Squamous Cell Cancer of Skin: Emerging Treatment Pathways

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2026 Dan Lydiatt Oncology Symposium:
Harnessing Your Immune System to Fight Head and Neck Cancer

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Squamous Cell Carcinoma

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Epidemiology

- Cutaneous squamous cell carcinoma (cSCC) is the second most common skin cancer[1]
- >1 million cases annually
- 3:1 males to females
- 50-60% of cases are in the head and neck

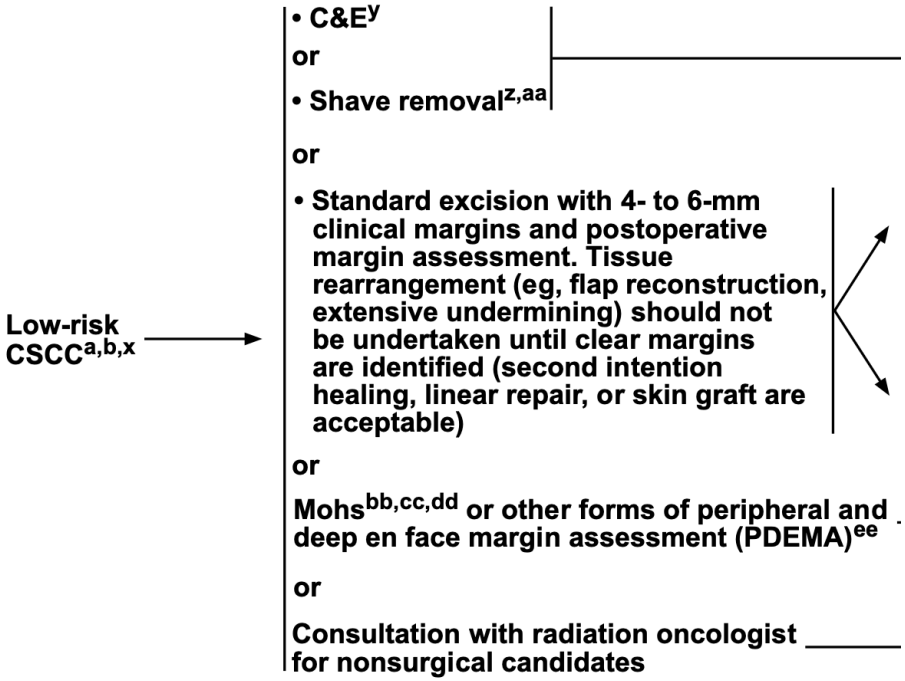
Risk Factors

- Ultraviolet radiation exposure[1]
- Advanced age – Patients >75 have 5-10 risk of cSCC than patients under 55
- White race – Non-Hispanic white patients 50-120x more likely to develop cSCC than black patients
- Immunosuppression (up to 100x risk)
- Genetic syndromes

Risk Stratification

Risk Group[j]	Low Risk	High Risk	Very High Risk
Treatment options	SCC-4	SCC-5	SCC-5 and SCC-6
H&P			
Location/diameter (cm)	Trunk, extremities <2 cm	Trunk, extremities 2 cm – ≤4 cm	>4 cm (any location)
		Head, neck, hands, feet, pretibia, and anogenital area (any size)[n]	
Clinical borders	Well-defined	Poorly-defined	
Primary vs. recurrent	Primary	Recurrent	
Immunosuppression	(-)	(+)	
Site of prior RT or chronic inflammation	(-)	(+)	
Rapid growth tumor	(-)	(+)	
Neurologic symptoms	(-)	(+)	
Pathology (SCC-A)			
Degree of differentiation	Well or moderately differentiated		Poorly differentiated
Histologic subtype[k]	(-)	(+)	(+)
Depth[l,m]: Thickness or level of invasion	<2 mm thick and no invasion beyond subcutaneous fat	2–6 mm depth and no invasion beyond subcutaneous fat	>6 mm or invasion beyond subcutaneous fat
Perineural involvement	(-)	(+)	Tumor cells within the nerve sheath of a nerve lying deeper than the dermis or measuring ≥0.1 mm
Lymphatic or vascular involvement	(-)	(-)	(+)

