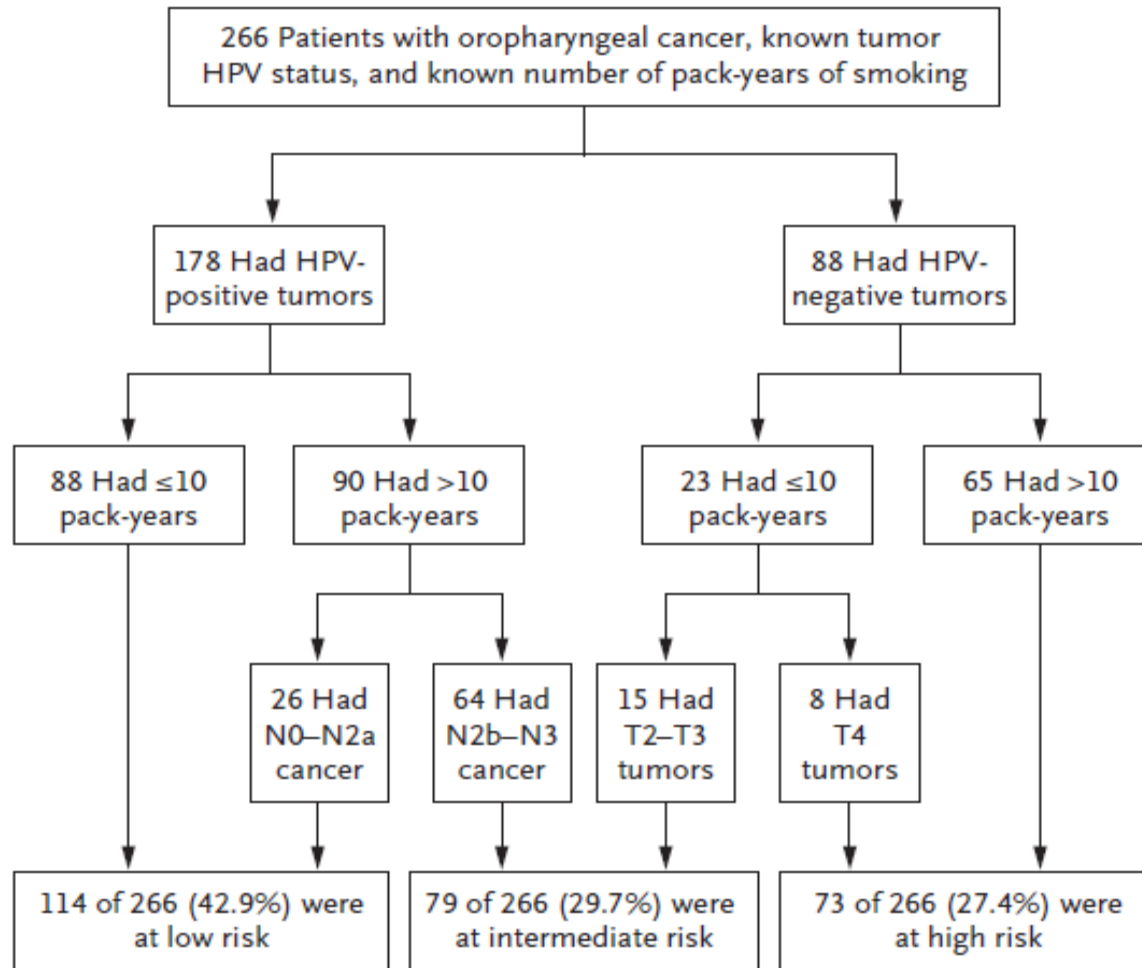


# Treatment Algorithm:

## Radiation as 1° Modality



# Stratification in SCCHN based on Risk of Death (from RTOG 0522): **HPV, Smoking, Stage**



**3-year OS**

**93%**

**71%**

**46%**



# PMH OPC 2001 – 2009

## Risk stratification: 505 HPV known cases focusing on DM

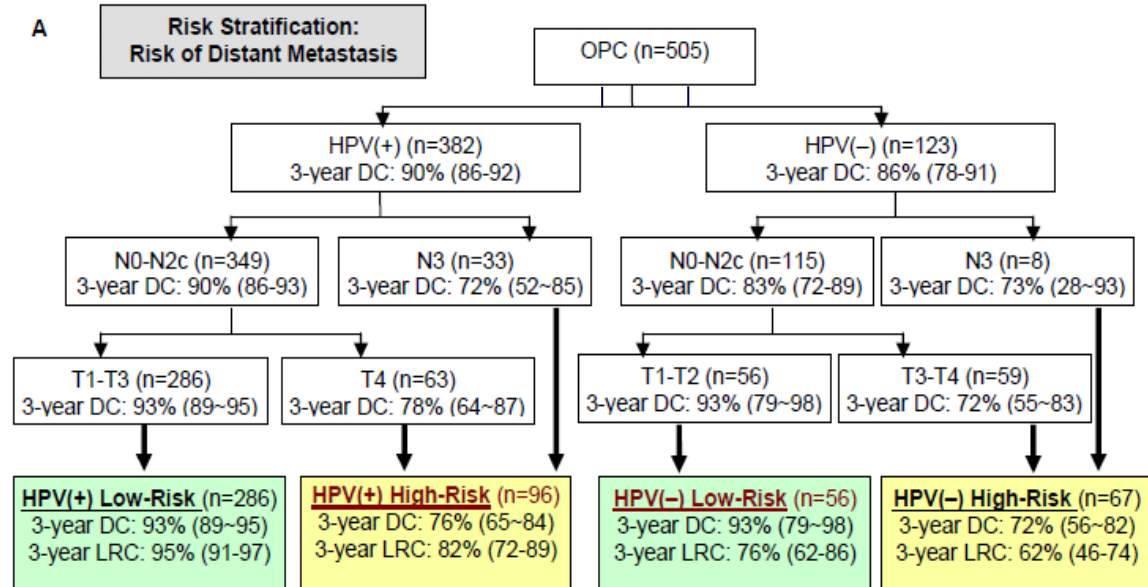
PMH 2001-2009:

