UPDATES ON THE SYSTEMIC THERAPY AND SEQUENCING FOR HEAD AND NECK CANCER

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Disclosures

- Grant/Research Support from Takeda.
- Consultant for AstraZeneca, Bristol-Myers Squibb, and Genentech.
- Stock ownership Johnson & Johnson

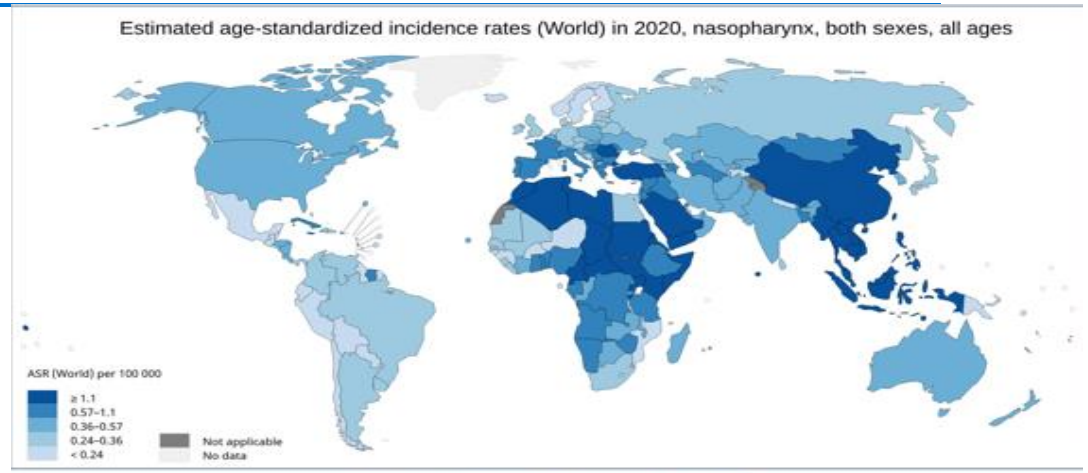
Objectives

- To discuss current SOC and sequencing for treatment of NPC, HNSCC, and DTC and where we are going for future treatment options.

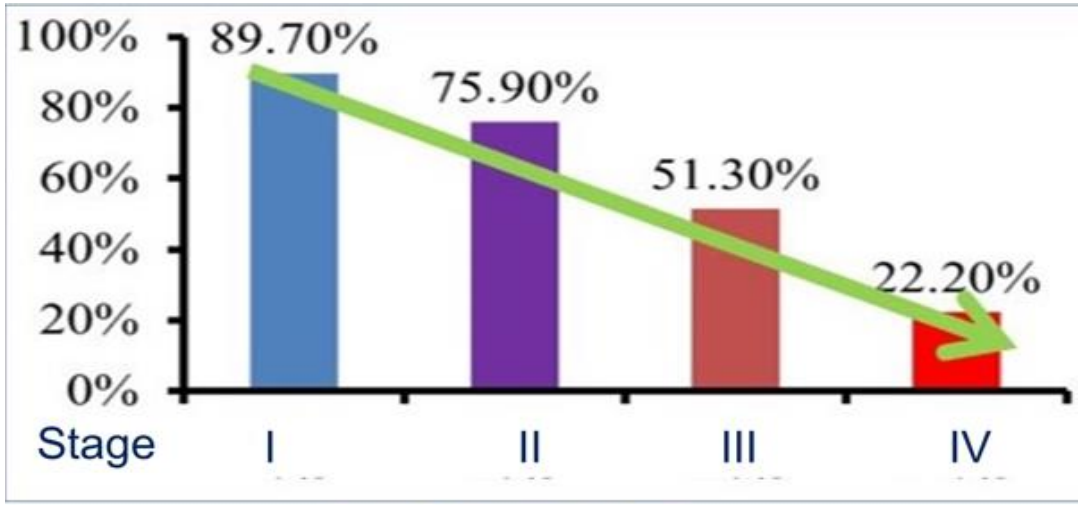
Nasopharynx Carcinoma
What are current treatment Recommendations?

Nasopharynx, Background

- 129,100 new cases/year and 73,000 deaths/year – worldwide
- Endemic areas in Asia and Africa, small pocket in South America – EBV related
    - WHO 3, non-keratinizing, undiff type and WHO 2 nonkeratinizing diff type
- Survival with CRT/Chemo has been significantly improved
- 20-30% of patients still have recurrence or develop metastatic disease and the prognosis is poor



Incidence of NPC worldwide in 2020[1]

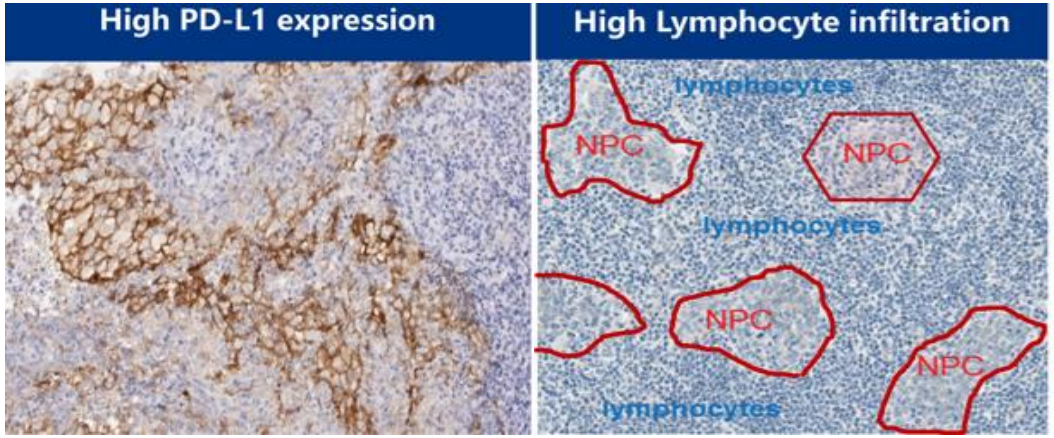


Mortality of NPC worldwide in 2020[1]

International Agency for Research on Cancer 2020, World Health Organization (https://gco.iarc.fr/today/ home
Ferlay J, et al. Int J Cancer 2019; 144L1941-52

Nasopharynx – Where are we now in the treatment of metastatic nasopharynx?

- **Clinical trials preferred vs Platinum based chemotherapy**
  - **Preferred regimens as SOC, Front-Line**
    - Gemcitabine/CDDP Category 1 NCCN
    - ➢ ORR -64% (42), PFS 7 mos (5.6), OS 29.1 mos (20.9)
    - Others – CDDP/FU, Platinum/Taxane, Platinum/Cetuximab, Gem/Carbo
  - **Subsequent lines**
    - Endemic NPC – Elevated PDL1 and Elevated TILs
    - Immunotherapy (generally non-keratinizing, PDL1 +, TMB-H)



Zhang L et al, Lancet 2016;388:1883-92
Larbcharoensub N et al. Am J Clin Oncol 2018;41:1204-10

SYSTEMIC THERAPY FOR NASOPHARYNGEAL CANCERS

- **The choice of systemic therapy should be individualized based on patient characteristics (eg, PS, goals of therapy).**

Induction[a]/Sequential Systemic Therapy

Preferred Regimens
- Gemcitabine/cisplatin (category 1)[1]
- Docetaxel/cisplatin/5-FU (dose-adjusted) (category 1 for EBV-associated disease, category 2A for non–EBV-associated disease)[2-4]

Other Recommended Regimens
- Cisplatin/5-FU[5]
- Cisplatin/epirubicin/paclitaxel
- Docetaxel/cisplatin (category 2B)[6]
- Following induction, agents used with concurrent systemic therapy/RT typically include weekly cisplatin[7] or carboplatin[8]

Systemic Therapy/RT Followed by Adjuvant Chemotherapy

Preferred Regimens
- Cisplatin + RT followed by cisplatin/5-FU[7,9]

Other Recommended Regimens
- Cisplatin + RT followed by carboplatin/5-FU[10]
- Cisplatin + RT without adjuvant chemotherapy (category 2B)[11]

Useful in Certain Circumstances
- If cisplatin ineligible or intolerant, carboplatin may be used as an alternative:
  - Carboplatin + RT followed by carboplatin/5-FU[8,12]

See Evidence Blocks for T0 (EBV+)-T1, N1-3; T2-T4 N0-3 nasopharyngeal cancer on NASO-B (EB-1)

Recurrent, Unresectable, or Metastatic Disease (with no surgery or RT option)

Preferred Regimens

First-Line[b]
- Cisplatin/gemcitabine (category 1)[13,14]

Other Recommended Regimens

First-Line[b]
- Combination Therapy
  - Cisplatin/5-FU[15,16]
  - Cisplatin or carboplatin/docetaxel[17] or paclitaxel[15]
  - Carboplatin/cetuximab[18]
  - Gemcitabine/carboplatin
- Single Agents
  - Cisplatin[19,20]
  - Carboplatin[21]
  - Paclitaxel[22]
  - Docetaxel[23,24]
  - 5-FU[20]
  - Methotrexate[16,25]
  - Gemcitabine[26]
  - Capecitabine[27]

Subsequent-Line
- Immunotherapy
  - Nivolumab if previously treated, recurrent or metastatic non-keratinizing disease (category 2B)[28,29]
  - Pembrolizumab if previously treated, PD-L1–positive, recurrent or metastatic disease (category 2B)[30]

See Evidence Blocks for recurrent, unresectable, or metastatic nasopharyngeal cancer on NASO-B (EB-2)

Useful in Certain Circumstances

Subsequent-line
- Pembrolizumab (for TMB-H tumors)[31]

[a]The categories of evidence and consensus for induction therapy vary depending on site. (See disease-specific site in the Head and Neck Table of Contents)
[b] If not previously used, these regimens may be considered in subsequent-lines, as other recommended regimens.