Low Risk – One Treatment



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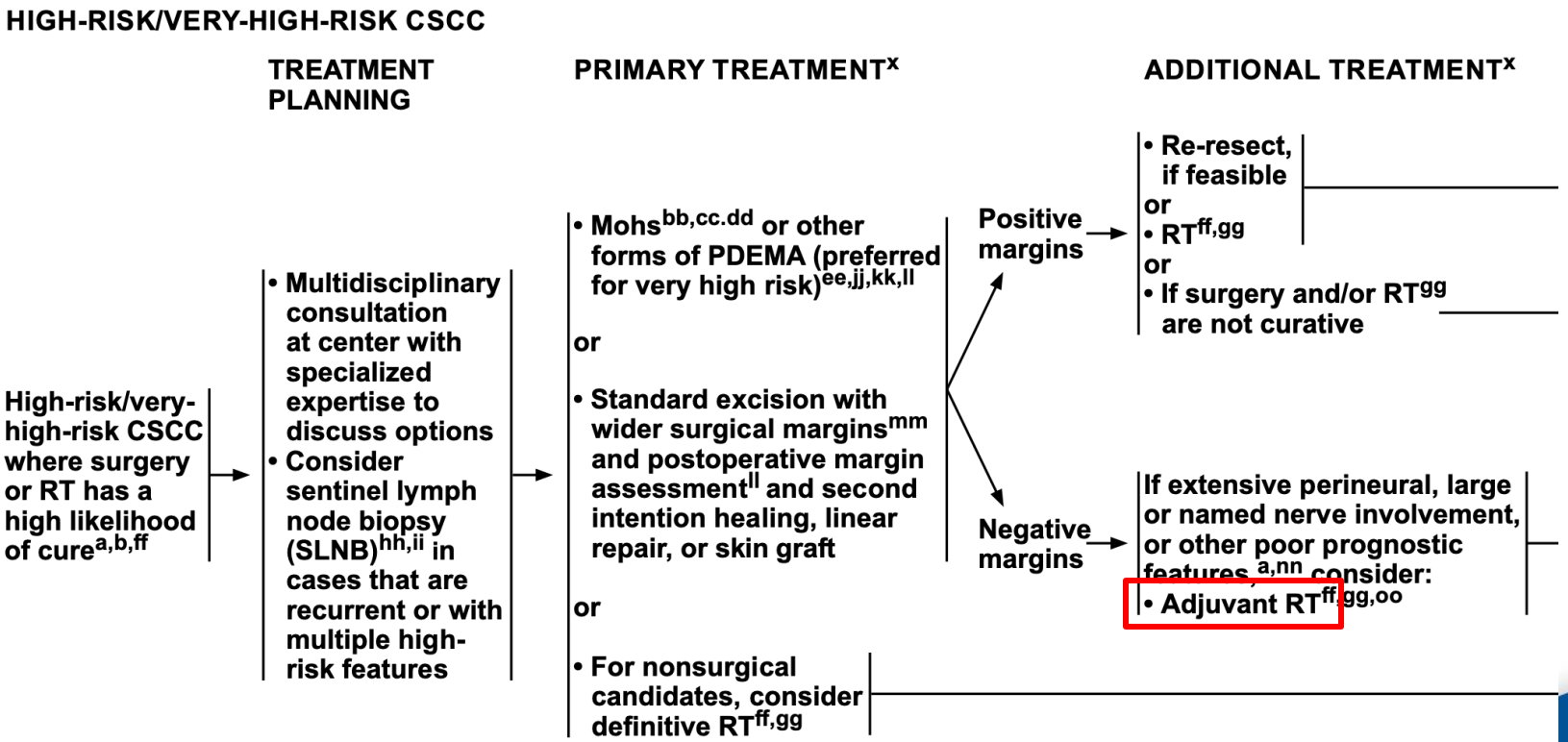
High Risk – Consider Radiation?



