# HNSCC Real world Practice Sharing & discussion

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1530-1600

MSD

台灣癌症安寧緩和醫學會
Taiwan Society of Cancer Palliative Medicine

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# Outline

Case 1

Case 2

Case 3

# Outline

Case 1

Case 2

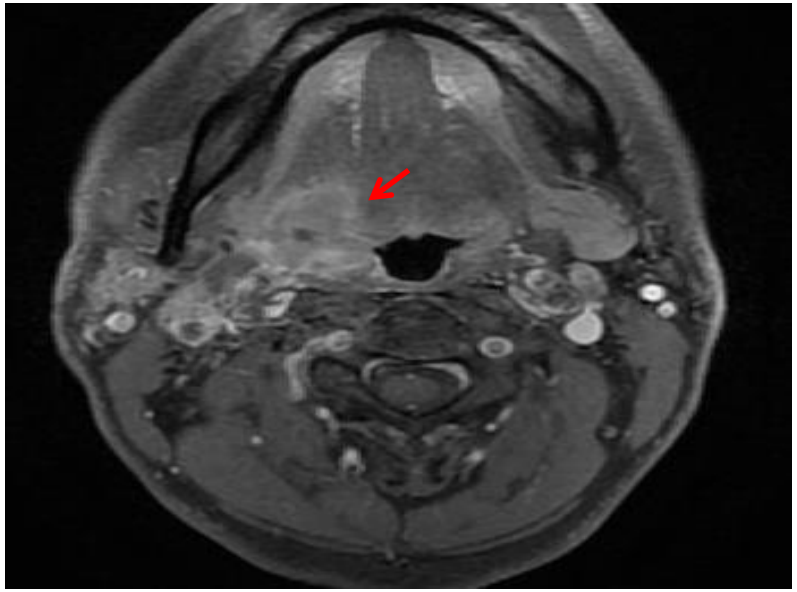
Case 3

# Case 1, M/49

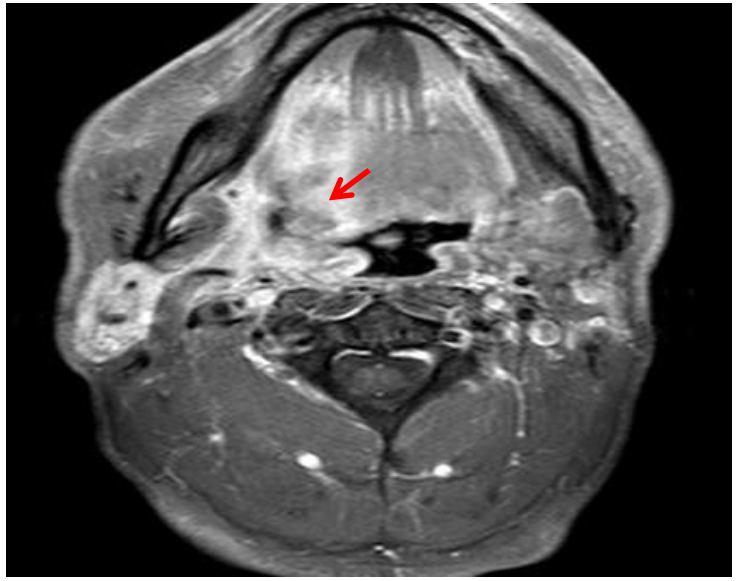
- history of 1.type II diabetes 2.hypertension 3. hyperlipidemia 4.CKD stage IV
- Squamous cell carcinoma of right tonsil, cT3N2bM0, stage III, s/p CCRT (cisplatin x3, shift to carboplatin x5, due to CKD) since February to April, 2018 (20180212-20180327), poor response with residual

- **2018/05/23** Wide excision of right tonsil and tongue + supraomohyoid neck dissection, right+ segmental mandibulectomy + PM flap, right and Tracheostomy,
- pT4aN3bM0, stage IVb and prepare adjuvant chemotherapy with **PF regimen** or **UFUR maintain** or **cetuximab treatment**

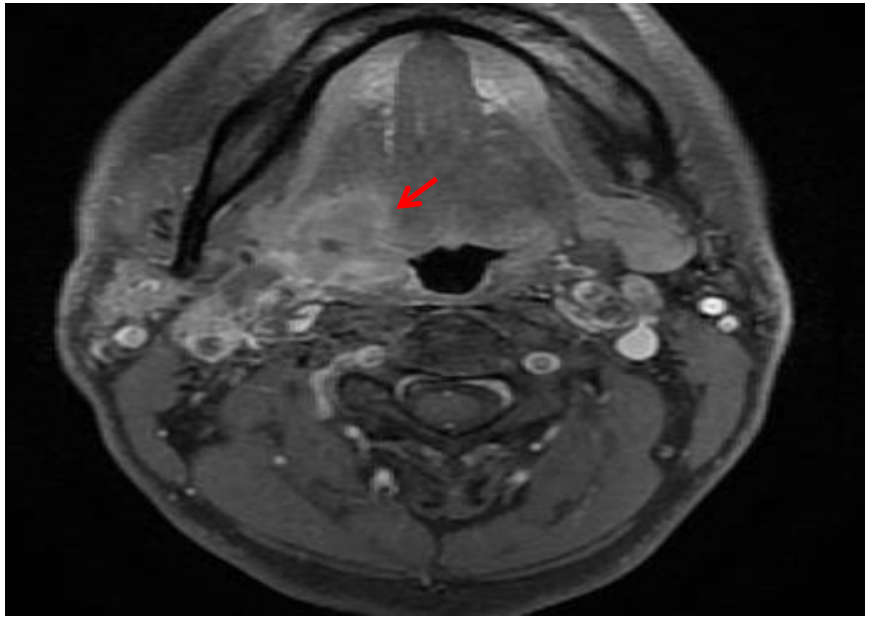
2018.1.31 initial diagnosis



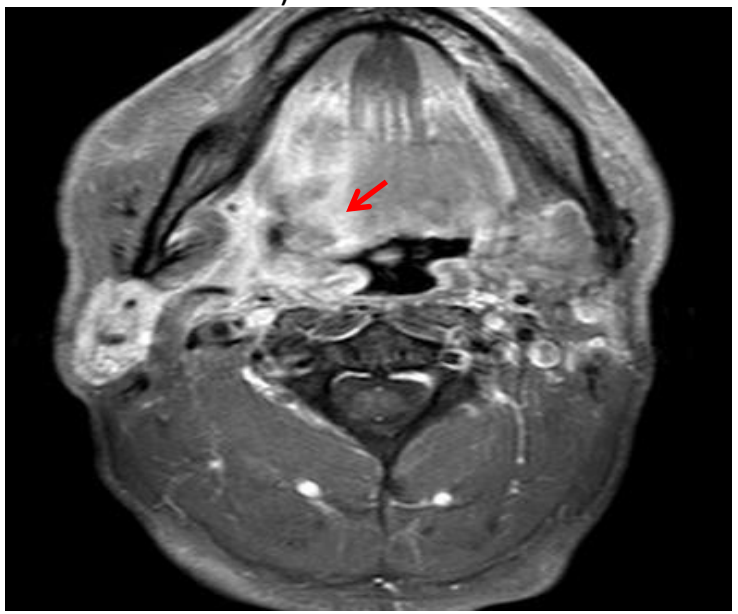
2018.5.16 1.5 month post CCRT (poor response with residual tumor)



