ASCO 2020 Review
Head and Neck Cancer

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Disclosures

- Consulting
  - Eisai
  - Regeneron
  - Loxo Oncology/Eli Lilly
- Research
  - Regeneron
  - Loxo Oncology/Eli Lilly

Outline

- H&N Squamous Cell Cancer
  - Locally Advanced Disease
  - Metastatic Disease
- Thyroid Cancer

Head and Neck Cancer
Locally Advanced Disease

Transoral Robotic Surgical Resection followed by Randomization to Low- or Standard-dose IMRT in Resectable p16+ Locally Advanced Oropharynx Cancer: A trial of the ECOG-ACRIN Cancer Research Group (E3311)

Robert Ferris

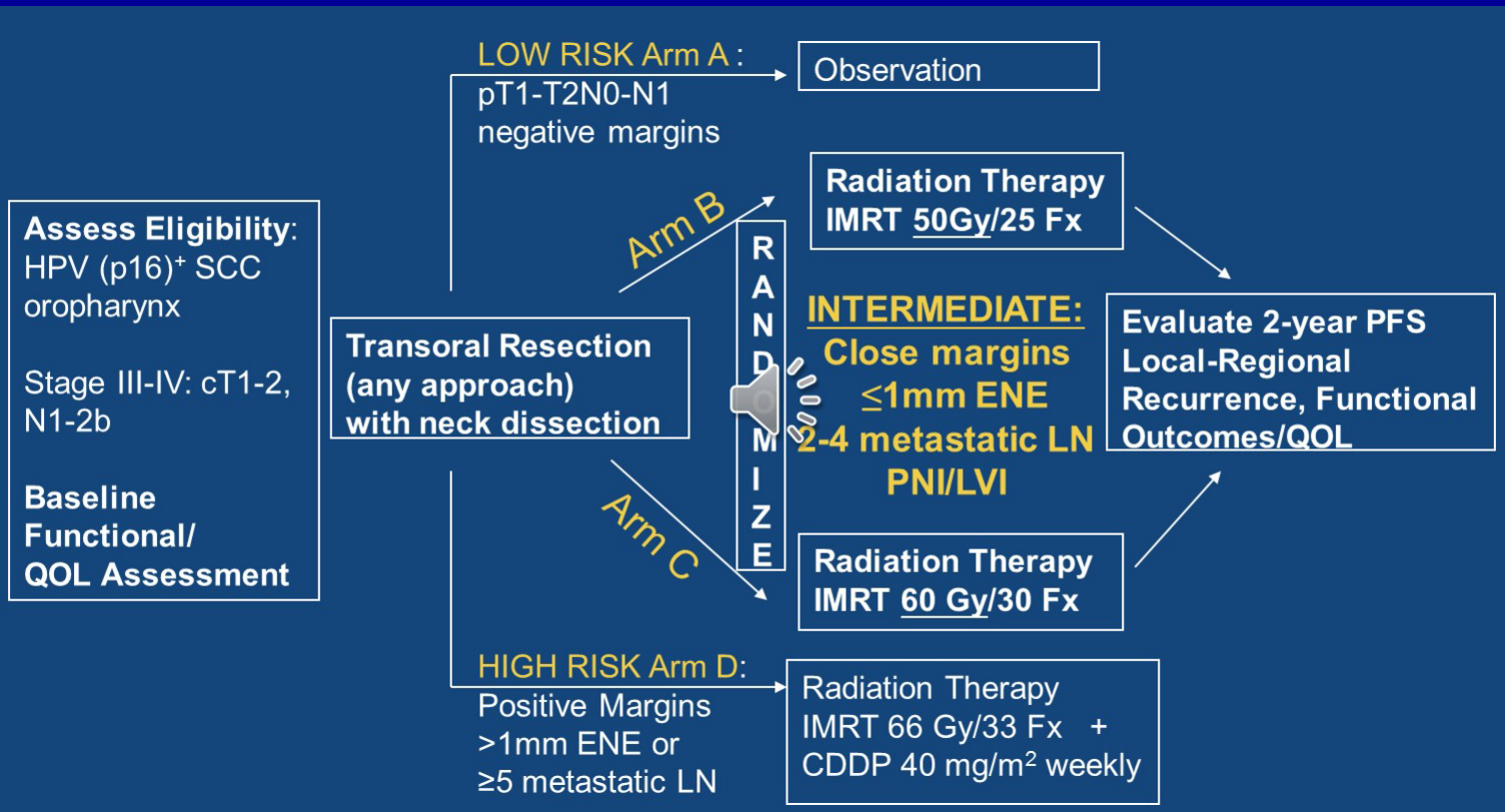
Study Design

- To evaluate in p16+ newly diagnosed OPC, Transoral Surgery followed by risk-adjusted post-operative therapy

	Pathologic Features
Arm A	Negative Margins (>3mm) N0-N1, No ENE
Arm B	Close Margins (<3mm), 2-4 (+) Nodes, ≤1mm ENE, PNI/LVI
Arm C	
Arm D	Positive Margins, >1mm ENE, ≥ 5 (+) Nodes

- Note that this is not comparable to chemo/RT due to Stage Migration

Trial Schema



Results

	N	2-year PFS	90% CI	Recurrences	LRF	DM
Arm A	37	93.9%	87.3-100	2	1	1
Arm B	102	95.0%	91.4-98.6	4	2	2
Arm C	104	95.9%	92.6-99.3	4	0	4
Arm D	110	90.5%	85.9-95.3	7	4	3

- There were 2 Treatment related deaths
  - 1 Surgical and 1 Arm D

Conclusion

- We can do large studies with Surgery as long as Surgery is the only option
- While PFS comparing post op 50 Gy vs 60 Gy looks about equal in a subgroup of patients
  - Not a non-inferiority study, so hypothesis generating
  - Do we really care?
    - QOL data was not presented
- Arm A treated with Surgery alone
  - Lowest risk group but looks possible worse than Arms B and C
- 2 year PFS in all groups look great
  - Patient Selection?
  - TORS approach Superior to chemo/RT?
  - Stage Migration?

Head and Neck Cancer Locally Advanced

Cisplatin HD every 3 weeks

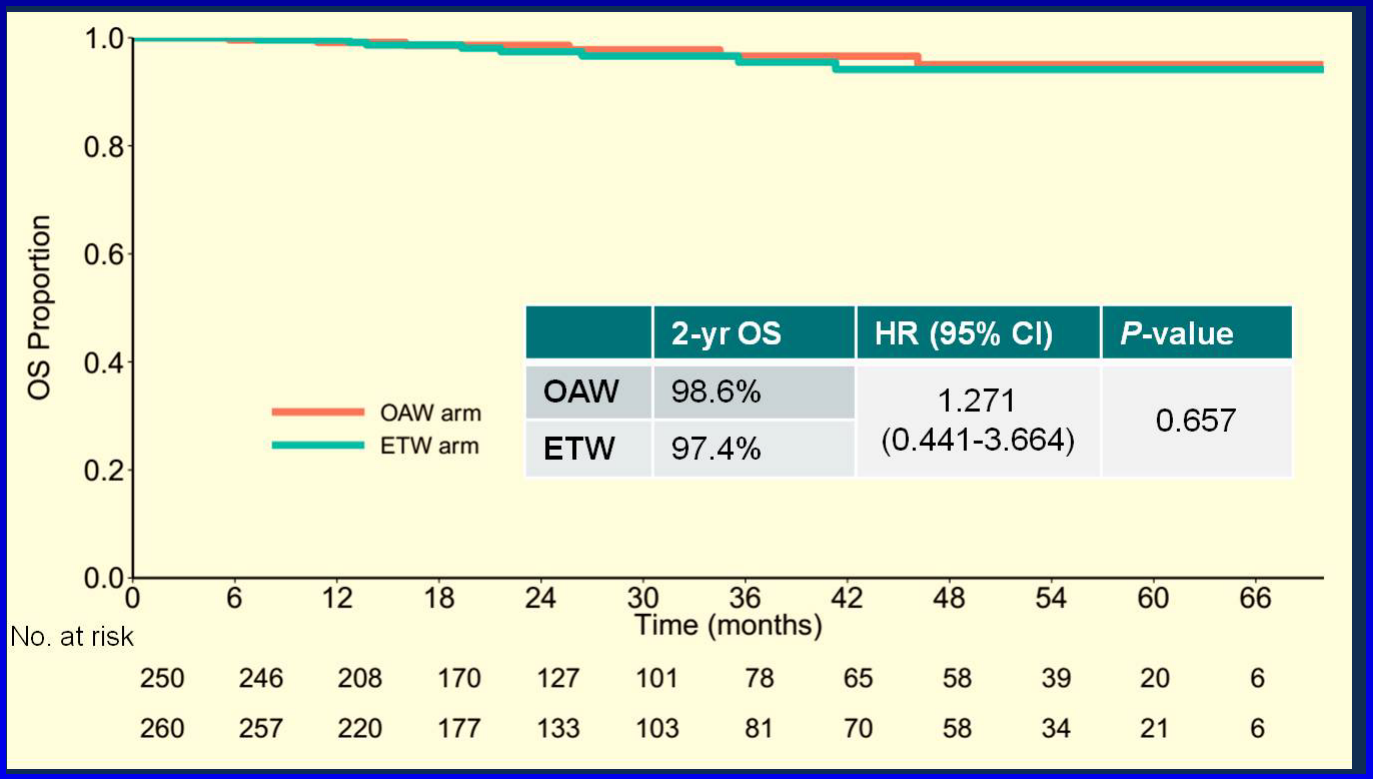
Vs

Cisplatin LD weekly

Nasopharynx (Hu Liang)