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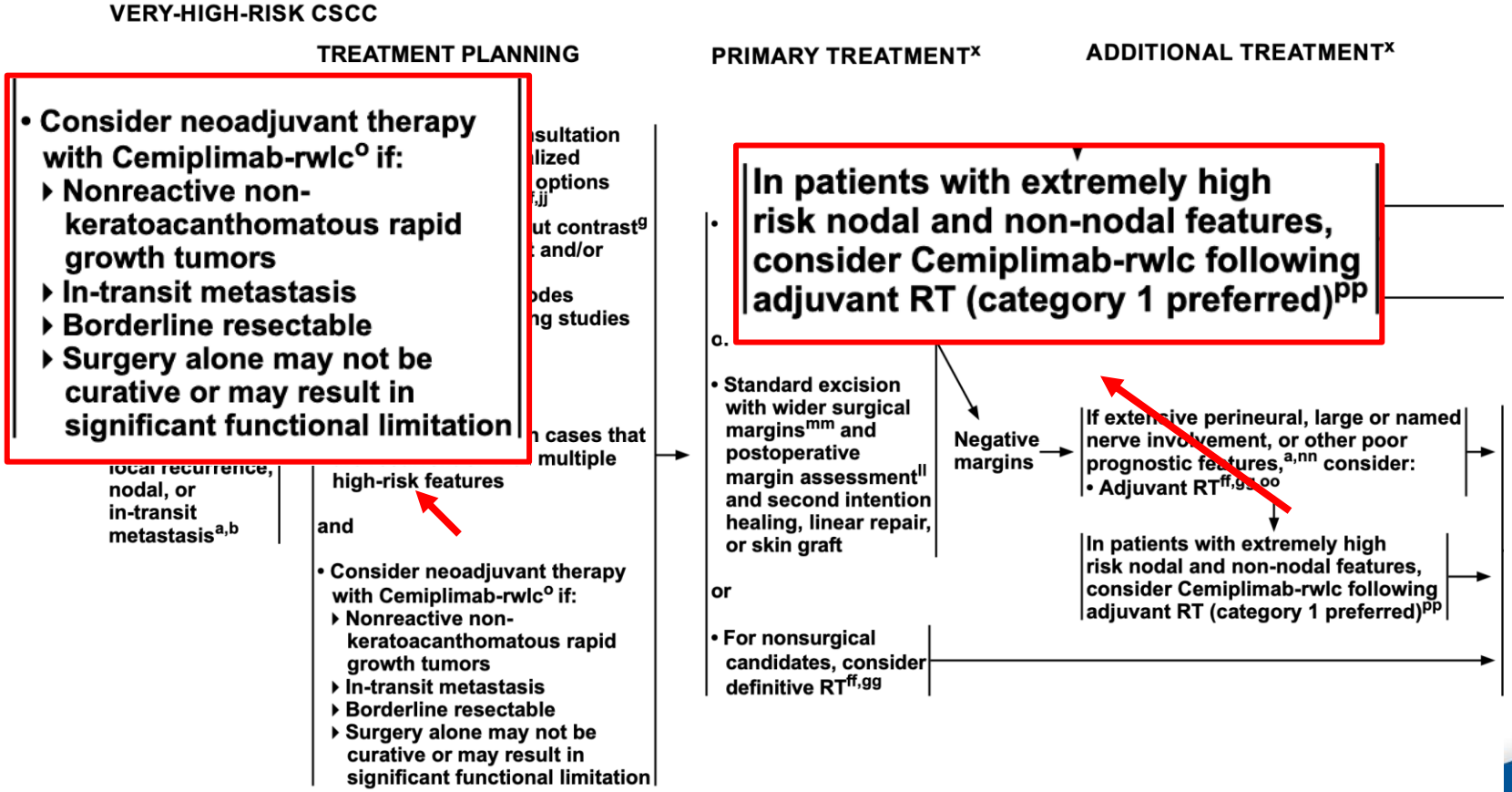
Adjuvant Therapy

- Adjuvant means “helper”
- This type of treatment comes after the main treatment
- The purposes can be to make cancer less likely to return and/or to lower the risk of dying from cancer

Very High Risk – Immunotherapy?