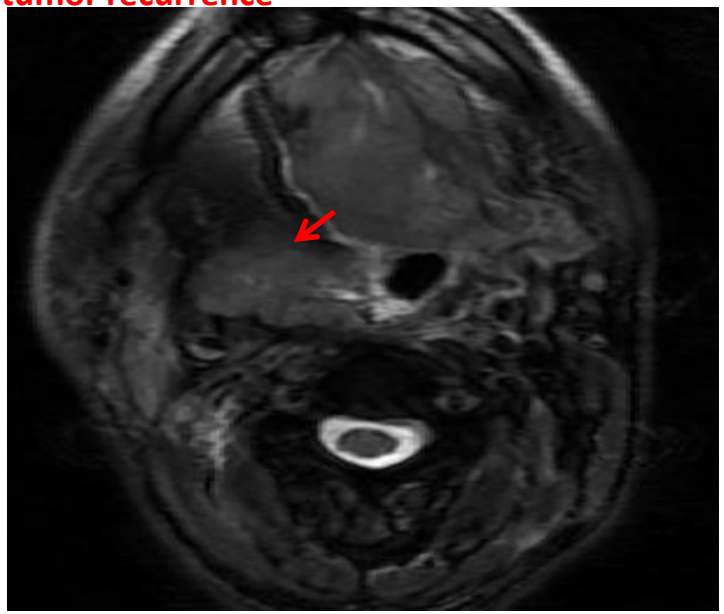
2018.1.31 initial diagnosis

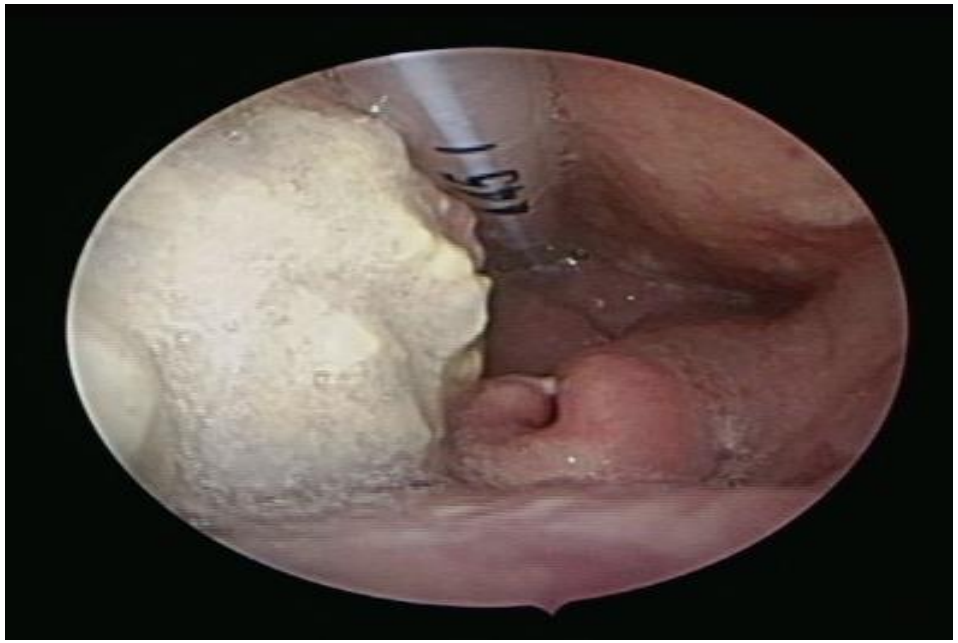


2018.5.16 1.5 month post CCRT (poor response with residual tumor)



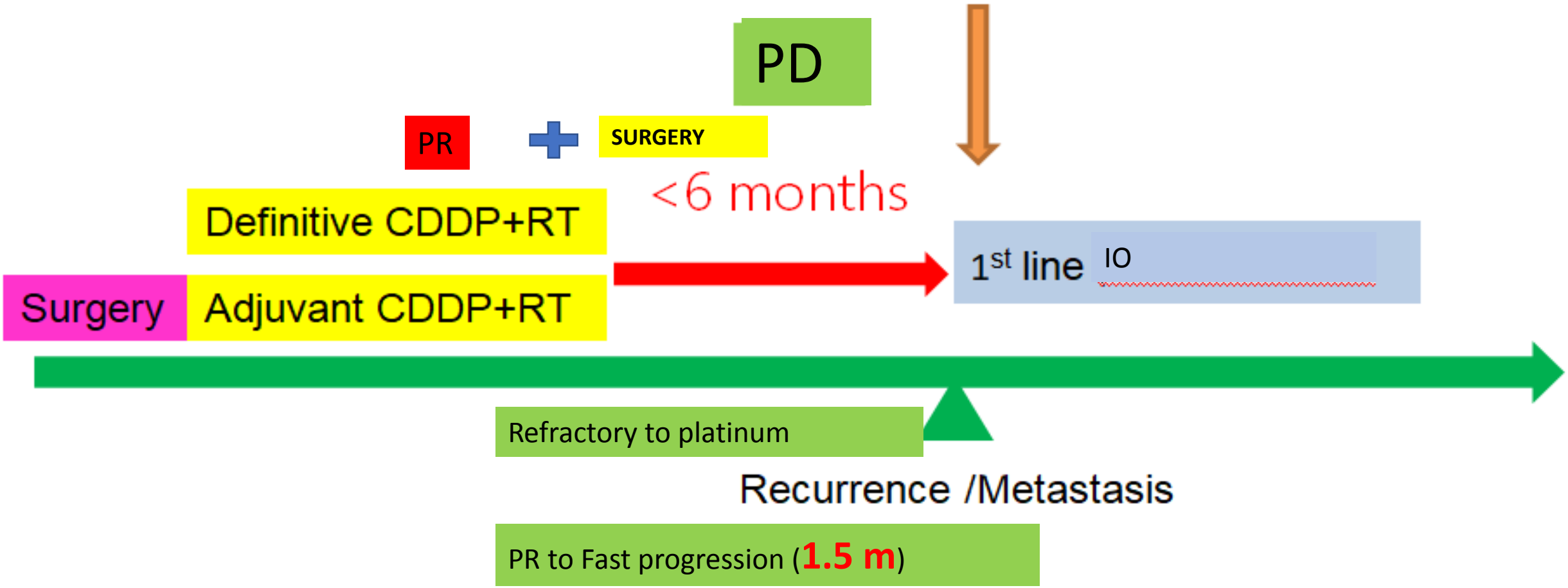
2018.7.08 post surgery **1.5 months** with **rapid tumor recurrence**





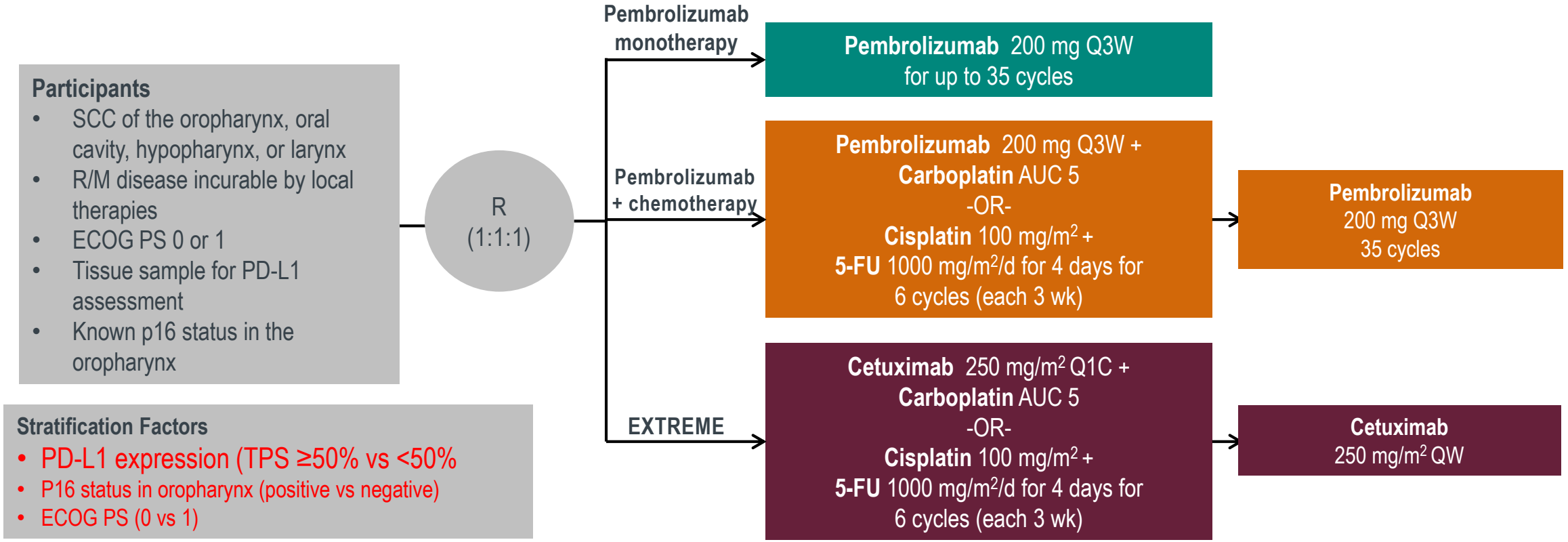
**early disease progression**
(nonsurgical treatment), ECOG:1-2

# 1st line for R/M SCCHN



# Keynote 048 trial design

- Randomized, open-label, **phase 3** study done at 200 medical centers in 37 countries

