Revolutionary Approaches to Improving Outcomes in Unresected LA SCCHN

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Welcome and Introductions

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Disclosures

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Consulting Fees: Adagene, Astellas, Cidara, Eisai, Genmab, Gilboa, iTeos, Lilly, MSD, Merck, Nectin Tx, Novartis, Nykode, Pangea Therapeutics, PCI Biotech, Replimune, Roche, Soteria, Tempus, Viracta

Employee of an ineligible company: Tempus Labs

Ownership Interest: Kinnate Biopharma, Primmune Therapeutics

Research: NCI

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Research: AstraZeneca, Boehringer Ingelheim, Replimune

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Consulting Fees: MSD

Research: AstraZeneca, BICARA Therapeutics, Bristol-Myers Squibb Company, FSTAR Therapeutics, Genentech, Gilead, KURA Oncology, Lilly, MSD, Pfizer, Regeneron, TopAlliance

LA SCCHN Overview

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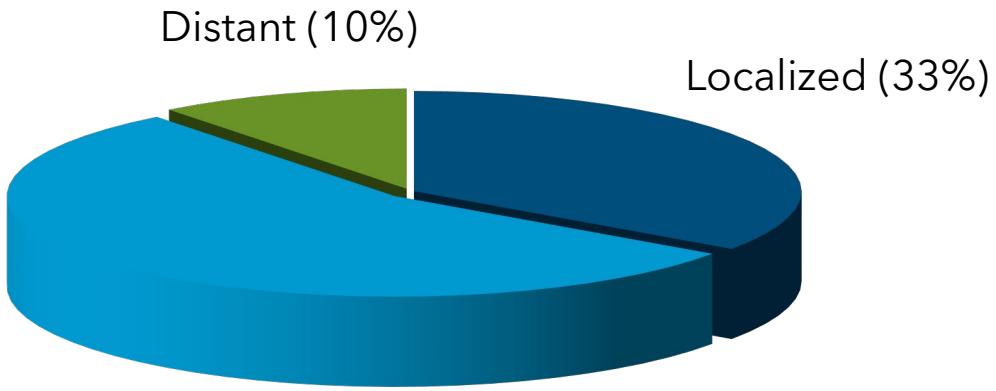
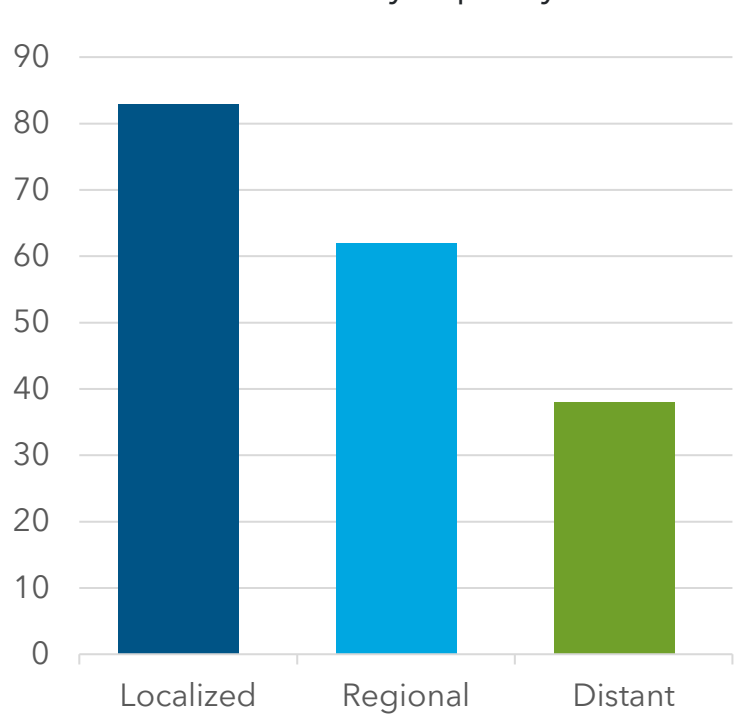
Locally Advanced Head and Neck Cancer

Stage at Diagnosis



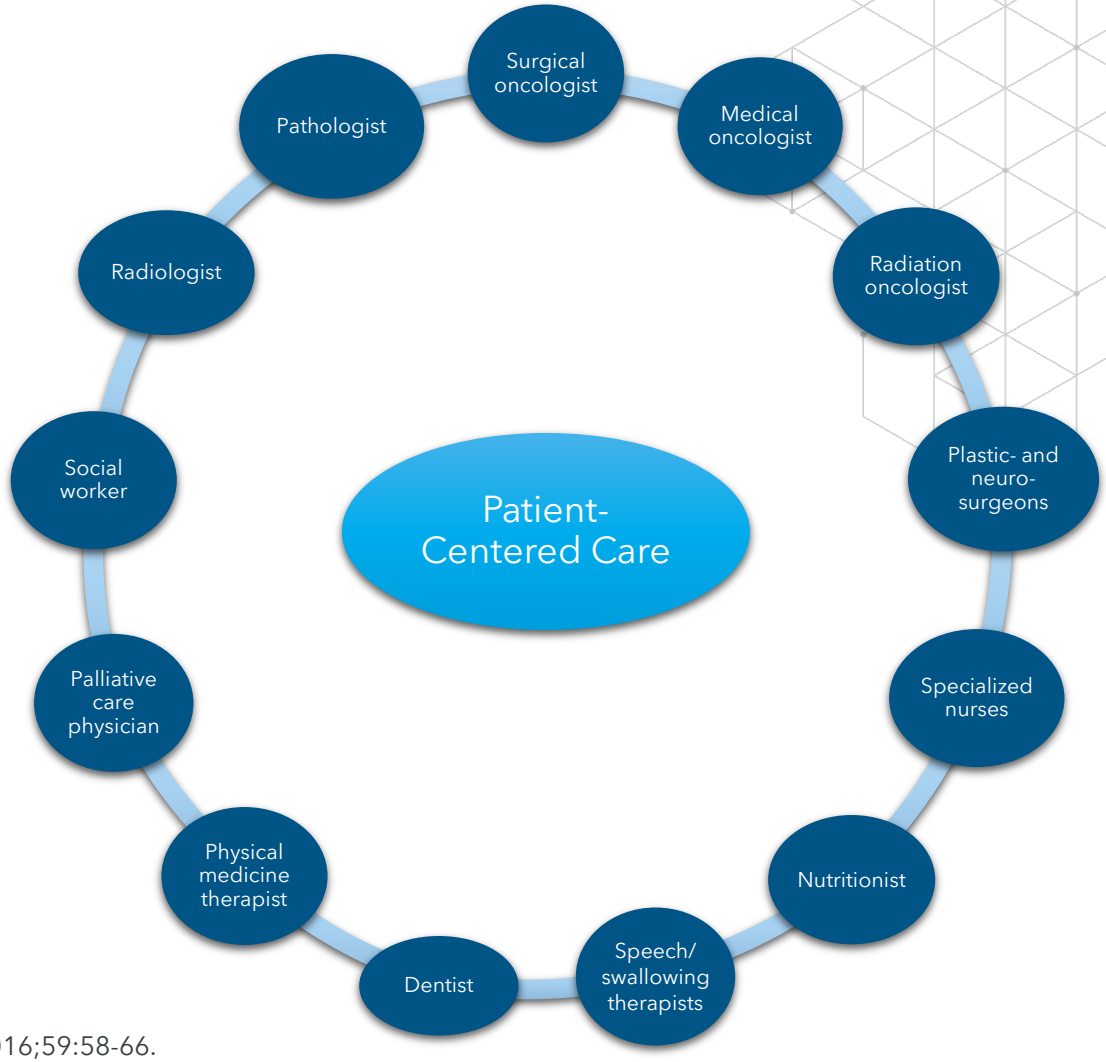
Five-Year Relative Survival Rates (US 2005 to 2011)



Adapted from Siegel RL, et al. *CA Cancer J Clin.* 2016;66(1):7-30. Chow LQM. *N Engl J Med.* 2020; 382:60-72.

LA SCCHN Requires a Multidisciplinary Treatment Approach

- Treatment of LA SCCHN is challenging because of the involvement of critical organs important for swallowing, speaking and breathing
- Patient evaluation by a multidisciplinary team (MDT) is essential for appropriate treatment decision-making
  - Treatment differs according to stage of disease, anatomical size and surgical resectability
  - Patient performance status, age, comorbidities, preference also impact choice of treatment
- Patients treated in high volume centers with expertise in multidisciplinary care have better outcomes



Chow LQM. *N Engl J Med.* 2020;382:60-72. Licitra L, et al. *Oral Oncol.* 2016;59:58-66.

LA SCCHN Non-Surgical Standard of Care

- Concurrent chemoradiotherapy (CRT) is superior to radiation alone with respect to loco-regional control and overall survival[1,2,3]
- Definitive concurrent CRT with high-dose (HD) cisplatin (100 mg/m^2 Q3W) to a dose of 70Gy over 6-7weeks is the preferred regimen[1,2]
- RTOG 91-11, laryngeal preservation randomized trial: the 2-year loco-regional control significantly was better with concurrent CRT (78%) vs induction chemo (IC)-RT (61%) vs RT alone (56%)[3]

1. NCCN Guidelines. Head and Neck Cancers (Version 2.2022). 2. Grégoire V, et al. *Ann Oncol.* 2010;21(5):v184-186. 3. Forestiere AA, et al. *New Engl J Med.* 2003;349:2091-2098.

Supportive Care is of Paramount Importance Along the Whole Disease Trajectory of LA SCCHN

Main issues in supportive care during CRT

- Nutritional assessment before and during CRT
- Nutritional enteral/parenteral support
- Prevention of swallowing problems related to RT
- Treatment of RT-induced pain
- Prevention and treatment of mucositis
- Prevention of major infections during chemotherapy and/or RT
- Psychological distress during treatment

Important role of MDT!

Bonomo P, et al. *Front Oncol.* 2019;9:926.

Current Landscape in LA SCCHN

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Outcomes for LA SCCHN

- Approximately two-thirds of patients with SCCHN present with locally advanced disease (stage III- IVB).
- Median Overall Survival is 20 months[1]
- Survival rate is poorer for HPV-negative vs. HPV-positive SCCHN:
  - HPV-negative: 5-year survival rate <25% for HPV-negative Stage IVA and IVB;[2] 8-year rate 30.2% for p16-negative Stage III, IV[3]
  - 5-year survival rate ~ 50% for HPV-positive Stage III;[4,5] 8-year survival rate 70.9% for p16+[3]

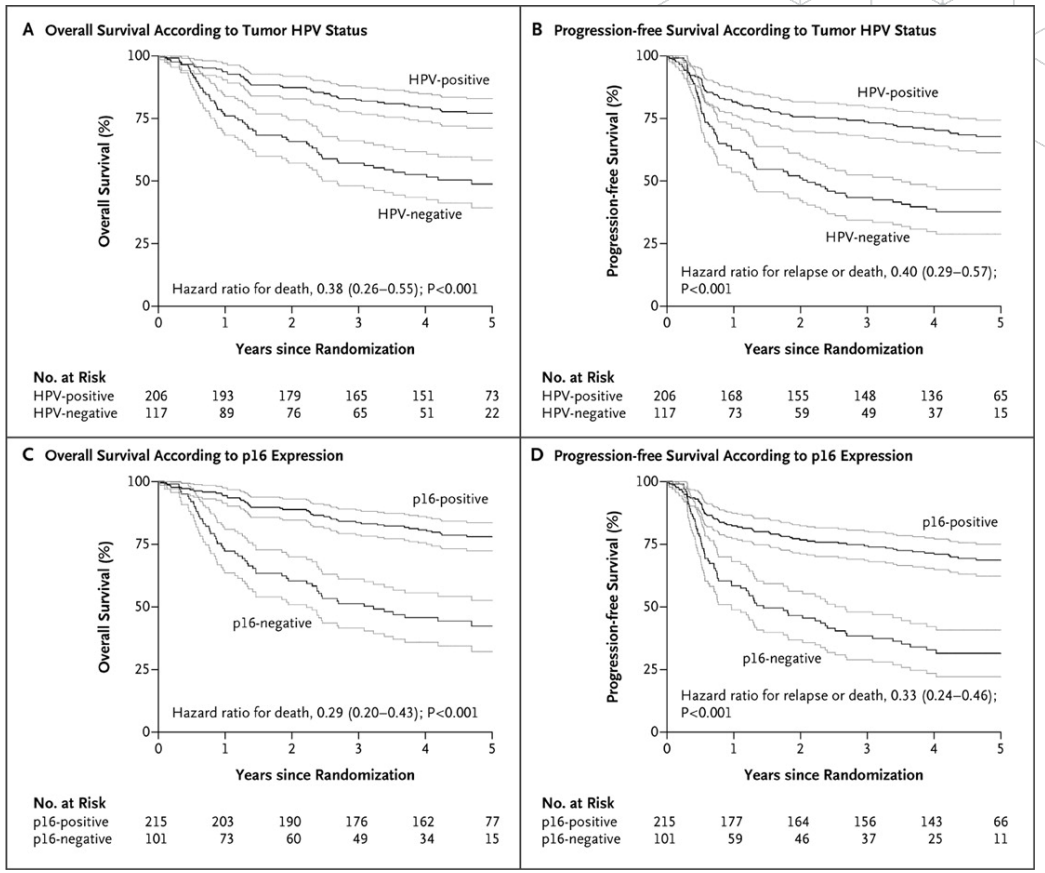


Fig. 1 from Reference 6, Ang et al.

1. Adelstein DJ, et al. *J Clin Oncol.* 2003;21(1):92-98.
2. Denis F, et al. *J Clin Oncol.* 2004;22(1):69-76.
3. Nguyen-Tan PF, et al. *J Clin Oncol.* 2014;32(34):3858-3867.
4. Vokes EE, et al. *J Natl Cancer Inst.* 2015;107(12):djv344.
5. O'Sullivan B, et al. *Lancet Oncol.* 2016;17(4):440-451.
6. Ang KK, et al. *N Engl J Med.* 2010;363(1):24-35.

Definitive Treatment Options for LA SCCHN

- Multi-modal treatment
- Surgery followed by adjuvant radiation +/- chemotherapy
- Definitive chemoradiotherapy
- Induction chemotherapy → chemoradiotherapy
- Neoadjuvant chemotherapy → surgery → radiation +/- chemotherapy

Slide Courtesy of Deborah J. Wong, MD, PhD

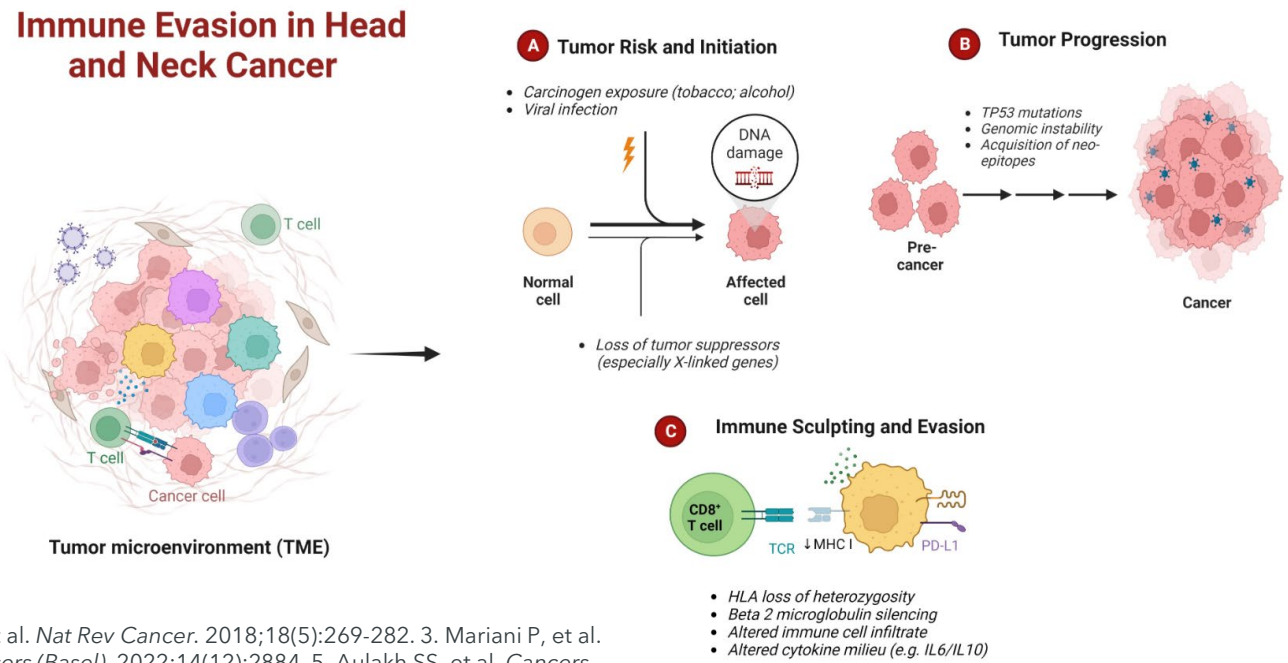
Non-Surgical Management of LA SCCHN

- Chemoradiotherapy
  - Cisplatin 100 mg/m^2 IV every 3 weeks on days 1, 22, 43
  - Cisplatin 40 mg/m^2 IV weekly
  - Definitive CRT: weekly cisplatin 40 mg/m^2 non-inferior to bolus cisplatin[1]
- Other chemotherapy: 5FU/platinum, Carboplatin/paclitaxel, 5FU/hydroxyurea
- Cetuximab: anti-EGFR[2]
  - Improved 3-year OS 10% vs RT alone, 32% increased locoregional control, decreased the risk of death by 26%, No difference in 1-year and 2-year rates of distant metastasis
- 50% of patients with LA-SCCHN will develop recurrent/metastatic disease with multimodal therapy

1. Sharma A, et al. *J Clin Oncol.* 2022;40(Suppl 16):6004. 2. Bonner JA, et al. *N Engl J Med.* 2006;354(6):567-578.

Negative Prognostic Factors for SCCHN

- Clinical Factors: HPV status, age, smoking, surgical margin status, tumor depth, extranodal disease
- High tumor mutational burden[1]
- Genetic mutations: *TP53* (84%), *CDKN2A*(59%), *FAT1*, *PIK3CA*, *NOTCH1*, *KMT2D*, *HRAS*[2]
- Recurrent alterations at oncogenes and tumor suppressor genes: *CCNL1*, *EGFR*, *MYC*, *CCND1*, and *TP53*
- Overexpression of oncogenes,
- Loss of heterozygosity
- Immune signatures:
  - Increased neutrophil : lymphocyte ratio[3]
  - Increased pro-inflammatory cytokines (IL-6) in the tumor microenvironment[4]
- Presence of detectable ctDNA[5]
- Inhibition of apoptosis[6]



1. Alexandrov LB, et al. *Nature*. 2013;500(7463):415-421. 2. Leemans CR, et al. *Nat Rev Cancer*. 2018;18(5):269-282. 3. Mariani P, et al. *J Oral Pathol Med*. 2022;51(1):39-51. 4. Kondoh N, Mizuno-Kamiya M. *Cancers (Basel)*. 2022;14(12):2884. 5. Aulakh SS, et al. *Cancers (Basel)*. 2022;14(12):2968. 6. Ferris RL, et al. *Cancer Treat Rev*. 2023;113:102492. 7. Kirtane K, et al. *J Clin Med*. 2022;11(24):7259.