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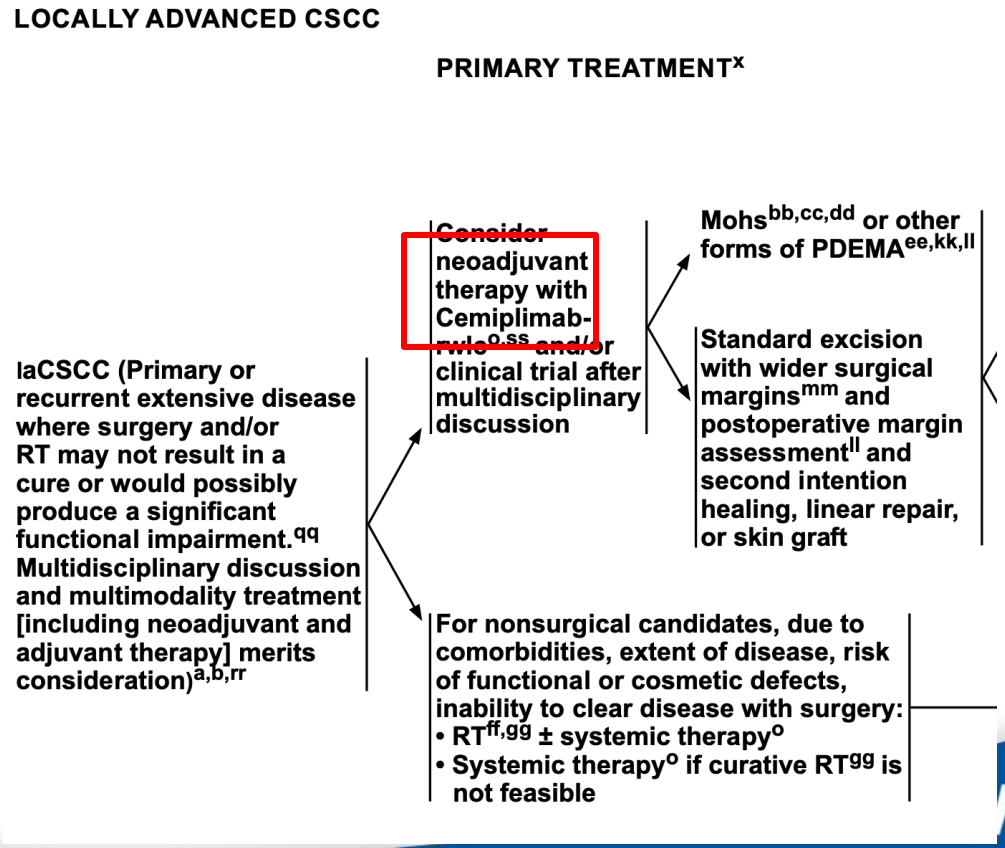
Locally Advanced – Immunotherapy Takes Center Stage



Why not use chemotherapy for cSCC?

Postoperative Concurrent Chemoradiotherapy Versus Postoperative Radiotherapy in High-Risk Cutaneous Squamous Cell Carcinoma of the Head and Neck: The Randomized Phase III TROG 05.01 Trial

- More than 300 patients with advanced cSCC[2]
- Half received radiation after surgery
- Half received chemotherapy and radiation after surgery
- No difference were found between groups in cancer outcomes

How about immunotherapy?

Immunotherapy and cSCC

- cSCC is known for having a lot of mutations in the DNA, likely from a lot of sun exposure
- This gives the immune system a lot of targets and suggests that it may work well for cSCC

Does immunotherapy work?

PD-1 Blockade with Cemiplimab in Advanced Cutaneous Squamous-Cell Carcinoma

- Small group of patients with cancer that had spread or could not be removed[3]
- All patients received cemiplimab (Libtayo), which blocks PD-1
- Over half of patients responded
- Many of the patients who responded had long lasting responses

Does adjuvant immunotherapy help?

Adjuvant Cemiplimab or Placebo in High-Risk Cutaneous Squamous-Cell Carcinoma

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- Patients with advanced cSCC treated with surgery and radiation[4]
- 415 patients, half got cemiplimab and half got a placebo
- Cemiplimab patients were 68% less likely to die or have the cancer come back

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Could we add immunotherapy before surgery?