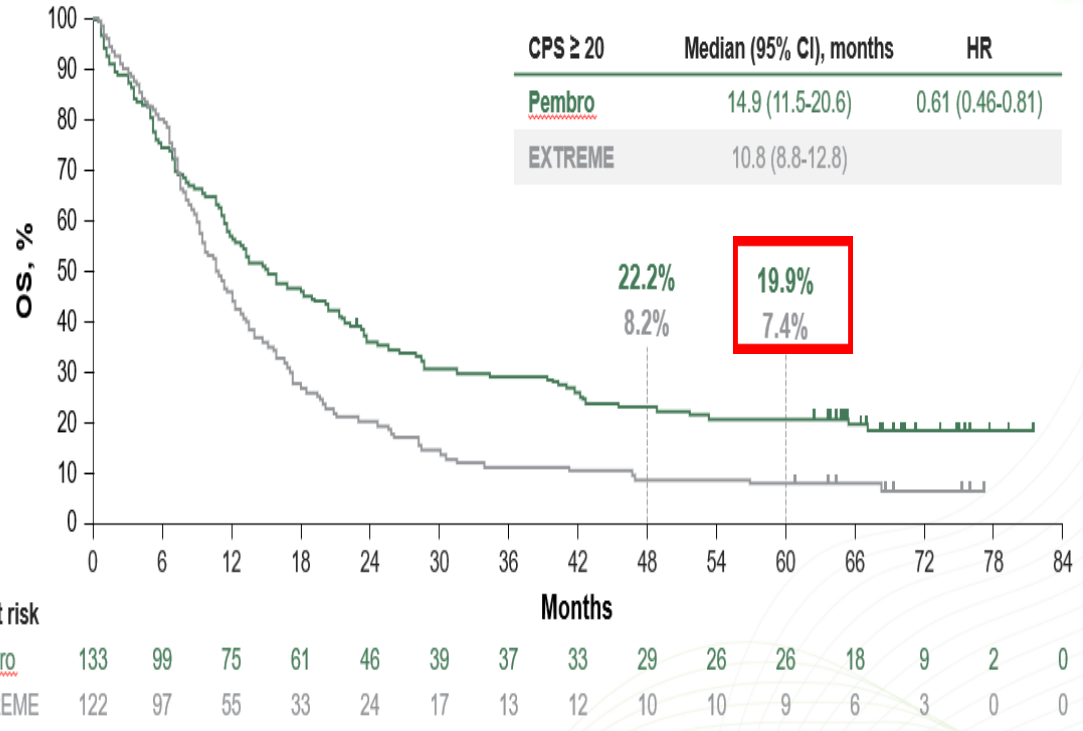



**Primary Endpoints:** **OS, PFS** per RECIST v1.1 (in CPS ≥20, CPS≥1, and total populations)
**Secondary Efficacy Endpoints:** PFS per RECIST v1.1 at 6 and 12 months, ORR (in CPS ≥20, CPS≥1, and total populations)

1. Burtness B et al. Lancet. 2019 Nov 23;394(10212):1915-1928.

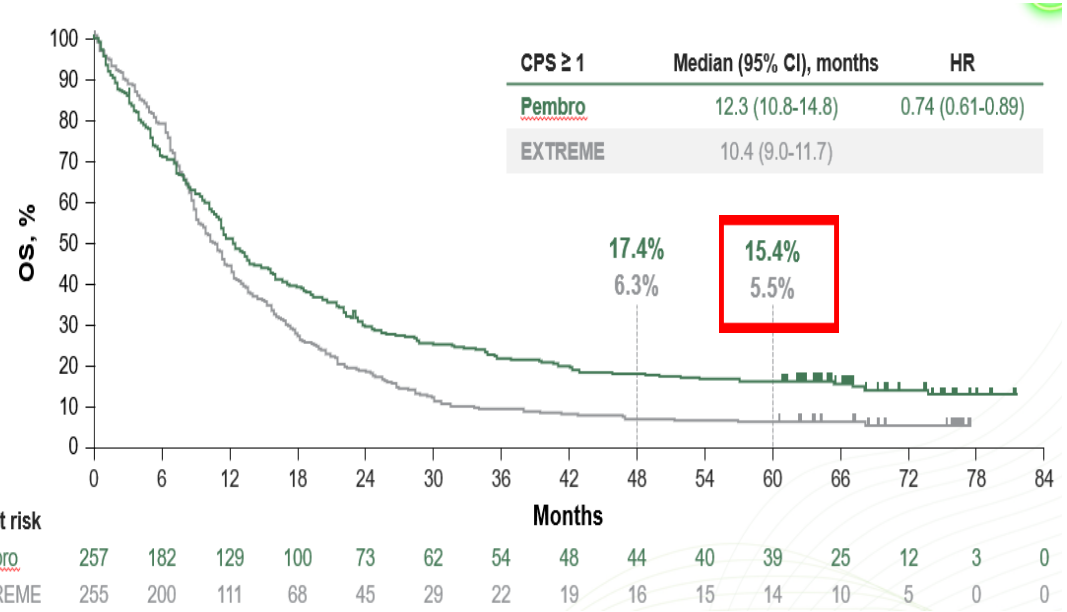
Pembrolizumab mono OS

# 5-Year OS



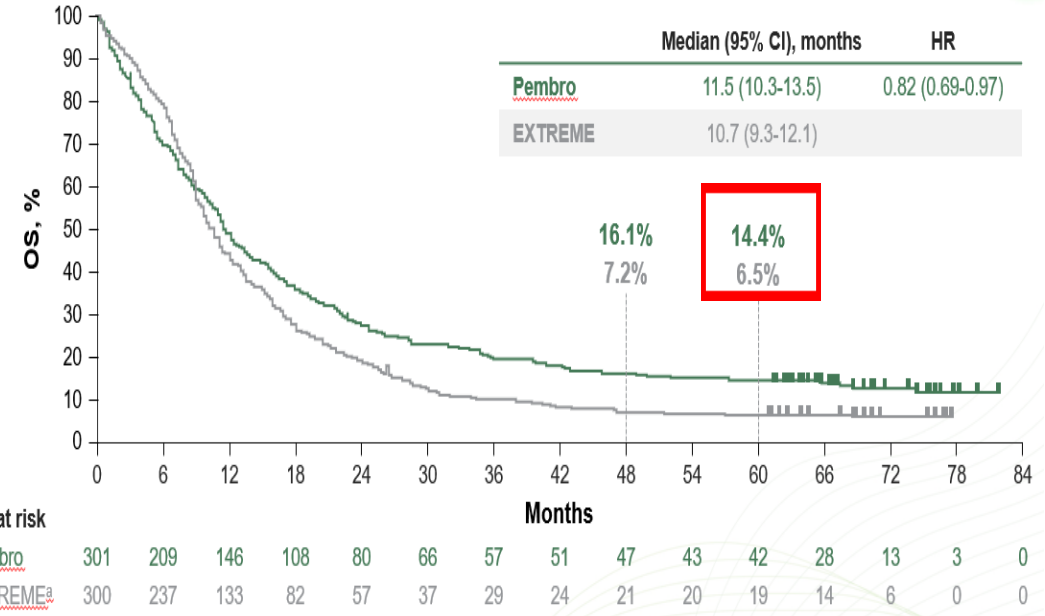

| CPS ≥ 20 | Median (95% CI), months | HR |
|---|---|---|
| Pembro | 14.9 (11.5-20.6) | 0.61 (0.46-0.81) |
| EXTREME | 10.8 (8.8-12.8) | |

| No. at risk | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Pembro | 133 | 99 | 75 | 61 | 46 | 39 | 37 | 33 | 29 | 26 | 26 | 18 | 9 | 2 | 0 |
| EXTREME | 122 | 97 | 55 | 33 | 24 | 17 | 13 | 12 | 10 | 10 | 9 | 6 | 3 | 0 | 0 |




| CPS ≥ 1 | Median (95% CI), months | HR |
|---|---|---|
| Pembro | 12.3 (10.8-14.8) | 0.74 (0.61-0.89) |
| EXTREME | 10.4 (9.0-11.7) | |