Treatment for LA SCCHN: Is More Better?

- Many attempts to improve outcomes, all negative.
  - No improvement with adjuvant chemotherapy
- RTOG 522: Cetuximab + cisplatin + RT vs Cisplatin-RT[1]
  - More frequent interruptions in radiation therapy (26.9% *v* 15.1%)
  - more grade 3 to 4 radiation mucositis (43.2% *v* 33.3%, respectively), rash, fatigue, anorexia, and hypokalemia, but not more late toxicity.
  - No differences in 30-day mortality (1.8% *v* 2.0%, respectively; *P* = .81), 3-year PFS (61.2% *v* 58.9%, respectively; *P* = .76), 3-year OS (72.9% *v* 75.8%, respectively; *P* = .32), locoregional failure (19.9% *v* 25.9%, respectively; *P* = .97), or distant metastasis (13.0% *v* 9.7%, respectively; *P* = .08).
- Lapatinib for resected SCCHN[2]
  - Lapatinib + Chemo-RT concurrently → 12 months maintenance – no improvement in DFS
- LUX Head and Neck – 18 months maintenance afatinib after chemo-RT +/- salvage surgery[3]
  - No improvement in DFS → Recruitment stopped after preplanned futility analysis
  - More toxicity compared to placebo (acneiform rash, stomatitis, diarrhea)

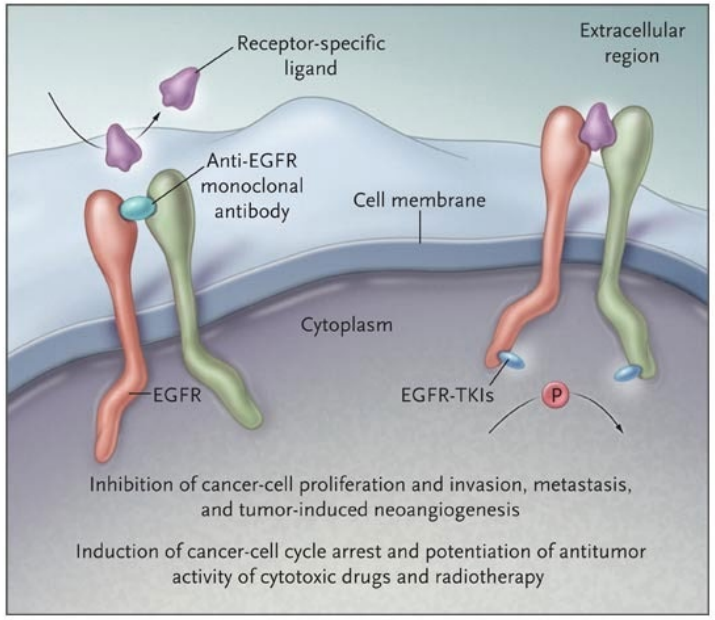


Figure from Ciardiello and Tortora[4]

1. Ang KK, et al. *J Clin Oncol*. 2014;32(27):2940-2950.
2. Harrington K, et al. *J Clin Oncol*. 2015;33(35):4202-4209.
3. Burtness B, et al. *JAMA Oncol*. 2019;5(8):1170-1180.
4. Ciardiello F, Tortora G. *N Engl J Med*. 2008;358(11):1160-1174.

Treatment for LA SCCHN: Anti-PD1?

Study Name	Phase	Agent	Comparator	Line of Therapy	% PD-L1 Positivity	Overall Survival
Checkmate-141	III	Nivolumab	I.C.[1]	Second line	any	7.5 vs. 5.1 mo
KEYNOTE-040	III	Pembrolizumab	I.C.	Second line	any	8.4 vs. 6.9 mo
KEYNOTE-048	III	P + C[2]	EXTREME[3]	First line	any	13.0 vs. 10.7 mo
KEYNOTE-048	III	Pembrolizumab	EXTREME	First line	PD-L1 CPS[4] ≥20	14.9 vs. 10.7 mo
KEYNOTE-048	III	Pembrolizumab	EXTREME	First line	PD-L1 CPS ≥1	12.3 vs. 10.3 mo

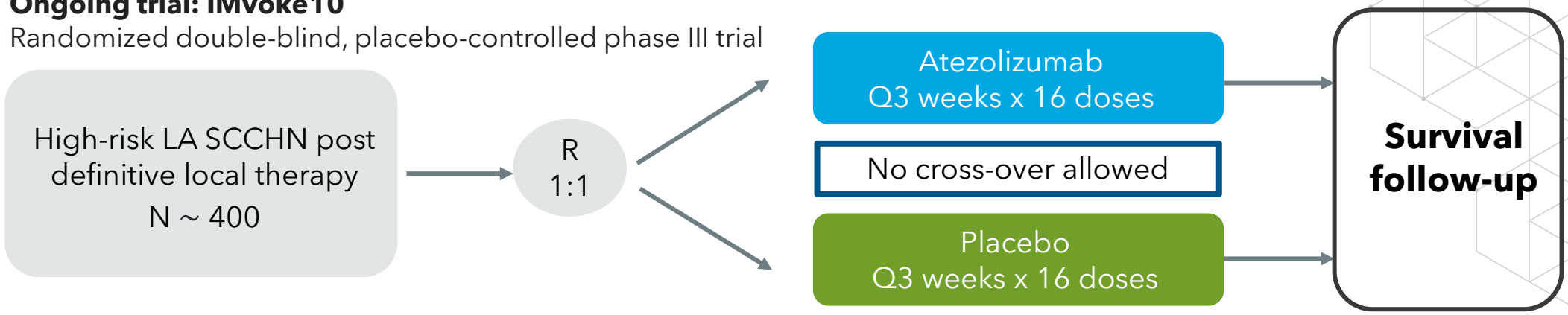
[1] I.C. – Investigator's Choice Therapy – cetuximab, docetaxel or methotrexate
[2] P + C – Pembrolizumab plus Chemotherapy (fluorouracil and platinum)
[3] EXTREME – platinum + fluorouracil + cetuximab
[4] CPS - combined positive score

Slide Courtesy of Deborah J. Wong, MD, PhD

Atezolizumab as Adjuvant Monotherapy After Definitive Therapy of LA SCCHN

Ongoing trial: IMvoke10

Randomized double-blind, placebo-controlled phase III trial



Stratification factors:
- HPV status
- Response to definitive local therapy
- Whether surgery was part of definitive therapy

High-risk definition:
- HPV negative = Stage IVA or IVB
- HPV positive = Stage III

Response post-definitive local therapy:
- Radiologic complete response (CR) / partial response (PR) / stable disease (SD) at the 10 – 12 week post-therapy scan

Co-primary endpoints:
- EFS
- OS

Secondary endpoints:
- EFS rates at 1 and 2 years, OS rates at 1,2, and 3 years, safety, PRO

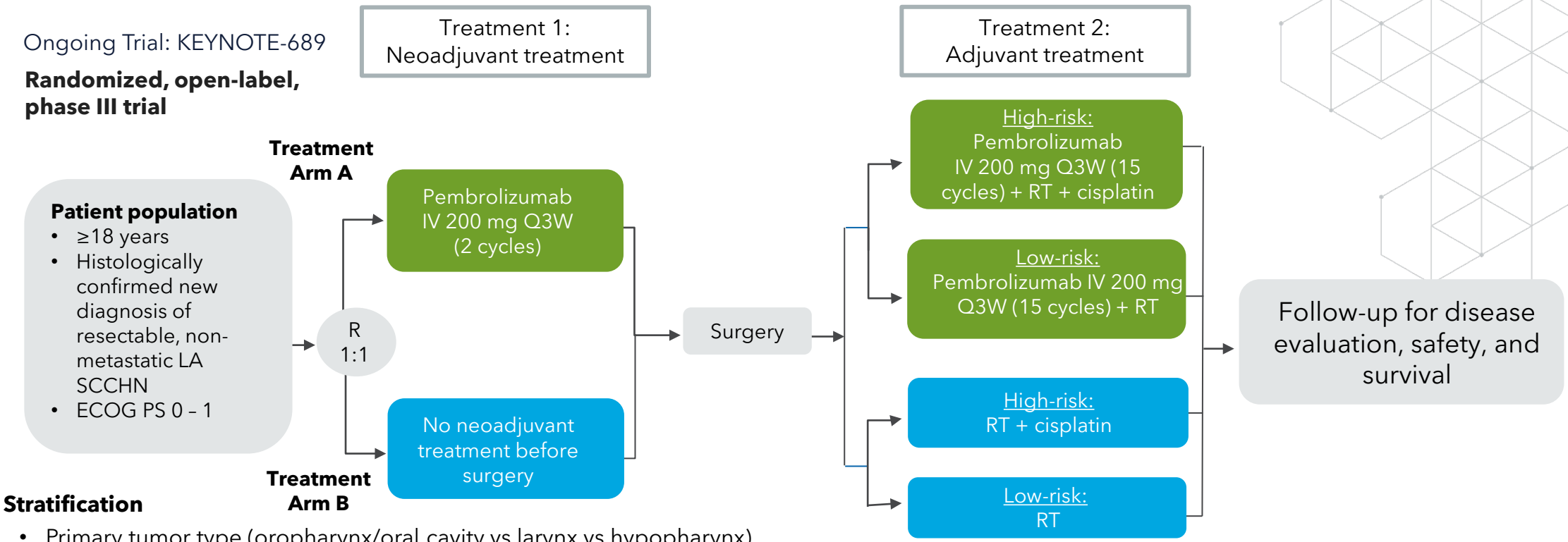
Exploratory objectives:
- Biomarkers, PK, and ADA

Haddad, R, et al. ESMO 2018. Abstract 1052. ClinicalTrials.gov Identifier: NCT03452137.

Neoadjuvant and Concurrent/Adjuvant Pembrolizumab in LA SCCHN

Ongoing Trial: KEYNOTE-689

Randomized, open-label, phase III trial



Stratification

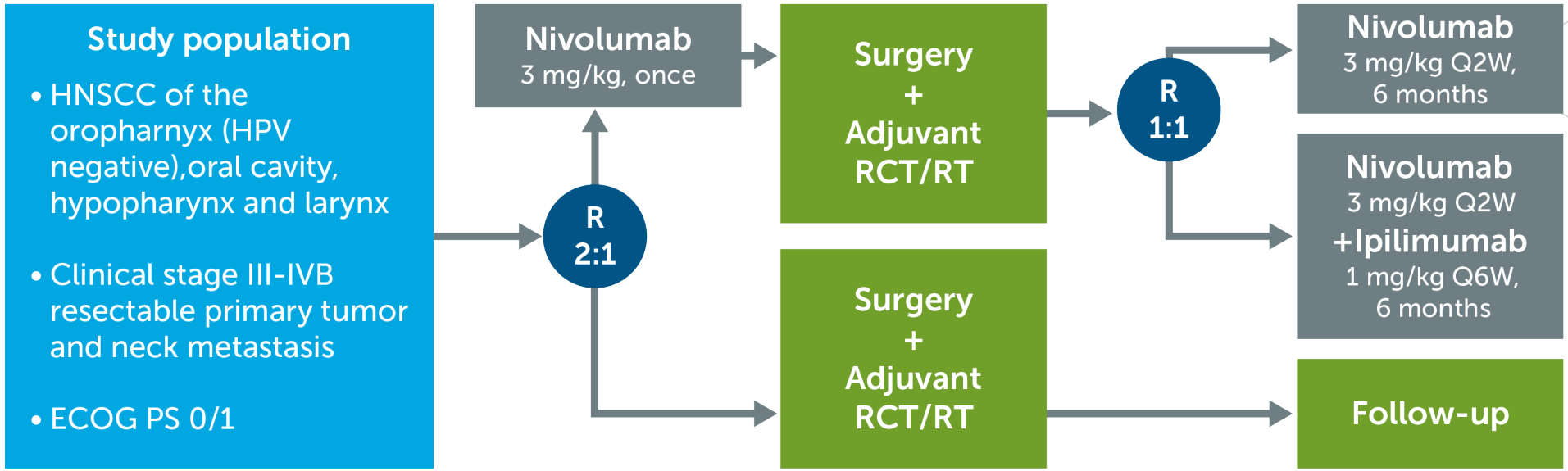
- Primary tumor type (oropharynx/oral cavity vs larynx vs hypopharynx)
- Tumor stage (III vs IVA)
- PD-L1 status (TPS ≥ 50% vs TPS <50%)
- HPV p16 status (oropharynx p16 positive vs oropharynx p16 negative or larynx/hypopharynx/oral cavity)

Uppaluri R, et al. ASCO 2019. Abstract TPS6090. ClinicalTrials.gov Identifier: NCT03765918.

Neoadjuvant Nivolumab and Adjuvant Nivolumab ± Ipilimumab in LA SCCHN

Ongoing Trial: IMSTAR-HN

Randomized, open-label, phase III trial



Primary endpoint: Disease free survival (DFS) at 3 years
Secondary endpoints: Locoregional control (LRC), distant metastasis free survival (DMFS), overall survival (OS), survival in PD-L1 subgroups, DFS in immunotherapy arms, acute toxicity and late morbidity, QoL

Busch CJ, et al. ASCO 2019. Abstract TPS6095. ClinicalTrials.gov Identifier: NCT03700905.

Summary and Conclusions

- Multimodal treatment of locally advanced SCCHN can be effective, but up to 50% of patients relapse.
- Beyond definitive or adjuvant chemoradiotherapy, no proven treatment strategies to improve outcomes have been identified.
- Prognostic factors for relapsed disease include clinical, genetic and immune factors.
- Novel immunotherapy and targeted therapy approaches are under investigation.

Raising Awareness of Emerging Evidence in LA SCCHN

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KEYNOTE-412 Study Design (NCT03040999)

Patients

- Newly diagnosed, pathologically proven, treament-naive unresected LA HNSCC
  - T3-T4 [N0-N3] or any N2a-3 [T1-T1] larynx/hypopharynx/oral cavity/ p16-negative oropharynx cancers
  - T4 or N3 p16-positive oropharynx cancer
- Evaluable tumor burden per RECIST v1.1
- ECOG PS 0 or 1
- Candidates for definitive high-dose cisplatin-based CRT

R (1:1) N=804

Pembrolizumab 200 mg IV Q3W + CRT[a] → Maintenance **Pembrolizumab** x 14 cycles

Placebo IV Q3W + CRT[a] → Maintenance **Placebo** x 14 cycles

Treament until

- PD or intolerance toxicity
- 17 cycles for pembrolizumab or placebo[b]
- Investigator/patient decision to withdraw

Stratification Factors
- Radiotherapy regimen (AFX vs SFX)
- Tumor site/p16 status (orthopharynx [p16+ vs p16-] or larynx/hypopharynx/oral cavity)
- Disease stage (III vs IV)

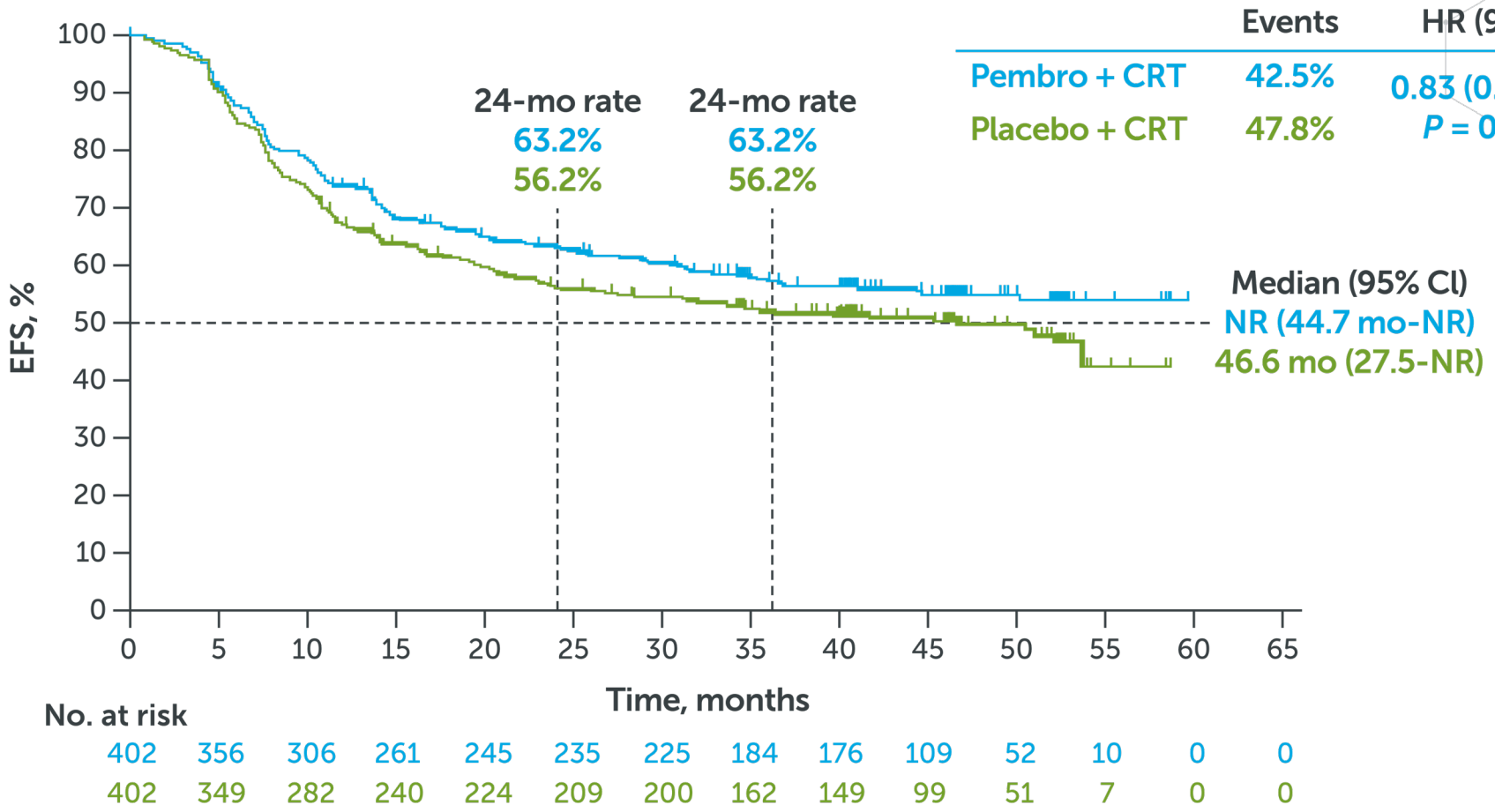
Primary endpoint
- Event-free survival (EFS)

Secondary endpoints included:
- OS
- Safety/tolerability

Post-treatment follow-up to assess
- Safety
- Disease status
- Survival

[a]CRT included cisplatin (100 mg/m2, Q3W) and accelerated fractionation (AFX) (70 Gy, 6 fractions/week for 5 weeks and then 5 fractions for the 6th week, 35 fractions total) or standard fractionation (SFX) (70 Gy, 5 fractions/week for 7 weeks, 35 fractions in total). [b]A pembrolizumab/placebo priming dose was given 1 week before CRT, followed by 2 doses during CRT and 14 doses of maintenance therapy after CRT, for a total of 17 doses.