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.
All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

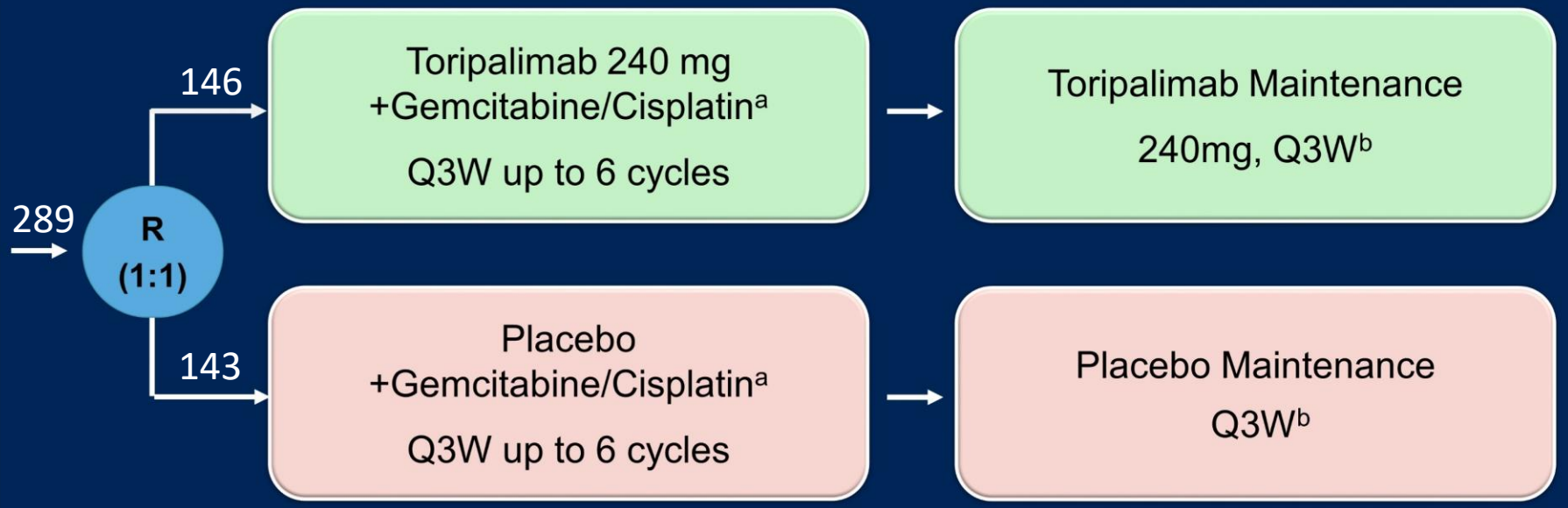
References

Nasopharynx,
What are we exploring to Improve outcomes?

JUPITER-02: Study Design
(ClinicalTrials.gov identifier: NCT03581786)

Key Eligibility Criteria

- Primary metastatic NPC or recurrent NPC after curative-intent therapy
- Treatment naïve for recurrent or metastatic (R/M) disease
- ECOG 0-1
- 18-75 yrs
- Measurable disease per RECIST v1.1



Stratification Factors

- Recurrent vs Primary metastatic
- ECOG PS 0 vs 1

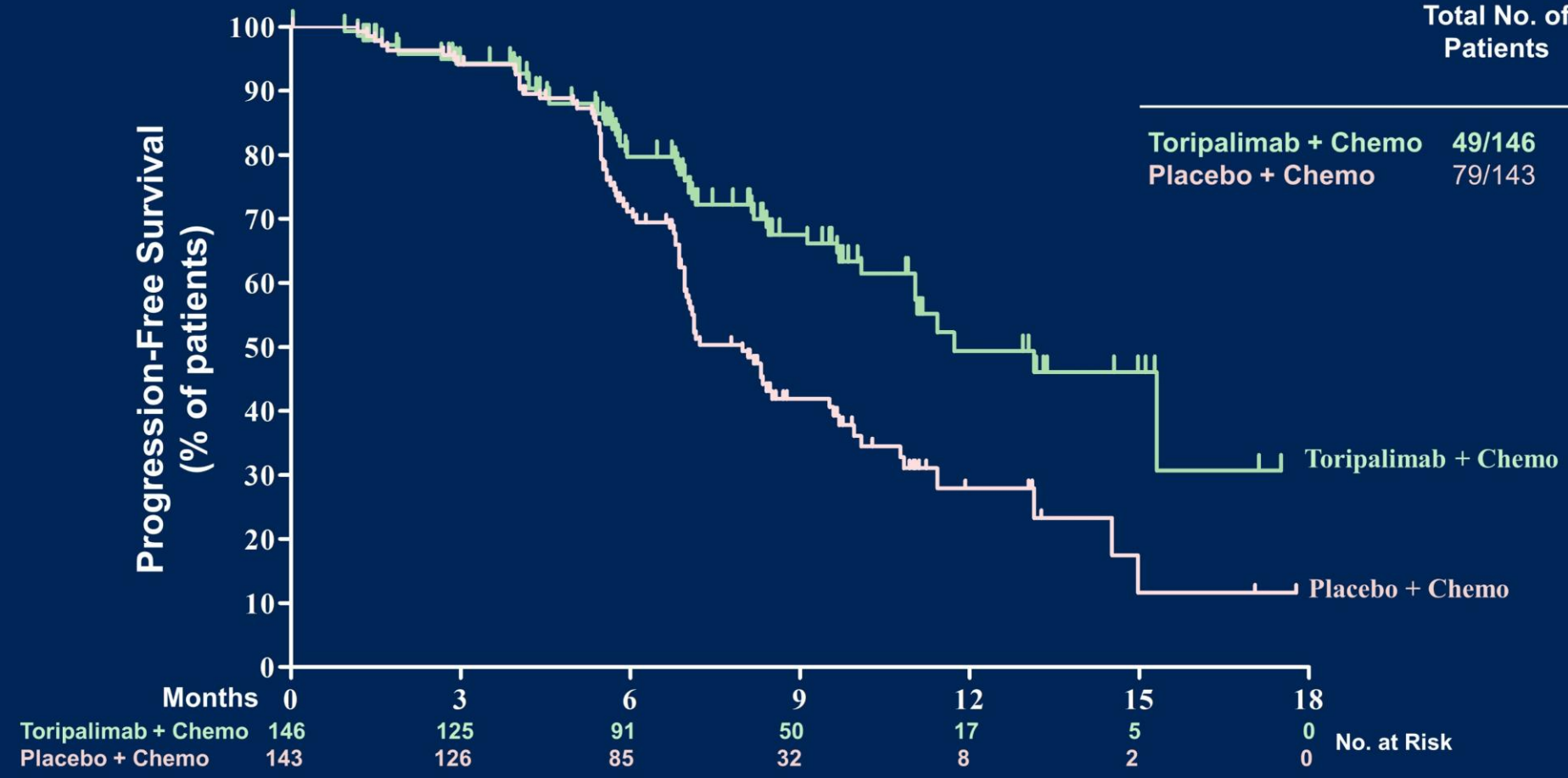
- Primary endpoint: PFS by a blinded independent review committee (BIRC) per RECIST v1.1
- Secondary endpoints: PFS by the Investigator, ORR, DoR, DCR, OS, and PFS & OS 1-year and 2-year rates

[a] Gemcitabine 1000mg/m^2 D1,8 +Cisplatin 80mg/m^2 D1
[b] Until progressive disease, excessive toxicity, withdrawal of consent or investigator's judgement or a maximum treatment of 2 years.

Progression-Free Survival by BIRC per RECIST v1.1

Interim Analysis Data cut-off Date: May 30, 2020

	No. of Events/ Total No. of Patients	Median Progression-free Survival, months (95% CI)	1-Yr Progression-free Survival Rate, % (95% CI)
Toripalimab + Chemo	49/146	11.7 (11.0, NE)	49.4 (36.4, 61.1)
Placebo + Chemo	79/143	8.0 (7.0, 9.5)	27.9 (18.0, 38.8)