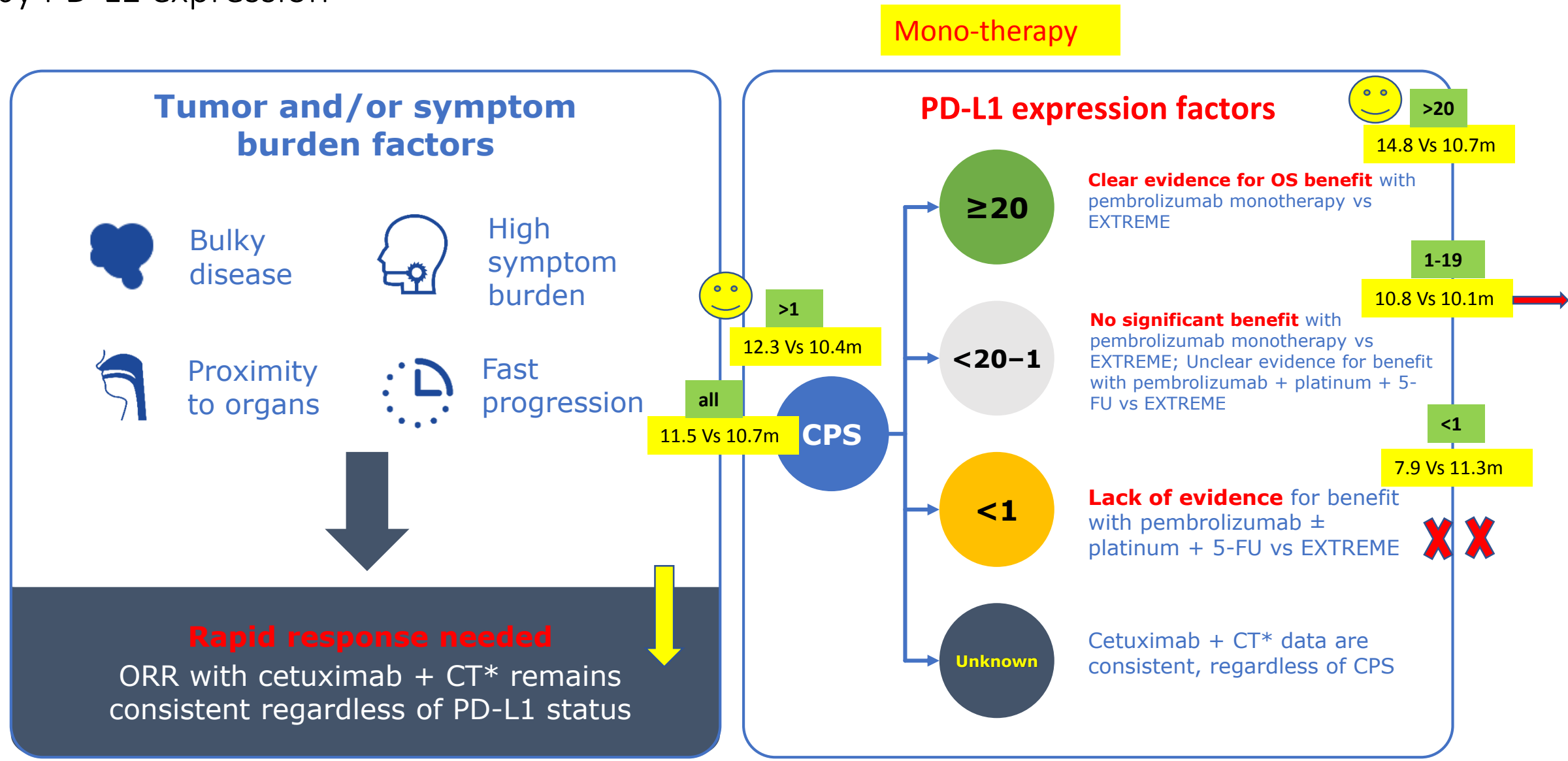
| No. at risk | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Pembro | 257 | 182 | 129 | 100 | 73 | 62 | 54 | 48 | 44 | 40 | 39 | 25 | 12 | 3 | 0 |
| EXTREME | 255 | 200 | 111 | 68 | 45 | 29 | 22 | 19 | 16 | 15 | 14 | 10 | 5 | 0 | 0 |




| | Median (95% CI), months | HR |
|---|---|---|
| Pembro | 11.5 (10.3-13.5) | 0.82 (0.69-0.97) |
| EXTREME | 10.7 (9.3-12.1) | |

| No. at risk | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Pembro | 301 | 209 | 146 | 108 | 80 | 66 | 57 | 51 | 47 | 43 | 42 | 28 | 13 | 3 | 0 |
| EXTREME[a] | 300 | 237 | 133 | 82 | 57 | 37 | 29 | 24 | 21 | 20 | 19 | 14 | 6 | 0 | 0 |