Event-Free Survival, ITT Population

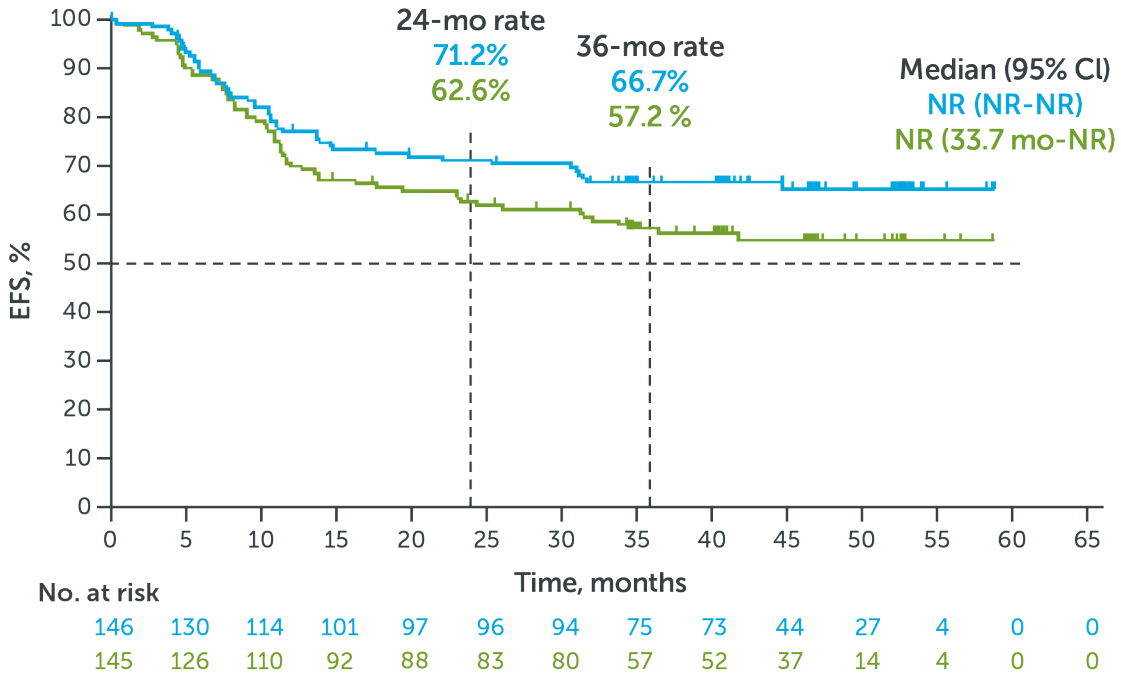


[a]*P* value did not meet the superiority threshold of one-sided a of 0.0242. Data cutoff date: May 31, 2022.
Machiels KN412 ESMO 2022.

EFS and OS in Patients with PD-L1 CPS ≥20 (Post Hoc Analysis)

EFS

	Events	HR (95% CI)
Pembro + CRT	32.3%	0.73 (0.49-1.06)
Placebo + CRT	42.1%	

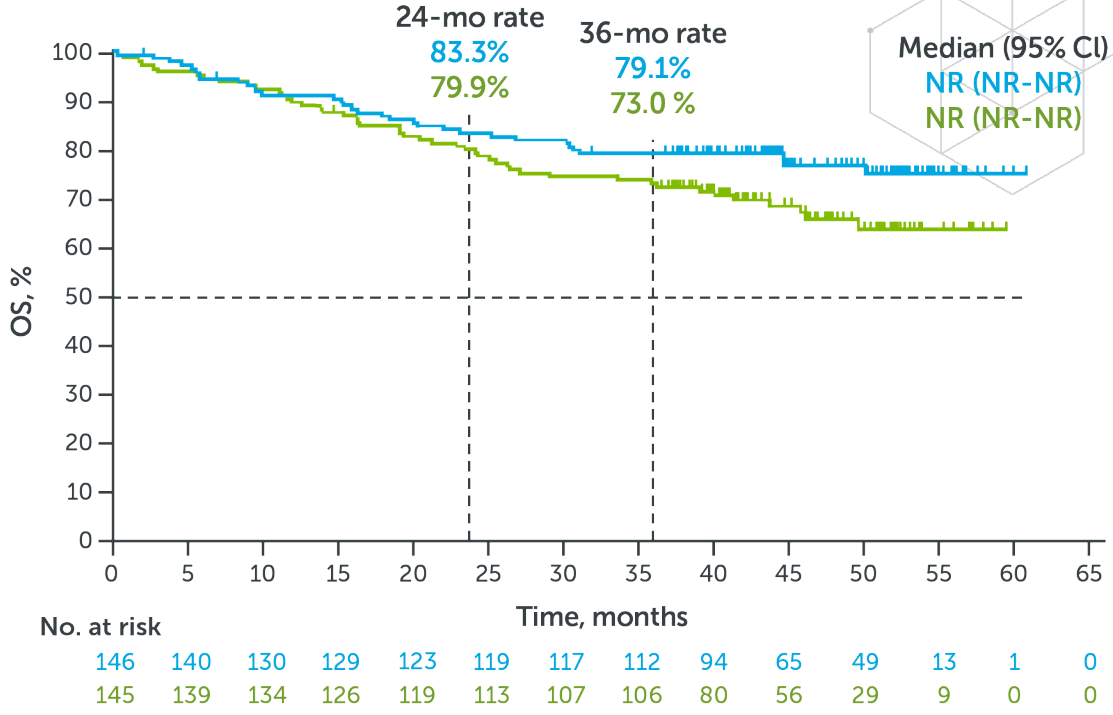


No. at risk

146	130	114	101	97	96	94	75	73	44	27	4	0	0
145	126	110	92	88	83	80	57	52	37	14	4	0	0

OS

	Events	HR (95% CI)
Pembro + CRT	22.6%	0.67 (0.43-1.04)
Placebo + CRT	32.4%	

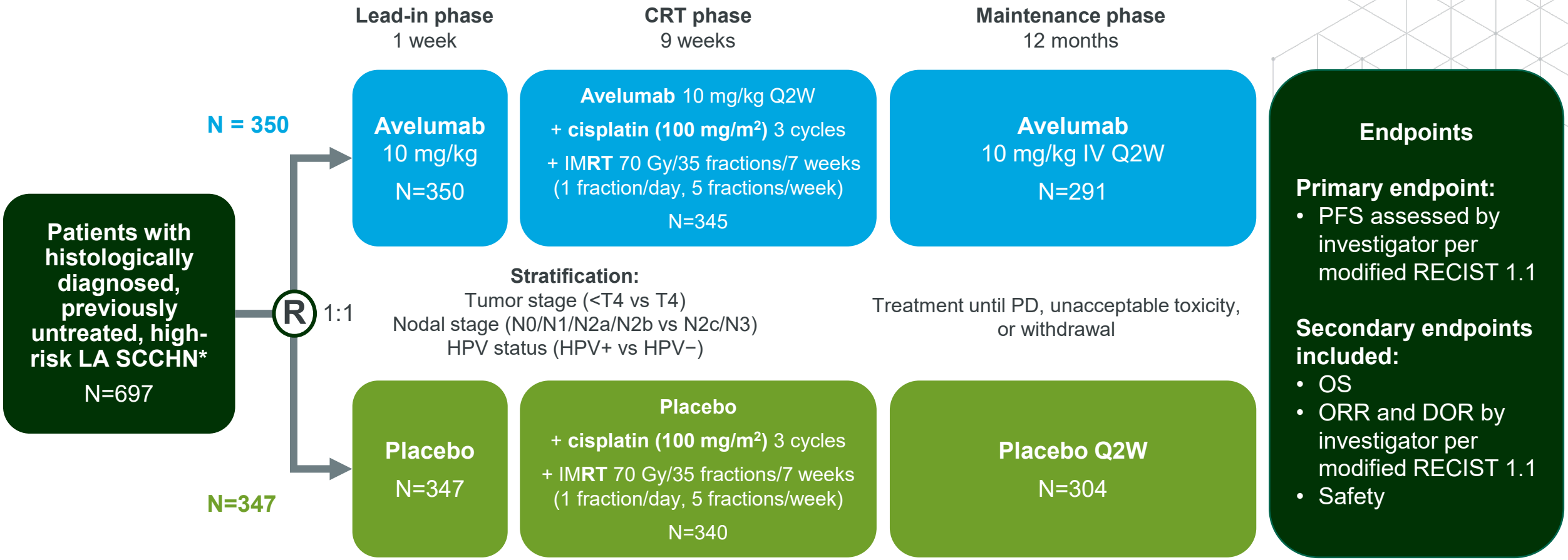


No. at risk

146	140	130	129	123	119	117	112	94	65	49	13	1	0
145	139	134	126	119	113	107	106	80	56	29	9	0	0

Data cutoff date: May 31, 2022.
Machiels KN412 ESMO 2022

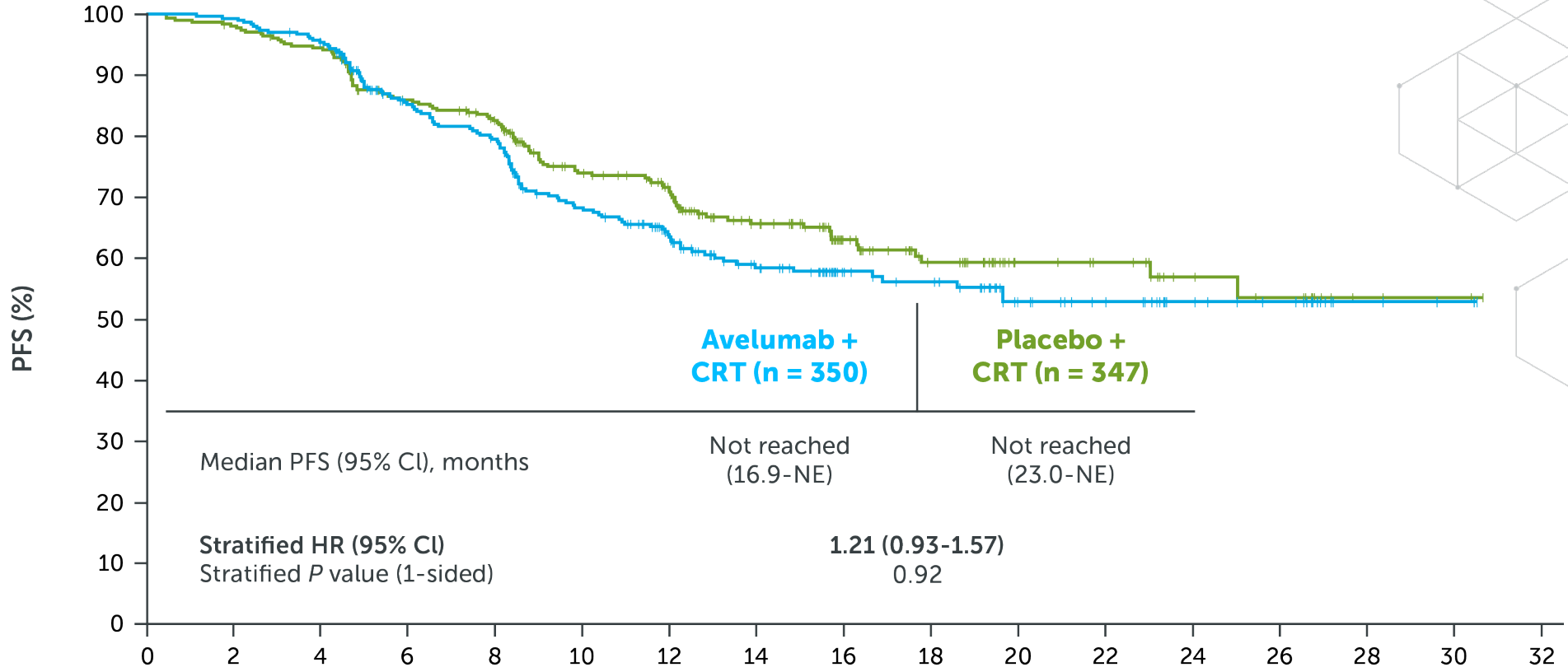
JAVELIN Head & Neck 100: Study Design



DOR, duration of response; HPV, human papillomavirus; IMRT, intensity-modulated radiation therapy; IV, intravenously; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; Q2W, every 2 weeks; R, randomized; RECIST 1.1, Response Evaluation Criteria in Solid Tumors version 1.1.
* High-risk LA SCCHN (oral cavity, oropharynx, larynx, or hypopharynx): HPV-negative disease stage III, IVa, IVb; nonoropharyngeal HPV-positive disease stage III, IVa, IVb; HPV-positive oropharyngeal disease T4 or N2c or N3 (TNM staging per AJCC, 7th edition).

Cohen EW, et al. Presented at ESMO 2020. Abstract 910O.

Primary Endpoint: PFS by Investigator per Modified RECIST 1.1



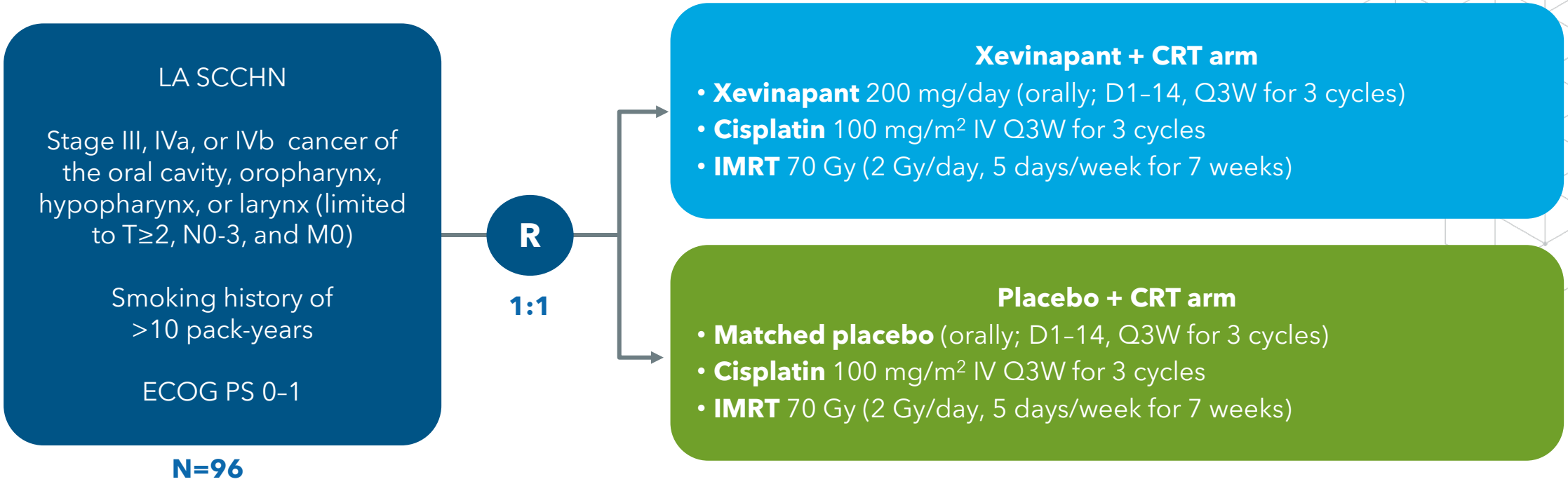
At risk

Avelumab + CRT	350	303	289	239	222	176	143	107	69	63	41	33	22	18	4	2	0
Placebo + CRT	347	303	291	257	241	200	172	121	75	56	31	28	18	15	3	2	0

NE, not estimable.

Cohen EW, et al. Presented at ESMO 2020. Abstract 910O.