weekly vs q 3 weeks

- Outcomes fairly similar between groups

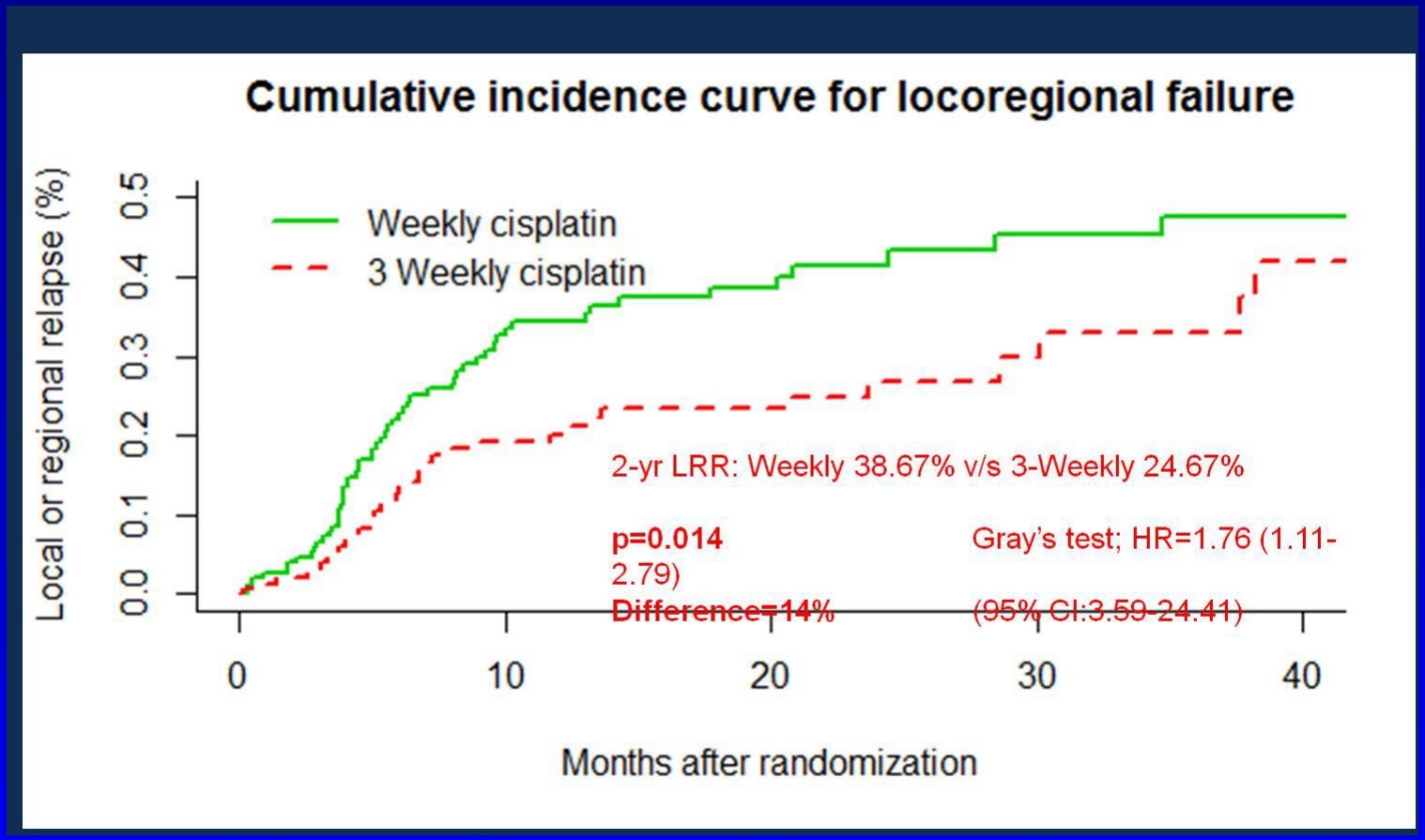


	2-yr OS	HR (95% CI)	*P*-value
OAW	98.6%	1.271 (0.441-3.664)	0.657
ETW	97.4%		

Nasopharynx (Hu Liang)
weekly vs q 3 weeks

Grade 3-4 Adverse Events			
	Weekly (n=249)	Every 3 Weeks (n=260)	P-value
Leukopenia	68 (27.3%)	42 (16.2%)	0.002
Thrombocytopenia	12 (4.8%)	3 (1.2%)	0.015
Nausea/Vomiting	28 (11.2%)	33 (12.7%)	0.615
Mucositis	89 (35.7%)	86 (33.1%)	0.527
Weight Loss	8 (3.2%)	5 (1.9%)	0.357

HNSCC (Noronha)
Weekly vs q 3 weeks

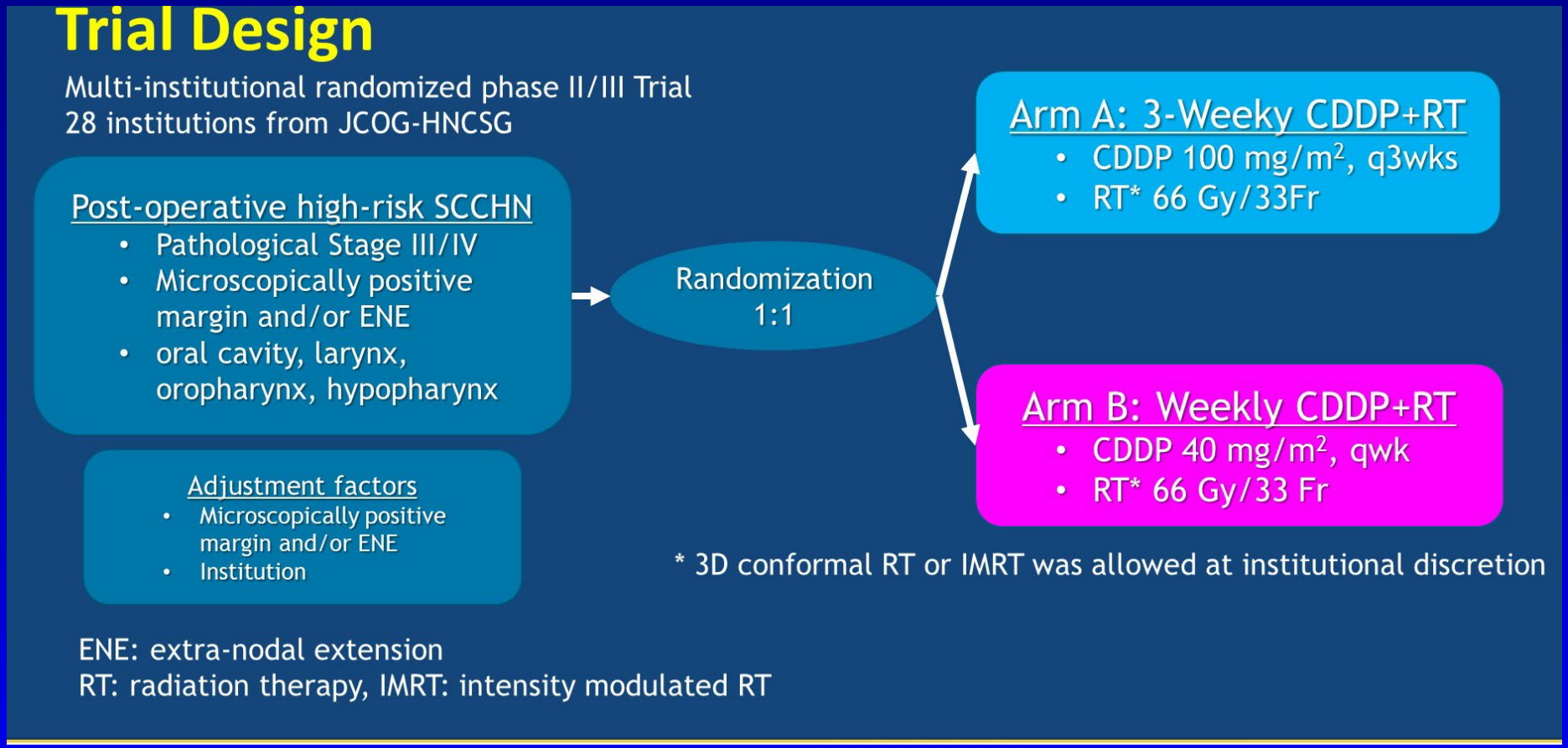


Phase II/III Trial of Postoperative Chemoradiotherapy Comparing 3-Weekly Cisplatin with Weekly Cisplatin in High-risk Patients with Squamous Cell Carcinoma of the Head and Neck (JCOG1008)

Kiyota

Japanese Clinical Oncology Group

Trial Design



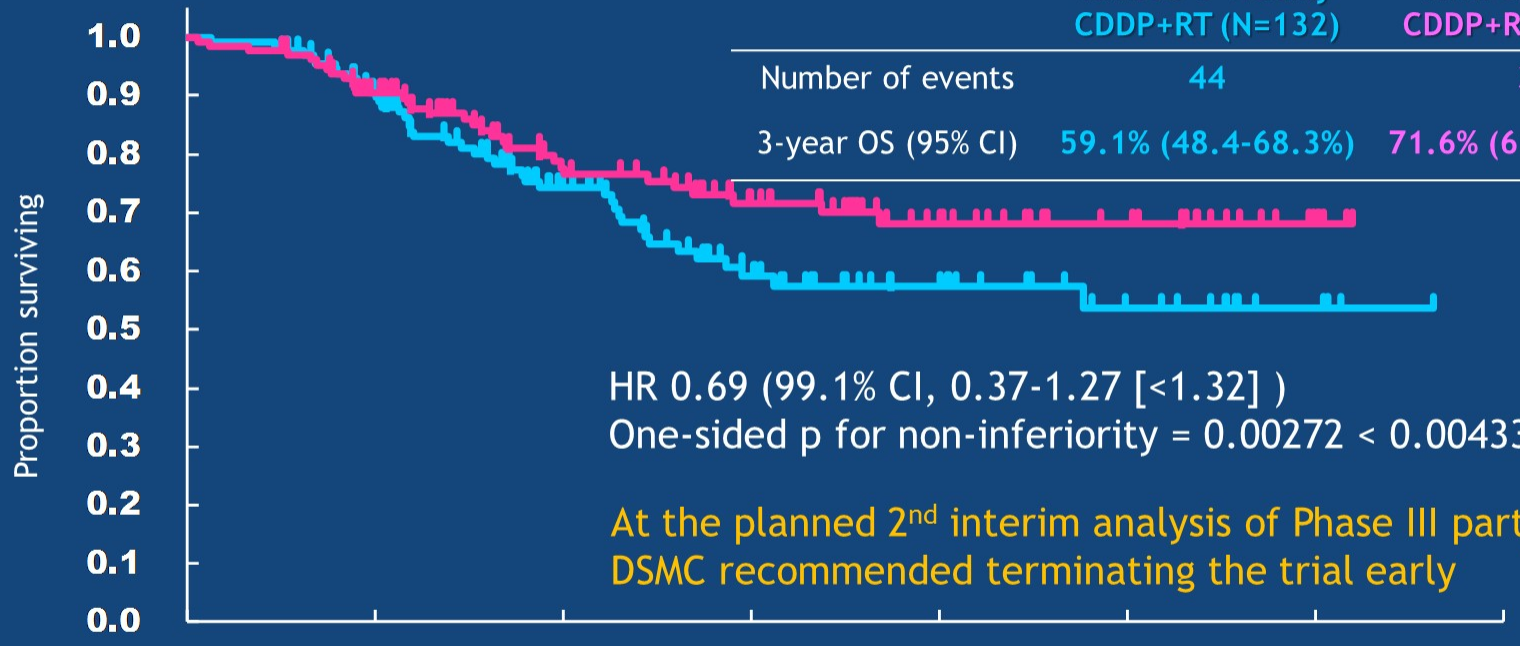
DSMC recommended terminating the trial early