- HPV(+): n=382
- HPV(-): n=123

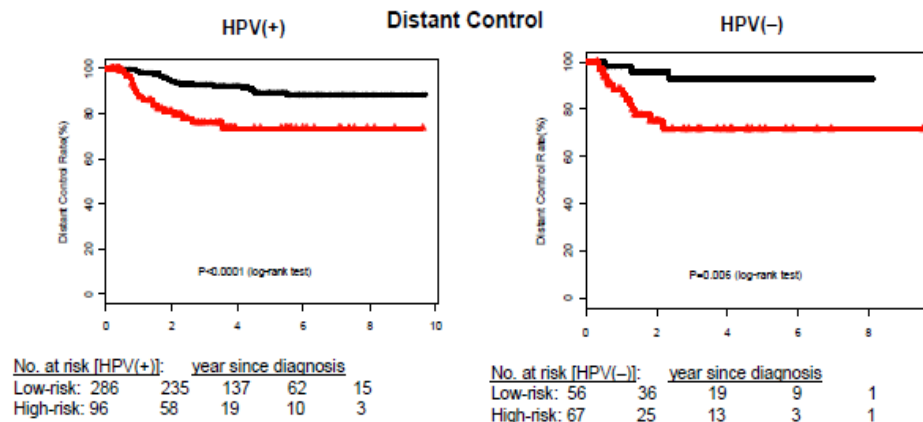
HPV(+) Low-risk:

- RT-alone: 150
- CRT: 136

A

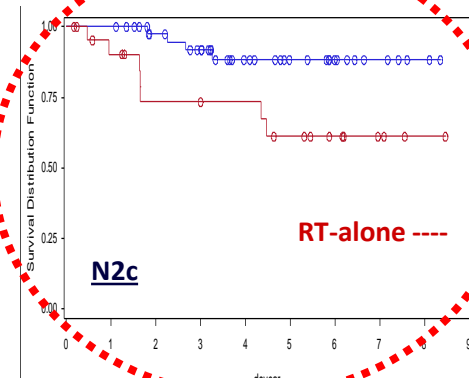
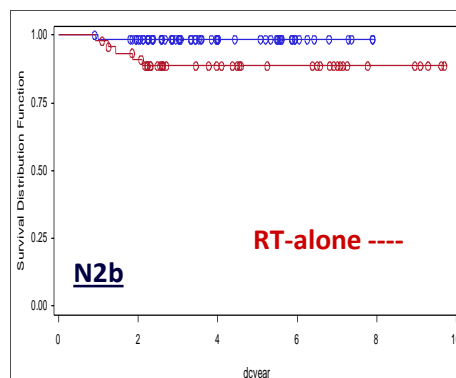
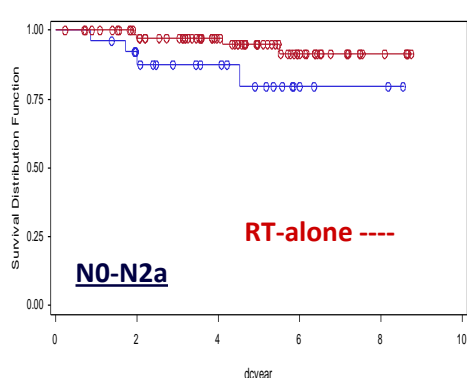


B



# Risk Stratification: HPV(+) Focusing on DM

- HPV(+) Low-risk of DM: not all suitable
  - Results reflect outcome of contemporary treatment
  - Not all low-risk HPV(+) subgroups appear suitable for treatment de-intensification with reduction/omission of chemotherapy
    - e.g. N2c is a definite concern



3-year DC Rate (95% CI)	N0-N2a (n=107)	N2b (n=112)	N2c (n=67)
RT alone	97% (89-99)	89% (75-95)	73% (47-88)
CRT	88% (66-96)	98% (90-99)	92% (77-97)
P value	0.07	<u>0.03</u>	<b>0.02</b>



# “Unmet Needs” in Locoregionally Advanced SCCHN

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- **Localized and locoregionally advanced disease:**
  - **High Risk:** Optimization of combined modality therapy for patients with high risk (goal: higher cure rates, less toxicity)
  - **Low Risk:** De-intensification of treatment for patients with favorable risk (goal: equal efficacy, less toxicity)