Randomized, Phase II Study of Xevinapant + CRT vs Placebo + CRT in Unresected LA SCCHN[1]



- **Primary endpoint:** LRC rate at 18 months after CRT (Δ>20% between arms with 0.8 power at 0.2 significance level)
- **Secondary endpoints:** PFS, duration of LRC, complete response rate, BOR, DCR, OS, safety

1. Sun X-S, et al. *Lancet Oncol.* 2020;21(9):1173–1178.

BOR, best observed response; CRT, chemoradiotherapy; D, day; DCR, disease control rate; ECOG PS, Eastern Cooperative Oncology Group performance status; Gy, Gray; IMRT, intensity modulated radiotherapy; IV, intravenous; LA SCCHN, locally advanced squamous cell carcinoma of the head and neck; LRC, locoregional control; M, metastasis; N, lymph node; OS, overall survival; PFS, progression-free response; Q3W, every 3 weeks; T, tumor.

Patient Characteristics[1]

Baseline characteristics	Xevinapant + CRT (n = 48)	Placebo + CRT (n = 48)
Age, mean (range), years	57 (39–70)	59 (56–63)
Smoking history		
Current/former smoker, %	100	100
Total pack-years (range)	40 (15–104)	40 (11–90)
Alcohol consumption		
Drinks per week (range)	21 (1–50)	21 (3–140)
ECOG PS, %		
0	56	56
1	42	44
Primary tumor location, n (%)		
Hypopharynx	7 (15)	10 (21)
Larynx	8 (17)	2 (4)
Oral cavity	2 (4)	3 (6)
Oropharynx	31 (65)	33 (69)
HPV-16 negative	28 (58)	28 (58)
HPV-16 positive	3 (6)	5 (10)
TNM stage, %		
III	15	17
IVa	73	67
IVb	13	17

Heavy smokers and high alcohol consumption

Few OPC HPV-16 positive

Predominantly Stage IVa disease

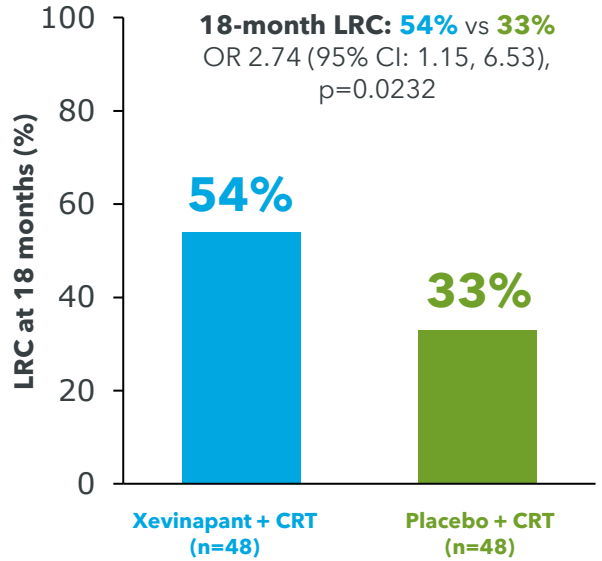
1. Sun X-S, et al. *Lancet Oncol.* 2020;21(9):1173–1178

CRT, chemoradiotherapy; ECOG PS, Eastern Cooperative Oncology Group performance status; HPV, human papillomavirus; OPC, oropharyngeal cancer; TNM, tumor, node, metastasis.

Xevinapant: Locoregional Control at 18 Months and Progression-Free Survival (3-Year Analysis*)

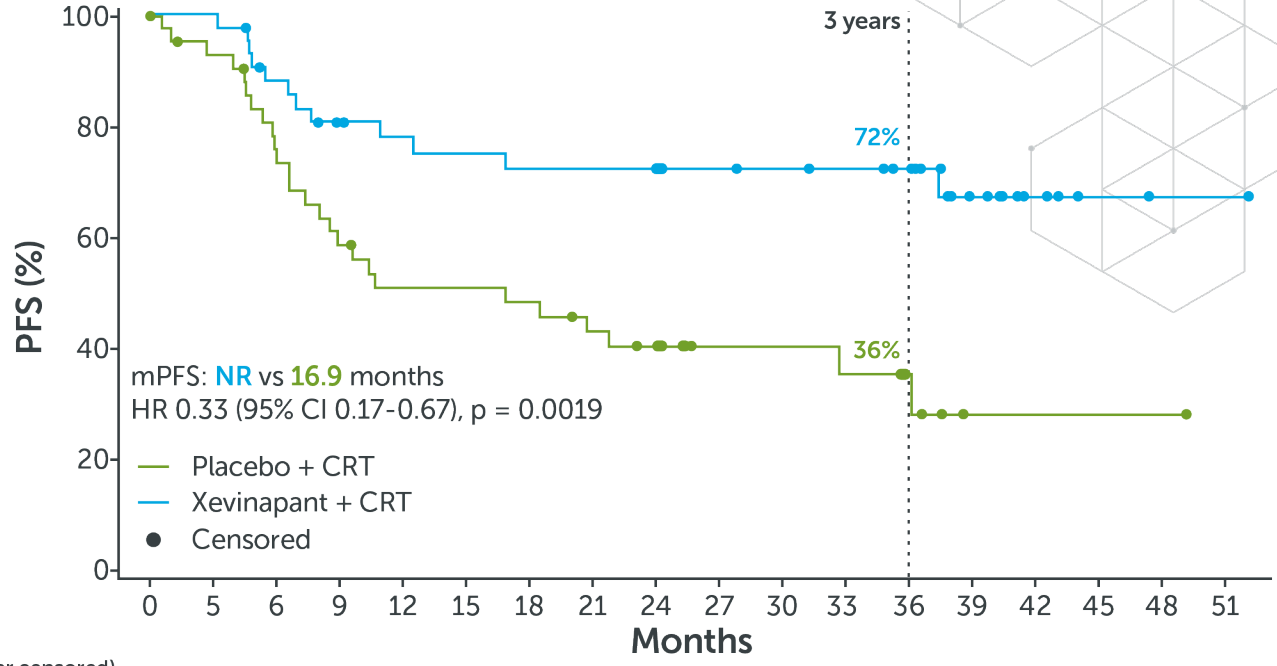
Primary endpoint was met

LRC at 18 months after CRT (ITT population)[1†]



*Analysed 3 years after the last patient started treatment. †Δ>20% between arms with 0.8 power at 0.2 significance level.
CI, confidence interval; CRT, chemoradiotherapy; HR, hazard ratio; ITT, intent-to-treat; LRC, locoregional control; (m)PFS, (median) progression-free survival; NR, not reached; OR, odds ratio.

PFS at 3 years[2*]



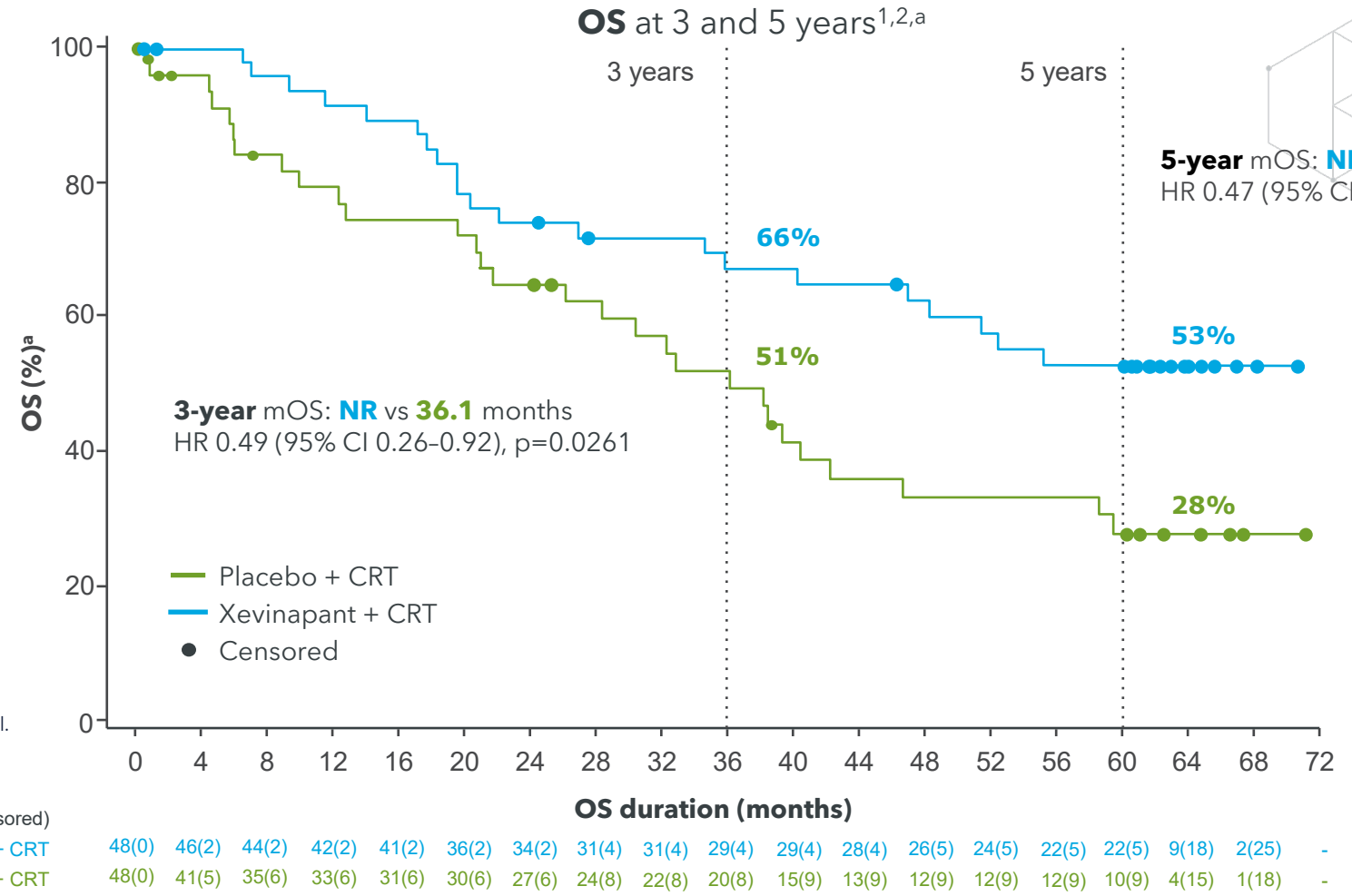
At risk (number censored)																
Xevinapant + CRT	48(0)	43(5)	36(7)	30(10)	28(11)	27(11)	26(11)	26(11)	26(12)	23(14)	22(15)	21(16)	18(19)	10(26)	5(31)	2(34)	1(35)	1(35)
Placebo + CRT	48(0)	39(6)	32(7)	24(7)	20(8)	20(8)	19(8)	16(9)	14(11)	8(16)	8(16)	7(16)	5(18)	1(21)	1(21)	1(21)	1(21)	-

1. Sun X-S, et al. *Lancet Oncol.* 2020;21(9):1173–1178; 2. Tao Y, et al. *Eur J Cancer.* 2023;183:24–37.

Xevinapant + CRT More Than Halved the Risk of Death After 3 and 5 Years of Follow-up vs Placebo + CRT[1,2]

Median OS was prolonged with xevinapant vs placebo[2]

[a]OS probability based on Kaplan-Meier estimate.CI, confidence interval; CRT, chemoradiotherapy; HR, hazard ratio; mOS, median OS; NR, not reached; OS, overall survival.



Risk of death was reduced by **53%** at 5 years HR 0.47

1. Bourhis J, et al. *Ann Oncol.* 2020;31:S1168. Abstract LBA 39. 2. Bourhis J, et al. *Ann Oncol.* 2022;33:S1400. Abstract LBA 33.

The Safety Profile of Xevinapant + CRT was Comparable to the Safety Profile of Placebo + CRT[1]

Most common TEAEs[a]	Xevinapant + CRT (n = 48), n (%)			Placebo + CRT (n = 47[b]), n (%)		
	Grade 1–2	Grade 3	Grade ≥4	Grade 1–2	Grade 3	Grade ≥4
Any	7 (15)	41 (85)	9 (19)	6 (13)	29 (62)	12 (25)
Mucositis	21 (44)	15 (31)	0	22 (47)	10 (21)	0
Dysphagia	10 (21)	24 (50)	0	19 (40)	10 (21)	0
Anemia	12 (25)	17 (35)	0	15 (32)	11 (23)	0
Weight loss	27 (56)	0	0	22 (47)	0	0
Radiation skin injury	24 (50)	1 (2)	0	17 (36)	3 (6)	0
Nausea	19 (40)	2 (4)	0	16 (34)	1 (2)	0
Xerostomia	19 (40)	1 (2)	0	18 (38)	0	0
Dermatitis	16 (33)	2 (4)	0	17 (36)	1 (2)	0
Neutropenia	4 (8)	7 (15)	4 (8)	4 (9)	11 (23)	2 (4)
Tinnitus	15 (31)	0	0	10 (21)	0	0
ALT increased	7 (15)	6 (13)	0	6 (13)	2 (4)	0
AST increased	6 (13)	3 (6)	0	2 (4)	1 (2)	0
Acute kidney injury	8 (17)	2 (4)	0	3 (6)	4 (9)	0
Blood creatinine increased	4 (8)	0	0	5 (11)	1 (2)	0
Renal failure	3 (6)	1 (2)	0	5 (11)	0	0
Chronic kidney disease	2 (4)	1 (2)	0	0	2 (4)	0

[a]TEAEs regardless of relation to study drugs of grade 1–2 occurring in at least 10% of patients, cisplatin-associated adverse events, and all grade 3, 4, and 5 events in the safety population; [b]one patient in the placebo group did not receive the study drug and was not included in the safety analysis; [c]renal insufficiency, febrile neutropenia, thrombocytopenia, peripheral sensory neuropathy, or severe vomiting; [d]in the placebo group, two (4%) deaths were due to adverse events (one multiple organ failure and one asphyxia; neither was considered to be related to treatment). CRT, chemoradiotherapy; TEAE, treatment-emergent adverse event.

- There were increases in mucositis, dysphagia, and anemia with xevinapant + CRT vs placebo + CRT, consistent with the radiosensitizing effect of xevinapant
- Xevinapant did not increase the frequency or severity of cisplatin-associated adverse events,[c] with the exception of grade 1–2 tinnitus
- No deaths due to adverse events occurred in the xevinapant group[d]

1. Sun X-S, et al. *Lancet Oncol.* 2020;21(9):1173–1178.

Phase II Data Summary

Efficacy

- **Xevinapant + CRT significantly improved LRC vs placebo + CRT for patients with unresected LA SCCHN (primary endpoint)[1]**
- The addition of xevinapant to CRT improved PFS and prolonged DoR[2]
- Xevinapant + CRT improved 5-year OS vs placebo + CRT[2]

Safety

The safety profile of the two arms were comparable, with expected increases in mucositis, dysphagia, and anemia in the xevinapant arm due to the radiosensitizing effect of xevinapant[1]

- Xevinapant treatment did not increase the frequency or severity of cisplatin-associated adverse events, with the exception of grade 1–2 tinnitus[1]
- Safety profile, including late-onset toxicity, was similar between arms[2]
- The addition of xevinapant to CRT did not compromise compliance vs placebo + CRT[1]

- CRT, chemoradiotherapy; DoR, duration of response; LA SCCHN, locally advanced squamous cell carcinoma of the head and neck; LRC, locoregional control; OS, overall survival; PFS, progression-free survival.

1. Sun X-S, et al. *Lancet Oncol.* 2020;21(9):1173–1178. 2. Bourhis J, et al. *Ann Oncol.* 2022;33:S1400. Abstract LBA 33.

Conclusions

- HNSCC is a locally advanced disease
  - Presents locoregionally
  - LRC paramount
- Cisplatin/RT remains SOC for platinum-eligible patients
- Concomitant RT/CRT and IO has not proven efficacious
- Xevinapant is a small molecule IAP inhibitor that has shown promising efficacy in a randomized phase 2 trial

A Comprehensive Analysis of IAPs

Kevin Harrington, MBBS, PhD

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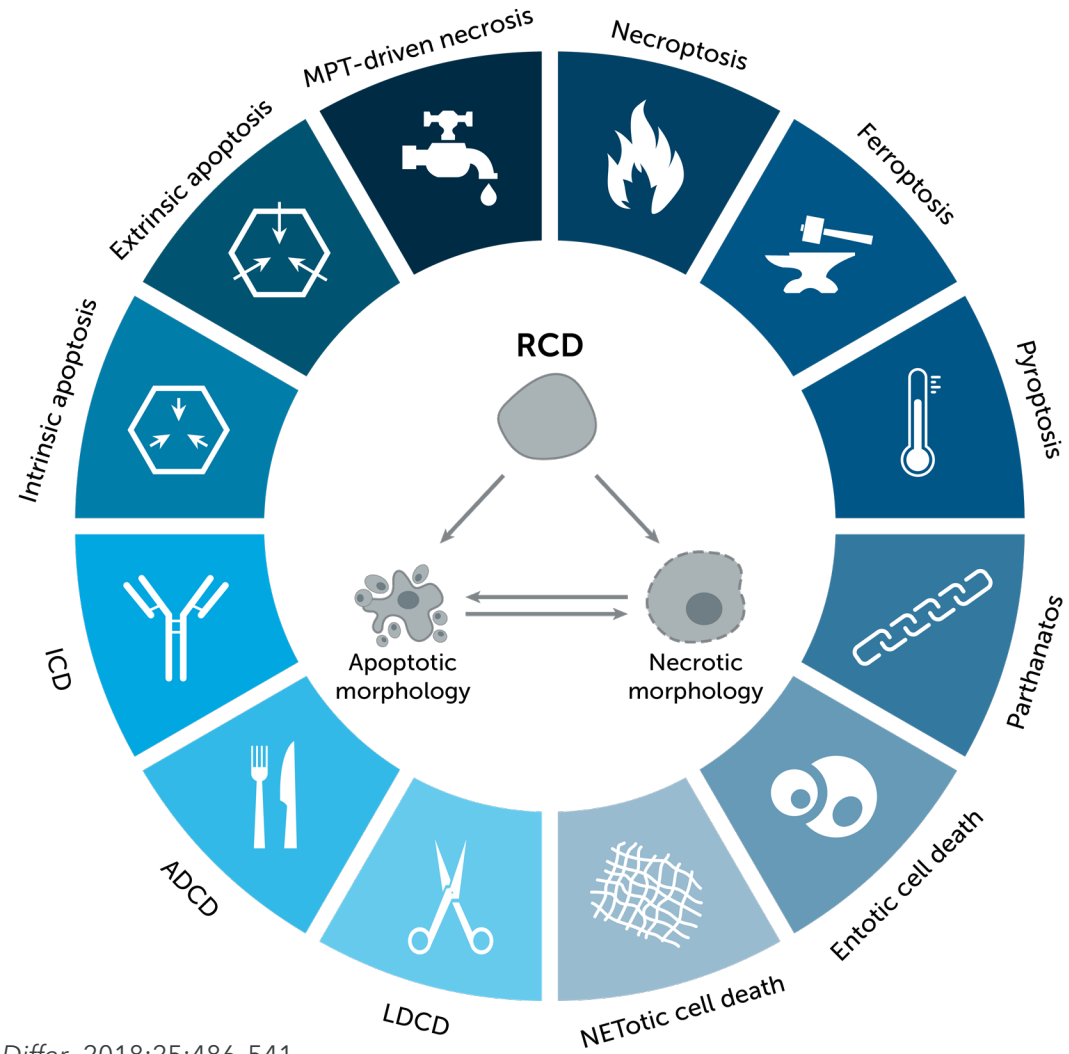
Mechanisms of Cell Death

ADCD, autophagy-dependent cell death; ICD, immunogenic cell death; LDCD, lysosome-dependent cell death; MPT, mitochondrial permeability transition; RCD, regulated cell death.