Overall Survival: OS (ITT)

JCOG Japan Clinical Oncology Group

Median follow-up period: 2.2 years

	Arm A: 3-Weekly CDDP+RT (N=132)	Arm B: Weekly CDDP+RT (N=129)
Number of events	44	32
3-year OS (95% CI)	59.1% (48.4-68.3%)	71.6% (61.7-79.4%)



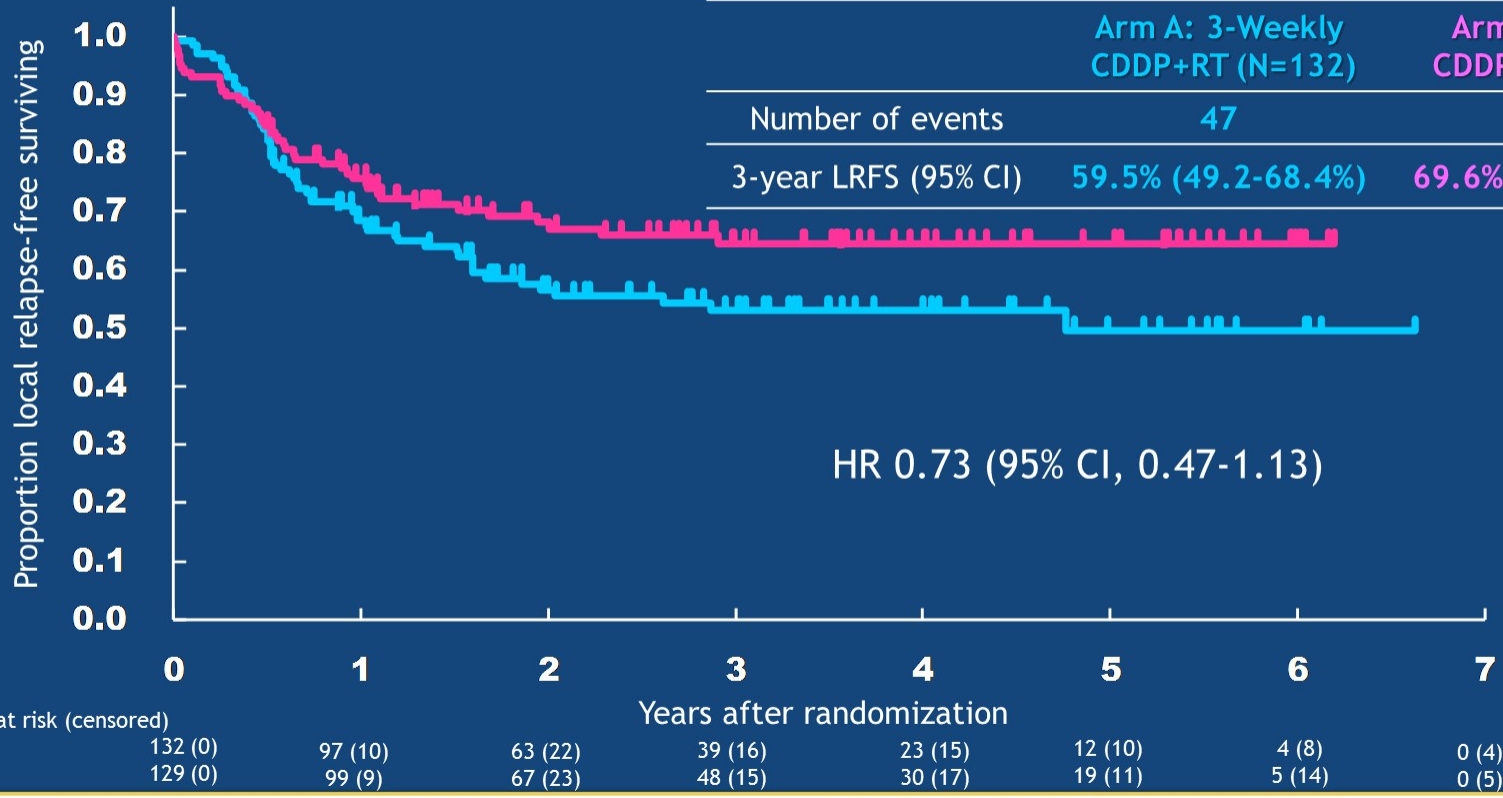
HR 0.69 (99.1% CI, 0.37-1.27 [<1.32])
One-sided p for non-inferiority = 0.00272 < 0.00433

At the planned 2nd interim analysis of Phase III part, DSMC recommended terminating the trial early

Patients at risk (censored)								
Arm A	132 (0)	110 (10)	67 (25)	39 (16)	23 (15)	12 (10)	4 (8)	0 (4)
Arm B	129 (0)	108 (9)	70 (25)	50 (15)	31 (17)	19 (12)	5 (14)	0 (5)

PRESENTED BY: Naomi Kiyota, MD, PhD, Kobe University Hospital, Japan, E-mail: nkiyota@med.kobe-u.ac.jp

Local Relapse-free Survival: LRFS (ITT)



	Arm A: 3-Weekly CDDP+RT (N=132)	Arm B: Weekly CDDP+RT (N=129)
Number of events	47	35
3-year LRFS (95% CI)	59.5% (49.2-68.4%)	69.6% (59.8-77.5%)

Patients at risk (censored)								
Arm A	132 (0)	97 (10)	63 (22)	39 (16)	23 (15)	12 (10)	4 (8)	0 (4)
Arm B	129 (0)	99 (9)	67 (23)	48 (15)	30 (17)	19 (11)	5 (14)	0 (5)

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Acute Non-hematological Toxicities*

Non-hematological	Arm A: 3-Weekly CDDP+RT (N=129)		Arm B: Weekly CDDP+RT (N=122)	
	Any grade	Grade3-4(%)	Any grade	Grade3-4
Mucositis	118 (91.5%)	30 (23.3%)	113 (92.6%)	34 (27.9%)
Dysphagia	75 (58.1%)	24 (18.6%)	59 (48.4%)	14 (11.5%)
Dermatitis	118 (91.4%)	19 (14.7%)	112 (91.8%)	14 (11.5%)
Nausea	87 (67.4%)	17 (13.2%)	57 (46.7%)	6 (4.9%)
Infection	25 (19.4%)	15 (11.6%)	18 (14.8%)	8 (6.6%)
Hyponatremia	119 (92.2%)	13 (10.1%)	100 (82.0%)	13 (10.7%)
Renal impairment	51 (39.5%)	0 (0%)	36 (29.5%)	0 (0.0%)
Hearing impairment	22 (17.1%)	5 (3.9%)	9 (7.4%)	2 (1.6%)
Peripheral neuropathy	7 (5.4%)	0 (0.0%)	2 (1.6%)	0 (0.0%)

- *Grade 3 or more toxicities which occurred in ≥10% patients or toxicities of special interest

PRESENTED BY: Naomi Kiyota, MD, PhD, Kobe University Hospital, Japan, E-mail: nkiyota@med.kobe-u.ac.jp

Characteristics

Characteristic		3-Week CDDP (132)	Weekly CDDP (129)
Primary Site	Oral Cavity	61	60
	Larynx	12	11
	Oropharynx	14	21
	Hypopharynx	45	37
Pathologic T	T1	13	7
	T2	26	40
	T3	25	23
	T4	68	59

Characteristics

Characteristic		3-Week CDDP (132)	Weekly CDDP (129)
Primary Site	Oral Cavity	61	60
	Larynx	12	11
	Oropharynx	**14**	**21**
	Hypopharynx	**45**	**37**
Pathologic T	T1	13	7
	T2	26	40
	T3	25	23
	T4	**68**	**59**

NOTE – Unequal distribution of Oropharynx/Hypopharynx cancers as well as T4 tumors

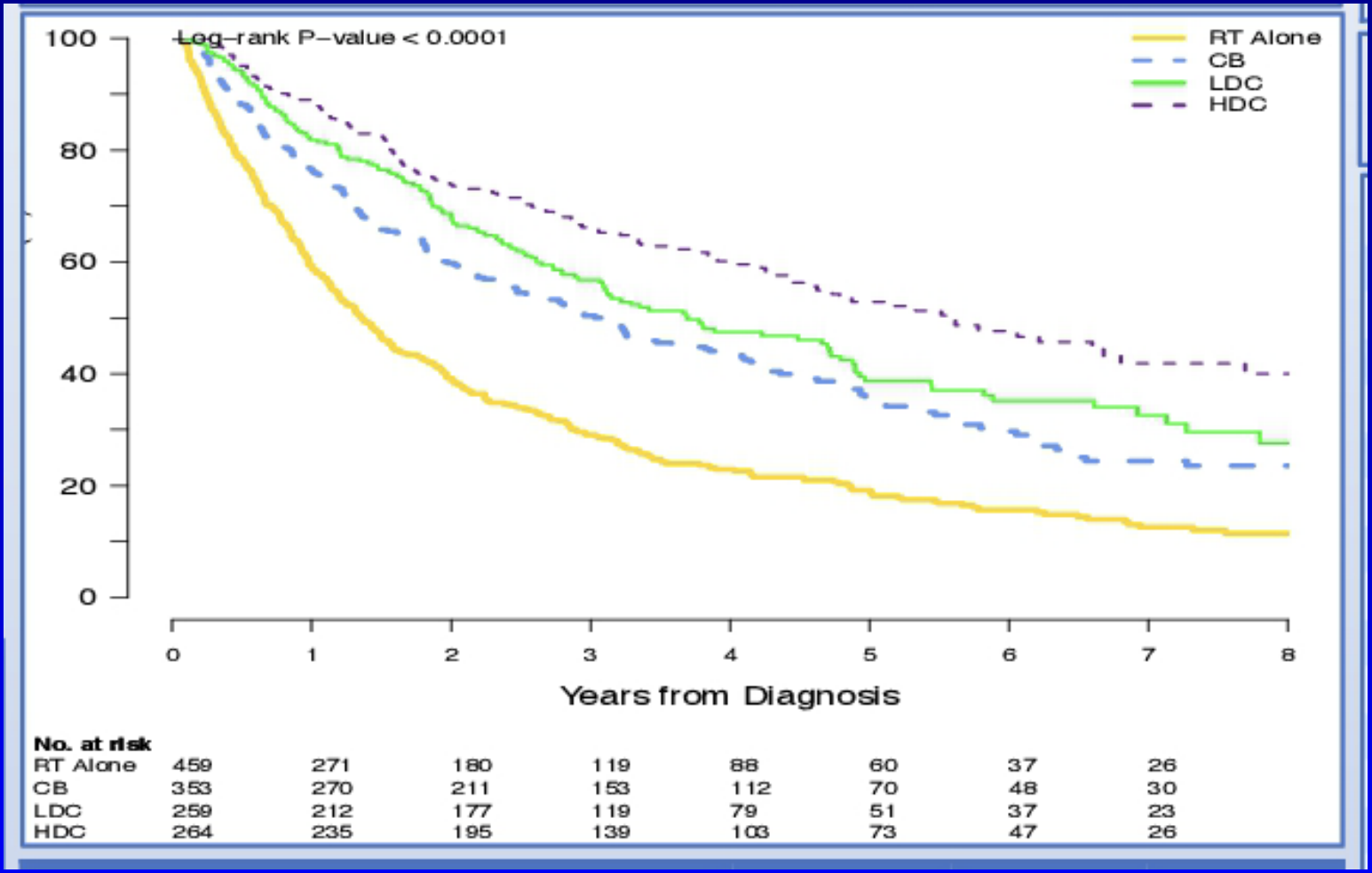
Cisplatin every three weeks versus cisplatin or carboplatin with definitive RT for HNSCC