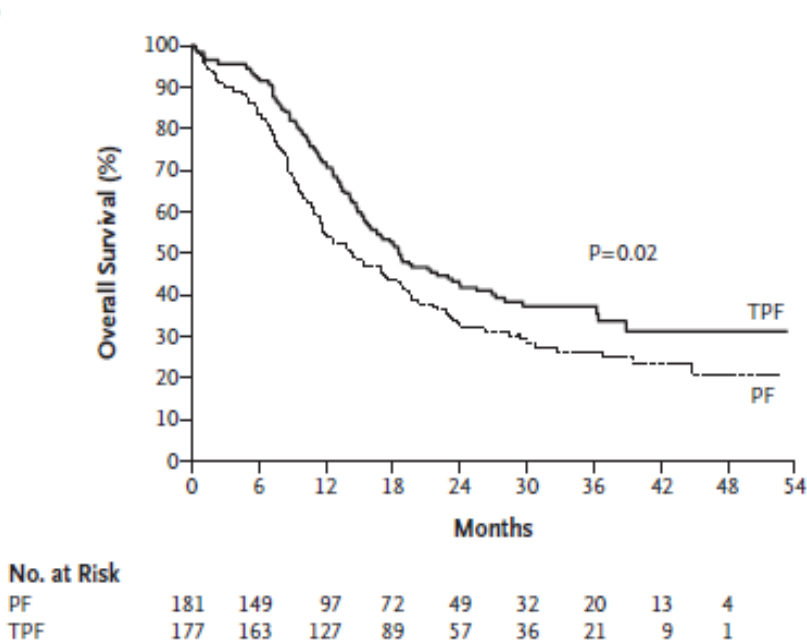


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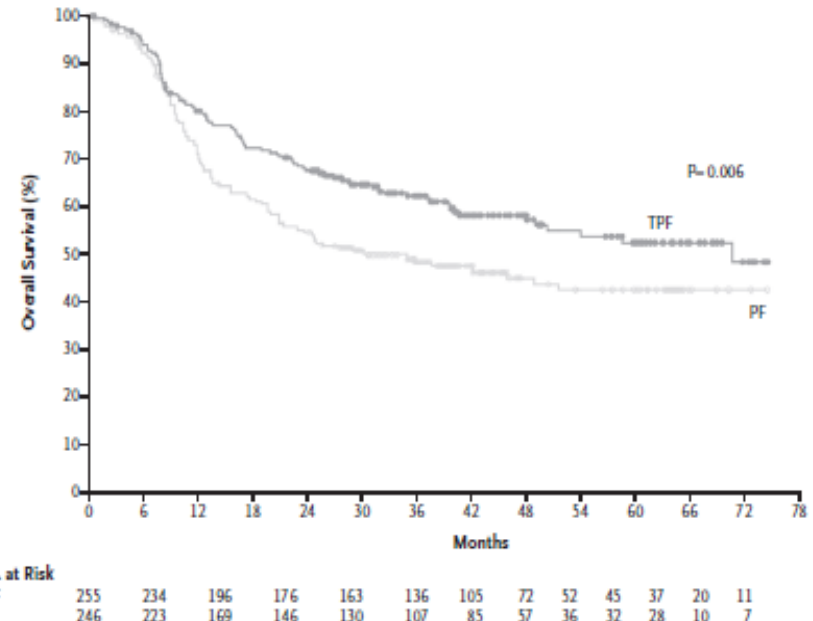
# **Sequential Therapy (Induction Chemotherapy + Concurrent Chem-oradiotherapy or Bio-radiotherapy)**



# Phase III Trials of **Different Sequential Therapies**



**TAX 323 (unresectable stage III/IV):**  
**Median OS for TPF vs PF**  
**= 18.8 mo vs 14.5 mo (HR 0.73, p=0.02)**



**TAX 324 (unresectable or organ preservation):**  
**Median OS for TPF vs PF**  
**= 71 mo vs 30 mo (HR 0.70, p=0.006)**



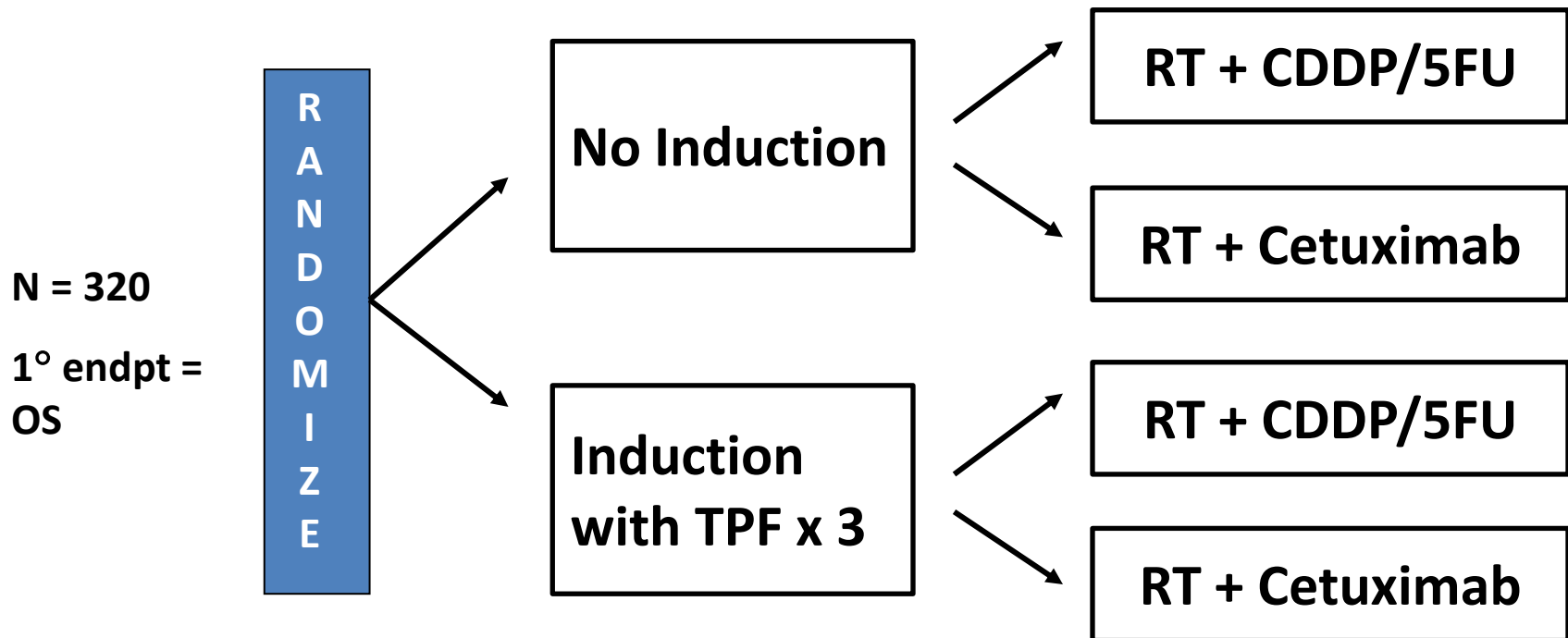
# Phase III Trials of Sequential Therapy vs CRT

Study	Phase	N	Induction Regimen	Concurrent Regimen	CR at end (%)	RSF or PFS	OS
DeCide (Cohen et al) <b>N2, N3 dx</b>	III	280 (400)	Docetaxel, Cisplatin, 5FU (TPF) x 2	Both arms: • Docetaxel, 5FU, Hydroxyurea + hyperfractionated RT	19% vs 15%	<b>3-yr RFS:</b> 67% vs 59%	<b>3-yr OS:</b> 75% vs 73% HR=0.91
Paradigm (Haddad et al) <b>Stage III or IV</b>	III	145 (300)	Docetaxel, Cisplatin, 5FU (TPF) x 3	Sequential arm: • Docetaxel wkly + Acc. Boost RT • Carboplatin wkly + Standard RT Concurrent arm: • Cisplatin wks 1, 4 + Acc. Boost RT	-	<b>3-yr PFS:</b> 67% vs 69%	<b>3-yr OS:</b> 73% vs 78%