Galluzzi L, et al. *Cell Death Differ.* 2018;25:486–541.

Mechanisms of Cell Death

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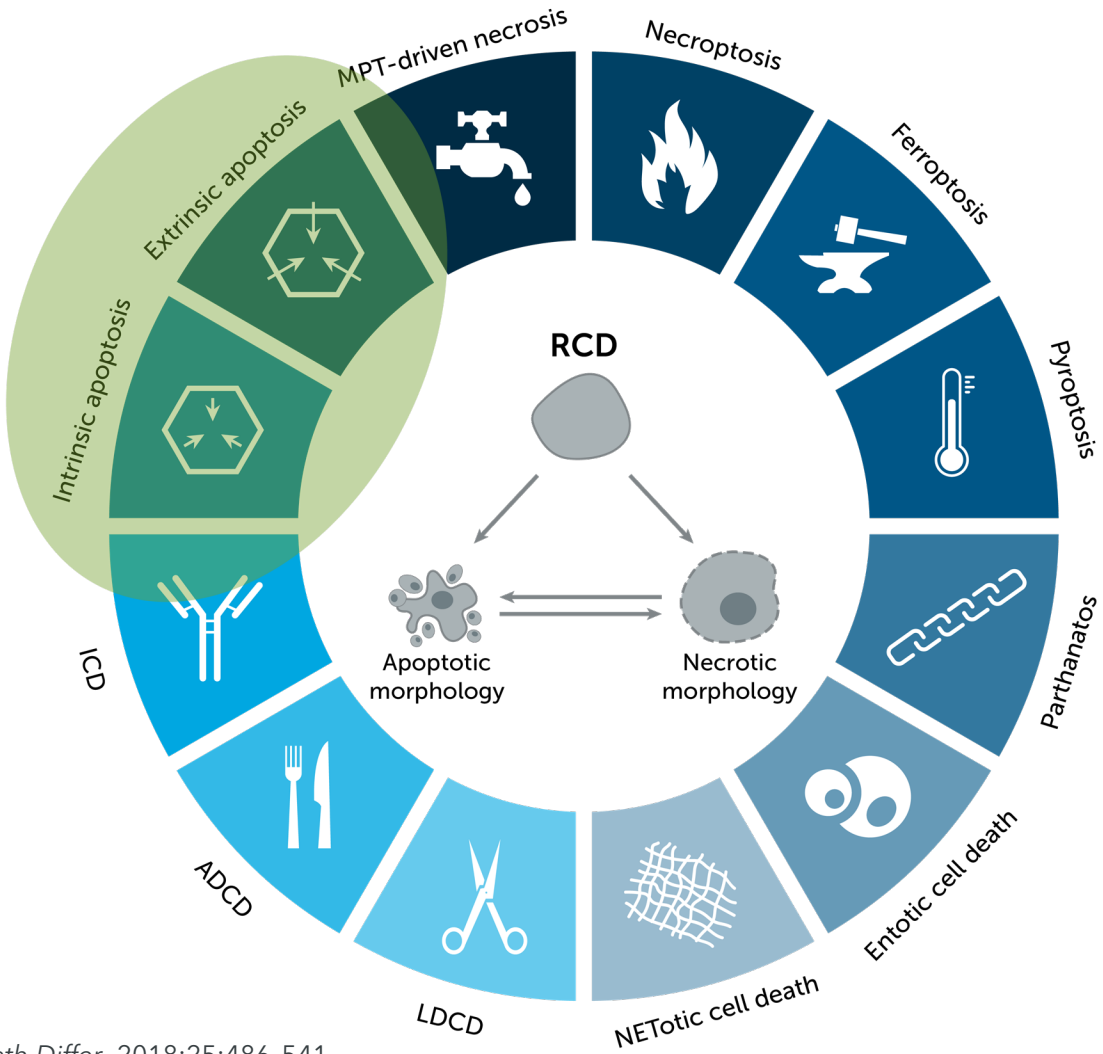


Galluzzi L, et al. *Cell Death Differ.* 2018;25:486–541.

Mechanisms of Combinatorial Therapy With (Chemo)radiotherapy Plus Immunotherapy

ATP, adenosine triphosphate; cGAS, cyclic GMP-AMP synthase; cGAMP, cyclic GMP-AMP; DC, dendritic cell; GzmB, granzyme B; HMGB1, high-mobility group box-1 protein; ICI, immune checkpoint inhibitor; IFN, interferon; IRF3, interferon regulatory factor 3; MHC, major histocompatibility complex; PFN, perforin; STING, stimulator of interferon genes; TAA, tumor-associated antigen.

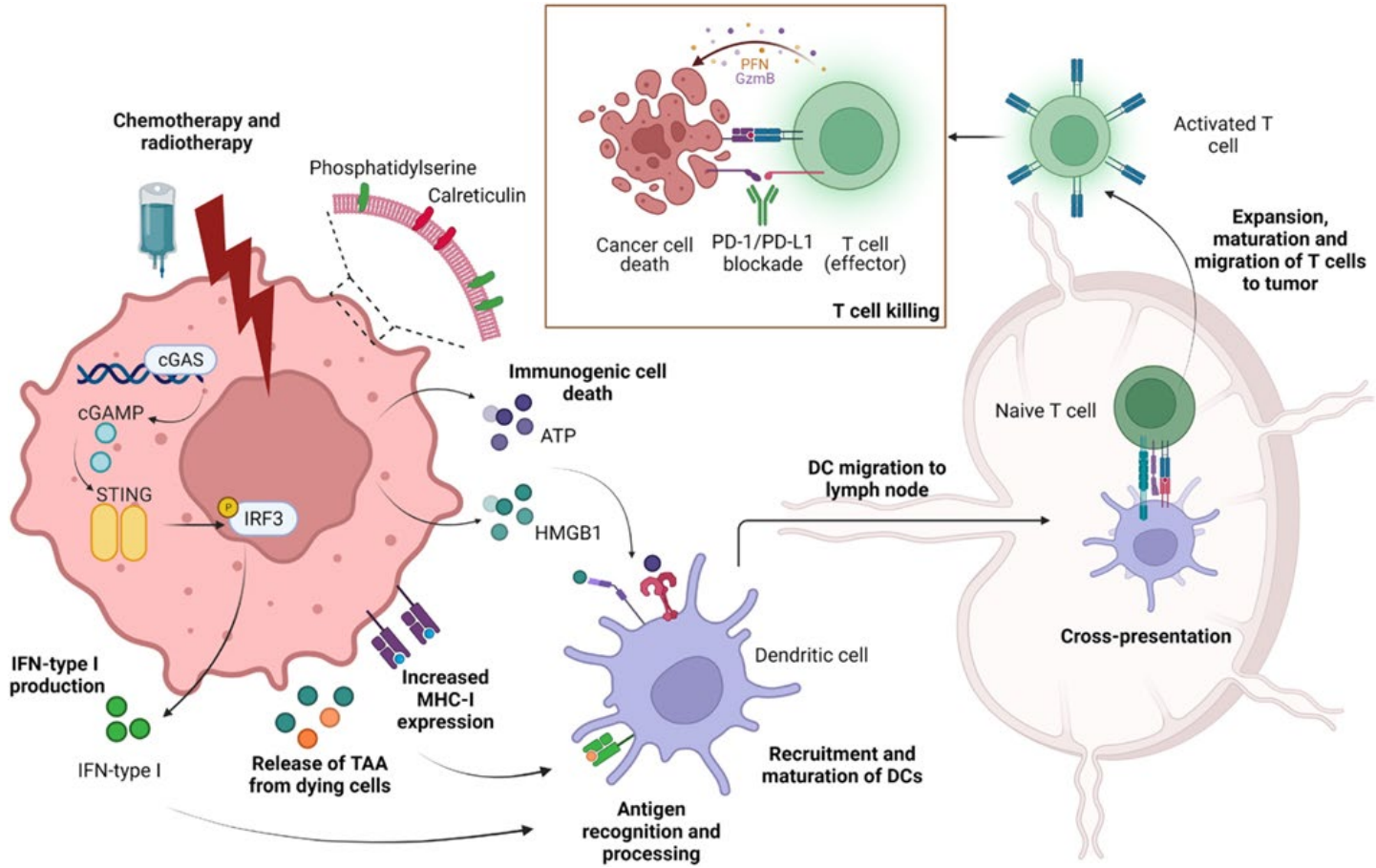
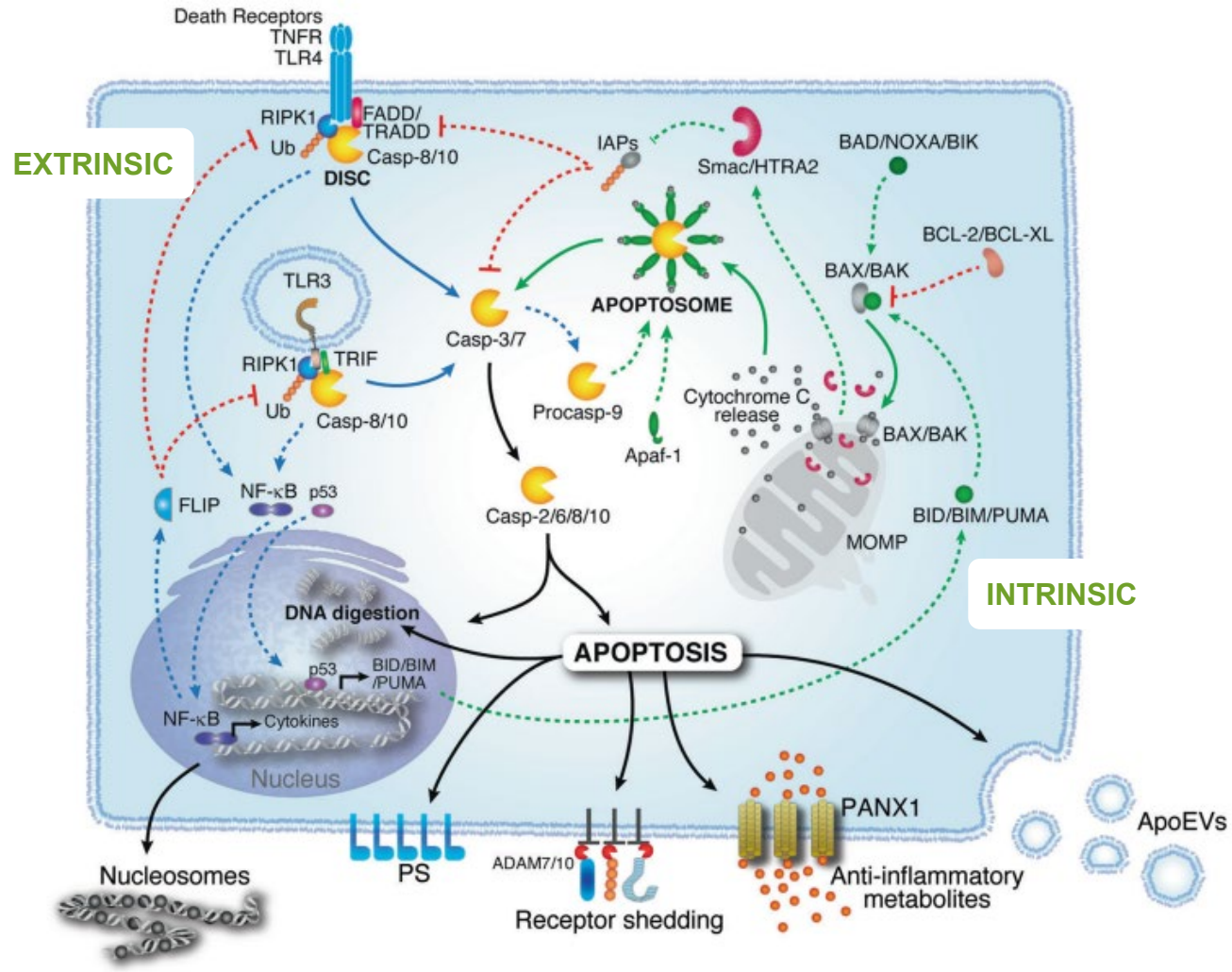


Figure from Nenclares P, et al. *Am Soc Clin Oncol Educ Book.* 2022;42:1–16.

Apoptotic Pathways



DISC, death-inducing signaling complex; FADD, FAS-associated death domain protein; IAP, inhibitor of apoptosis proteins.

Bertheloot D, et al. *Cell Mol Immunol.* 2021;18:1106–1121.

Apoptotic Pathways (Cont.)

Intrinsic Pathway

- Intracellular sensing of cell viability
- Continuous audit of balance of pro- and anti-apoptotic factors
- Responsive to DNA damage
- Mediated through mitochondrion
- Signal involves cytochrome C release from mitochondrion
- Generation of apoptosome
- Signature is caspase 9
- Executioner is caspase 3

Extrinsic Pathway

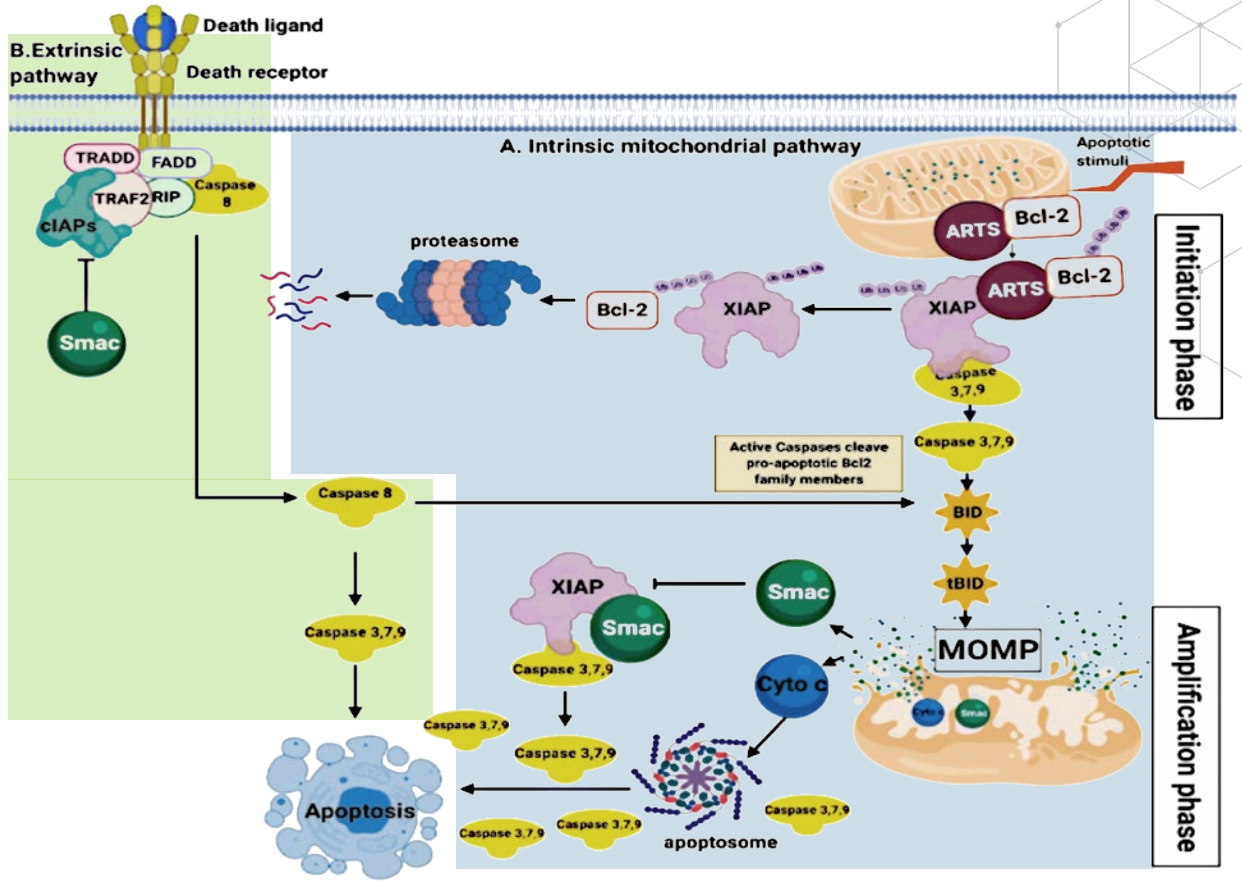
- Extracellular death ligands act on death receptors
- Activates FADD
- Mediated through generation of activated caspase 8
- Executioner is caspase

FADD, FAS-associated death domain protein.

Elmore S. *Toxicol Pathol.* 2007;35:495-516.

Apoptosis: Intrinsic and Extrinsic Pathways

- The involvement of overexpression of members of the inhibitor of apoptosis protein family as an anti-apoptotic mechanism
- XIAP/SMAC linkage between extrinsic and intrinsic pathway



cIAP, cellular inhibitor of apoptosis proteins; XIAP, X-linked inhibitor of apoptosis.