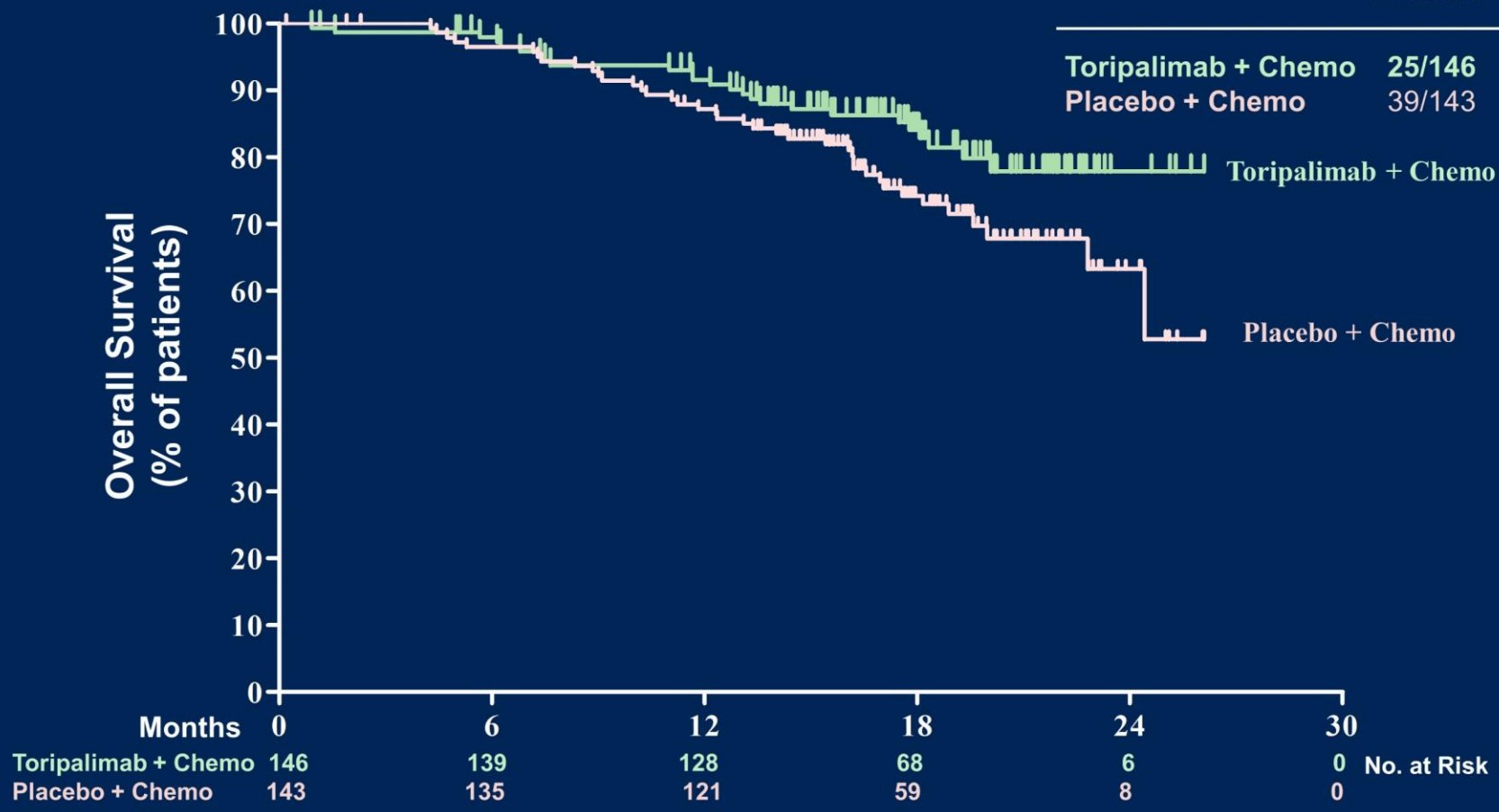
Stratified HR for disease progression or death,

0.52 (95% CI 0.36-0.74); P=0.0003

Overall Survival Update

Nine-month OS update after PFS Interim Analysis on Feb 18, 2021

	No. of Deaths/ Total No. of Patients	Median Overall Survival (95% CI) *mo*	1-Yr Overall Survival Rate % (95% CI)	2-Yr Overall Survival Rate % (95% CI)
Toripalimab + Chemo	25/146	NE (NE, NE)	91.6 (85.6, 95.1)	77.8 (68.0, 85.0)
Placebo + Chemo	39/143	NE (22.8, NE)	87.1 (80.4, 91.7)	63.3 (49.8, 74.1)



Stratified HR for death,

0.603 (95% CI 0.364-0.997); P=0.0462

Study Design (NCT03707509)

Key eligibility criteria:

- Aged 18-75 years;
- Pathologically confirmed R/M-NPC;
- Had not received previous systemic therapy for R/M-NPC (disease progression at least 6 months after induction, adjuvant, or concurrent chemoradiotherapy were eligible);
- ECOG performance status of 0 or 1;
- At least one measurable lesion according to RECIST version 1.1;

R 1:1

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Camrelizumab (200 mg on day 1)
+ gemcitabine (1000 mg/m^2 on days 1 and 8)
+ cisplatin (80 mg/m^2 on day 1)

Q3W for 4-6 cycles

Camrelizumab (200 mg on day 1)

Q3W until disease progression, unacceptable toxicity, withdrawal of consent

Stratification factors:

- Liver metastases (yes *vs* no).
- Previous radical concurrent chemoradiotherapy (yes *vs* no).
- ECOG performance status (0 *vs* 1)

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Placebo
+ gemcitabine (1000 mg/m^2 on days 1 and 8)
+ cisplatin (80 mg/m^2 on day 1)

Q3W for 4-6 cycles

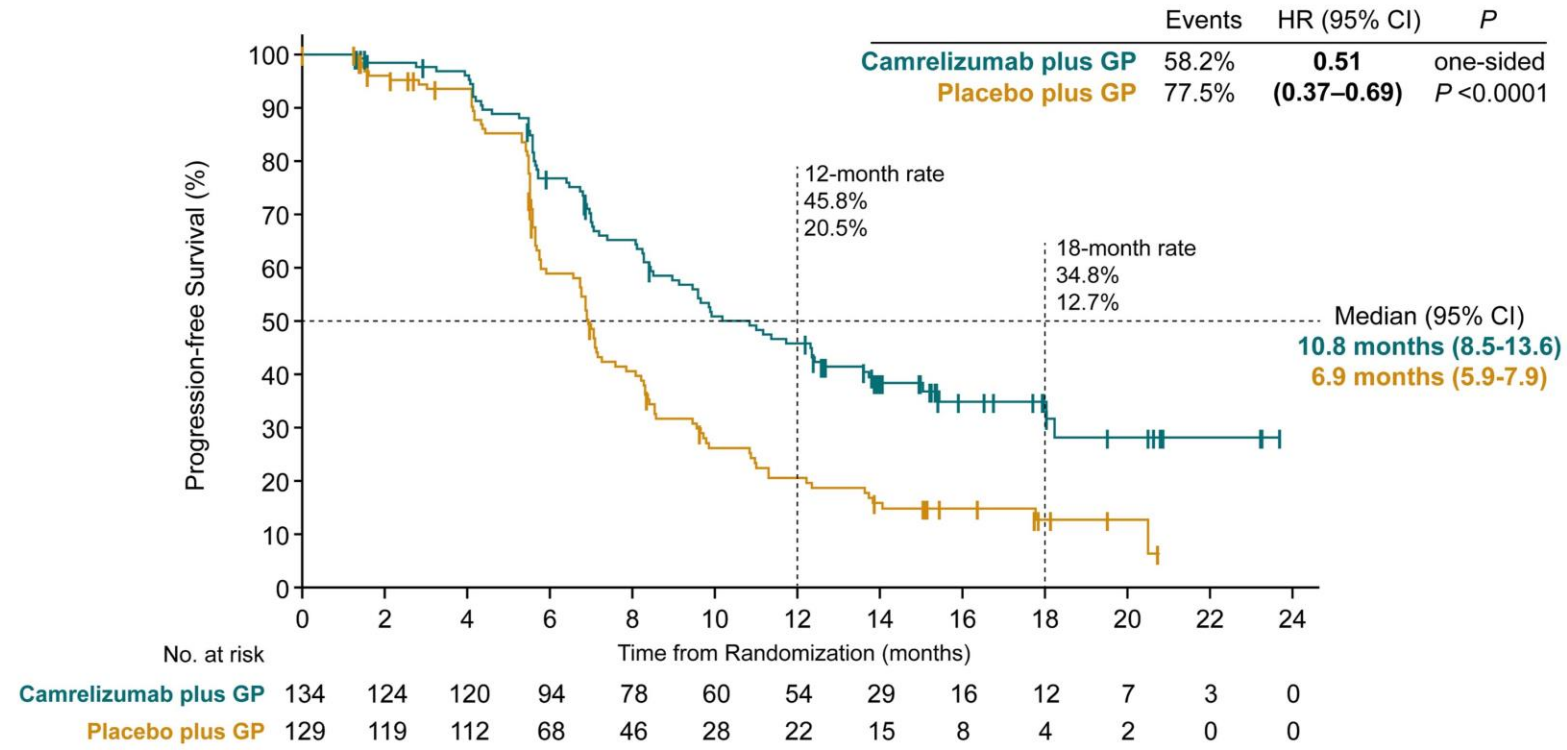
Placebo

Q3W until disease progression, unacceptable toxicity, withdrawal of consent

- Primary endpoint: independent review committee (IRC)-assessed PFS
- Secondary endpoints: investigator-assessed PFS, ORR, DCR, DoR, OS and safety

ECOG, Eastern Cooperative Oncology Group; RECIST, Response Evaluation Criteria in Solid Tumors; DCR, disease control rate; DoR, duration of response

PFS per IRC



- **Camrelizumab plus GP improved PFS compared with placebo plus GP, with a 49% lower risk of disease progression or death.**

Data cutoff on Dec 31, 2020

1st line NPC – Summary and Conclusion

- Addition of Toripalimab or Camrelizumab to GC prolongs survival

66.4%	GC	GC-T	GC	GC-C	p
mPFS	8.0 mos	11.7 mos	6.9 mos	10.8 mos	0.0003/<0.0001
DoR	5.7 mos	10.0 mos	5.7 mos	9.9 mos	
mOS	NR	NR	22.6 mos	NR	
ORR	66.4%	77.4%	80.6%	88.1%	0.03/NS

- No new safety signals
- GC remains SOC first line
- Addition of Checkpoint inhibitor appears to improve PFS in patients with endemic NPC in front line with GC. Studies ongoing in US.
- Role of maintenance systemic therapy remains to be defined

SYSTEMIC THERAPY FOR NASOPHARYNGEAL CANCERS

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2nd line not well defined, CPI if indicated
Or a chemo not previously used.