# Ongoing Phase III Trials of **Sequential Therapy** - 1

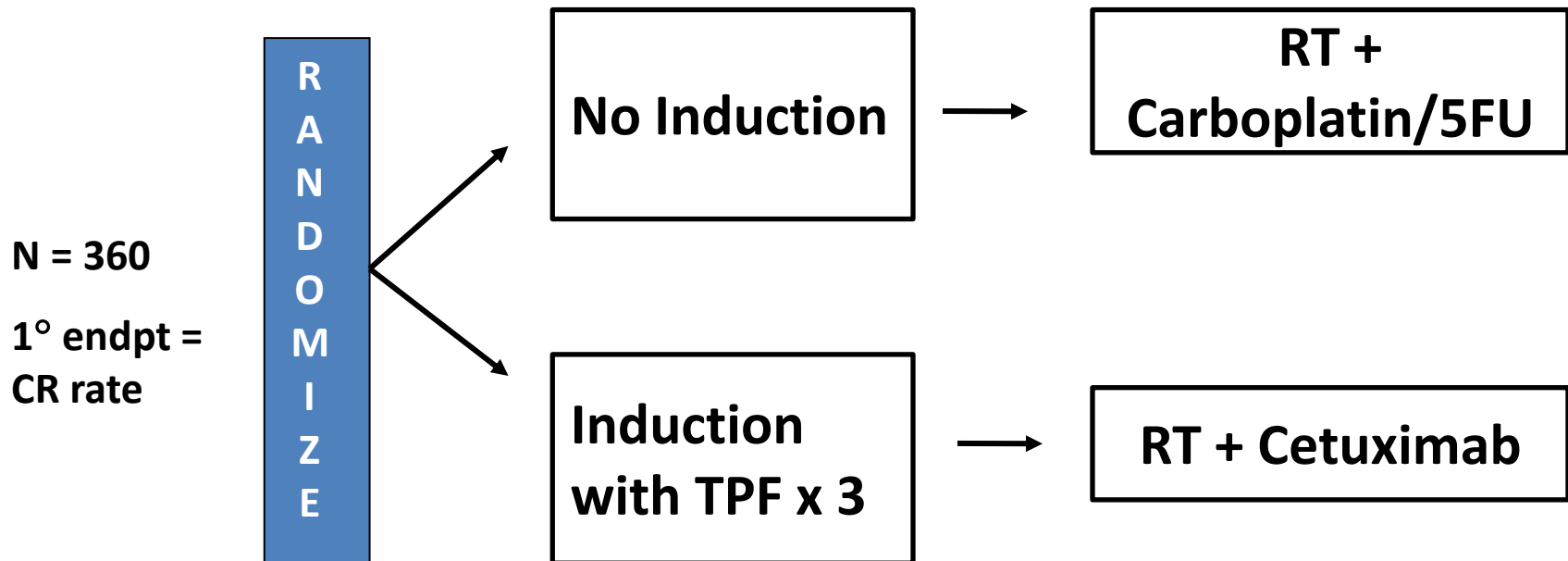
- Strategy - Factorial Design: **1) sequential therapy vs concurrent therapy? 2) chemoRT vs bioRT?**
  - GSTTC (Italian) H&N07 – NCT01086826



# Ongoing Phase III Trials of **Sequential Therapy** - 2

- Strategy: **1) sequential therapy vs concurrent therapy?**  
**2) chemoRT vs bioRT?**

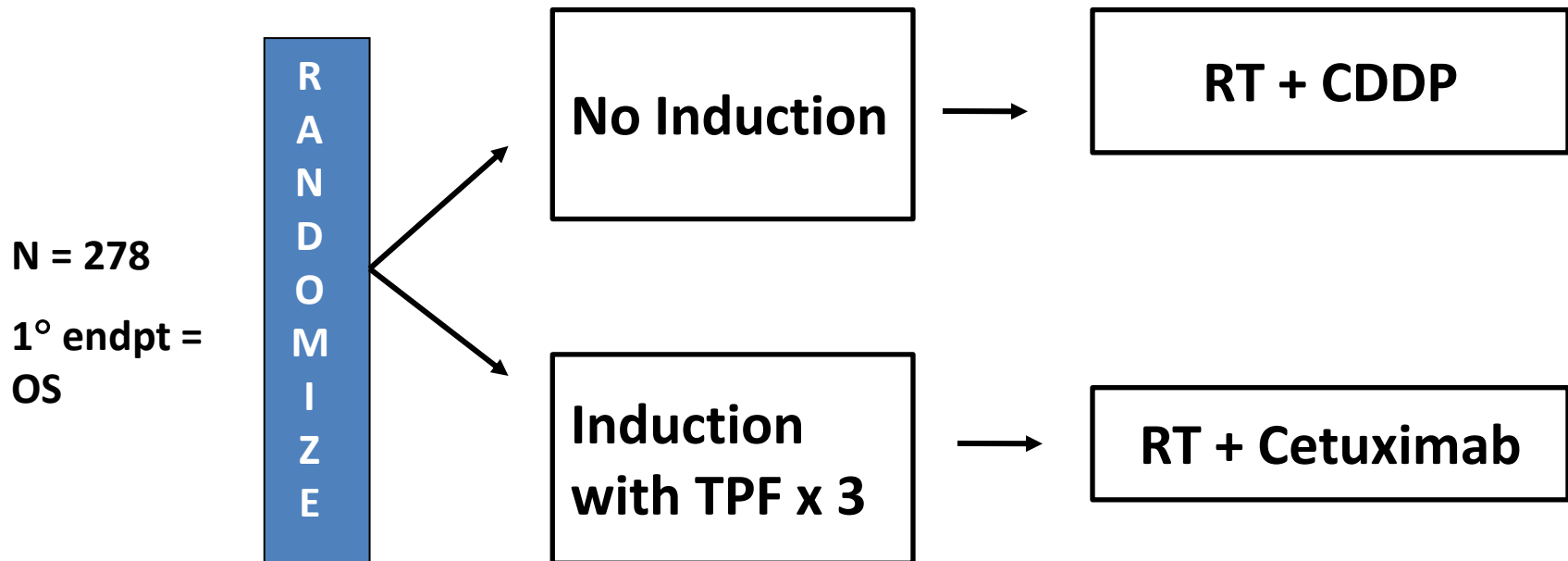
– GORTEC 2007-02 – NCT01233843



# Ongoing Phase III Trials of **Sequential Therapy** - 3

- Strategy: **1) sequential therapy vs concurrent therapy?**  
**2) chemoRT vs bioRT?**