Abbas R, et al. *Cells.* 2020;9:663.

Downstream Effects of Formation of the Apoptosome

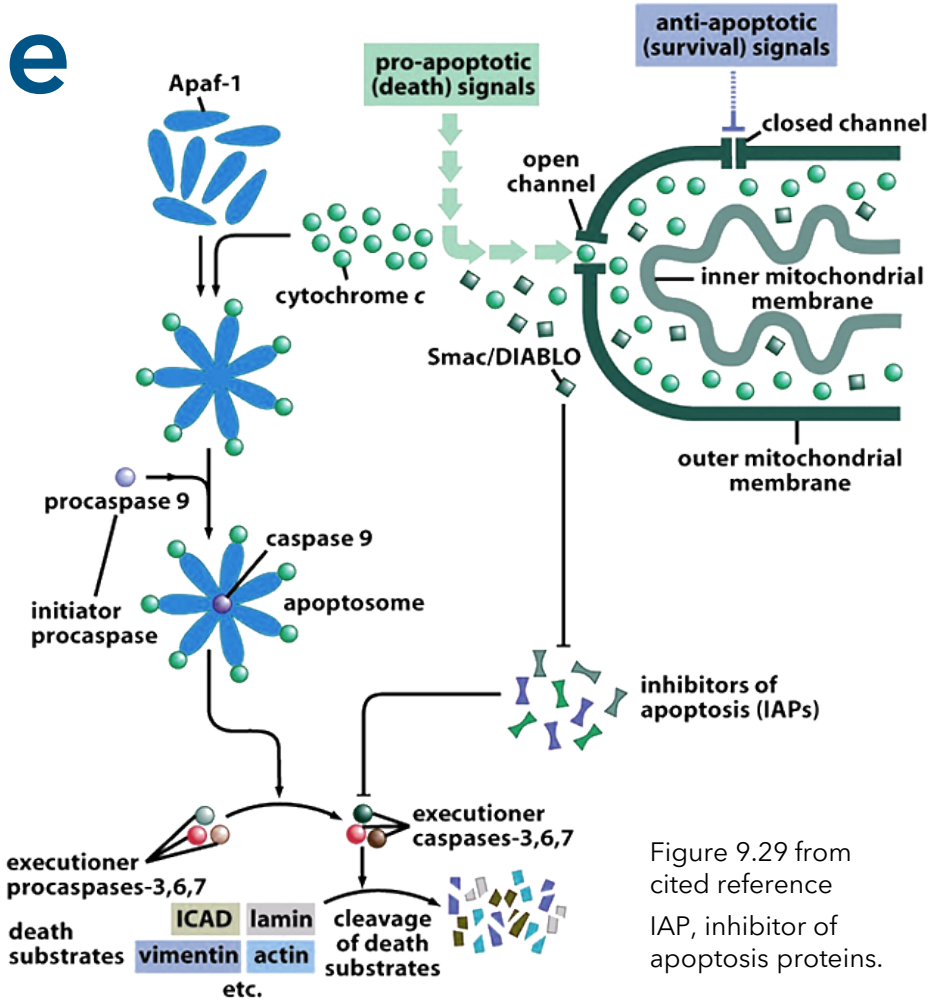


Figure 9.29 from cited reference

IAP, inhibitor of apoptosis proteins.

Weinberg R. *The Biology of Cancer.* New York: Garland Science; 2007.

General Scheme of Control

Pro-apoptotic signals
eg DNA damage, hypoxia, growth factor withdrawal

Extrinsic pathway
eg death receptor

Noxa, Puma, Bad, Hrk, Bim, Bmf, Bik

Bid

Bcl-2 etc

Anti-apoptotic proteins control activity of Bax/Bak

Bax/Bak

Cell primed for apoptosis

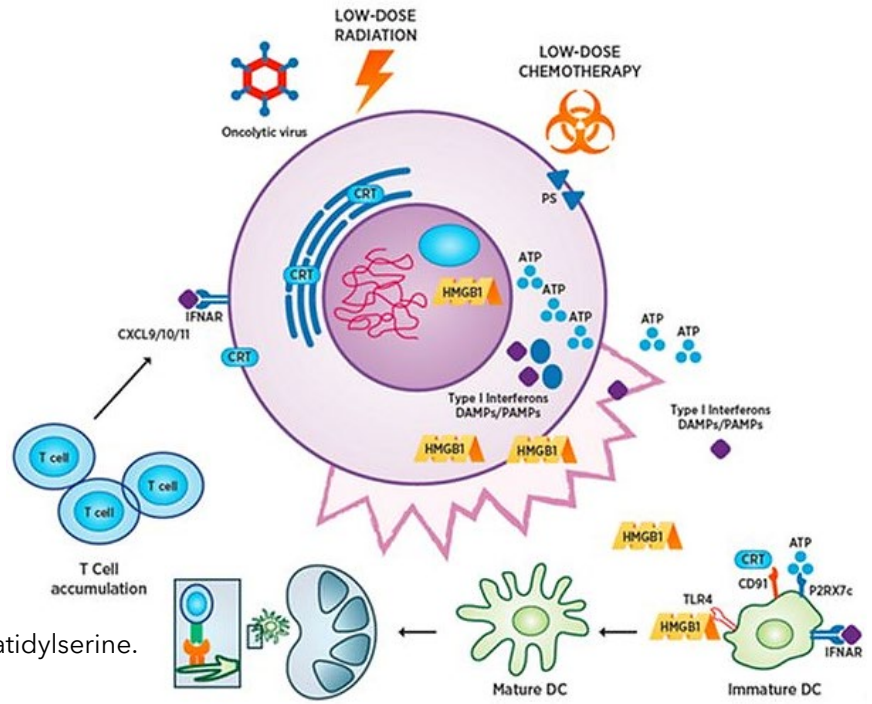
IAPs – Inhibition of apoptosis

APOPTOSIS

Elmore S. *Toxicol Pathol.* 2007;35:495–516.

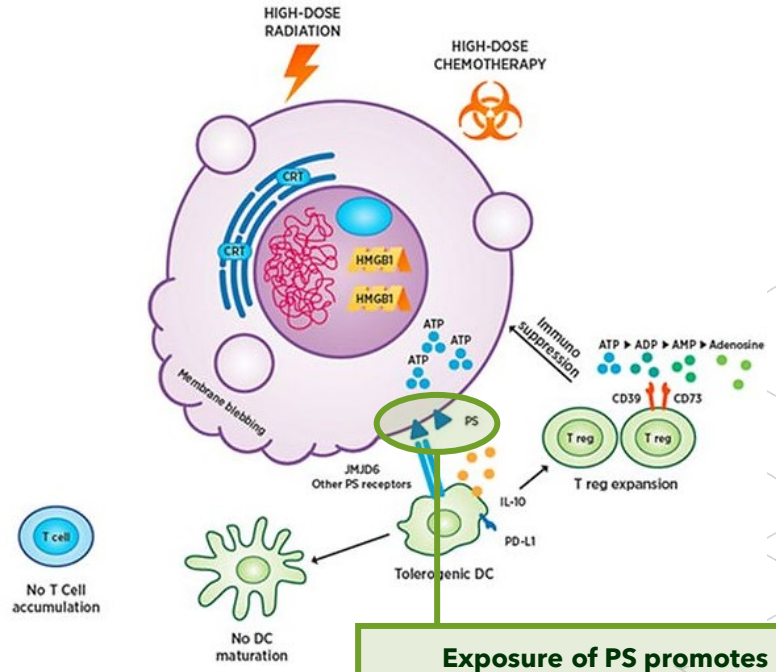
Promoting Immunogenic (Versus Tolerogenic) Cell Death

Immunogenic Cell Death



PS, phosphatidylserine.

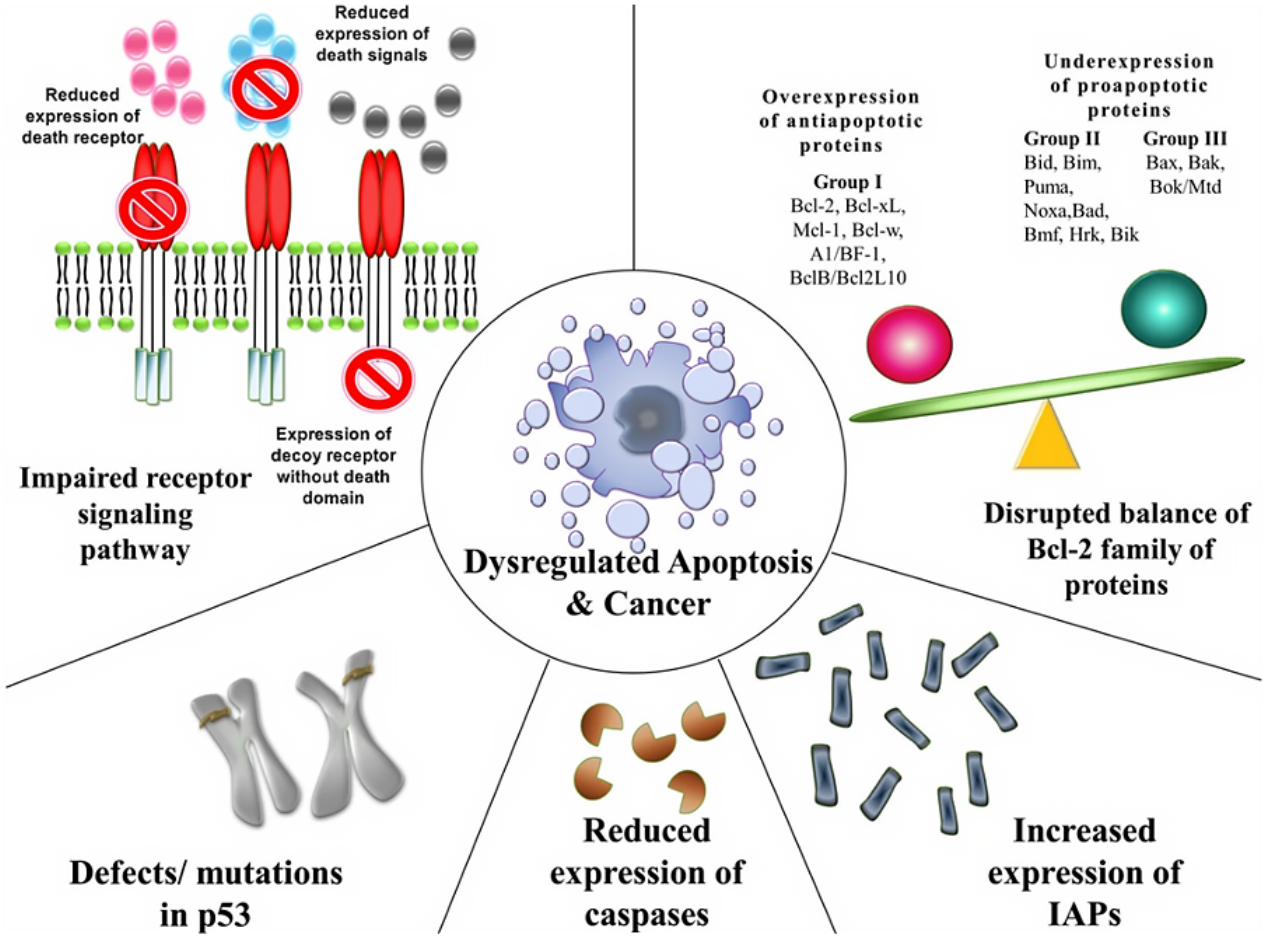
Tolerogenic or Non-Immunogenic Cell Death



Exposure of PS promotes the tolerogenic removal of cell corpses

Bedognetti D, et al. *J Immunother Cancer*. 2019;7:131.

Cancer's Resistance to Apoptosis: The Role of IAPs



IAP, inhibitor of apoptosis proteins.

Wong RS. *J Exp Clin Cancer Res.* 2011;30:87.

IAP Inhibitors Modify Two Hallmarks of Cancer

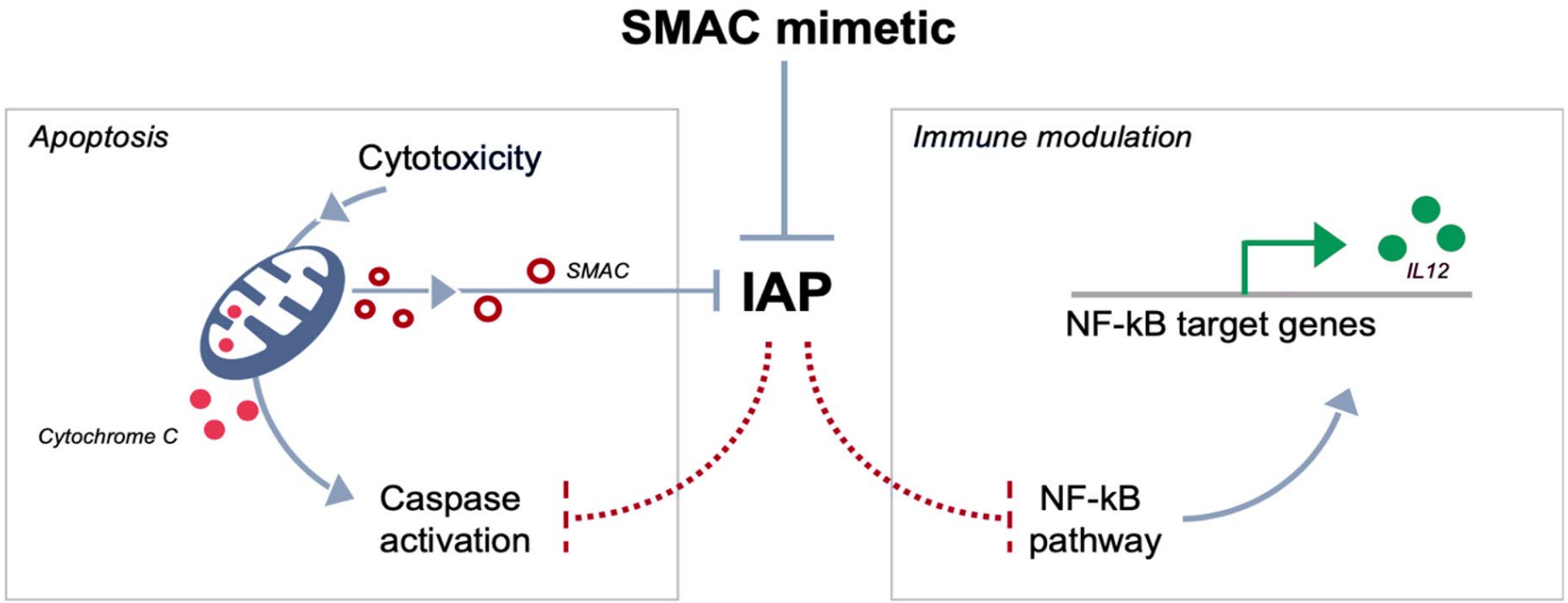


Figure from DeMaggio A, 2020

POTENTIAL INTERACTION WITH CHEMORADIOTHERAPY

POTENTIAL INTERACTION WITH IMMUNOTHERAPY

IAP, inhibitor of apoptosis proteins

DeMaggio A, 2020. Available at: https://www.blu-amp.com/home/blog/pipeline/ESMO%202020%20Preview%2C%20part%202%3A%20new%20and-or%20notable. Accessed August 2023.

IAP Inhibitors Overcome Resistance to Apoptosis

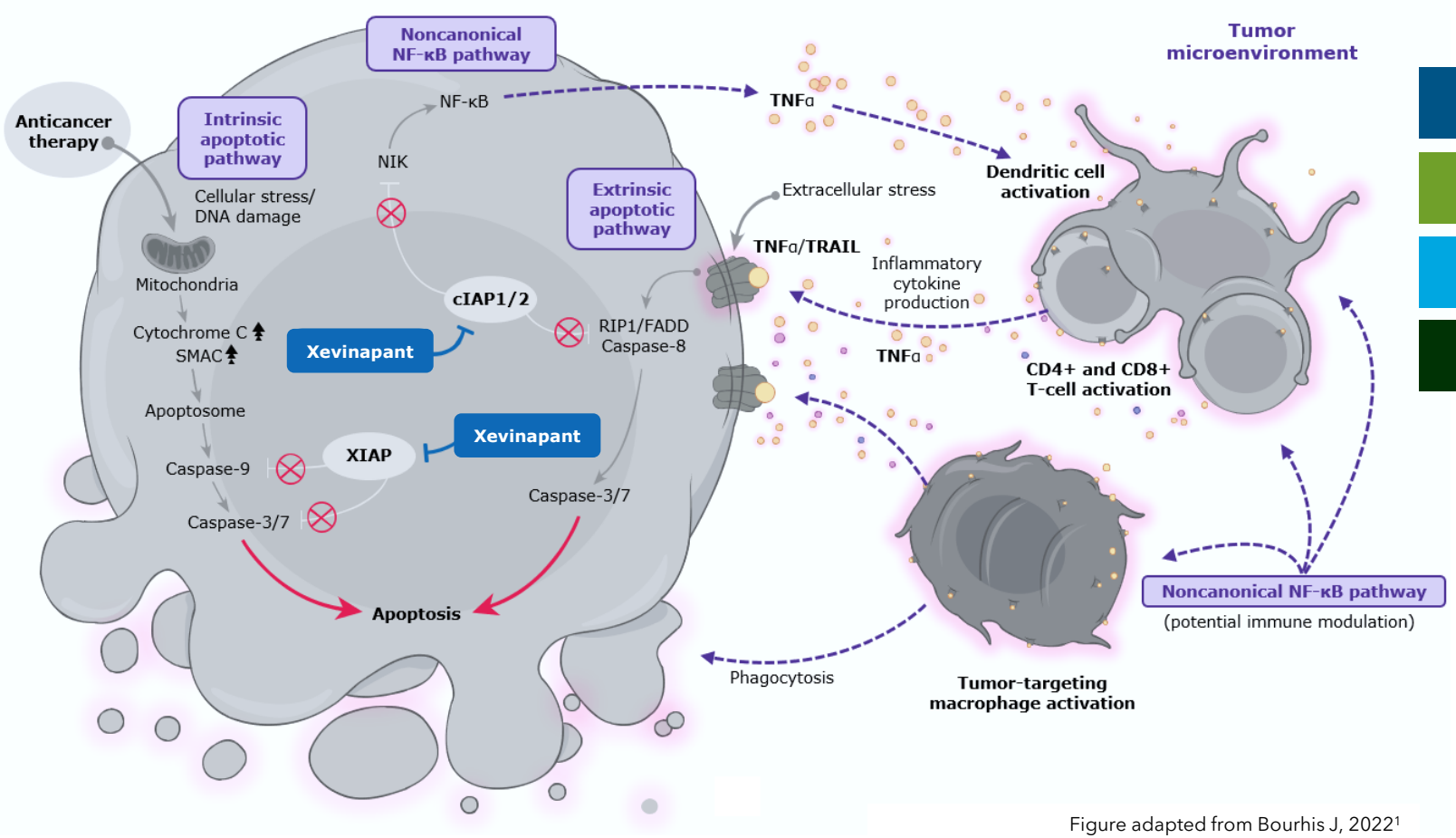


Figure adapted from Bourhis J, 2022[1]

- Xevinapant[1]
- Tolinapant[2]
- Birinapant[3]
- LCL161[4]

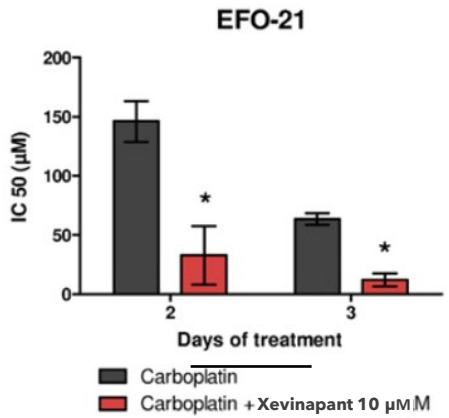
CD, cluster of differentiation; cIAP1/2, cellular IAP 1 and 2; FADD, Fas-associated protein with death domain; IAP, inhibitor of apoptosis protein; NF-κB, nuclear factor kappa B; NIK, NF-κB-inducing kinase; RIP1, receptor interacting serine/threonine kinase 1; SMAC, second mitochondria-derived activator of caspases; TNFα, tumour necrosis factor alpha; TRAIL, TNF-related apoptosis-inducing ligand; XIAP, X-linked IAP.