See Evidence Blocks for recurrent, unresectable, or metastatic nasopharyngeal cancer on NASO-B (EB-2)

Useful in Certain Circumstances

Subsequent-line
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References

Ongoing Trials Phase III R/M NPC

Trial identifier	Ph	Study title	Patient selection	Primary end point
NCT02611960	III	Pembrolizumab versus standard of care (capecitabine, gemcitabine or docetaxel)	Subsequent line (N = 233)	OS
NCT03707509	III	Cisplatin gemcitabine ± Camrelizumab	1st line (N = 250)	PFS
NCT03581786	III	Cisplatin gemcitabine ± Toripalimab	1st line (N = 280)	PFS
NCT04458909	III	Cisplatin gemcitabine ± Nivolumab	1st line (N = 316)	OS

Other Treatments in Development NPC

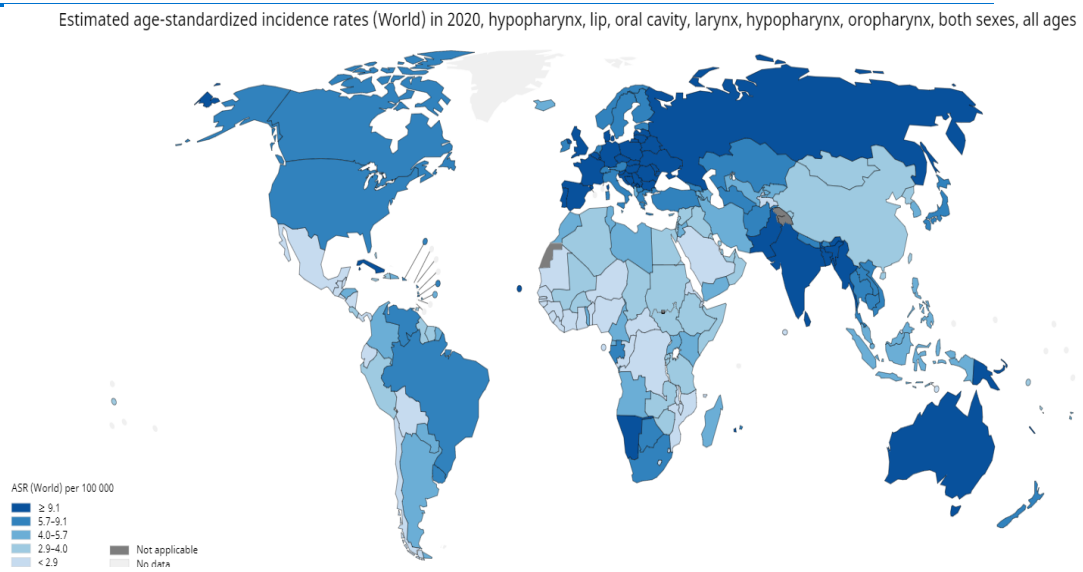
- Other IO and IO combinations with PD
- Vaccines,
- TILs, Allogeneic EBV T cells
- CCR4 antagonists, other signaling inhibitors coupled with CPI
- Bispecific or Antibody-drug conjugates

HNSCC, non-NPC

What are current treatment Recommendations?

HNSCC, Background

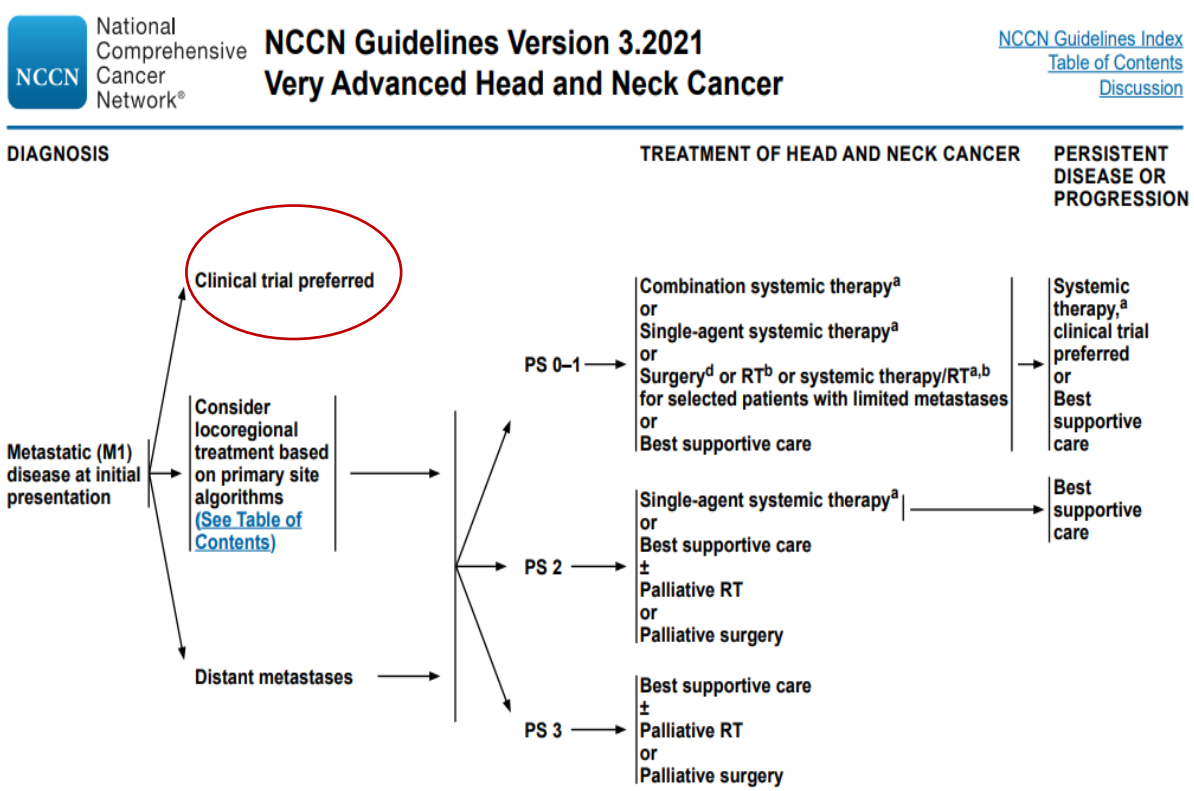
- Non-NPC HNSCC 744,994 new cases/year and 364,339 deaths/year – worldwide
- Heterogenous group of malignancies
  - Tobacco/ETOH
  - HPV (US, Canada, Australia, Brazil, Europe)
- 50% of patients still have recurrence or develop metastatic disease and the prognosis is poor

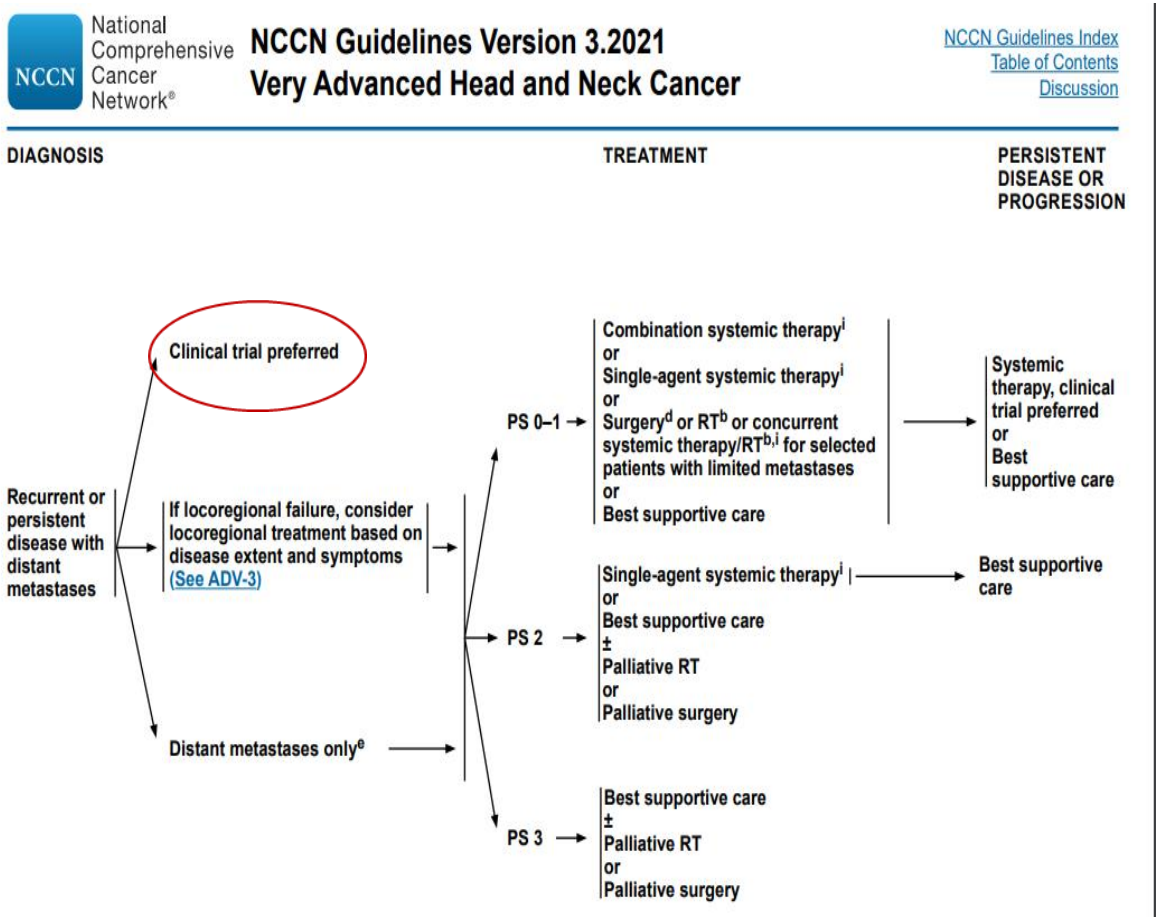


Site	New Cases	Deaths
Lip/Oral Cavity	377,713	177,757
Larynx	184,615	99,840
Oropharynx	98,412	48,143
Hypopharynx	84,254	38,599
Non-NPC HNSCC	744,994	364,339

International Agency for Research on Cancer 2020, World Health Organization (https://gco.iarc.fr/today/ home

HNSCC – Where are we now in the treatment of metastatic HNSCC?