– **GONO INTERCEPTOR – NCT00999700**



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# Chemo-Additive Strategy

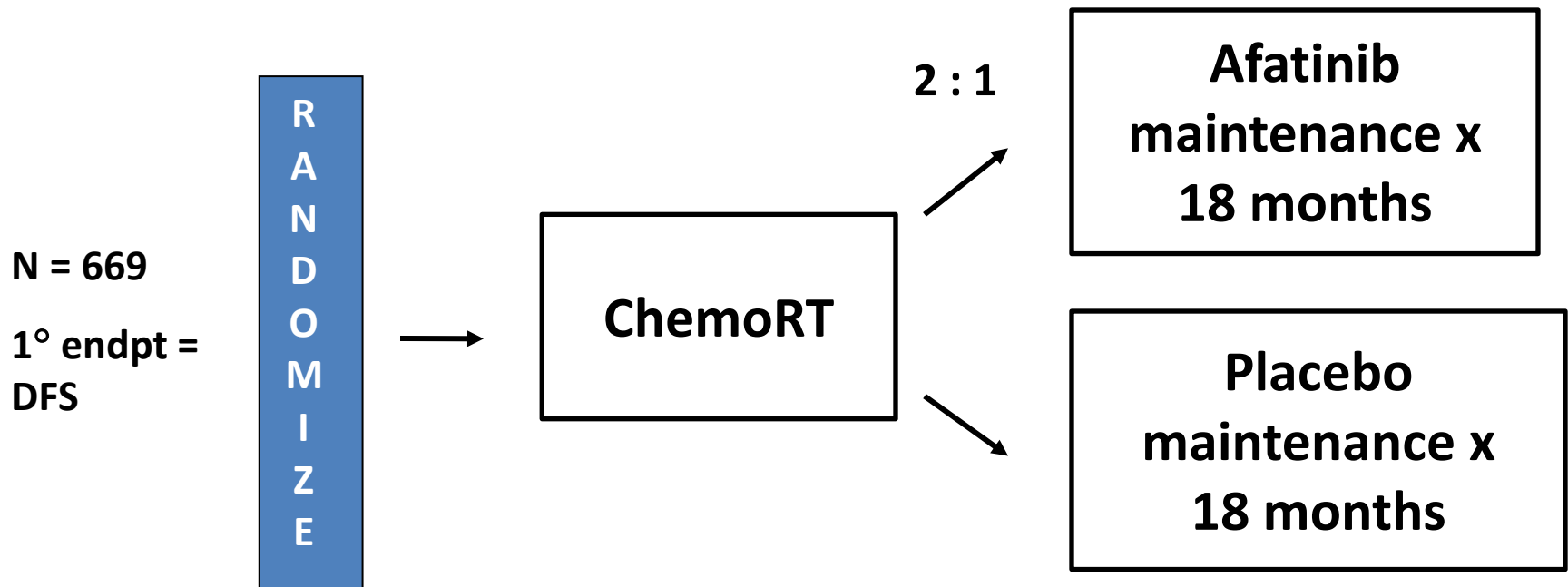


# Spectrum Trial – HPV Analysis

	ITT (n = 657)	HPV+ (n = 83)	HPV- (n = 294)
<b>OS</b> P-MAB + CT vs CT (mo) Stratified HR (95% CI)	11.1 vs 9.0 0.87 (0.73-1.05)	10.9 vs 12.1 1.02 (0.59-1.77)	11.8 vs 8.7 0.71 (0.54-0.94)
Interaction test	p = 0.144		
<b>PFS</b> P-MAB + CT vs CT (mo) Stratified HR (95% CI)	5.8 vs 4.6 0.78 (0.66-0.92)	5.5 vs 5.3 1.25 (0.74-2.12)	6.3 vs 5.1 0.64 (0.5-0.83)
Interaction test	p = 0.018		
<b>ORR</b> P-MAB + CT vs CT (mo) P-value odds ratio	36 vs 25 0.007	41 vs 25 0.21	37 vs 27 0.11

# Ongoing Phase III Trials in Locoregionally Advanced SCCHN (Chemo-Additive) - 1

- Strategy: **Following concurrent chemoRT, maintenance PAN-HER inhibition vs placebo?**
  - LUX-Head&Neck 2 – NCT01345669 (excludes base of tongue or tonsil and  $\leq 10$  pack years of tobacco)