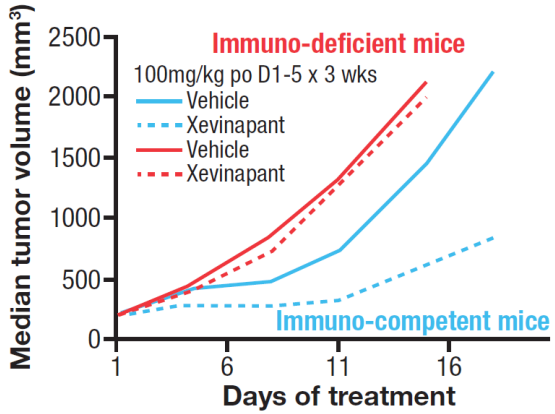
1. Bourhis J, et al. *Future Oncol.* 2022;18:1669–1678; 2. Ferrari N, et al. *Blood Adv.* 2021;5:4003–4016;
3. Kearney CJ, et al. *Cell Death Differ.* 2017;24:1705–1716; 4. Chesi M, et al. *Nat Med.* 2016;22:1411–1420.

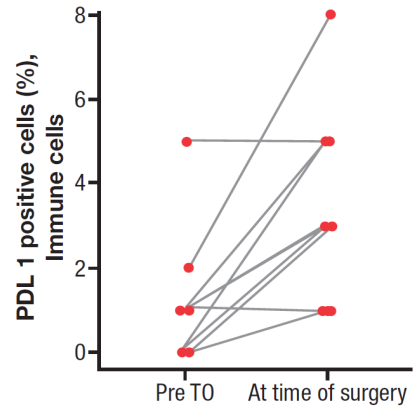
IAP Inhibitors Can Trigger Cancer Cell Death

Xevinapant

- Reverses carboplatin resistance in cancer cells models and triggers apoptotic or necroptotic cell death[1]
- In mice models, activity dependent on the host immune system[2]
- Increases levels of PD-L1 and tumor infiltrating lymphocytes from tumours resected from patients[2]





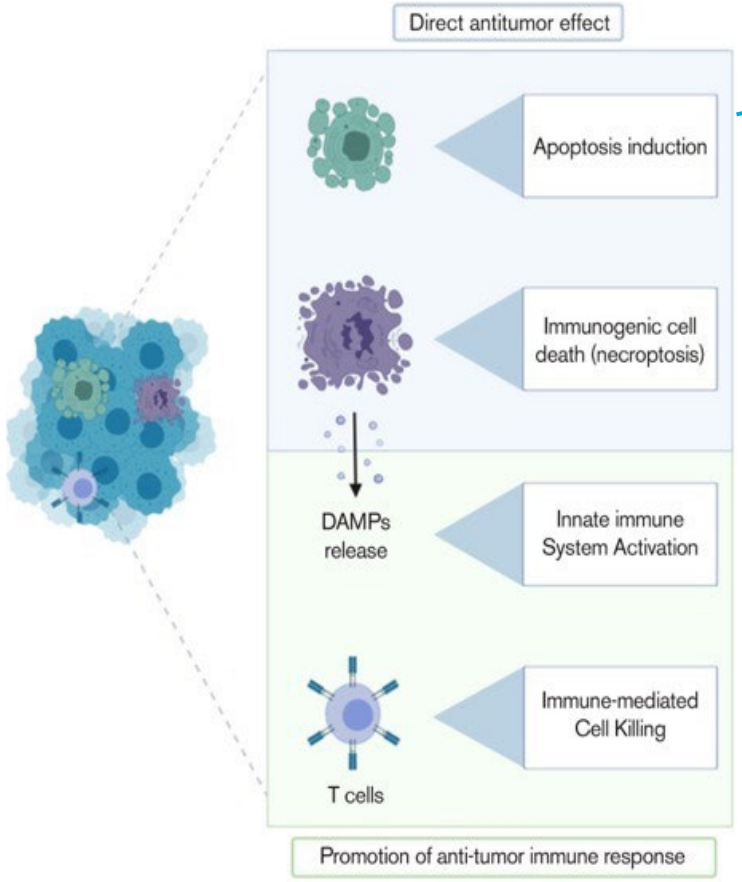


IAP, inhibitor of apoptosis proteins; PD-L1, programmed death-ligand 1.

1. Thibault B, et al. *Sci Rep.* 2018;8:17862; 2. Azaro-Pedrazzoli A, et al. *Ann Oncol.* 2020;31(Suppl_4):S462–S504.

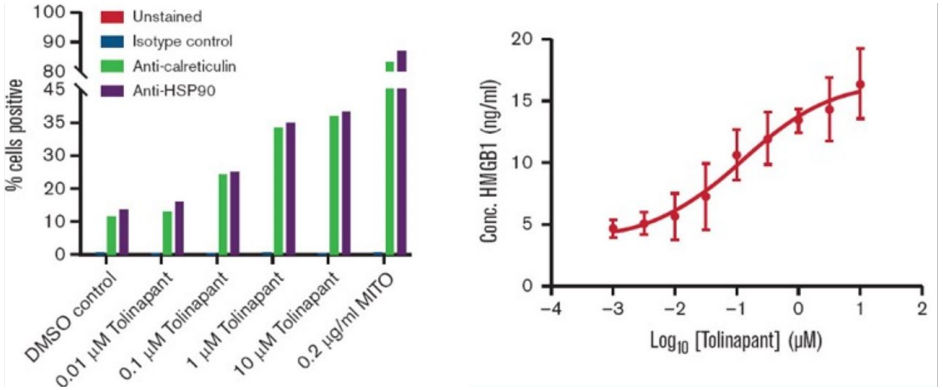
IAP Inhibitors Induce Necroptosis in Tumor Cells

Induction of immunogenic forms of cell death in vitro – DAMPs release



Tolinapant

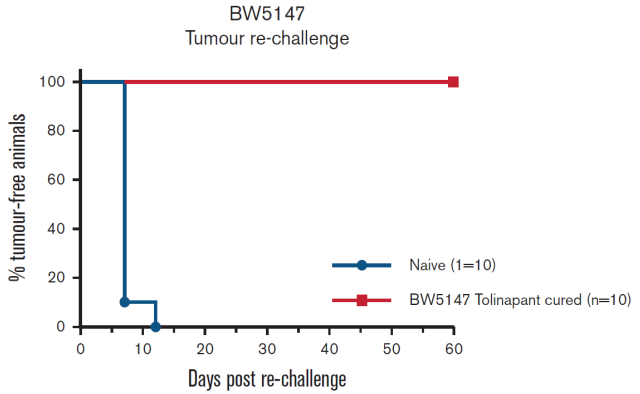
BW5147 cells after 24-hour treatment with tolinapant



Cell surface calreticulin or HSP90

HMGB1 in cell supernatants

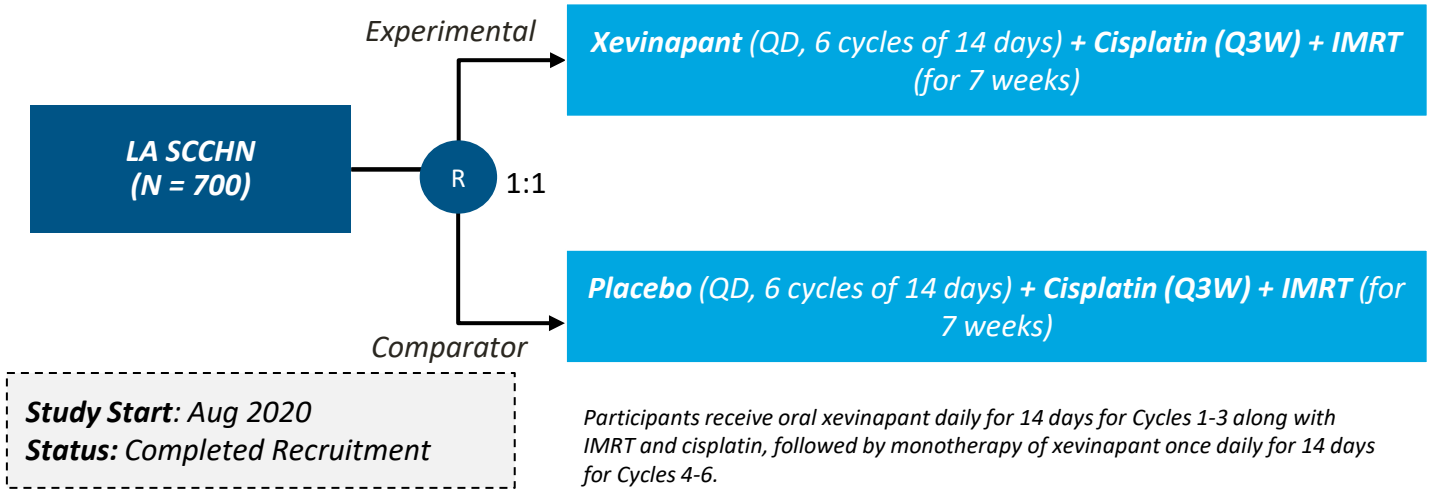
Tumor-free mice after challenge with tumor cells



DAMP, damage-associated molecular pattern; IAP, inhibitor of apoptosis proteins.

Ferrari N, et al. *Blood Adv*. 2021;5:4003–4016.

Xevinapant: Design of TrilynX Phase III Trial



Study Start: Aug 2020
Status: Completed Recruitment

Participants receive oral xevinapant daily for 14 days for Cycles 1-3 along with IMRT and cisplatin, followed by monotherapy of xevinapant once daily for 14 days for Cycles 4-6.

Primary Endpoints
EFS

Key Secondary Endpoints
PFS, OS, LRC, safety. QoL, others

Key Inclusion Criteria	Key Exclusion Criteria
• >18 years • Stage III, IVa or IVb suitable for definitive CRT, of at least one of the following sites: oropharynx, hypopharynx and larynx • Oropharyngeal Cancer (OPC) participants, primary tumors must be HPV-negative as determined by p16 expression (IHC) • ECOG performance score of 0 or 1 • Evaluable tumor burden (measurable and/or non-measurable tumor lesions) assessed by CT-scan or MRI based on RECIST v 1.1 • Peripheral neuropathy < grade 2 • Adequate hematologic, renal and hepatic function	• Primary tumor of nasopharyngeal, paranasal sinuses, nasal or oral cavity, salivary, thyroid or parathyroid gland pathologies, skin or unknown site • Metastatic disease (stage IVc) • Prior definitive or adjuvant Radiotherapy (RT) and/or radical surgery to the head and neck region which may jeopardize the primary tumor irradiation plan, or any other prior HNSCC systemic treatment • Weight loss of >10% during the last 4 weeks prior to randomization (unless nutritional support), OR plasmatic albumin < 3.0 g/dL • Allergy to Debio 1143, cisplatin or study formulations

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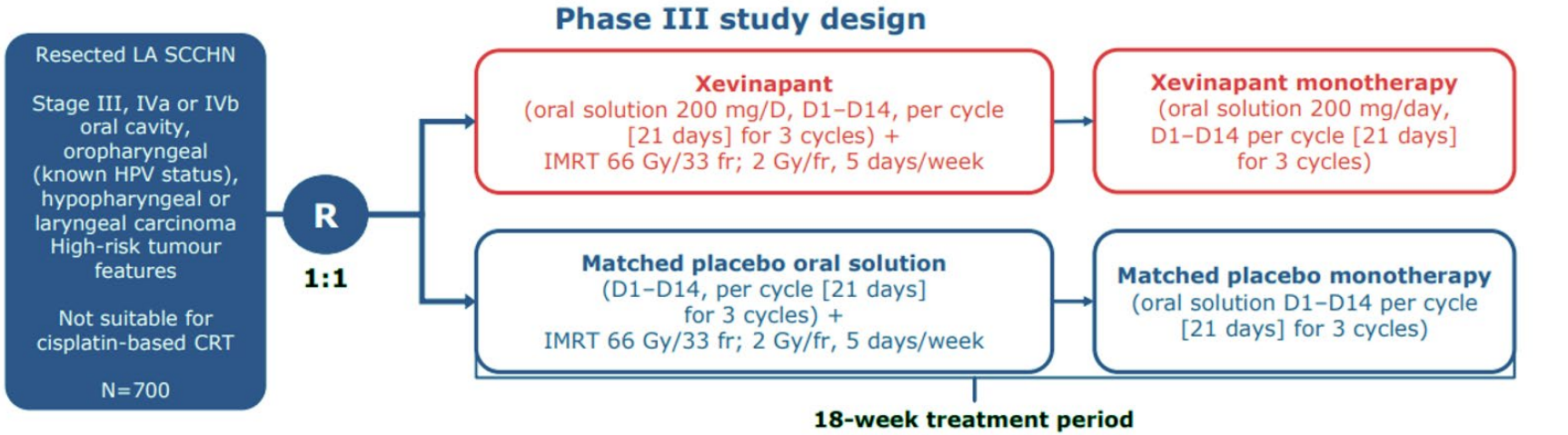
Clinicaltrials.gov. NCT04459715. https://www.clinicaltrials.gov/study/NCT04459715. Accessed August 2023.

Xevinapant: Design of X-RayVision Trial

Phase III, randomised study of xevinapant + IMRT vs placebo + IMRT for resected high-risk, cisplatin-ineligible LA SCCHN patients



PRIMARY OBJECTIVE:	To demonstrate **superior efficacy of xevinapant vs placebo** when added to RT in high-risk resected LA SCCHN

Primary endpoint: Disease-free survival

Secondary endpoints: Overall survival, time to subsequent cancer treatments, safety, HRQoL

Clinicaltrials.gov. NCT05386550. https://clinicaltrials.gov/ct2/show/NCT05386550. Accessed August 2022.

Understanding Clinical Trials and Their Endpoints in LASCCHN

Ezra E.W. Cohen, MD

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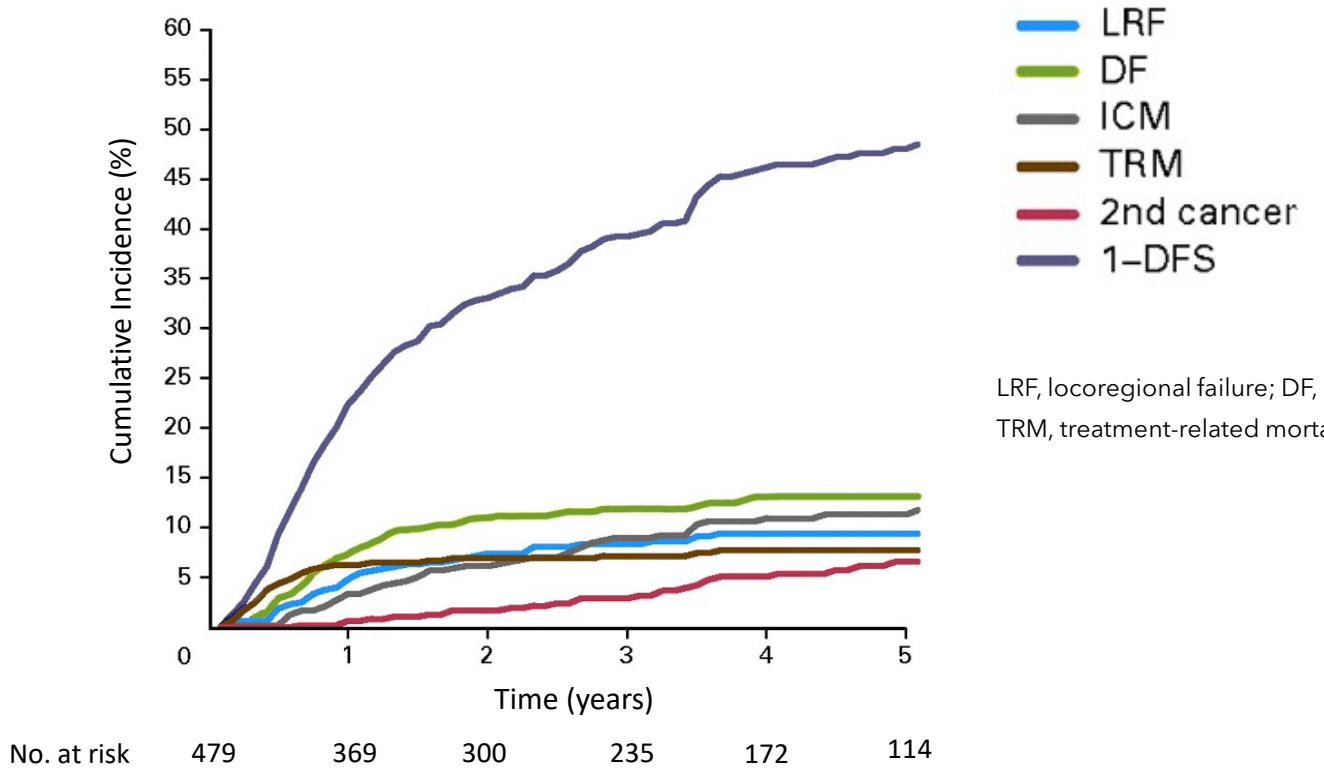
Endpoints in LA-HNSCC Trials

- Overall Survival
  - Gold standard
  - Easily defined and assessed
  - Unbiased
  - Competing risks can confound survival
  - Longer follow-up
  - Relatively larger sample size
- HRQOL
- Progression-free, Event-free, Disease-free survival
- Time to Progression, Time to Treatment Failure
- Locoregional control
- Distant control

Cumulative Incidence Curves of Individual Events (Additive to the Complement of Disease-Free Survival (1-DFS)



LRF, locoregional failure; DF, distant failure; ICM, intercurrent mortality; TRM, treatment-related mortality; 2nd cancer, second malignancy

Mell LK, et al. *J Clin Oncol.* 2010;28 (1):15-20.