McCusker
University of Maryland

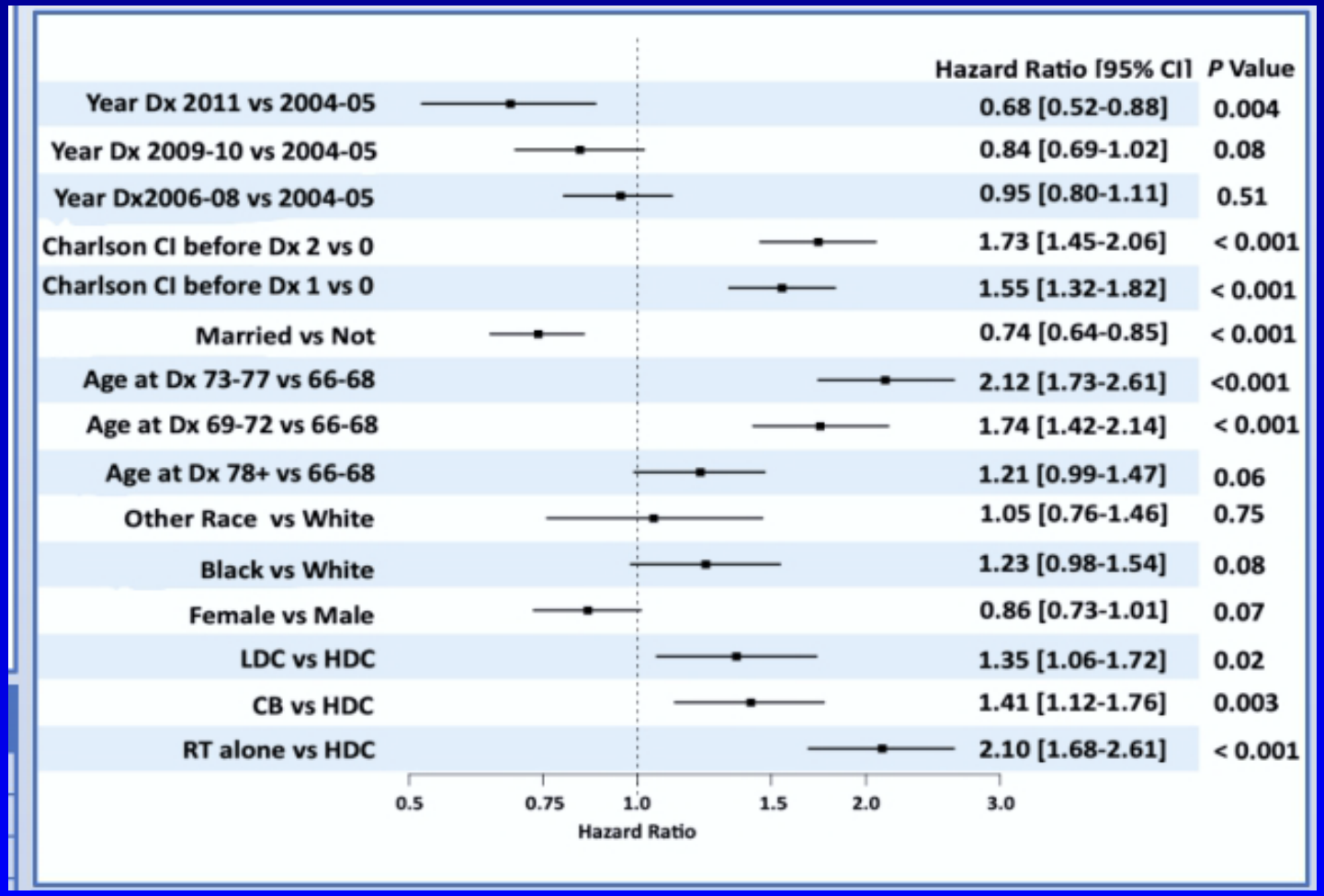
Methods

- Patients dx 2004-2011 with stages III-VI HNCC in linked SEER-Medicare Database
- Confined to oropharynx, hypopharynx, or larynx
- Definitive Radiation Therapy

Overall Survival



Forest Plot with HR's estimated by the propensity score weighted Cox regression model



Conclusion

- After 2 phase III randomized studies showing inferiority by toxicity or efficacy with weekly CDDP compared to 3-week, a study is now positive
- All studies have their flaws
- Further studies need to be done (NRG)
  - Question about enthusiasm for these studies
- Standard of care now -
  - Argue should be HD 3-week Cisplatin

Randomised Phase III study of Dysphagia-Optimised Intensity Modulated Radiotherapy (DO-IMRT) versus Standard IMRT (S-IMRT) in Head and Neck Cancer

Christopher Nutting

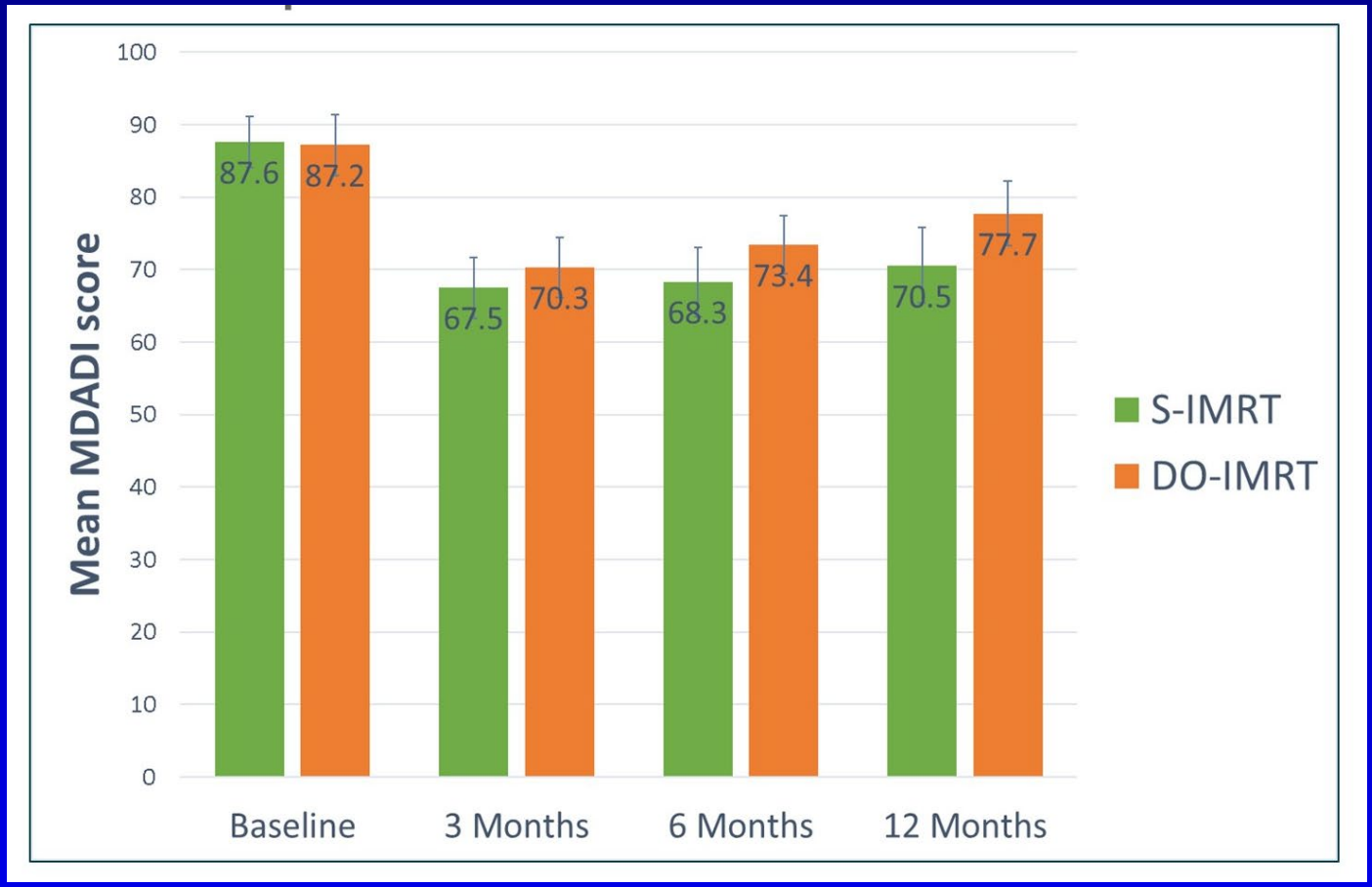
Background

- Persistent swallowing problems after chemo/RT for pharynx cancer common
- Hypothesized reduced dose to the pharyngeal constrictor muscles would improve swallowing function
  - Volume of the superior & middle pharyngeal constrictor muscle or inferior PCM outside the high-dose clinical target volume was set a mandatory mean dose constraint <50Gy

Endpoints

- Primary Outcome
  - Diff in mean MD Anderson Dysphagia Inventory (MDADI) composite score at 12 months after treatment completion
- Secondary endpoints
  - Multiple QOL
  - Tumor control and overall survival
- Sample Size -> 102
  - Detect 10 point improvement in MDADI score

MDADI Composite Score Over Time



Improvement of 7.2 by 12 months (p=0.037)

Conclusion

- Change in IMRT fields lead to improvement in swallowing function
- No difference in clinical cancer outcomes
  - Small study, so not able to prove noninferior
- Changing Radiation Fields can be as important as dose reduction