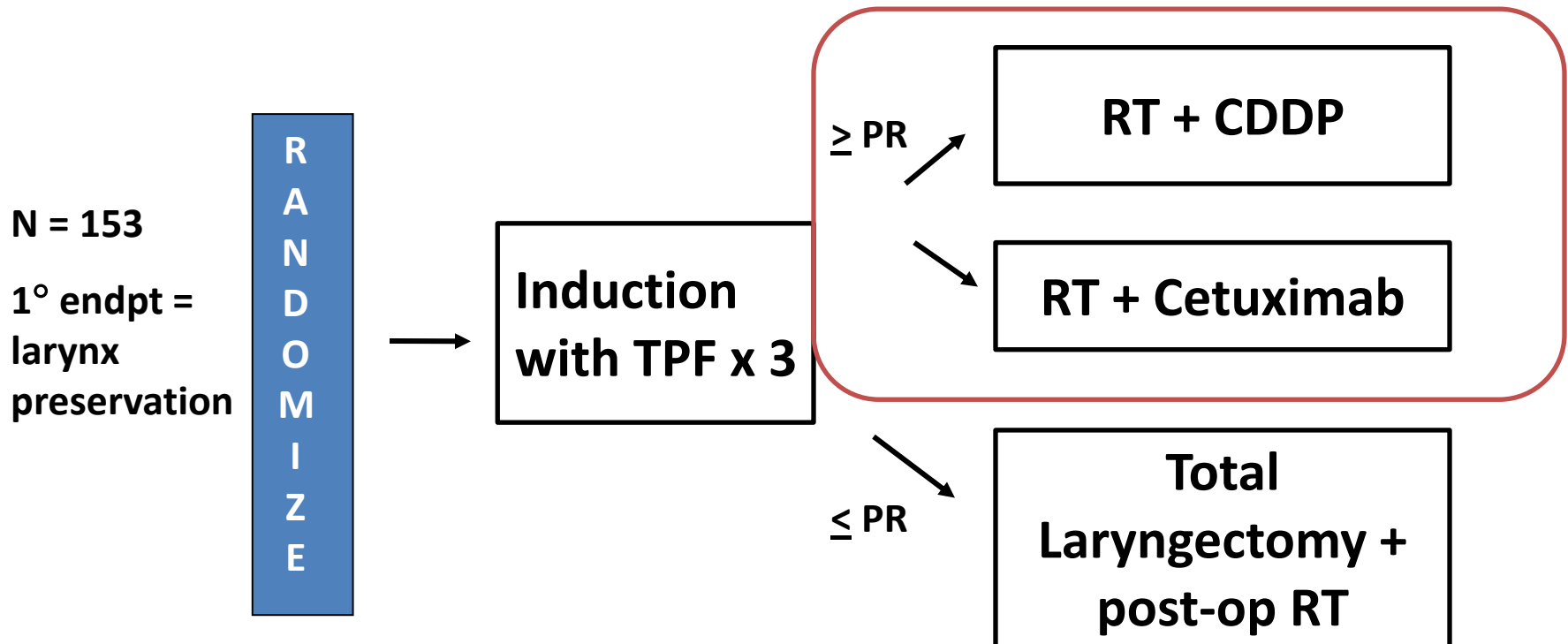
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# **Concurrent Therapy Utilizing Anti-EGFR Therapies**



# Randomized Phase II Trial of Laryngeal Preservation: TREMPLIN

- **Strategy: Sequential therapy + concurrent chemoRT vs sequential therapy + concurrent bioRT (Chemo-Sparing)?**



# Randomized Phase II Trial of Laryngeal Preservation:

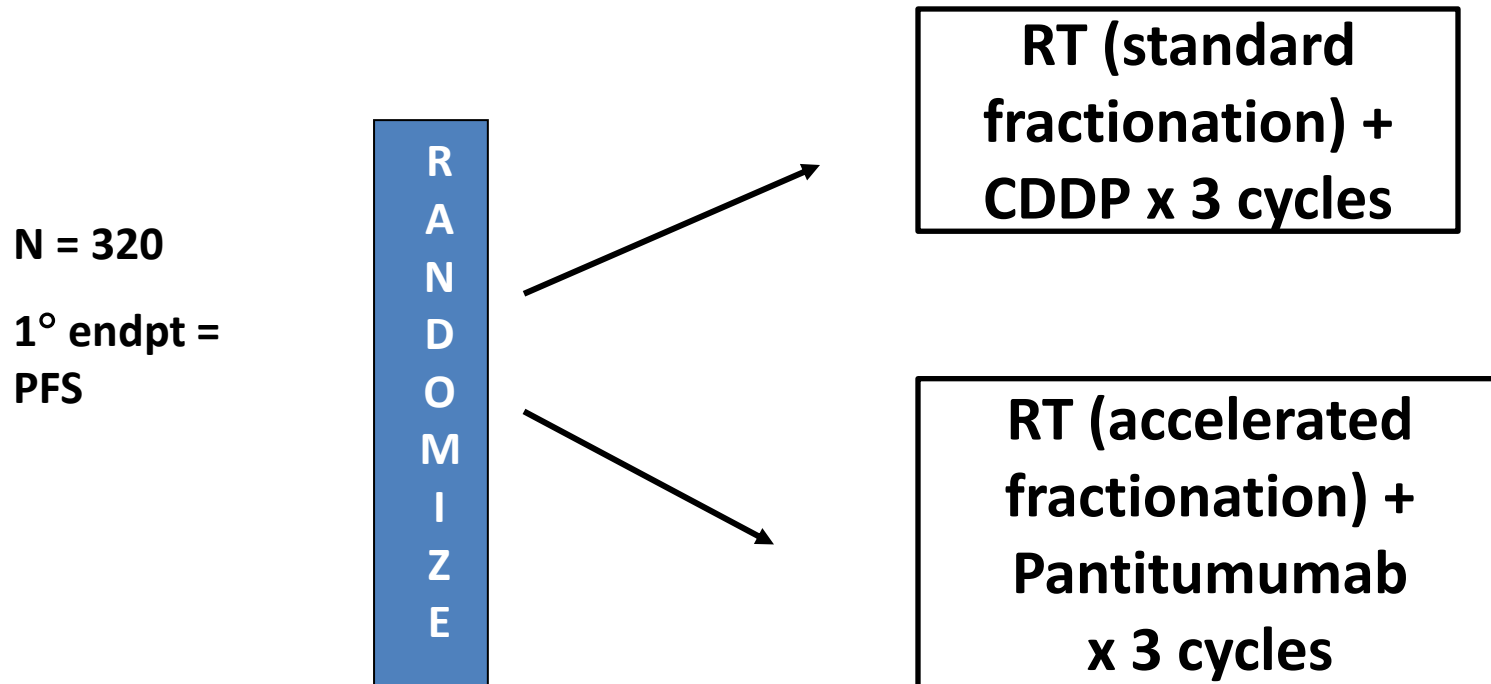
## TREMPLIN

Parameter	CDDP Arm (n = 60)	Cetuximab Arm (n = 56)
Compliance (got all cycles)	43%	71%
Grade 3-4 mucositis	47%	45%
Grade 3-4 in-field skin toxicity	26%	57%
Protocol modification due to acute toxicity	57%	29%
Late renal toxicity (all grade 1)	22%	0
Local +/- regional failures at median follow-up of 3 years	11.7%	21.4% (log-rank 0.14)
1° Endpoint: Larynx preservation at 3 months	95%	93%
Larynx function preservation at 18 months	87%	82%
Overall survival at 18 months	92%	89% (log-rank 0.44)