PRINCIPLES OF SYSTEMIC THERAPY FOR NON-NASOPHARYNGEAL CANCERS
(Lip, Oral Cavity, Oropharynx, Hypopharynx, Glottic Larynx, Supraglottic Larynx, Ethmoid Sinus, Maxillary Sinus, Occult Primary)

- **The choice of systemic therapy should be individualized based on patient characteristics (eg, PS, goals of therapy).**

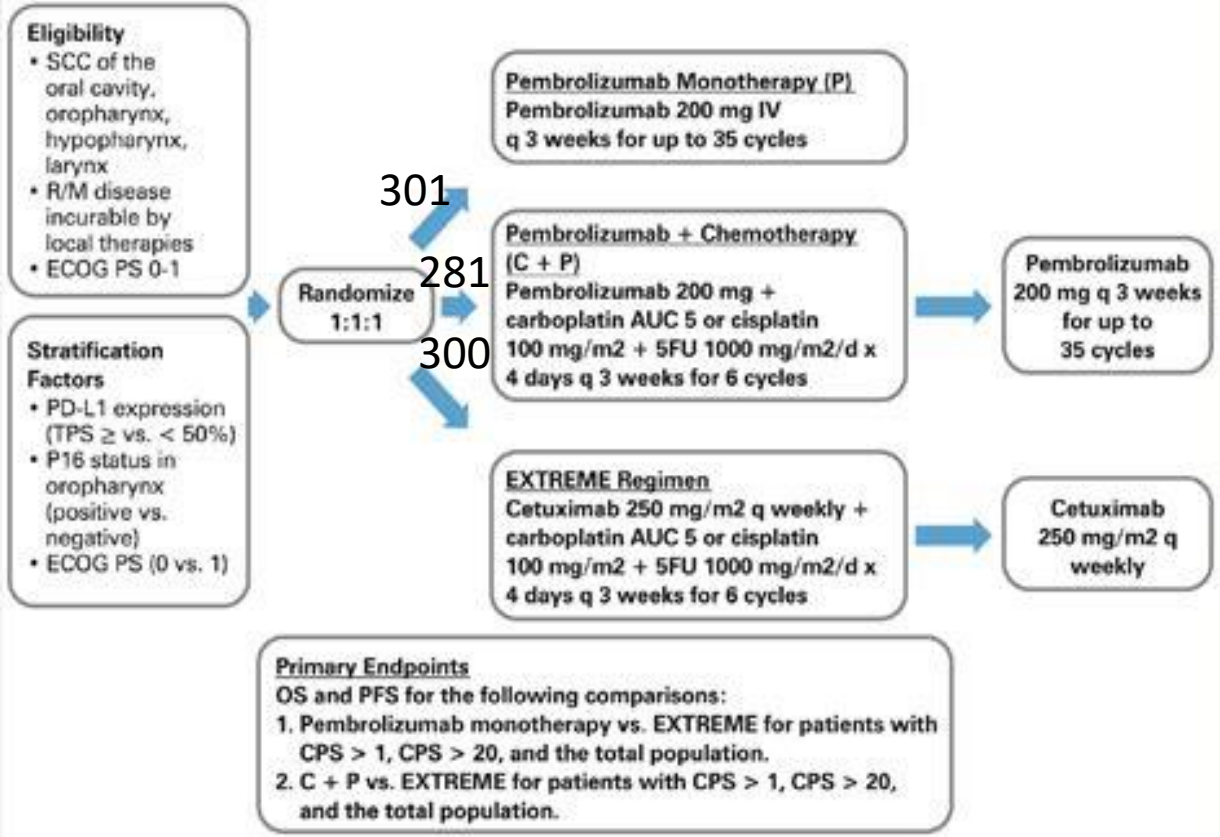
Recurrent, Unresectable, or Metastatic (with no surgery or RT option)

Preferred Regimens	Other Recommended Regimens (First- and Subsequent-Line)	Useful in Certain Circumstances (First- and Subsequent-Line)
First-line[c] • Pembrolizumab/platinum (cisplatin or carboplatin)/5-FU (category 1)[c,29] • Pembrolizumab (for tumors that express PD-L1 with CPS ≥1) (category 1 if CPS ≥ 20)[c,29] **Subsequent-Line (if not previously used)** • Nivolumab[30] (if disease progression on or after platinum therapy) (category 1) • Pembrolizumab[31-33] (if disease progression on or after platinum therapy) (category 1)	**Combination regimens** • Cetuximab/platinum (cisplatin or carboplatin)/5-FU[34] (category 1) • Cisplatin/cetuximab[35] • Cisplatin or carboplatin/docetaxel[36] or paclitaxel[37] • Cisplatin/5-FU[37,38] • Cisplatin or carboplatin/docetaxel/cetuximab[39] • Cisplatin or carboplatin/paclitaxel/cetuximab[40] • Pembrolizumab/platinum (cisplatin or carboplatin)/paclitaxel (category 2B)[29,37] • Pembrolizumab/platinum (cisplatin or carboplatin)/docetaxel (category 2B)[29,36] **Single Agents** • Cisplatin[35,41] • Carboplatin[42] • Paclitaxel[43] • Docetaxel[44,45] • 5-FU[41] • Methotrexate[38,46] • Cetuximab[47] • Capecitabine[48] • Afatinib[49] (subsequent-line only, if disease progression on or after platinum therapy) (category 2B)	• For select ethmoid/maxillary sinus cancers (small cell, SNEC, high-grade olfactory esthesioneuroblastoma, SNUC with neuroendocrine features): ▸ Cisplatin/etoposide or carboplatin/etoposide[14] ▸ Cyclophosphamide/doxorubicin/vincristine (category 2B) • Pembrolizumab (for MSI-H tumors)[50]

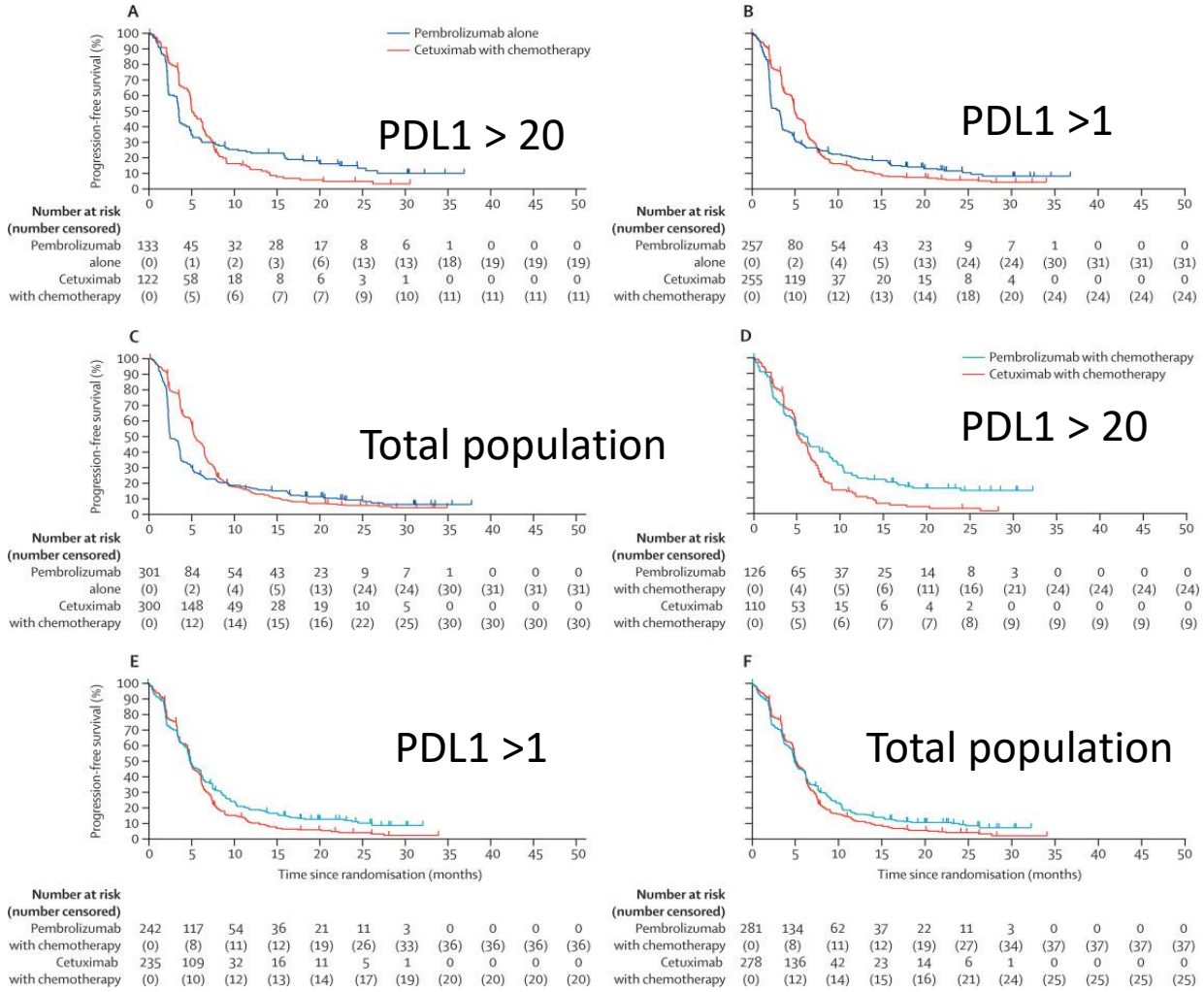
[c] If not previously used, these regimens may be considered in subsequent-lines, as other recommended regimens.