- **Randomized studies in Radiation are feasible**

Head and Neck Cancer Metastatic

Keynote-048

Harrington

Protocol-Specified Final Results of the KEYNOTE-048 Trial of Pembrolizumab as First-Line Therapy for Recurrent/ Metastatic Head and Neck Squamous Cell Carcinoma (R/M HNSCC)

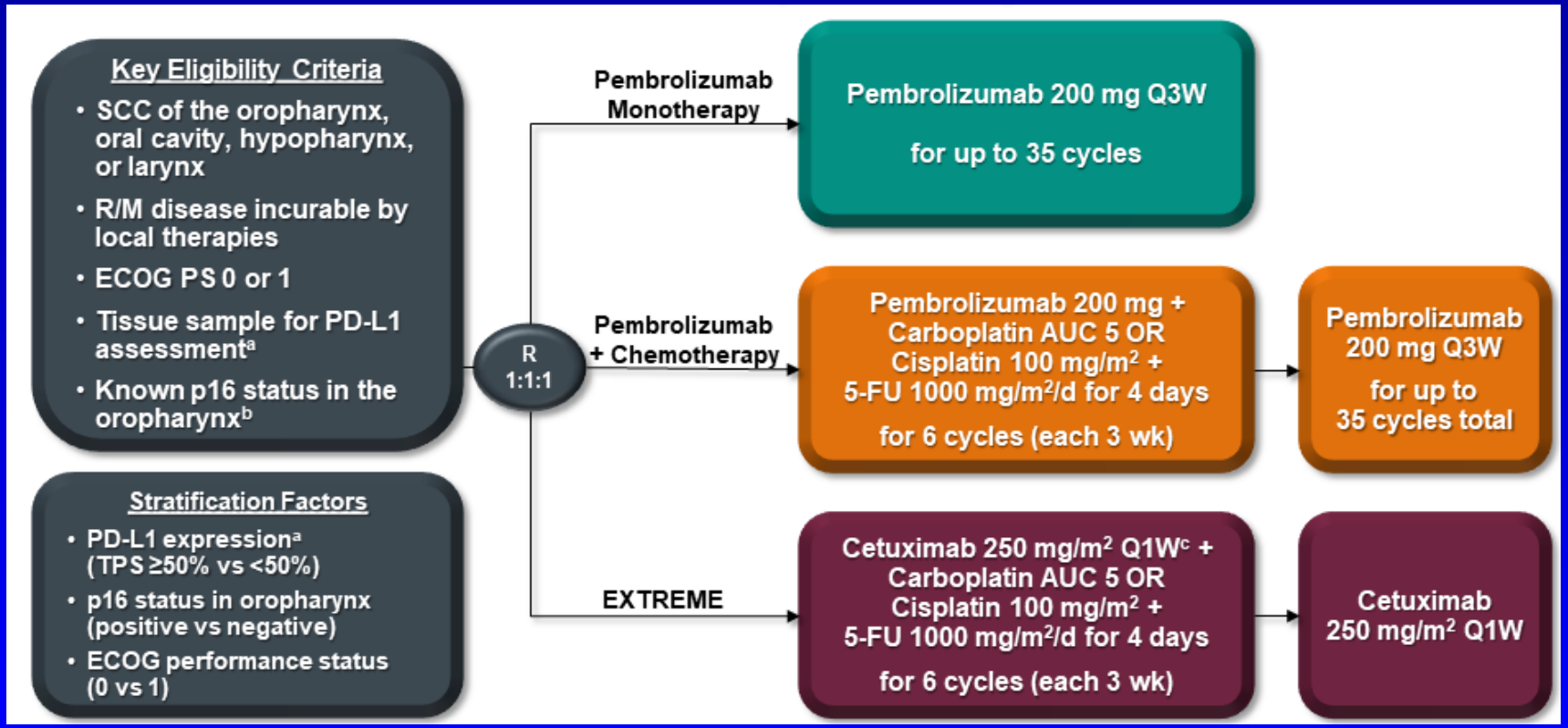
Danny Rischin[1], Kevin Harrington,[2] Richard Greil,[3] Denis Soulières,[4] Makoto Tahara,[5] Gilberto de Castro,[6] Amanda Psyrri,[7] Neus Basté,[8] Prakash Neupane,[9] Åse Bratland,[10] Thorsten Fuereder,[11] Brett GM Hughes,[12] Ricard Mesia,[13] Nuttapong Ngamphaiboon,[14] Tamara Rordorf,[15] Wan Zamaniah Wan Ishak,[16] Yayan Zhang,[17] Fan Jin,[17] Burak Gumuscu,[17] Barbara Burtness[18]

[1]Peter MacCallum Cancer Centre, Melbourne, VIC, Australia; [2]The Institute of Cancer Research/The Royal Marsden NHS Foundation Trust National Institute of Health Research Biomedical Research Centre, London, UK; [3]Paracelsus Medical University, Salzburg Cancer Research Institute, and Cancer Cluster Salzburg, Salzburg, Austria; [4]Centre Hospitalier de l'Université de Montréal, Montréal, QC, Canada; [5]National Cancer Center Hospital East, Kashiwa, Japan; [6]Instituto do Cancer do Estado de Sao Paulo, Sao Paulo, Brazil; [7]National Kapodistrian University of Athens, Attikon University Hospital, Athens, Greece; [8]Vall d'Hebron University Hospital, Barcelona, Spain; [9]University of Kansas Medical Center, Kansas City, KS, USA; [10]Oslo University Hospital, Oslo, Norway; [11]Medical University of Vienna, Vienna, Austria; [12]Royal Brisbane and Women's Hospital and University of Queensland, Brisbane, QLD, Australia; [13]Catalan Institute of Oncology, Hospitalet de Llobregat, Barcelona, Spain; [14]Ramathibodi Hospital, Mahidol University, Bangkok, Thailand; [15]University Hospital, Zurich, Switzerland; [16]University Malaya, Kuala Lumpur, Malaysia; [17]Merck & Co., Inc., Kenilworth, NJ, USA; [18]Yale School of Medicine and Yale Cancer Center, New Haven, CT, USA

Presented By Danny Rischin at 2019 ASCO Annual Meeting

Keynote-048 Design

- Total of 882 subjects randomized
- Chemo/Pembro arm was held for 2 months so it has a few less patients



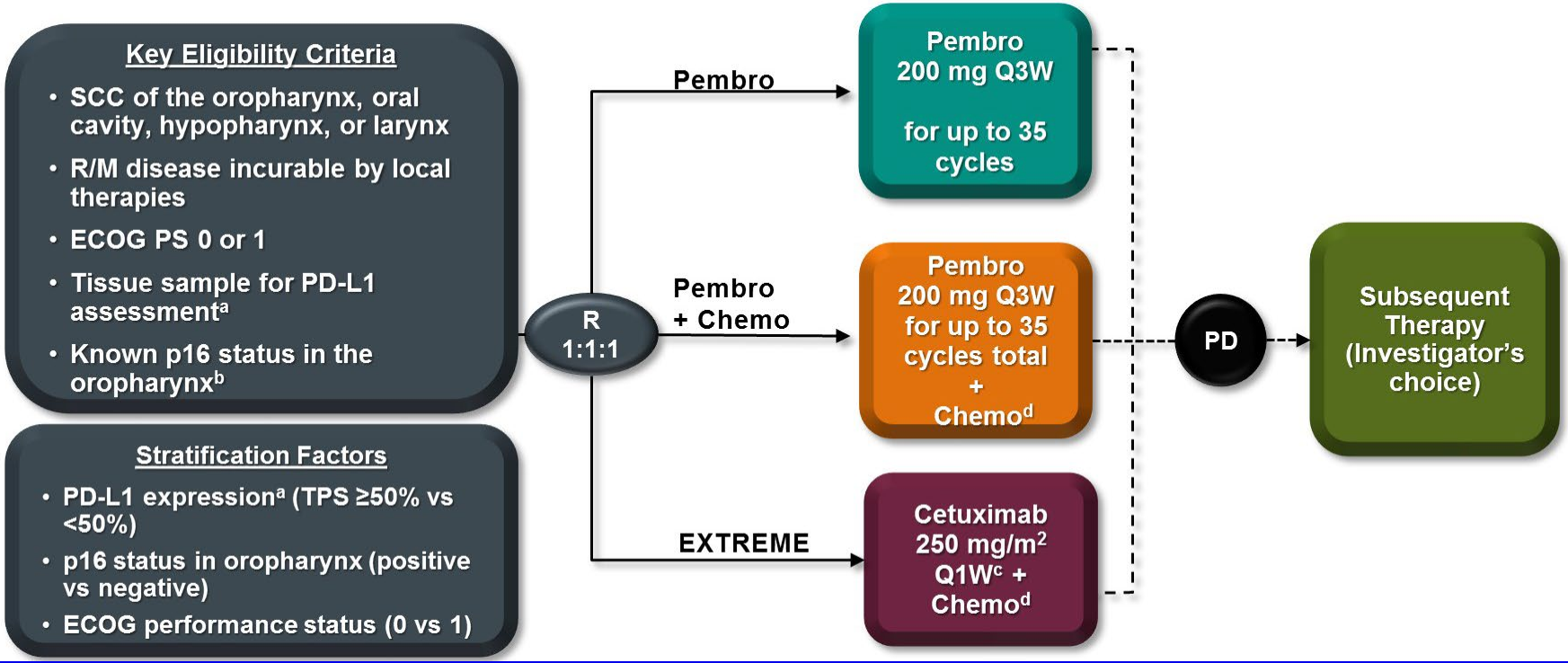
Summary of Overall Survival Keynote 048

Population	HR (95% CI)
Pembrolizumab monotherapy vs EXTREME	
PD-L1 CPS $\geq$ 20	0.58 (0.44-0.78)
PD-L1 CPS $\geq$ 1	0.74 (0.61 – 0.90)
Total Population	0.83 (0.70 – 0.99), p=0.0199
Pembrolizumab + chemotherapy vs EXTREME	
PD-L1 CPS $\geq$ 20	0.60 (0.45-0.82); p=0.0004
PD-L1 CPS $\geq$ 1	0.65 (0.53-0.80); p<0.0001
Total Population	0.72 (0.60 – 0.87)

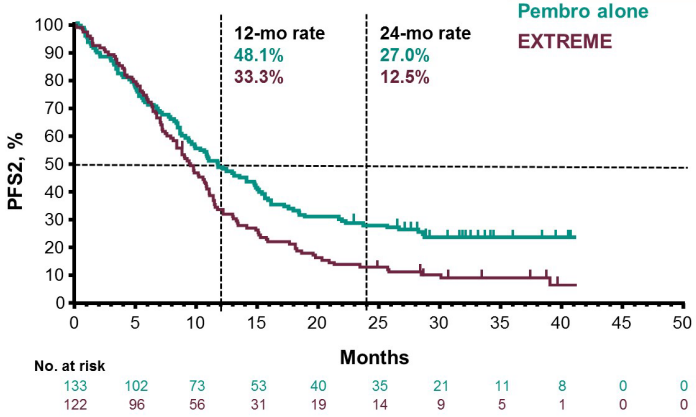
If no p-value, statistical testing was not performed