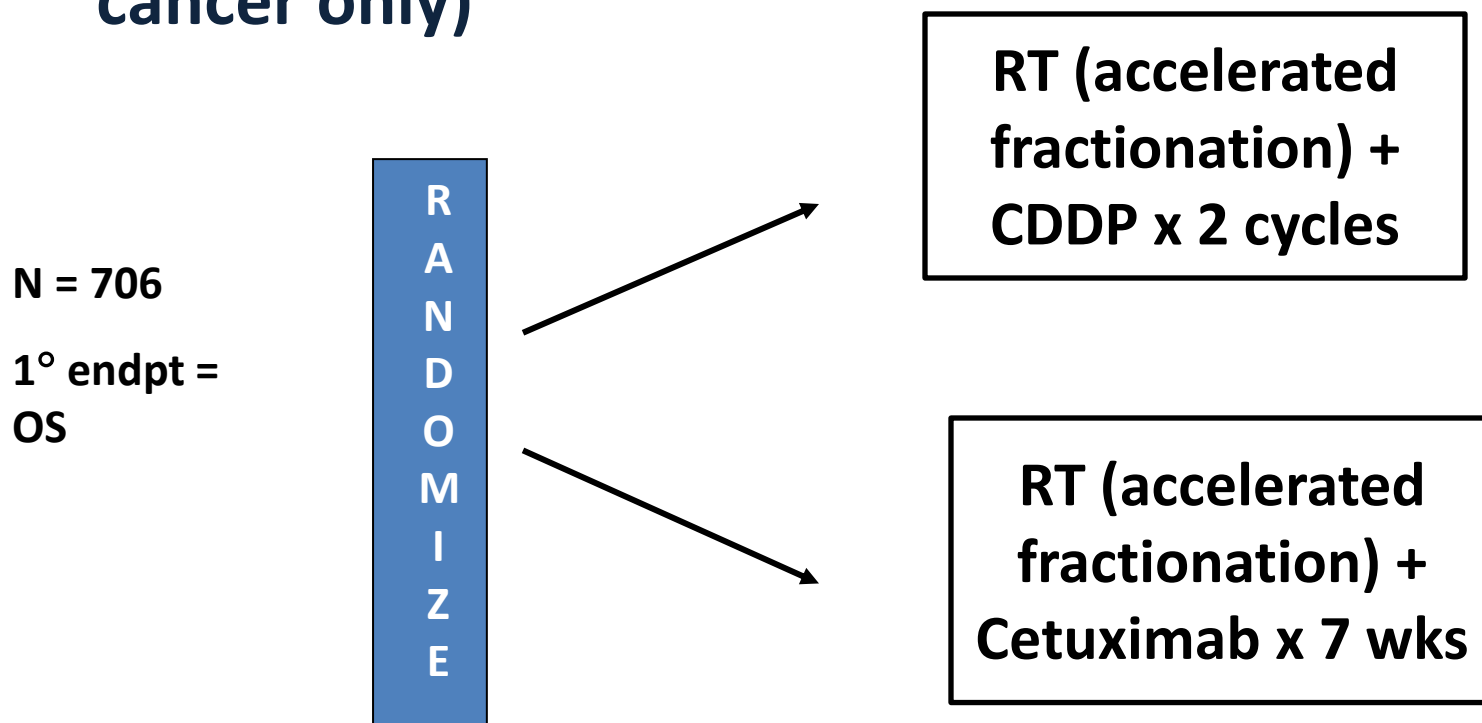
# Recently Completed Phase III Trials in Locoregionally Advanced SCCHN (Chemo-Sparing)

- Strategy: **Concurrent chemoRT vs concurrent bioRT?**
  - NCIC CTG (Canadian) HN6 – NCT00820248



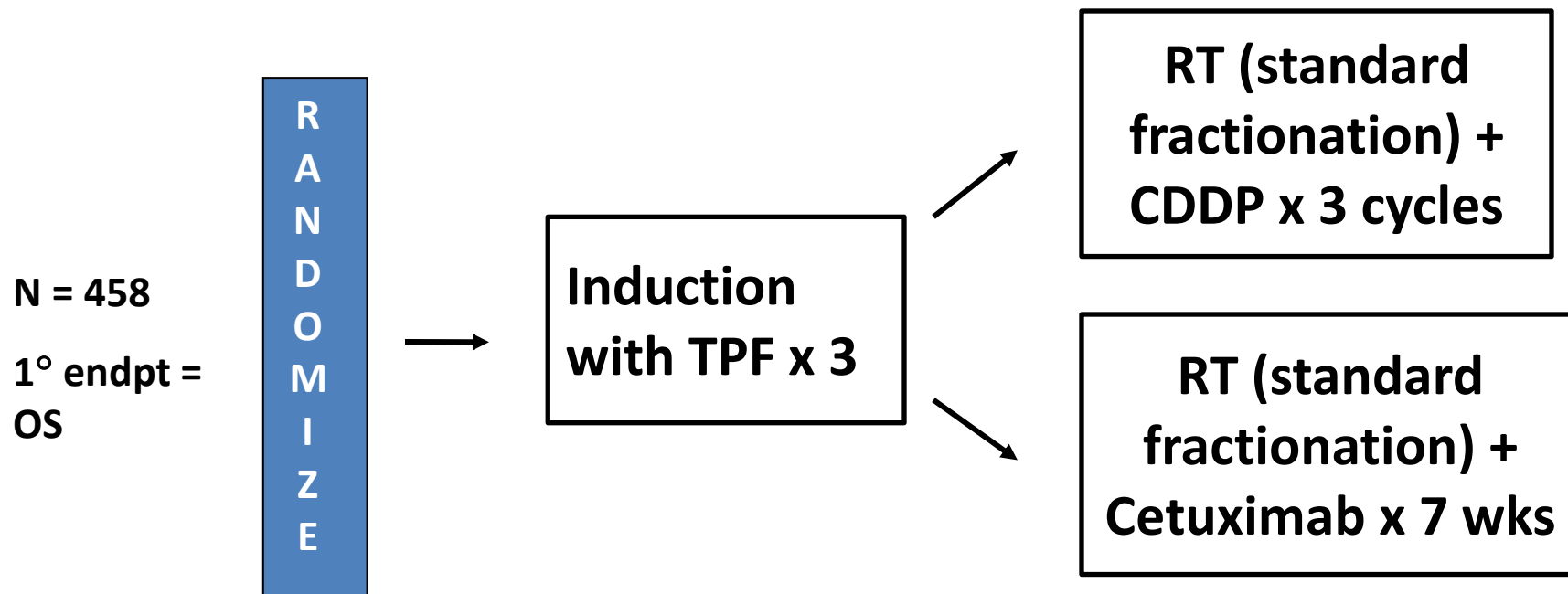
# Ongoing Phase III Trials in Locoregionally Advanced SCCHN (Chemo-Sparing) - 1