Keynote 048

Figure. KEYNOTE-048 Schema



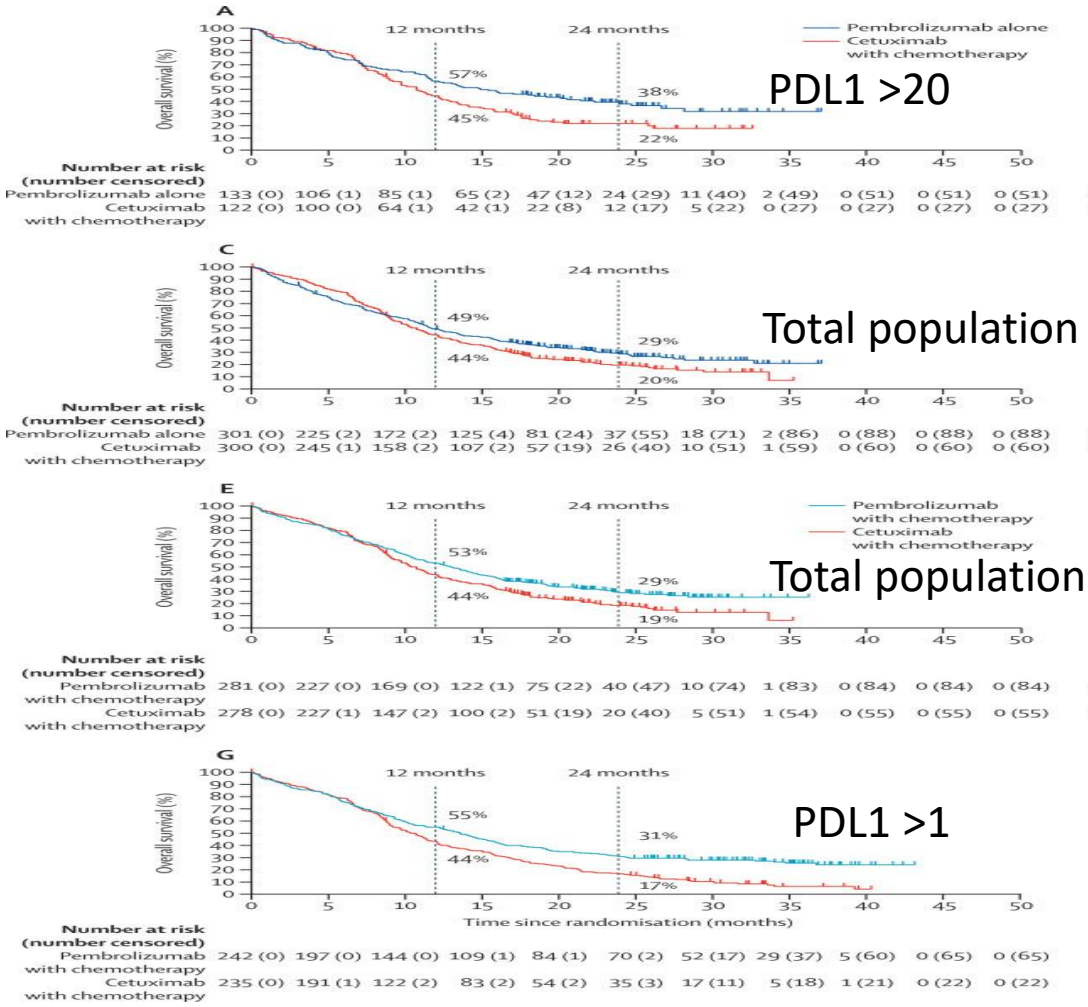
Abbreviations: AUC, area under the curve; C + P, platinum (cisplatin or carboplatin)/5-fluorouracil plus pembrolizumab; CPS, combined positive score; EXTREME, platinum/5-fluorouracil plus cetuximab; ECOG PS, Eastern Cooperative Oncology Group performance status; 5-FU, fluorouracil; IV, intravenous; OS, overall survival; PFS, progression-free survival; R/M, recurrent/metastatic; SCC, squamous cell carcinoma; TPS, tumor proportion score.



	Pembro	EXTREME	CF-Pembro
PFS(CPS >20)	3.4 mos	5.0 mos	5.8 mos
PFS(CPS >1)	3.2 mos	5.0 mos	5.0 mos
All	2.3 mos	5.2 mos	4.9 mos

Burtness B, et al. Lancet 2019;394:1915-28

KEYNOTE 048 Overall survival



ORR	Pembro	Extreme	CF-Pem
CPS>20	23%	36%	43%
CPS >1	19%	35%	36%

	Pembro	EXTREME	CF-Pembro
OS(CPS >20)	12m – 57%	45%	57%
	24m – 38%	27%	35%
OS(CPS >1)	12m – 51%	44%	55%
	24m – 30%	19%	31%
All	12m – 49%	44%	53%
	24m – 29%	20%	29%

Burtness B, et al. Lancet 2019;394:1915-28

PRINCIPLES OF SYSTEMIC THERAPY FOR NON-NASOPHARYNGEAL CANCERS
(Lip, Oral Cavity, Oropharynx, Hypopharynx, Glottic Larynx, Supraglottic Larynx, Ethmoid Sinus, Maxillary Sinus, Occult Primary)

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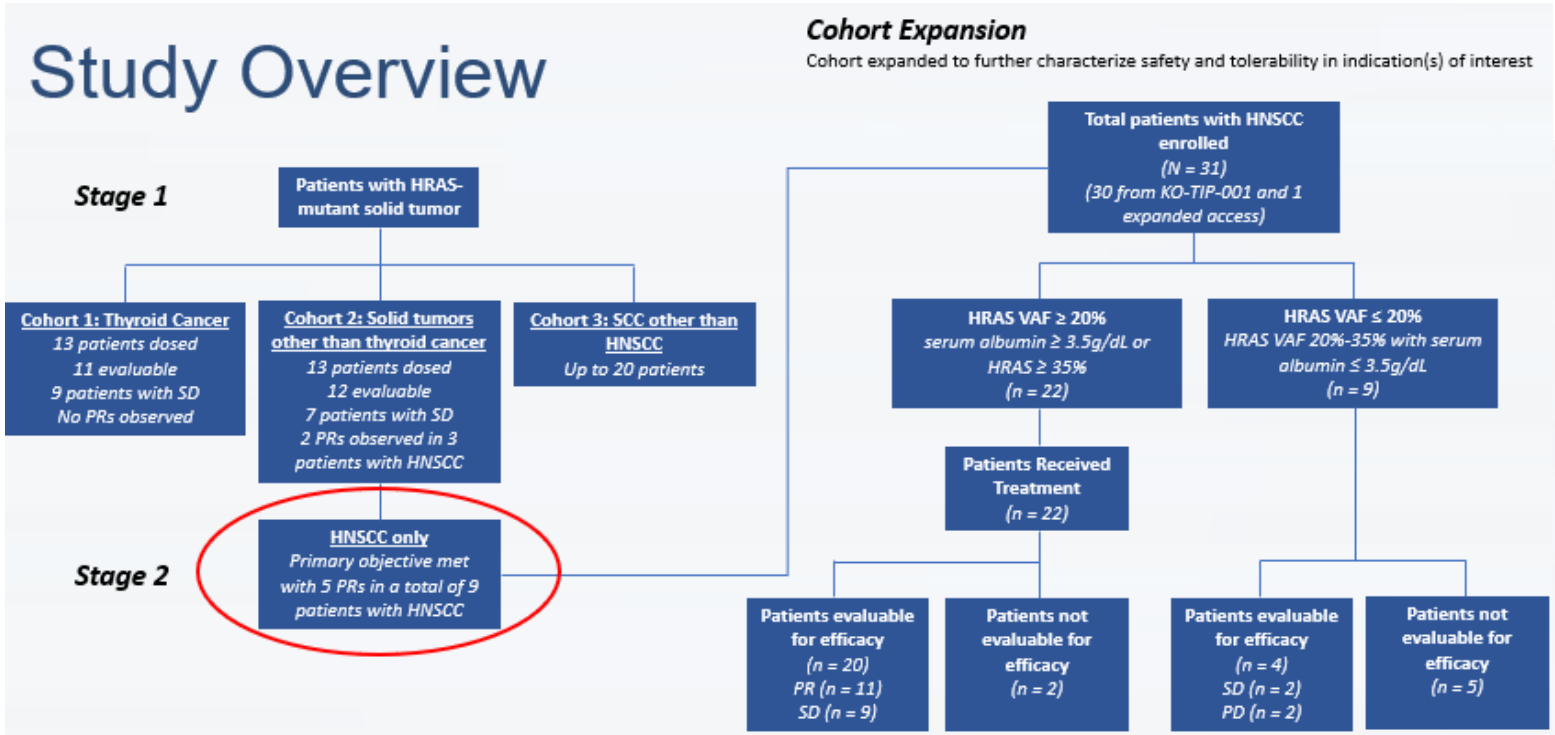
2nd line not well defined
EXTREME vs CPI if not used front line
OTW Dealers choice

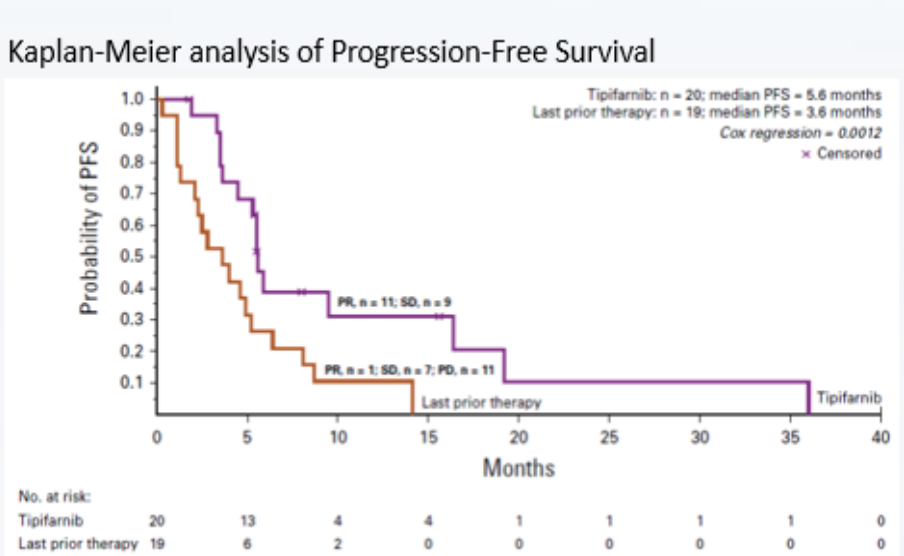
[c] If not previously used, these regimens may be considered in subsequent-lines, as other recommended regimens.