# Treatment choices for 1L R/M SCCHN should be guided by need for rapid response, and by PD-L1 expression[19,21]

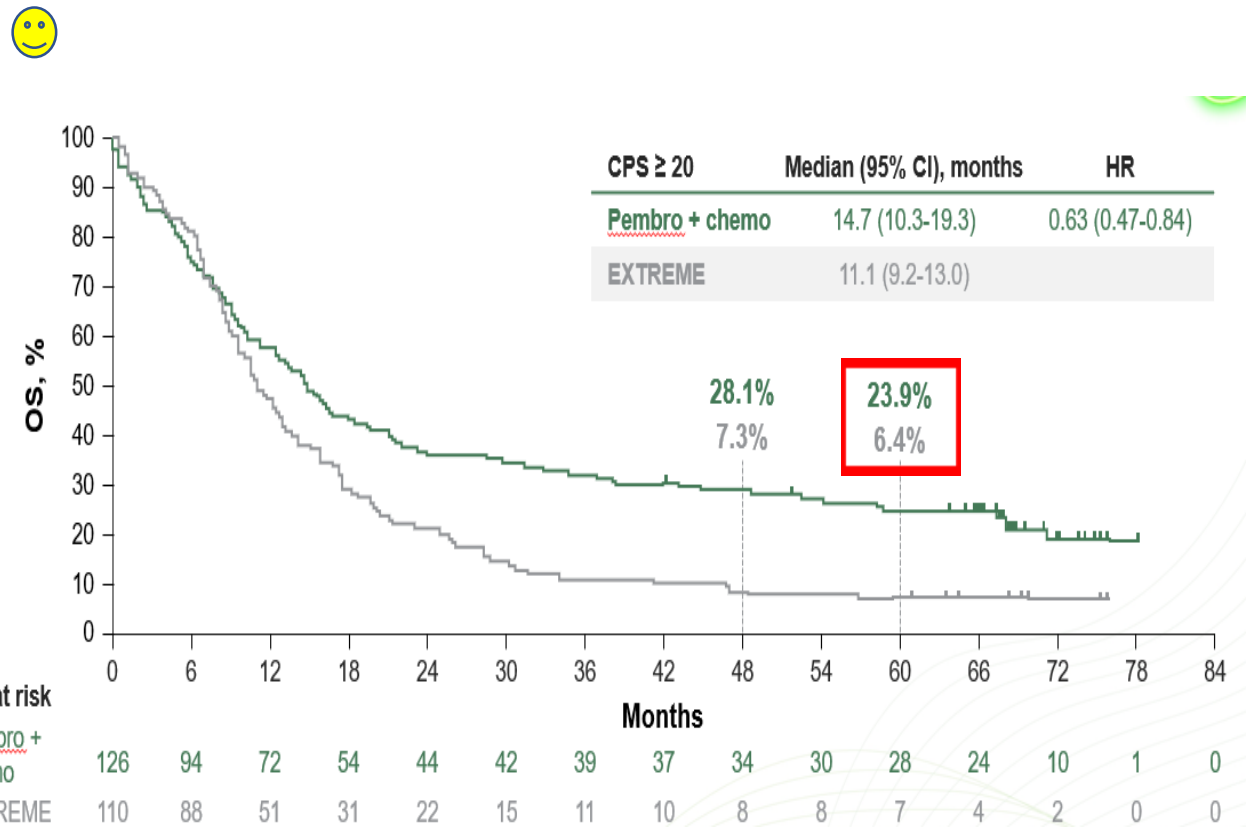


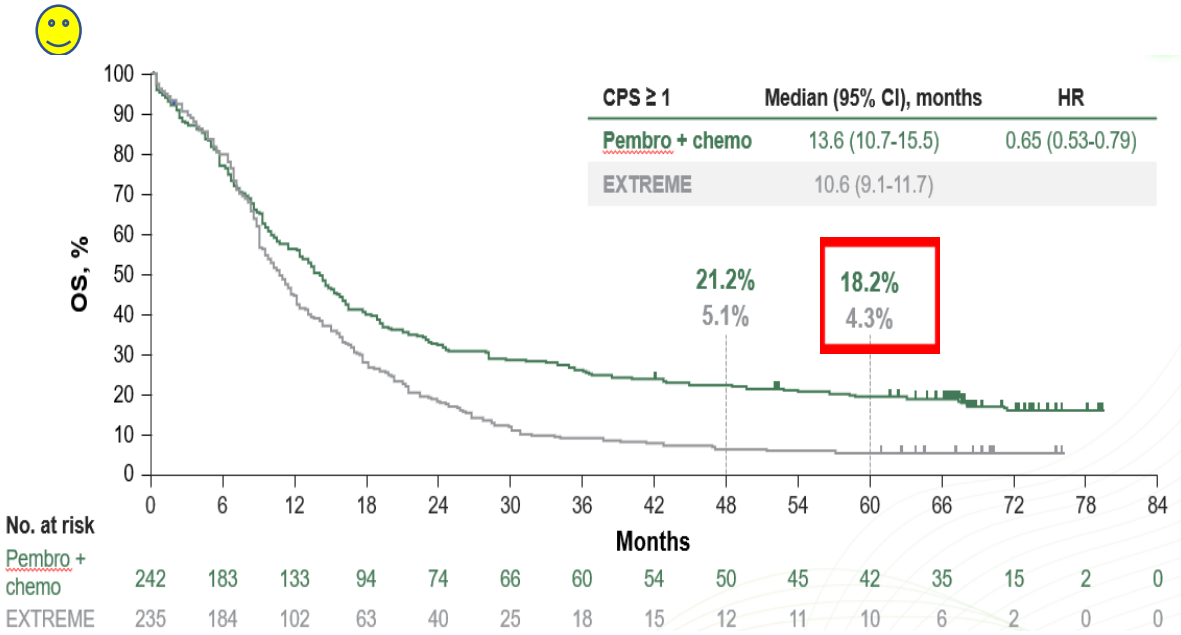

- *Platinum-based CT; Symptom burden icon by lastspark, RU from the Noun Project; Fast icon by Alexander Wiefel from the Noun Project.

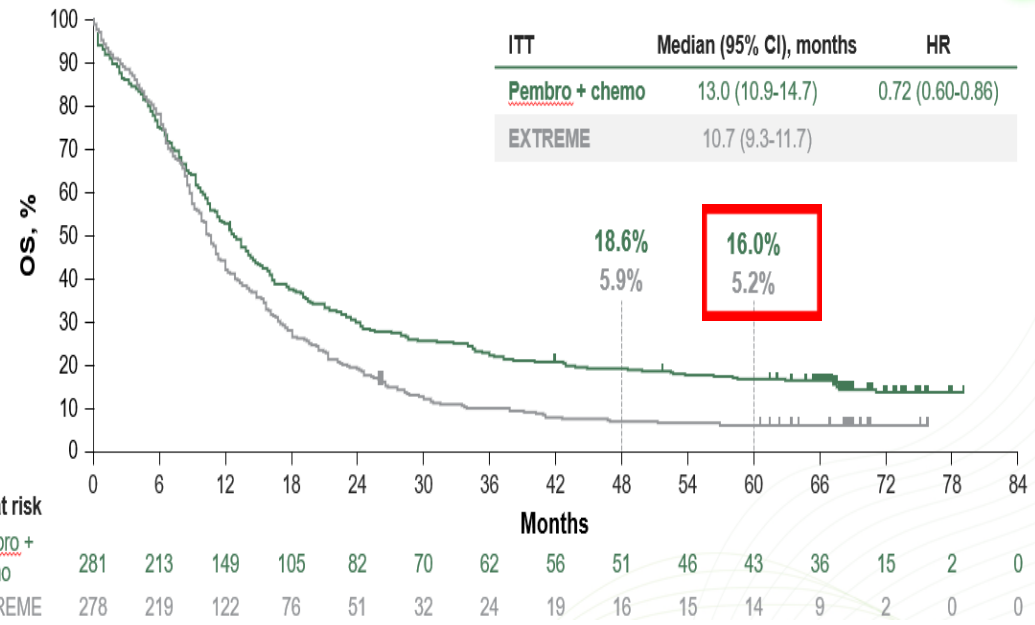

- 19. Burtness B, et al. **ESMO 2018** (Abstract No. LBA8_PR – presentation); 21. Rischin D, et al. **ASCO 2019** (Abstract No. 6000 – presentation).

Pembrolizumab combo OS

# 5-Year OS



# Treatment choices for 1L combination R/M SCCHN

Combo-therapy

## Tumor and/or symptom burden factors

- Bulky disease
- High symptom burden
- Proximity to organs
- Fast progression

**Rapid response needed**

ORR with cetuximab + CT* remains consistent regardless of PD-L1 status

## PD-L1 expression factors

CPS

- **≥20** — **Clear evidence for OS benefit** with pembrolizumab monotherapy vs EXTREME
  - >20: 14.7 Vs 11.0m
- **<20–1** — **No significant benefit** with pembrolizumab monotherapy vs EXTREME; Unclear evidence for benefit with pembrolizumab + platinum + 5-FU vs EXTREME
  - 1-19: 12.7 Vs 9.9m
  - >1: 13.6 Vs 10.4m
- **<1** — **Lack of evidence** for benefit with pembrolizumab ± platinum + 5-FU vs EXTREME
  - <1: 11.7 Vs 10.7m
- **Unknown** — Cetuximab + CT* data are consistent, regardless of CPS

all: 13.0 Vs 10.7m

ORR:30-35-40%

- *Platinum-based CT; Symptom burden icon by lastspark, RU from the Noun Project; Fast icon by Alexander Wiefel from the Noun Project.


- 19. Burtness B, et al. ESMO 2018 (Abstract No. LBA8_PR – presentation); 21. Rischin D, et al. ASCO 2019 (Abstract No. 6000 – presentation).

# KEYNOTE-048 5yr Data Summary – Deep dive into detail

| Endpoint | Pembrolizumab vs EXTREME | | | | | | Pembrolizumab + Chemo vs EXTREME | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | ITT | | CP S≥ 1 | | CPS≥20 | | ITT | | CPS ≥ 1 | | CPS ≥ 20 | |
| Event, n | Pembro | EXTREME | Pembro | EXTREME | Pembro | EXTREME | Pembro +Chemo | EXTREME | Pembro +Chemo | EXTREME | Pembro +Chemo | EXTREME |
| | 301 | 300 | 257 | 255 | 133 | 122 | 281 | 278 | 242 | 235 | 126 | 110 |
| **mOS at 5 years (%)** | 14.4% | 6.5% | 15.4% | 5.5% | 19.9% | 7.4% | 16.0% | 5.2% | 18.2% | 4.3% | 23.9% | 6.4% |
| **mOS (months)** (95% CI) | 11.5 (10.3-13.5) | 10.7 (9.3-12.1) | 12.3 (10.8-14.8) | 10.4 (9.0-11.7) | 14.9 (11.5-20.6) | 10.8 (8.8-12.8) | 13.0 (10.9-14.7) | 10.7 (9.3-11.7) | 13.6 (10.7-15.5) | 10.6 (9.1-11.7) | 14.7 (10.3-19.3) | 11.1 (9.2-13.0) |
| HR | 0.82 (0.69-0.97) | | 0.74 (0.61-0.89) | | 0.61 (0.46-0.81) | | 0.72 (0.60-0.86) | | 0.65 (0.53-0.79) | | 0.63 (0.47-0.84) | |
| **mPFS (months)** (95% CI) | 2.3 (2.2-3.3) | 5.3 (4.9-6.2) | 3.2 (2.2-3.4) | 5.0 (4.8-6.1) | 3.4 (3.2-4.1) | 5.3 (4.9-6.3) | 4.9 (4.7-6.0) | 5.3 (4.9-6.2) | 5.1 (4.7-6.2) | 5.0 (4.8-6.1) | 5.8 (4.7-7.6) | 5.3 (4.9-6.4) |
| HR | 1.29 (1.09-1.52) | | 1.14 (0.95-1.37) | | 0.97 (0.74-1.26) | | 0.95 (0.80-1.13) | | 0.87 (0.72-1.05) | | 0.78 (0.59-1.04) | |
| **ORR (%)** (95% CI) | 16.9 (12.9-21.7) | 36.0 (30.6-41.7) | 19.1 (14.5-24.4) | 34.9 (29.1-41.1) | 23.3 (16.4-31.4) | 36.1 (27.6-45.3) | 37.0 (31.4-42.9) | 36.3 (30.7-42.3) | 38.0 (31.9-44.5) | 35.7 (29.6-42.2) | 45.2 (36.4-54.3) | 38.2 (29.1-47.9) |
| **DoR (months)** (range) | 22.6 (1.5+ to 75.5+) | 4.5 (1.2+ to 73.9+) | 23.4 (1.5 to 75.5+) | 4.5 (1.2+ to 73.9+) | 23.4 (2.7 to 75.5+) | 4.3 (1.2+ to 38.2+) | 6.7 (1.6+ to 73.8+) | 4.3 (1.2+ to 66.5+) | 6.7 (1.6+ to 73.8+) | 4.3 (1.2+ to 66.5+) | 7.1 (2.1+ to 73.8+) | 4.2 (1.2+ to 38.2+) |
| **TRAE Grade 1-2 (%)** | 41.3 | 27.5 | | | | | 23.9 | 27.5 | | | | |
| **TRAE Grade 3-5 (%)** | 17.0 | 69.3 | | | | | 71.7 | 69.3 | | | | |

The study concluded that 1L pembro and pembro + chemo continues to suggest clinical benefit with a manageable safety profile in R/M HNSCC and further supports treatment with pembrolizumab and pembrolizumab + chemotherapy as first-line SOC in R/M HNSCC.