- Strategy: **Concurrent chemoRT vs concurrent bioRT?**
  - **RTOG 1016 – NCT01302834 (p16 + oropharyngeal cancer only)**



# Ongoing Phase III Trials in Locoregionally Advanced SCCHN (Chemo-Sparing) - 2

- Strategy: **Following induction chemo, concurrent chemoRT vs concurrent bioRT?**
  - TTCC (Spanish) 2007-01 – NCT00716391

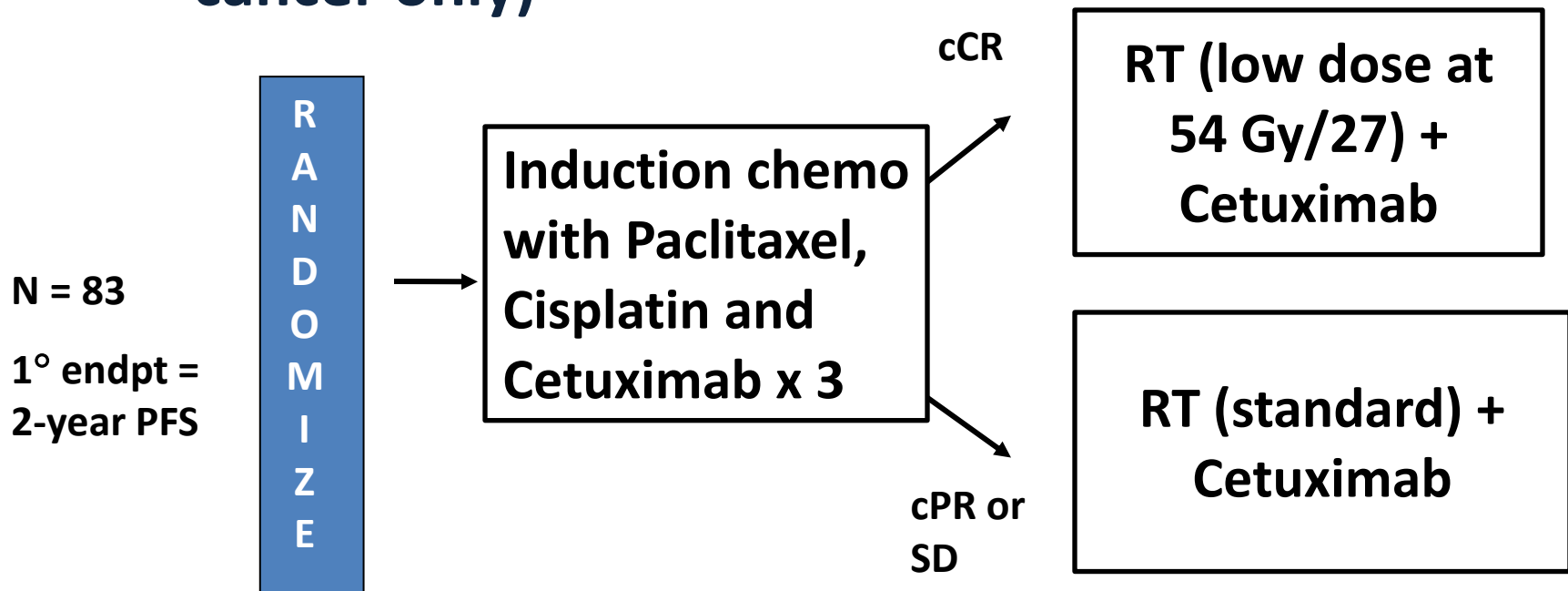


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# **De-Intensification for Low-Risk Disease**

# Recently Completed Phase II Trial in Locoregionally Advanced SCCHN (Radio-Sparing)

- Strategy: Following induction chemo, de-intensify RT in combination with cetuximab?
  - ECOG 1308 – NCT01084083 (p16 + oropharyngeal cancer only)



# Transoral Robotic Surgery (TORS)



- Surgeon sits in a console and controls micromanipulators -> move the arms of a robot placed at the patients bedside
- Highly magnified 3-D view of the surgical field
- Precise, scaled and filtered motions to the operating arms
- Needs hands-on course training and quality assurance





# Transoral Robotic Surgery (TORS)

- **Advantages:**

- Less invasive, avoids mandibulotomy and its associated morbidity
- Decreased manipulation and dissection of healthy tissues, improved cosmetic outcome
- Decreased need for tracheotomies
- Early return to oral intake
- Shortened hospital stay

# Early Stage SCCHN

**TORS +/-  
post op RT**

**vs**

**RT**

**Low risk  
e.g. T1-2, N0-1**

**TORS +  
post op  
(C)RT**

**vs**

**CRT**

**Intermediate  
risk e.g. T1-3,  
N2-3, HPV+**

# **Summary: Strategies to Optimize Therapy in High Risk Locoregionally Advanced SCCHN**

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- **Intensification of chemotherapy and radiotherapy – we are at or near limit**
- **Finding more effective systemic agents to replace or add to current regimens**
- **Understanding the biology of SCCHN and finding the right drug for the right target**
- **Targeting primary and acquired resistance mechanisms**



# Summary: Strategies to Optimize Therapy in **Low Risk** Locoregionally Advanced SCCHN

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- De-intensification of chemotherapy and radiotherapy – balance of preserving high cure rates while reducing acute and late toxicities
- Understanding the biology of SCCHN so that patients who relapse despite having low risk can be identified early