HNSCC, non-NPC
What are we exploring to Improve outcomes?

Molecularly Driven 2nd line and Beyond



PFS



Efficacy n=20	Outcome	%(95% CI)
PFS	5.6 mos	3.6-16.4
OS	15.4 mos	15.4-29.7
ORR	(11/20)55%	31.5-76.9

Ho AL, et al. J Clin Oncol. 2021;39(17):1856-1864

Ongoing Trials Phase III R/M HNSCC - Targeted

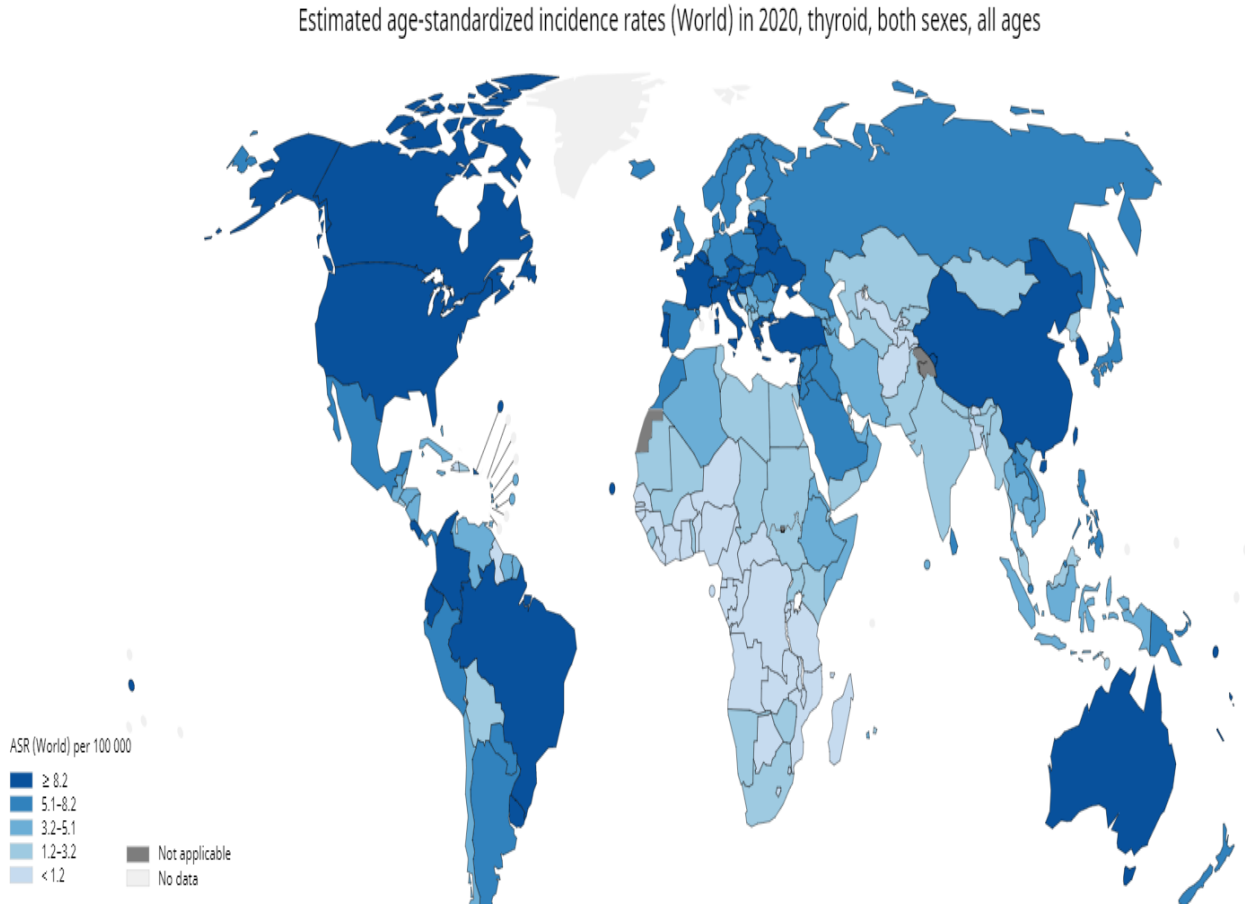
Trial Identifier	Ph	Study Title	MOA	Pt Selection	Primary Endpt
04338399	III	BURAN	PI3K/Taxane	2nd line/483	OS
02741570	III	Nivo/Ipi vs Extreme	CTLA4/PDL1	1st line/947	OS
	III				OS
00588770	III	Chemo+/-Bev	VEGF	1st line/403	OS
04199104	III	LEAP-10 Pembro +/- Len	PD1/VEGF-TKI	1st line/500	ORR/PFS/OS
04590963	III	INTERLINK-1	EGFR mab +/- Mab to NKG2A (NK cells/CTL)	2+ line Failed CPI/624	OS

Other Treatments in Development HNSCC, non-NPC

- Other IO and IO combinations with PD (LAG-3, CTLA4, ICOS, STING, TIGIT)
- Vaccines,
- TILs, CART, gene therapy
- CCR4, PI3K, HRAS, PARP, EZH2, STAT, EPHB antagonists, other signaling inhibitors coupled with CPI
- Bispecific or Antibody-drug conjugates

HNSCC, Background

- Thyroid cancer 586,202 new cases/year and 43,646 deaths/year – worldwide
- Heterogenous group of malignancies
  - Differentiated TCA, Sporadic
    - Papillary
    - Follicular (Hurthle cell)
    - Medullary
  - MEN familial syndrome
  - Anaplastic/Insular Thyroid Cancer
- RAI Resistance - Molecular Targeted Agents for BRAF V600e, RET, NTRK
- RAI Resistance - Non-mutated, Metastatic DTC options update for



International Agency for Research on Cancer 2020, World Health Organization (https://gco.iarc.fr/today/ home

NCCN Guidelines Version 2.2021
Thyroid Carcinoma – Papillary Carcinoma

NCCN Guidelines Index
Table of Contents
Discussion

TREATMENT OF LOCALLY RECURRENT, ADVANCED, AND/OR METASTATIC DISEASE NOT AMENABLE TO RAI THERAPY

Structurally persistent/recurrent locoregional or distant metastatic disease not amenable to RAI therapy

- Continue to suppress TSH with levothyroxine[i]
- For advanced, progressive, or threatening disease, genomic testing to identify actionable mutations (including *ALK, NTRK*, and *RET* gene fusions), DNA mismatch repair (dMMR), microsatellite instability (MSI), and tumor mutational burden (TMB)
- Consider clinical trial

Unresectable locoregional recurrent/ persistent disease

Soft tissue metastases (eg, lung, liver, muscle) excluding CNS metastases (see below)

- Consider systemic therapy
  - For progressive and/or symptomatic disease, consider lenvatinib (preferred)[ee] or sorafenib[ff,gg]
  - Larotrectinib or entrectinib for patients with *NTRK* gene fusion-positive advanced solid tumors
  - Selpercatinib or pralsetinib for patients with *RET*-fusion positive tumors
  - Pembrolizumab for patients with tumor mutational burden-high (TMB-H) (≥10 mutations/megabase [mut/Mb]) tumors
  - Other therapies are available and can be considered for progressive and/or symptomatic disease if clinical trials or other systemic therapies are not available or appropriate[hh,ii]
- Consider resection of distant metastases and/or EBRT (SBRT/ IMRT[m]/other local therapies[dd] when available to metastatic lesions if progressive and/or symptomatic (For locoregional disease, see PAP-8)
- Disease monitoring is often appropriate in asymptomatic patients with indolent disease assuming no brain metastasis.[gg] (See PAP-7)
- Best supportive care (See NCCN Guidelines for Palliative Care)