Limitation: This post hoc analysis was exploratory in nature and occurred after the protocol-specific final analysis. No formal statistical testing was planned for this analysis and, therefore, no conclusions can be drawn.

ITT, intention-to-treat; CPS, combined positive score; OS, overall survival; PFS, progression-free survival; ORR, objective response rate; DoR, duration of response; TRAE, treatment-related adverse event; R/M HNSCC, recurrent or metastatic head and neck squamous cell carcinoma; pembro, pembrolizumab; SOC, standard-of-care

1. Makoto Tahara et al. Presented at: European Society of Medical Oncology Virtual Congress Science Program; 2022.

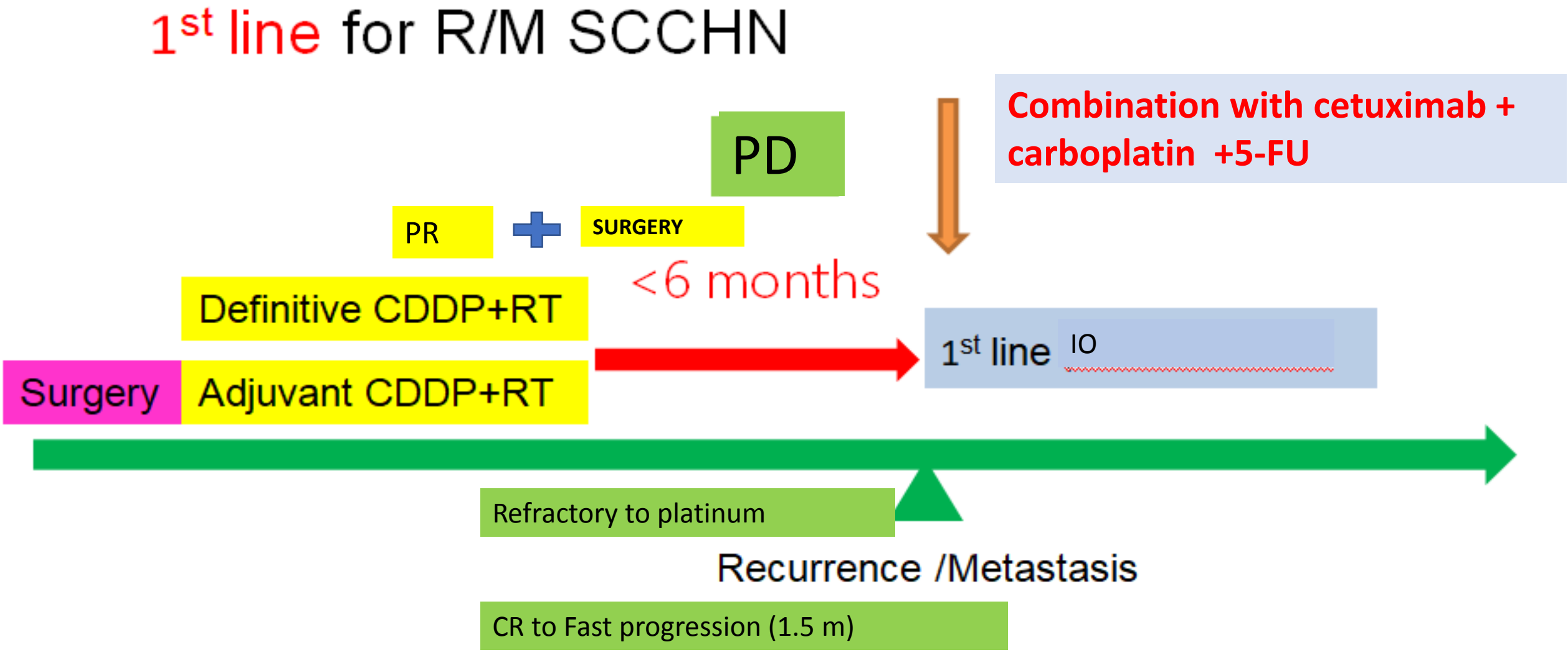
KEYTRUDA (pembrolizumab)

- Pembrolizumab,d1 (self-paid) + Cetuximab + carboplatin + 5-FU, d1,d8,d15, tri-weekly since July 11, 2018 (20180711, 20180801, 20181011, 20181106, 20181113, 20181120, 20181127, 20181204, 20181211, 20190226, 20190319, 20190410, 20190502).

- Grade 1-2 CINV and anorexia after previous treatment.

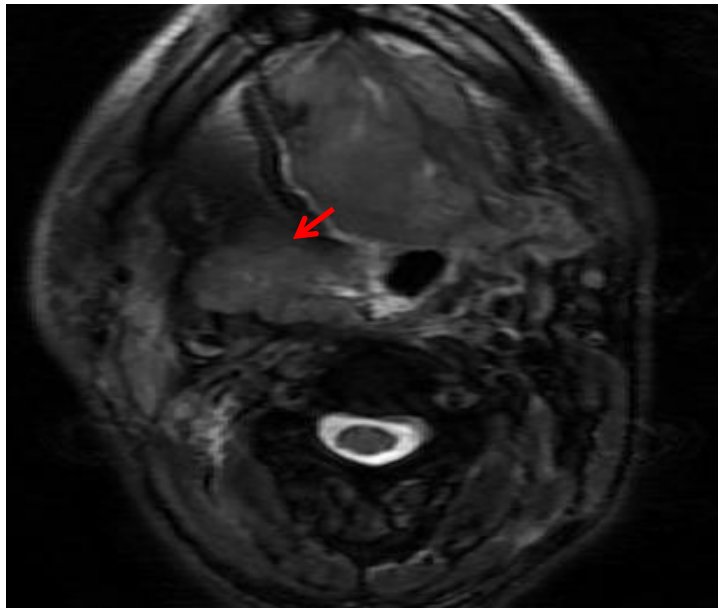
CPS>1

# 1st line for R/M SCCHN

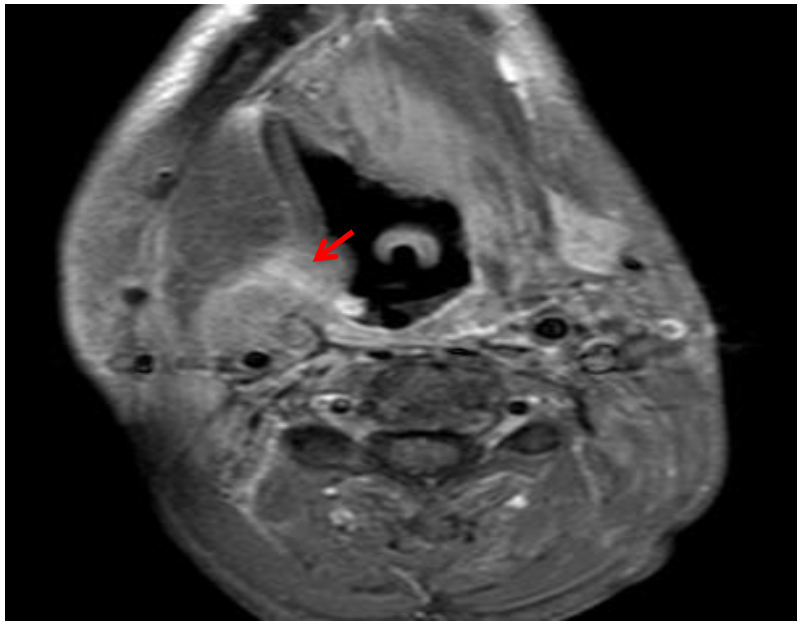


Pembrolizumab,d1 (self-paid) + Cetuximab + carboplatin + 5-FU, d1,d8,d15, tri-weekly (20180711-20190502) for 10 months.