NO BENEFIT WITH PFS IN ANY ARM

First Subsequent Therapy Following Progression of Disease



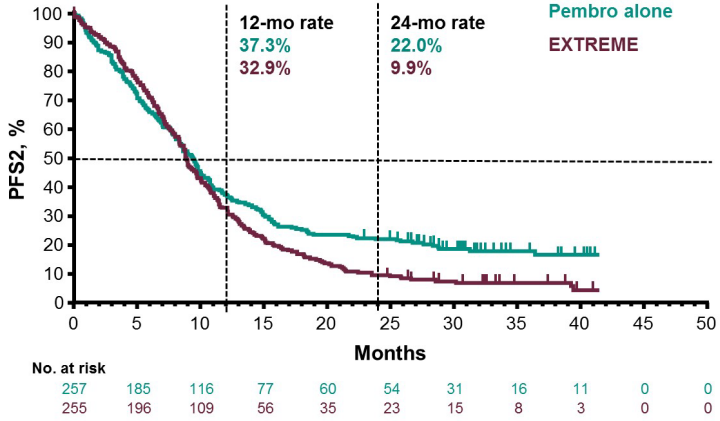
PFS2: Initially Randomized, Pembro vs EXTREME, CPS ≥20 Population



	Events	HR (95% CI)
Pembro alone	76.7%	0.64 (0.48-0.84)
EXTREME	91.0%	

Median (95% CI)
11.7 mo (9.1-14.8)
9.4 mo (7.9-10.8)

PFS2: Initially Randomized, Pembro vs EXTREME, CPS ≥1 Population



	Events	HR (95% CI)
Pembro alone	80.9%	0.80 (0.66-0.96)
EXTREME	92.5%	

Median (95% CI)
9.4 mo (8.3-10.2)
8.8 mo (8.3-9.8)

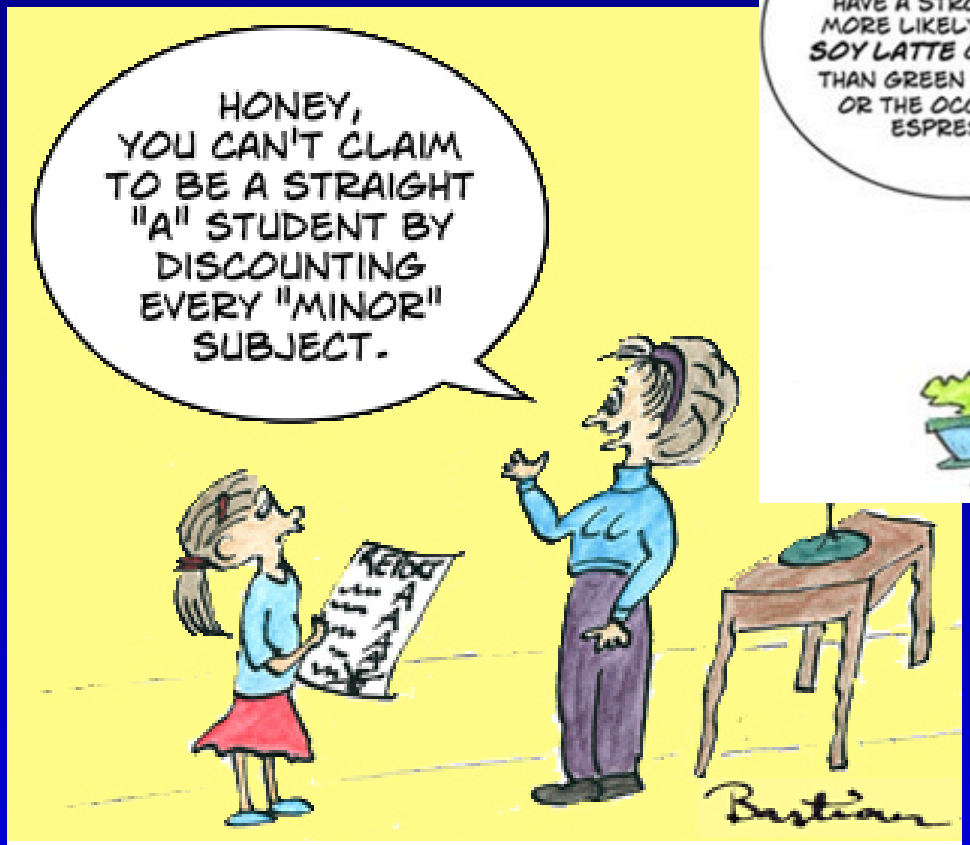
Similar Data with comparison of Pembro+Chemo vs EXTREME

First Subsequent Therapy

n (%)	Pembro Monotherapy n = 301	Pembro + Chemotherapy n = 281	EXTREME n = 300
Any new anticancer treatment[a]	148 (49.2)	115 (40.9)	159 (53.0)
Chemotherapy	135 (44.9)	88 (31.3)	102 (34.0)
EGFR inhibitor	59 (19.6)	37 (13.2)	19 (6.3)
Immune checkpoint inhibitor	6 (2.0)	12 (4.3)	50 (16.7)
Other immunotherapy	1 (0.3)	0 (0.0)	6 (2.0)
Kinase inhibitor	1 (0.3)	7 (2.5)	1 (0.3)
Other	2 (0.7)	1 (0.4)	2 (0.7)

Conclusion

- Pointless and misleading study done to try show a PFS benefit when initial study did not
- Data showing benefit after immunotherapy with chemo not shown
- Data showing how the subset of patients who received immunotherapy after EXTREME not shown
- Note –
  - Initial Protocol only included PFS as primary endpoint. Changed in middle of study
  - Still not data how CPS 0 or CPS 1-19 did



JULIE WAS EXCITED WHEN HER DAUGHTER FAILED HISTORY. AT LAST A TEACHABLE MOMENT ON THE NEED FOR UNBIASED CONSIDERATION OF ***ALL*** THE EVIDENCE!

Low-Cost oral metronomic versus intravenous chemotherapy in recurrent/metastatic/inoperable HNSCC

Minon

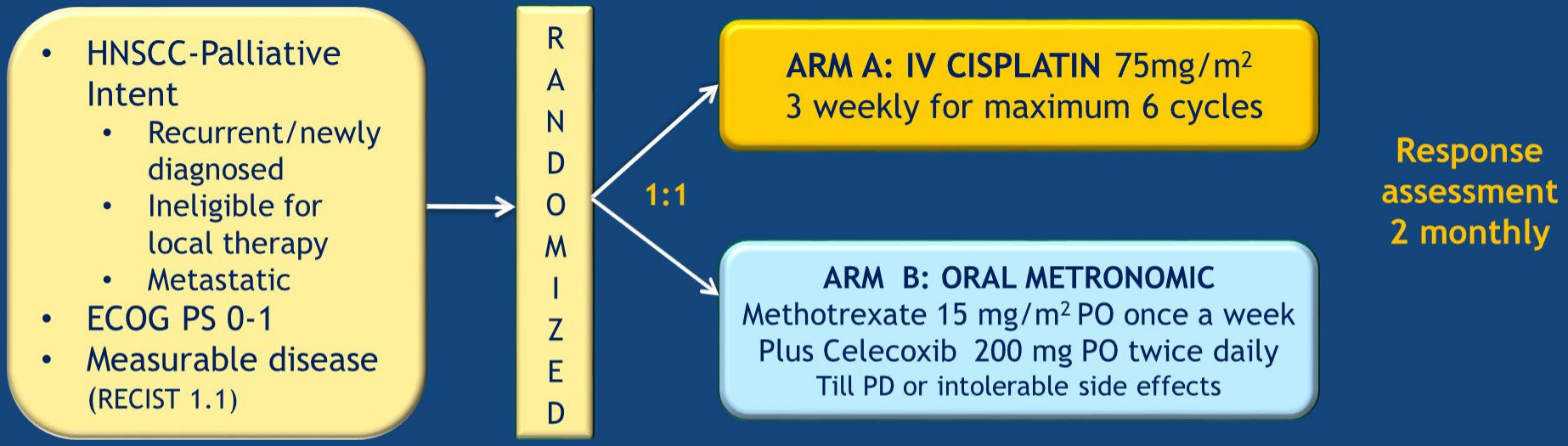
Tata Memorial Hospital, India

Background

- Standard Treatment
  - EXTREME – Cisplatin/5FU/**Cetuximab**
  - Keynote048 – Cisplatin/5FU/**Pembrolizumab**
  - FDA – Cisplatin-Based Therapy
- Low/Middle Income Countries
  - Rare access to these agents
  - Even **IV** Treatment may not be accessible

- Phase II study at Tata Memorial Hospital
  - Oral Methotrexate/Celecoxib vs IV Cisplatin
  - Favorable for Oral Regimen