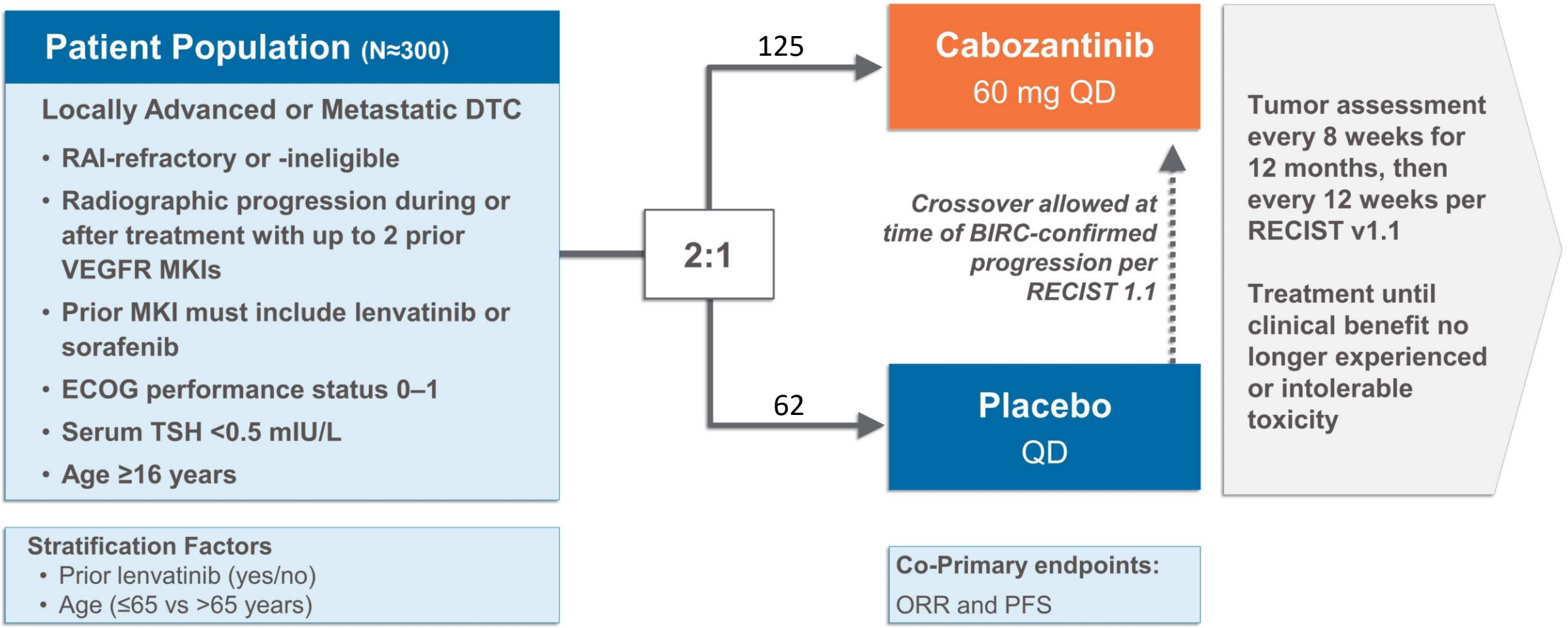
Bone metastases → See PAP-10

CNS metastases → See PAP-10

Lirov R, et al. Drugs 2017;77733-45
Durante C, et al. J Clin Endocrinol Metab 2006;91:2892-9

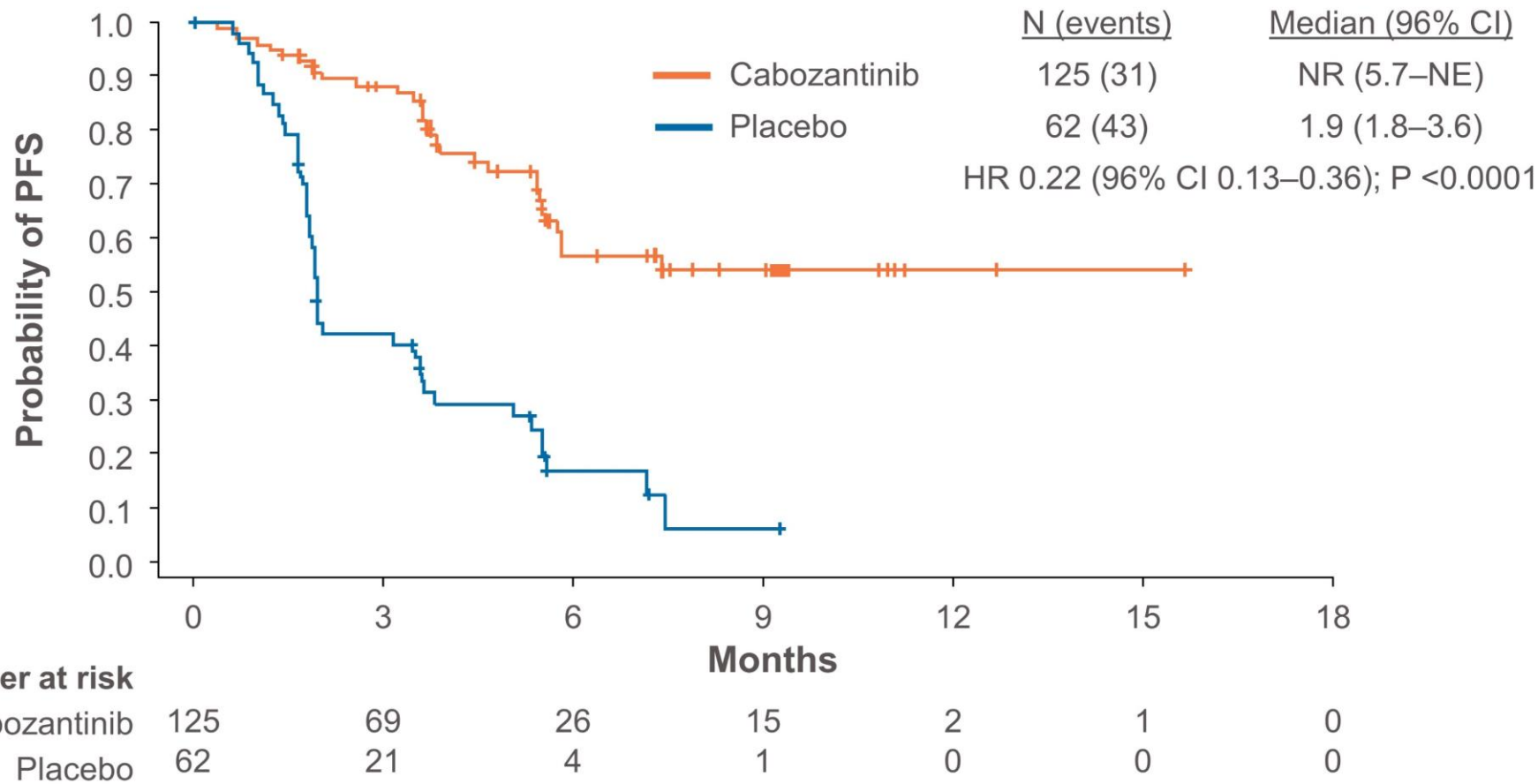
[i] See Principles of TSH Suppression (THYR-A).
[m] See Principles of Radiation and RAI Therapy (THYR-C).
[dd] Ethanol ablation, cryoablation, RFA, etc.
[ee] In a subset of patients (>65 years of age), lenvatinib showed an overall survival benefit compared to placebo. Brose MS, et al. J Clin Oncol 2017;35:2692-2699.
[ff] The decision of whether to use lenvatinib (preferred) or sorafenib should be individualized for each patient based on likelihood of response and comorbidities.
[gg] Kinase inhibitor therapy may not be appropriate for patients with stable or slowly progressive indolent disease. See Principles of Kinase Inhibitor Therapy (THYR-B).
[hh] Commercially available small-molecule kinase inhibitors (such as axitinib, everolimus, pazopanib, sunitinib, vandetanib, vemurafenib [*BRAF* positive], dabrafenib [*BRAF* positive], or cabozantinib [all are category 2A]) can be considered if clinical trials are not available or appropriate.
[ii] Cytotoxic chemotherapy has been shown to have minimal efficacy, although most studies were small and underpowered.

COSMIC-311 Study Design



BIRC, blinded independent radiology committee; ECOG, Eastern Cooperative Oncology Group; QD, once daily; RECIST, Response Evaluation Criteria in Solid Tumors; TKI, tyrosine kinase inhibitor; TSH, thyroid-stimulating hormone

Progression-Free Survival by BIRC (ITT Population)



Primary endpoint of PFS was met at planned interim analysis (critical p-value of 0.00036)

Median follow-up 6.2 months; HR, hazard ratio; NE, not estimable; NR, not reached; PFS per RECIST v1.1

Cosmic Conclusions

- Cabozantinib significantly improved PFS compared to placebo in previously-treated RAI refractory DTC
- ORR favored cabozantinib (15% vs 0)
- AE's c/w known safety profile cabozantinib

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use CABOMETYX safely and effectively. See full prescribing information for CABOMETYX.

CABOMETYX® (cabozantinib) tablets, for oral use
Initial U.S. Approval: 2012

RECENT MAJOR CHANGES

Indications and Usage, Renal Cell Carcinoma (1.1)	01/2021
Indications and Usage, Differentiated Thyroid Cancer (1.3)	09/2021
Dosage and Administration (2.2, 2.5)	01/2021
Dosage and Administration (2.4, 2.5)	09/2021
Warnings and Precautions, Hepatotoxicity (5.7)	01/2021
Warnings and Precautions, Adrenal Insufficiency (5.8)	01/2021
Warnings and Precautions, Thyroid Dysfunction (5.13)	09/2021
Warnings and Precautions, Hypocalcemia (5.14)	09/2021

INDICATIONS AND USAGE

CABOMETYX is a kinase inhibitor indicated for the treatment of

- patients with advanced renal cell carcinoma (RCC) (1.1)
- patients with advanced renal cell carcinoma, as a first-line treatment in combination with nivolumab (1.1)
- patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib (1.2)
- adult and pediatric patients 12 years of age and older with locally advanced or metastatic differentiated thyroid cancer (DTC) that has progressed following prior VEGFR-targeted therapy and who are radioactive iodine-refractory or ineligible (1.3)

Clinical Trials – Phase III, RAI-resistant TCA w/o molecular Targets

- Donafenib (RAF inhibitor, Multi-TKI)
- Vandetinib (VEGF inhibitor Multi-TKI)

THANK YOU

QUESTIONS?