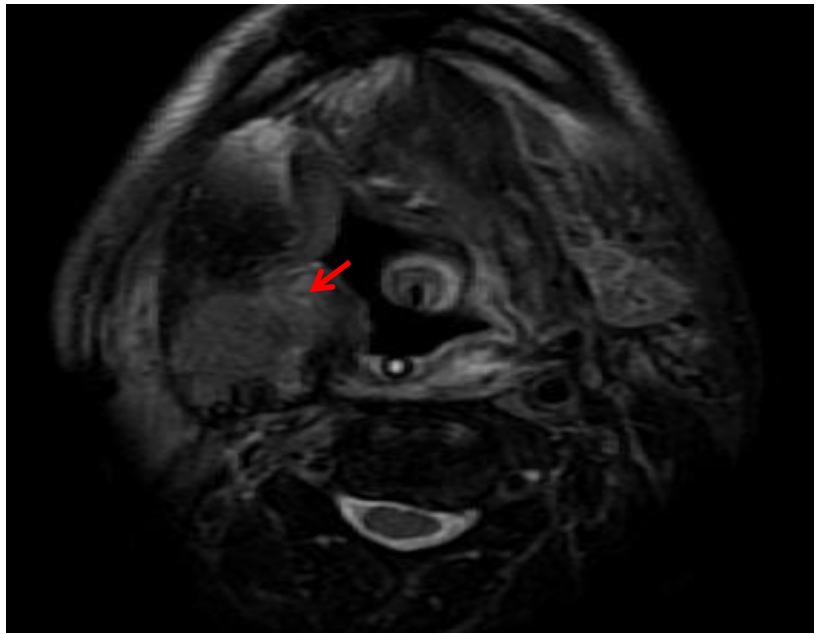
2018..07.08 post surgery with rapid tumor recurrence



2019.1.18 **SD** (I/O for 6 months)



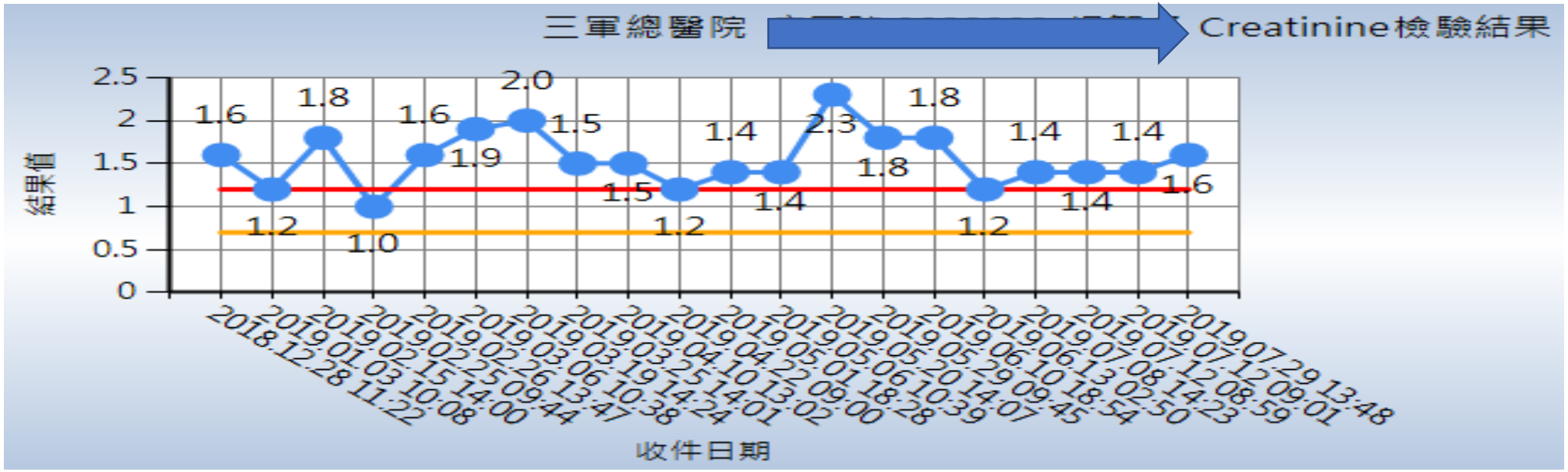
2019.5.21 **PD** (I/O for 10 months)



Neck MRI: Recurrent tumor in the oral cavity with metastatic nodes in the right neck.

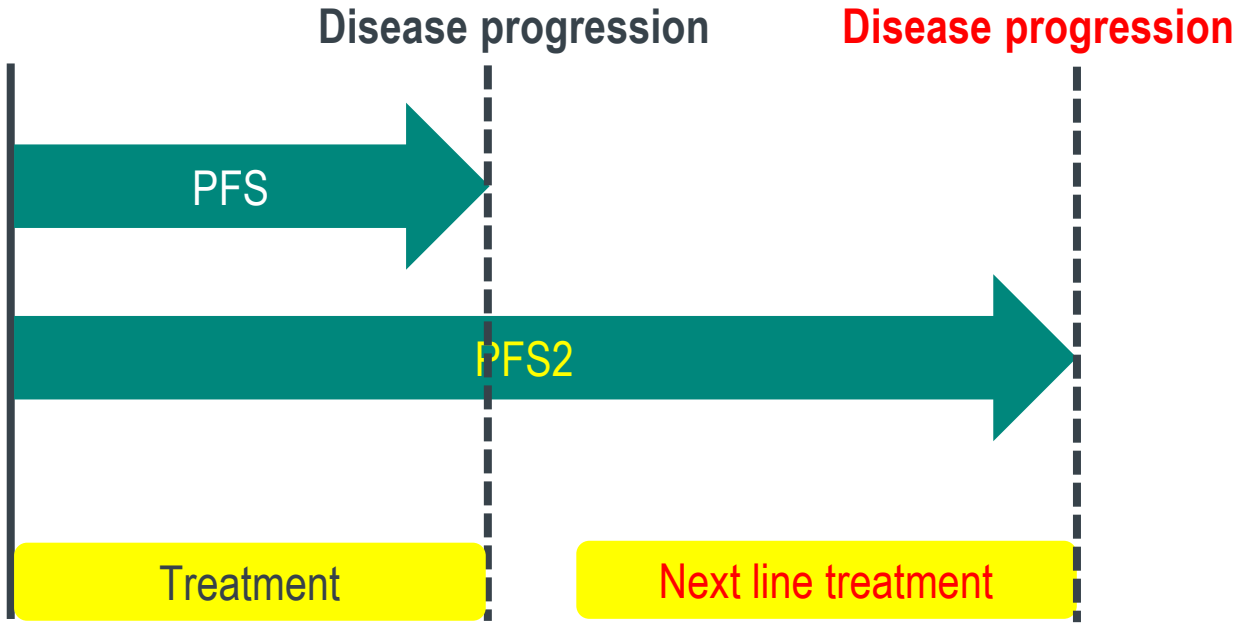
- NP biopsy 2019/06/03: Squamous cell carcinoma, moderately to poorly differentiated.
- Then,  intermittent dyspnea in recent 2+ weeks.

- **Pembrolizumab**, tri-weekly (self-paid) + **Afatinib** 40 mg 1 # po qod (self-paid)  since June to July (201906-202003)
- Transfer to other hospital.
- At least **PFS2**:20 months (201807-202003)



# What is PFS2, how is it used, and what is the significance of this endpoint?

- PFS2 was defined in KEYNOTE-048 as the time from **randomization** to subsequent disease progression after initiation of an anti-cancer therapy subsequent to discontinuation of study-specified treatments, or death from any cause, whichever occurs first. If progression after next-line therapy cannot be measured, a PFS event is defined as end or discontinuation of next-line treatment or death from any cause, whichever occurs first.
- It is used to assess impact of crossover on overall survival assessment and can also be used to assess whether therapy in one line positively or negatively affects efficacy of the next line of therapy.




2020 ASCO

# 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) |

[a]A patient is counted only once for each therapy group, but a patient could be counted in more than one therapy group.
Data cutoff: February 25, 2019 (final analysis).