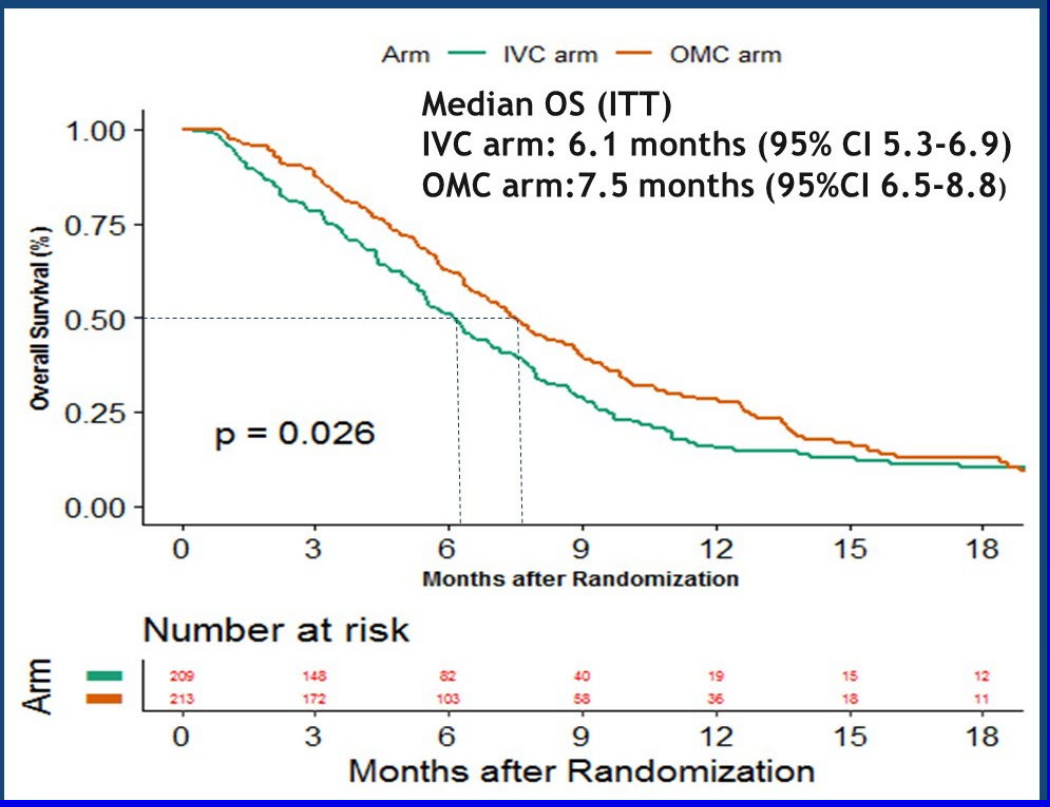
Study Design



Phase III, Open label, Randomized
Non-Inferiority
Stratification: Site, prior Rx

Primary Endpoint: OS
Secondary Endpoint: PFS,RR, Toxicity, QoL

Overall Survival



- 6-month OS (ITT)
  - IVC Arm: 50.89%
  - OMC Arm: 62.26%
  - Non-inferiority: p<0.001
  - Superiority: p=0.026
- Response Rate
  - IVC: 9.6%
  - OMC: 13.1%

Author	Drugs	N	Overall Response	Survival median (months)
Jacobs	CDDP	83	17%	5.0
	5-FU	83	13%	6.1
	CDDP/5-FU	79	32%	5.5
Forastiere	Methotrexate	88	10%	5.6
	Carboplatin/5-FU	86	21%	5.0
	CDDP/5-FU	87	32%	6.6
Clavel	CDDP	113	15%	5.3
	CDDP/5-FU	116	31%	6.2
	CDDP/MTX/Bleo/Vincr	127	34%	8.2

Efficacy and tolerance of carboplatin-cetuximab in patients with metastatic/recurrent HNSCC unfit for EXTREME

Le Roy

Hospitaux de Paris

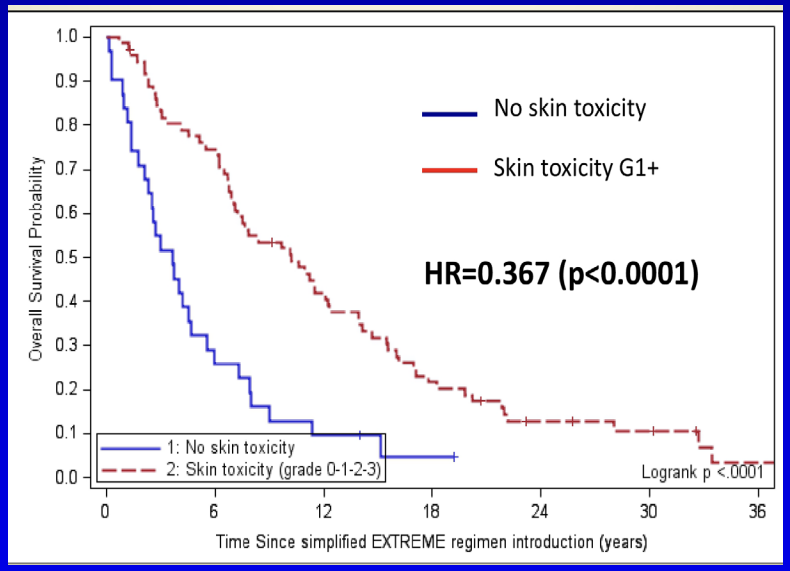
Background/Population

- Retrospective Review at 3 French academic hospitals 2007-2017
- Primary Endpoint is overall survival

- 103 Patients
- Median Age is 63 years old
- PS 2-3: 40%

Efficacy
Carboplatin/Cetuximab

- Overall Response Rate of 39.1%
- Median Overall Survival of 7.2 months
  - PS 0-1: 10.1 months
  - PS 2-3: 4.6 months
- Median PFS of 3.7 months



Conclusion

- There is also an older study by Hitt with cetuximab and paclitaxel showing a > 50% response rate
- These studies question the need for cisplatin and EXTREME showing good activity in patients receiving single agent chemotherapy with or without a targeted therapy (cetuximab)

Thyroid Cancer

Clinical activity of the RET inhibitor pralsetinib in patients with RET fusion+ solid tumors

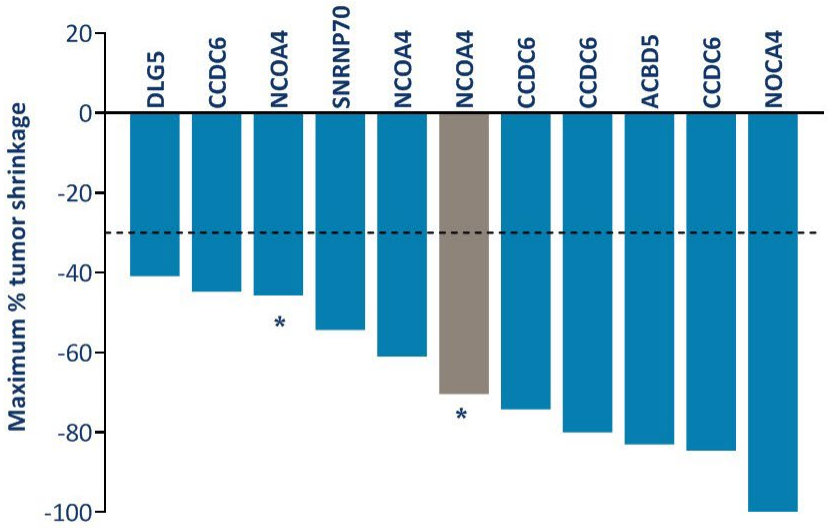
Subbiah

Background

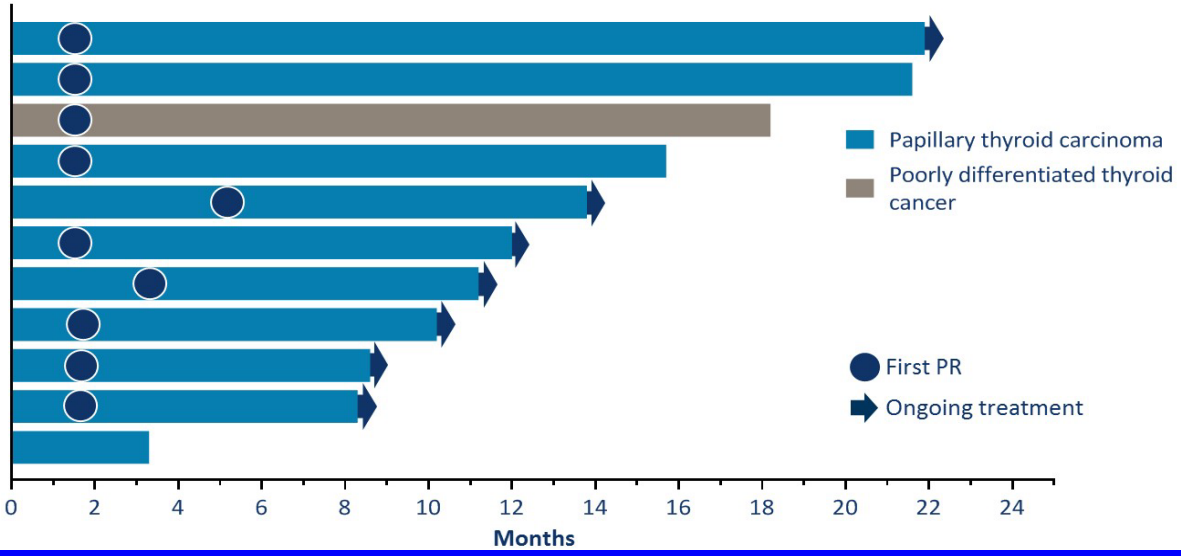
- RET fusion genes seen in 10-20% of papillary thyroid cancers
  - Less frequent in aggressive disease
- RET mutations are seen in 50-60% of medullary thyroid cancers (somatic and germline)
- Standard therapies that target RET (vandetanib, cabozantinib, etc…) have significant toxicities related to concurrent VEGFR targeting
- New drugs being developed that selectively target RET

Pralsetinib

RET fusion thyroid cancer



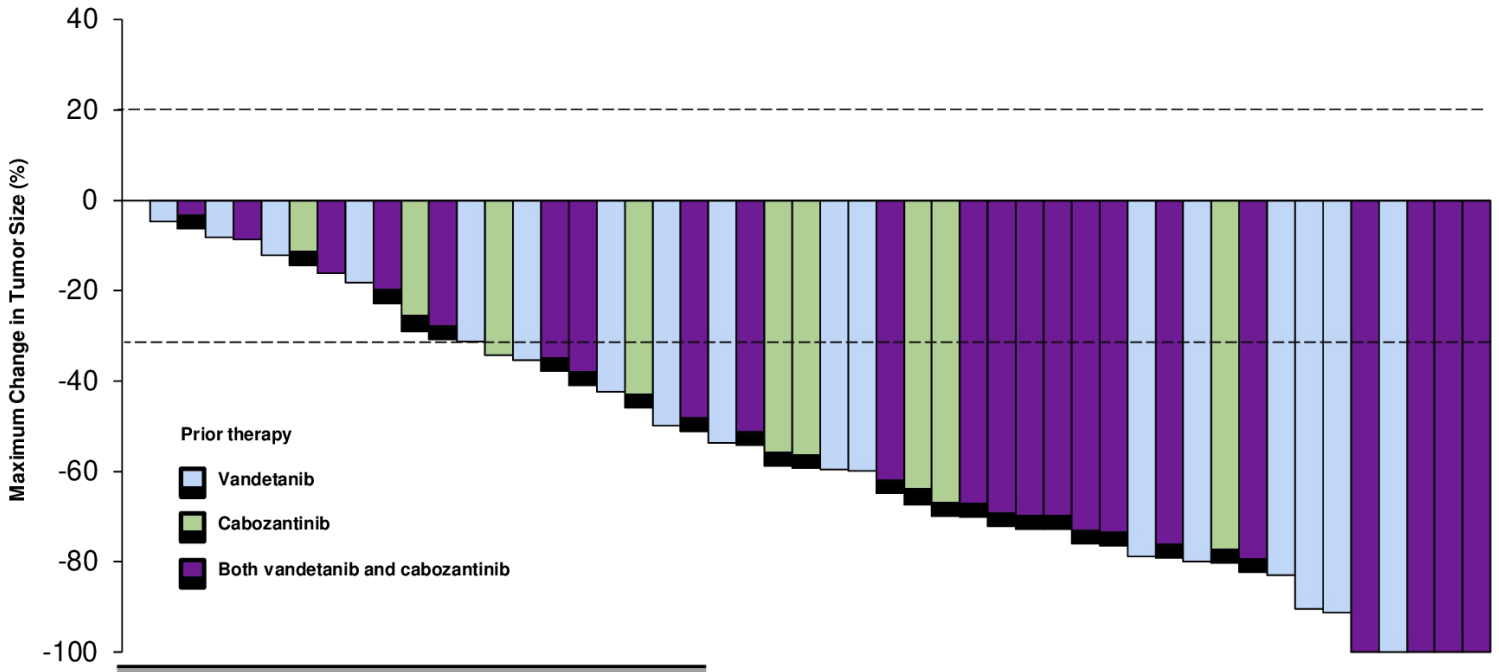
Best response, (response evaluable), %	RET fusion-positive thyroid cancer (n=11)†
ORR (95% CI)	91 (59–100)
PR	91
SD	9
PD	0
DCR (95% CI)	100 (72–100)