EFS/DFS

- DFS: time from randomization until disease recurrence or death from any cause
  - Appropriate when a large percentage of patients achieve CR
- EFS: time from randomization to any of the following events: progression of disease that precludes surgery, local or distant recurrence, or death due to any cause

- Earlier assessment and smaller sample size compared to OS
- Objective and quantitative assessment

- Assessment bias
- Definitions vary
- Timing of assessments influence time to event
- Includes death from other causes

Why EFS/DFS/LRC Matter in HNSCC?

- HNSCC is a locoregional disease
  - 90% of patients present with local or locoregional disease
    - > Metastatic disease at presentation is uncommon
  - Symptoms reflect locoregional disease
  - Patterns of recurrence predicate intervention
    - > Locoregional disease is often symptomatic
    - > Distant disease responds better to IO when tumor burden is lower

Endpoint Utilization

- Le Tourneau et al. examined all published randomized trials from 1978-2008 in the English literature
  - 40 trials total
  - 25 trials used LRC as endpoint
    - > 2nd most common endpoint
    - > Heterogeneous definition – e.g., CR at end of treatment, salvage surgery, pathologic response, location of recurrence, etc.
  - 17 trials used DFS as endpoint

Le Tourneau C, et al. *J Clin Oncol.* 2009;27(35):5965-5971.

Surrogate Endpoints for Overall Survival in Locally Advanced Head and Neck Cancer: Meta-Analyses of Individual Patient Data

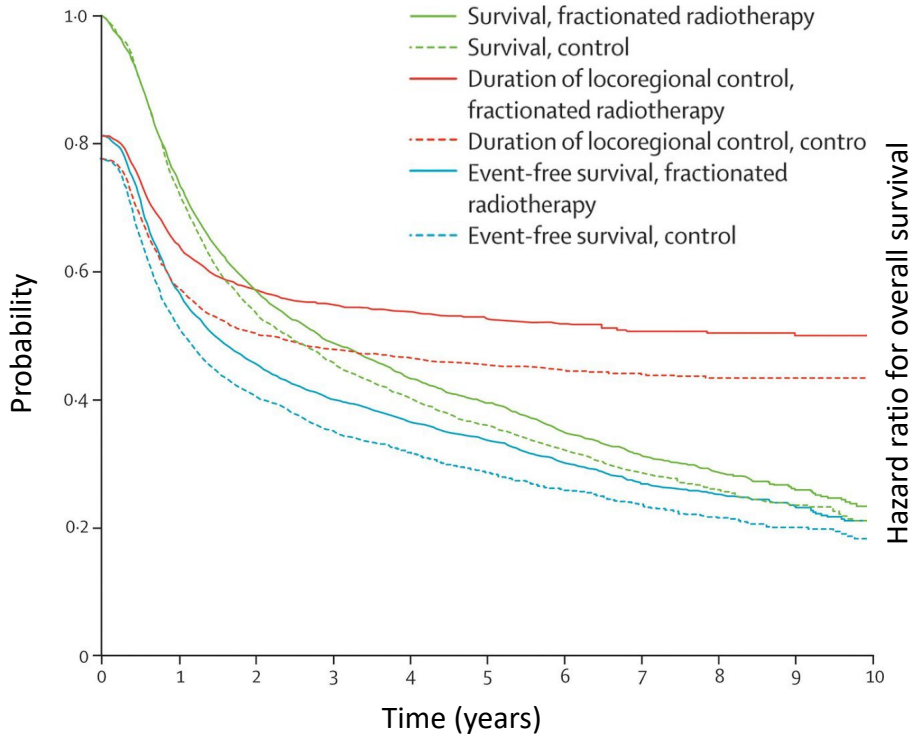
	Duration of locoregional control			Event-free survival		
	Individual, □ (95% CI)	Trial, R (95% CI)	Trial (2 years), R (95% CI)	Individual, □ (95% CI)	Trial, R (95% CI)	Trial (2 years), R (95% CI)
Radiotherapy	0·76 (0·76–0·76)	0·94 (0·89–1·00)	0·90 (0·81–0·99)	0·86 (0·86–0·86)	0·98 (0·97–1·00)	0·95 (0·90–1·00)
Concomitant chemotherapy	0·76 (0·76–0·77)	0·72 (0·60–0·85)	0·70 (0·57–0·83)	0·86 (0·86–0·86)	0·86 (0·79–0·93)	0·75 (0·64–0·87)
Induction chemotherapy	0·76 (0·75–0·76)	0·53 (0·28–0·78)	0·59 (0·36–0·81)	0·90 (0·90–0·90)	0·79 (0·66–0·92)	0·52 (0·26–0·77)
Adjuvant chemotherapy	0·65 (0·64–0·65)	0·84 (0·67–1·01)	0·75 (0·49–1·01)	0·82 (0·82–0·82)	0·93 (0·85–1·01)	0·83 (0·65–1·01)

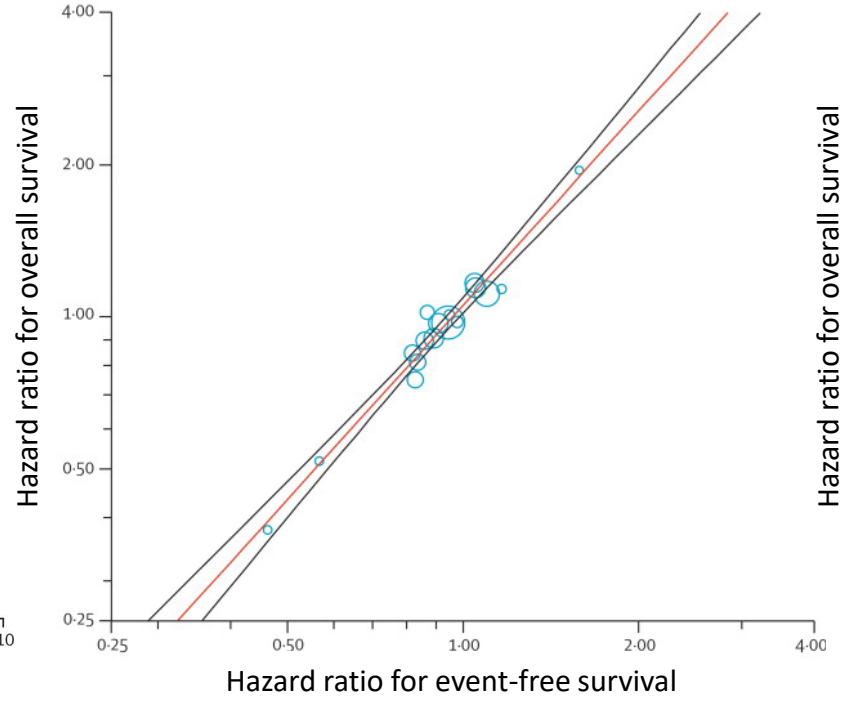
□=rank correlation between surrogate and overall survival. R=correlation between treatment effects on the surrogate and treatment effects on overall survival. Trial (2 years)=correlations between treatment effects censoring events of the surrogate at 2 years after randomisation and deaths 5 years after randomisation.

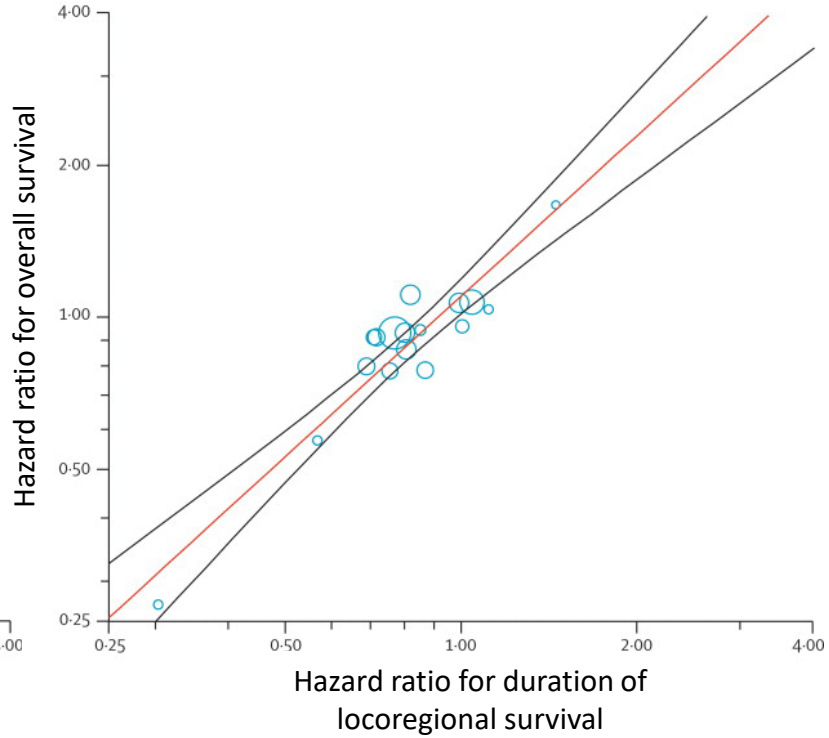
Correlation coefficients for the candidate surrogate endpoints and overall survival in the different meta-analyses

Michiels S, et al. *Lancet Oncol.* 2009;10(4):341-350.

RT Trials

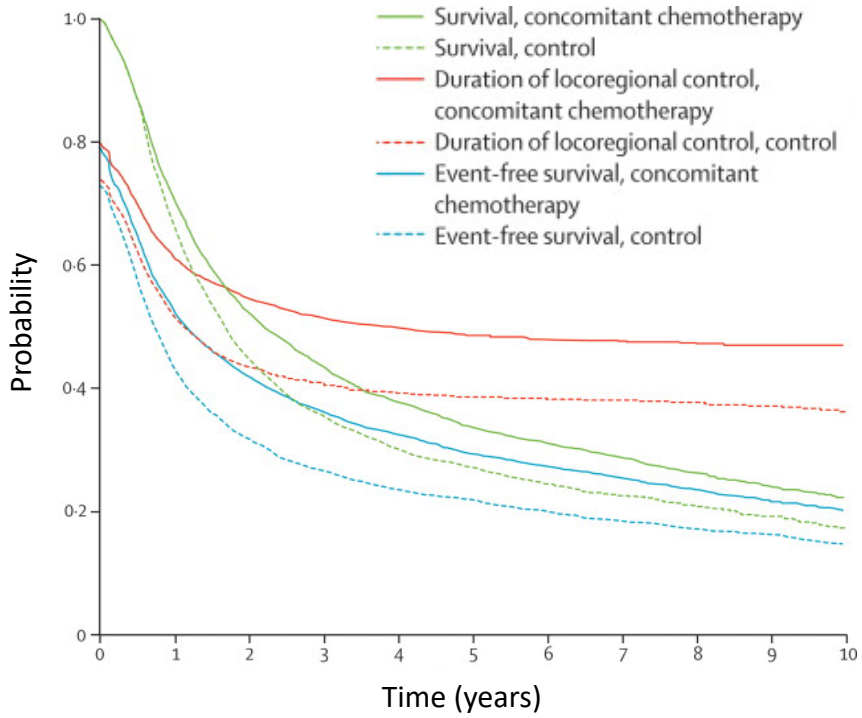


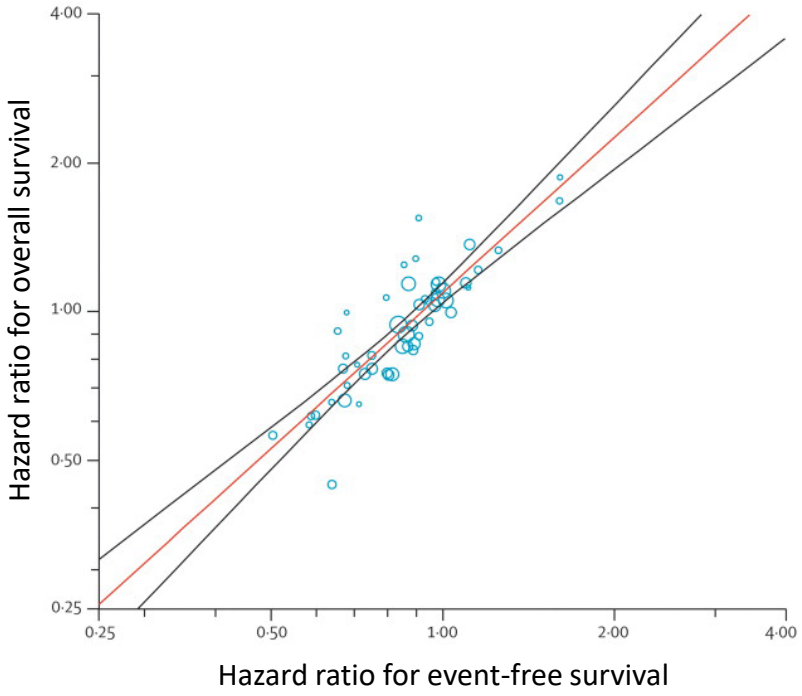


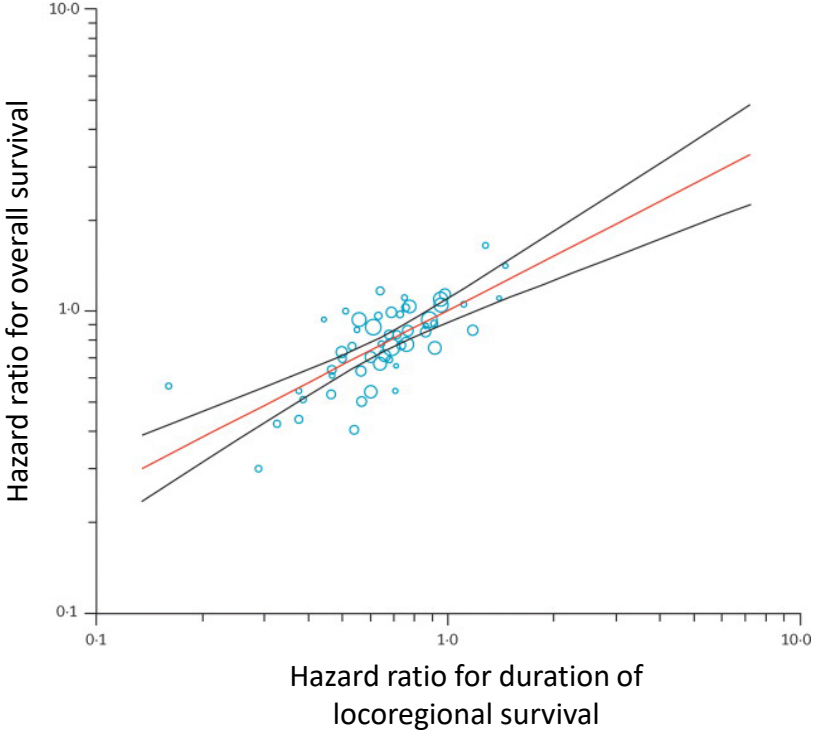


Michiels S, et al. *Lancet Oncol.* 2009;10(4):341-350.

CRT Trials







Michiels S, et al. *Lancet Oncol.* 2009;10(4):341-350.

Endpoint Definitions in Recent Trials

- KN412
  - EFS is defined as the time from the date of randomization to the date of first record of progression per RECIST v1.1 by blinded independent central review ([a] locoregional progression or recurrence or [b] distant metastasis), salvage surgery at the primary tumor site when invasive cancer is present, neck dissection performed >20 weeks after completion of CRT when invasive cancer is present, or death from any cause.
- TrilynX
  - EFS by BIRC: time from randomization to the occurrence of death, clinical or radiological progression, primary treatment failure, radiological or clinical relapse after achieving a loco-regional CR or the occurrence of secondary cancers

Conclusions

- Continued unmet need to improve efficacy in unresected LA-HNSCC
- Shifting timing of IO and RT might prove beneficial
- EFS/DFS appear to be excellent surrogate endpoints for OS in LA-HNSCC
  - Inherent benefit of no recurrence even if salvageable

Panel Discussion and Audience Q&A

Ezra Cohen, MD
University of California,
San Diego Health
San Diego, CA

Kevin Harrington, MBBS, PhD
The Institute of Cancer Research
London, UK

Deborah J. Wong, MD, PhD
UCLA Health
Los Angeles, CA

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Our Message Worth Sharing

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Our Message Worth Sharing

Dr. Cohen

- Clinical significance of early endpoints

Dr. Harrington

- How IAPs have the potential to change SOC

Dr. Wong

- Where the current landscape is going

Thank You!

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