Rationale for giving immunotherapy before treatment

- Neo-adjuvant means a “helper” treatment before the main treatment
- It is thought that its better to help the immune system learn about the tumor before it is cut out to develop a stronger response

Neoadjuvant Cemiplimab for Stage II to IV Cutaneous Squamous-Cell Carcinoma

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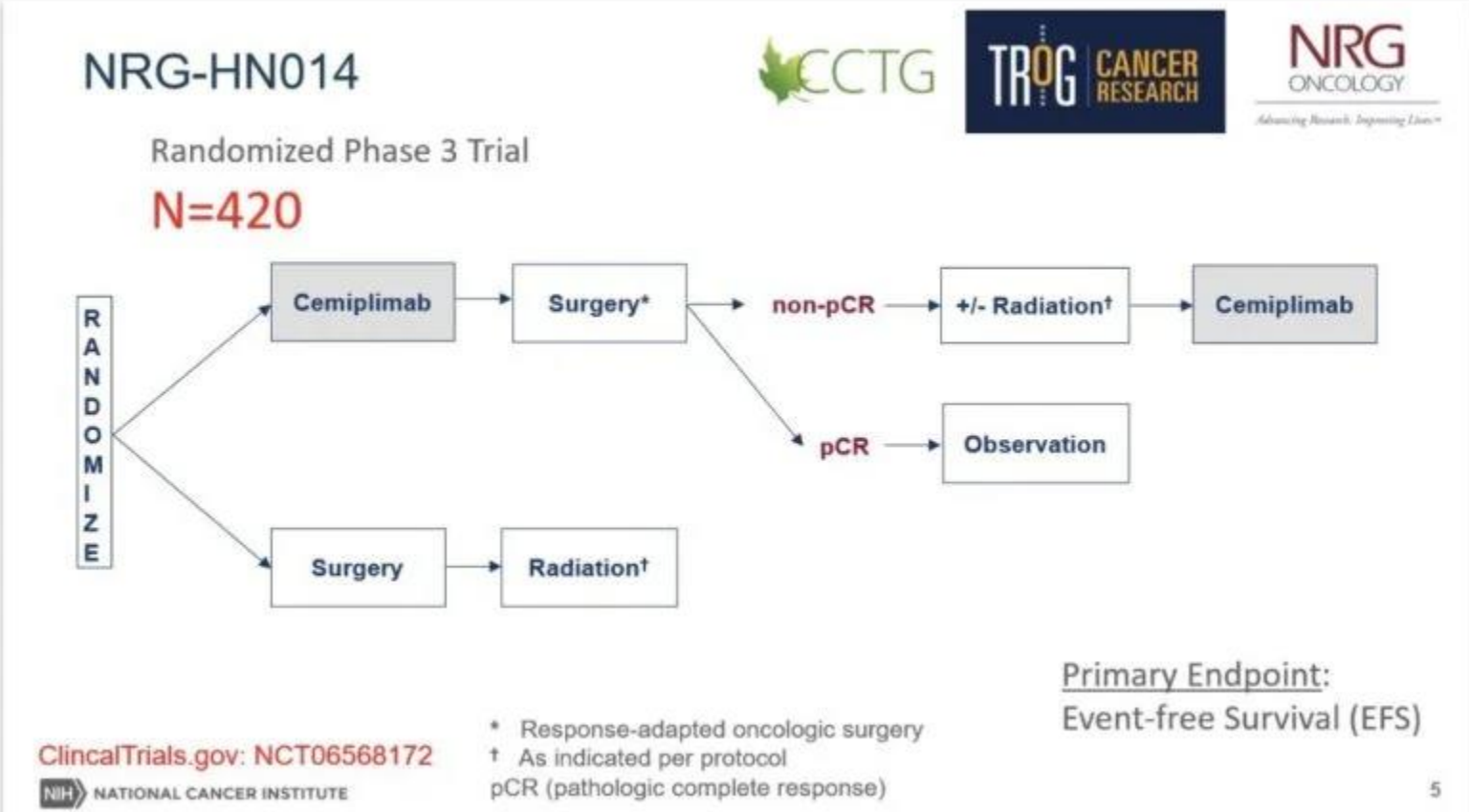
- ~80 patients with cSCC were treated with cemiplimab followed by surgery[5]
- 51% complete pathologic response, pathological major response in 13%

The Next Frontier

- Does adding immunotherapy before surgery actually make people more likely to survive?
- Does the response of the tumor predict how the patient will do?
- Can we change what we do if the tumor responds well
  - No radiation
  - Less surgery
  - No surgery

State of the Art



Unanswered Questions

- Which are the right patients to use immunotherapy for?
- How long do we need to use the treatment for?
- Are there blood tests that can measure or even predict a response?
- How can we help patients with compromised immune systems?

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