Selpercatinib in patients with RET-altered thyroid cancers

Manisha Shah

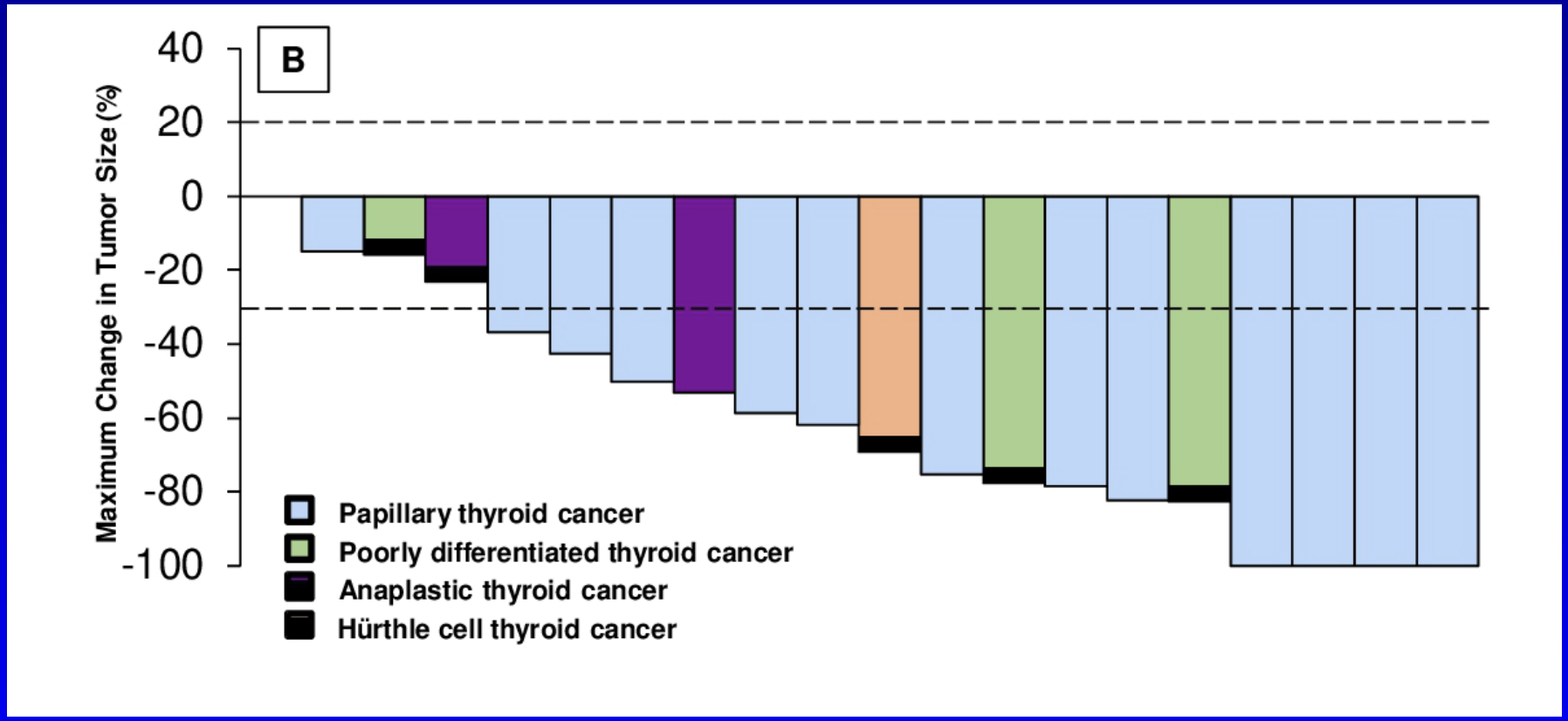
Selpercatinib
Pretreated MTC



	RET-mutant MTC Prior Vandetanib / Cabozantinib (n=55)
ORR by IRC, % (95% CI)	**69 (55–81)**
Best response by IRC, n (%)	
Complete response (CR)	5 (9)
Partial response (PR)	33 (60)
Stable disease (SD)	14 (26)
Progressive disease (PD)	1 (2)
Not evaluable (NE)	2 (4)

Data cutoff: 16-Dec-2019. For each patient, the maximum change in tumor size, defined as the best % change from baseline in the sum of diameters for all target lesions, is represented by a vertical bar in the waterfall plot. 7 patients are not shown as 2 discontinued prior to post-baseline imaging assessments, and 5 had non-measurable disease at baseline. Abbreviations: IRC, independent review committee; ORR, objective response rate.

Selpercatinib
Pretreated Follicular Cell Thyroid Cancer



Selpercatinib
Pretreated MTC

	Pretreated (vandet/cabo)	Treatment Naïve
Number	55	88
Best Overall Response	69% (9% CR)	73% (11% CR)
Progression-free Survival		
Median, months (95% CI)	NE (24-NE)	24 (NE-NE)
Median follow up, months	17	11
1-Yr PFS Rate % (95% CI)	82 (69-90)	92 (82-97)

*Independent Review of Scans

Selpercatinib
RET-fusion Thyroid Cancer

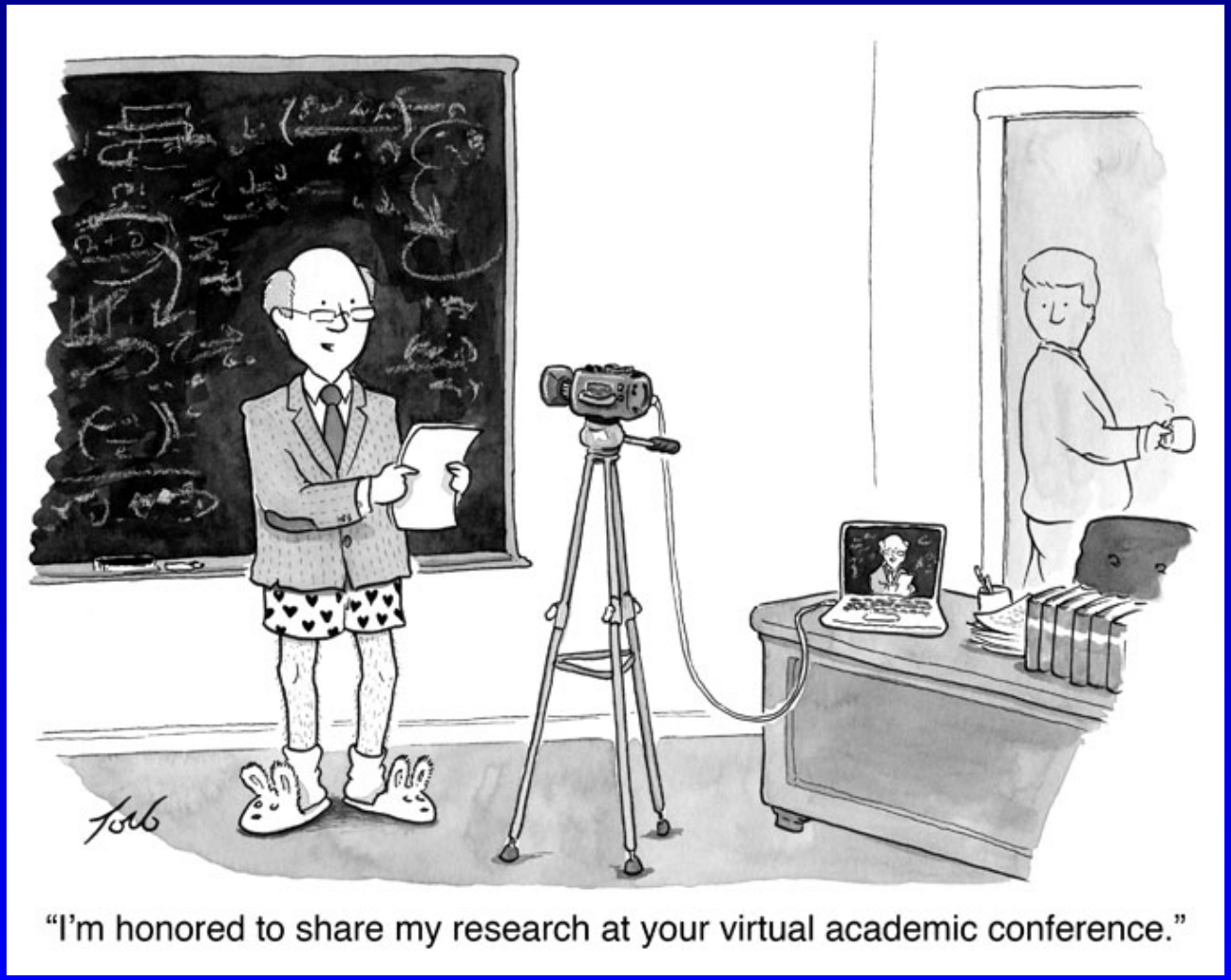
	Previously Treated
Number	19
Best Overall Response	79% (5% CR)
Progression-free Survival	
Median, months (95% CI)	NE (10-NE)
Median follow up, months	19
1-Yr PFS Rate % (95% CI)	61 (33-81)

*Independent Review of Scans

Conclusion

- These new RET inhibitors represent the new standard of care for RET altered thyroid cancer
- Selpercatinib has been FDA approved already for all lines of therapy
- There are still questions about sequencing of treatment and mechanisms of resistance

Thank You!



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