# Pembrolizumab With or Without Chemotherapy in Recurrent or Metastatic Head and Neck Squamous Cell Carcinoma: Updated Results of the Phase III KEYNOTE-048 Study[1]

| | Pembrolizumab vs Cetuximab-Chemotherapy No. (%) | | Pembrolizumab-Chemotherapy vs Cetuximab-Chemotherapy (n=278) | |
|---|---|---|---|---|
| Subsequent Anticancer Therapy | Pembrolizumab (n=301) | Cetuximab-Chemotherapy (n=300) | Pembrolizumab-Chemotherapy (n=281) | Cetuximab-Chemotherapy (n=278) |
| Any[a] | 150 (49.8) | 161 (53.7) | 199 (42.3) | 147 (52.9) |
| Chemotherapy | 138 (45.8) | 121 (40.3) | 100 (35.6) | 110 (39.6) |
| Taxane | 83 (27.6) | 94 (31.3) | 72 (25.6) | 86 (30.9) |
| Nontaxane | 134 (44.5) | 71 (23.7) | 65 (23.1) | 65 (23.4) |
| Antimetabolite | 100 (33.2) | 39 (13.0) | 45 (16.0) | 34 (12.2) |
| Platinum-based | 122 (40.5) | 47 (15.7) | 45 (16.0) | 43 (15.5) |
| EGFR inhibitor | 74 (24.6) | 20 (6.7) | 52 (18.5) | 18 (6.5) |
| Chemotherapy plus EGFR inhibitor | 67 (22.3) | 13 (4.3) | 44 (15.7) | 11 (4.0) |
| Kinase inhibitor | 5 (1.7) | 3 (1.0) | 7 (2.5) | 3 (1.1) |
| ICI | 19 (6.3) | 76 (25.3) | 23 (8.2) | 70 (25.2) |
| Anti-PD-1/PD-L1 | 19 (6.3) | 75 (25.0) | 21 (7.5) | 69 (24.8) |
| Anti-B7-H3 | 1 (0.3) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Anti-CTLA-4 | 1 (0.3) | 6 (2.0) | 1 (0.4) | 5 (1.8) |
| Anti-TIGIT | 0 (0.0) | 0 (0.0) | 1 (0.4) | 0 (0.0) |
| Other immunotherapy | 3 (1.0) | 6 (2.0) | 1 (0.4) | 5 (1.8) |
| Other therapy | 2 (0.7) | 7 (2.3) | 4 (1.4) | 5 (1.8) |

[a] Patients could have received more than one subsequent anticancer therapy overall or of a specific category.

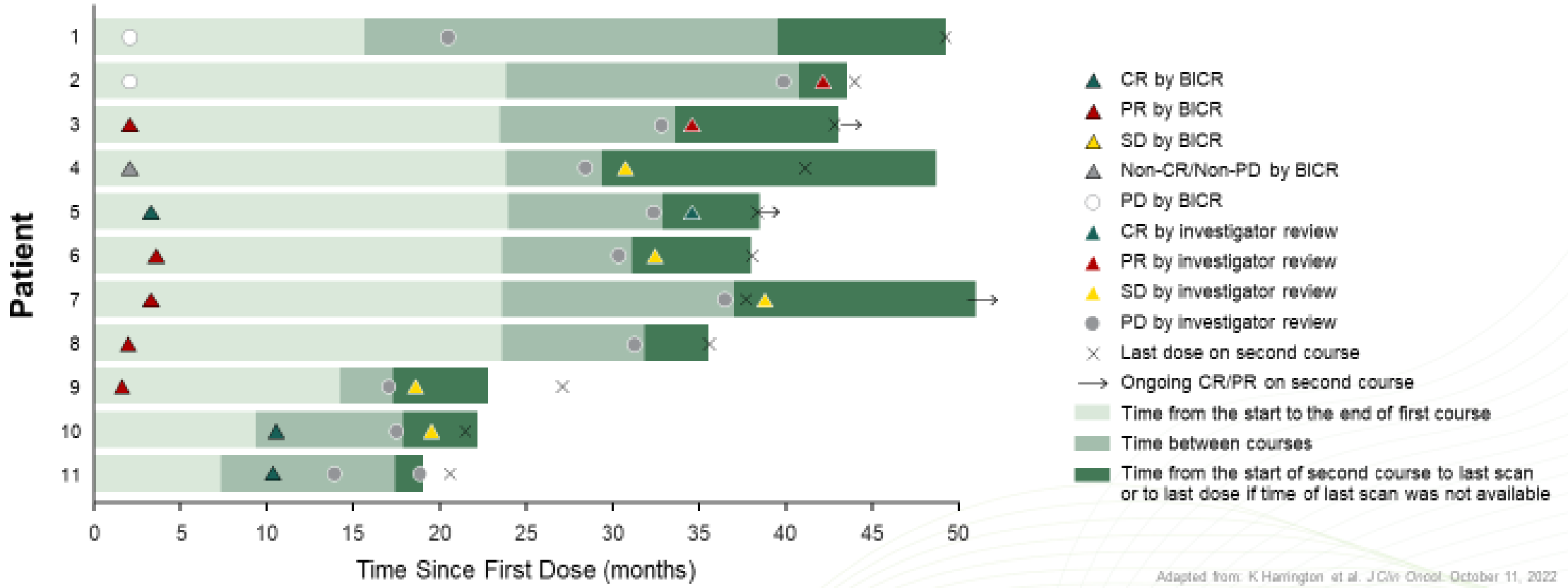
ICI, immune checkpoint inhibitors; EGFR, epidermal growth factor receptor; PD-1, programmed cell death-1 ligand 1; PD-L1, programmed death ligand-1; B7-H3, B7 homolog 3; CTLA-4, Cytotoxic T-lymphocyte Antigen-4; TIGIT, T-cell immunoglobulin and ITIM domain

1. K Harrington et al. *J Clin Oncol*. October 11, 2022

KEYTRUDA® (pembrolizumab)

# Pembrolizumab With or Without Chemotherapy in Recurrent or Metastatic Head and Neck Squamous Cell Carcinoma: Updated Results of the Phase III KEYNOTE-048 Study[1]

## Pembrolizumab second-course response characteristics

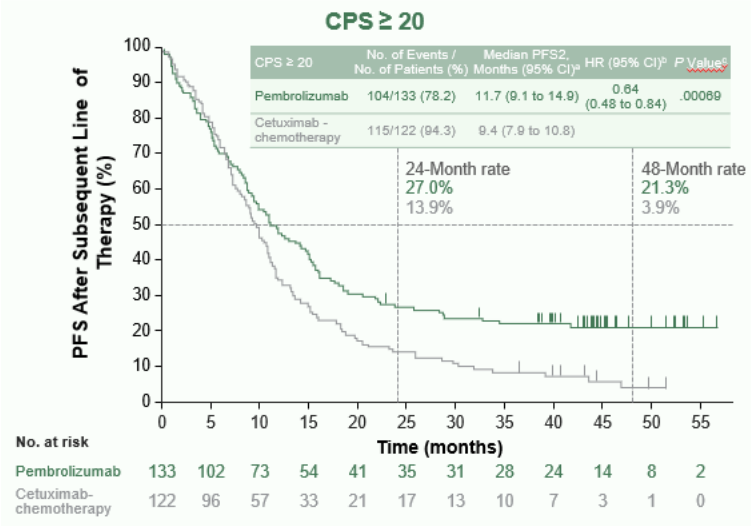


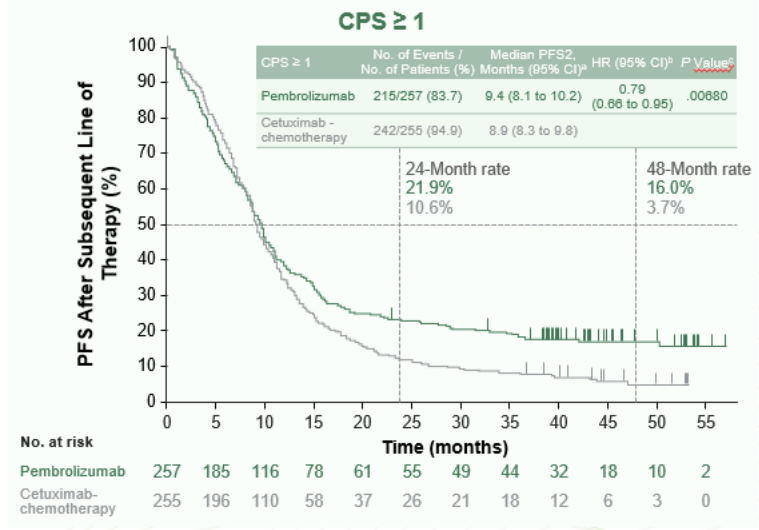

Adapted from: K Harrington et al. J Clin Oncol. October 11, 2022

Data cutoff date: February 18, 2020
CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; BICR: Blinded Independent Central Review
1. K Harrington et al. J Clin Oncol. October 11, 2022

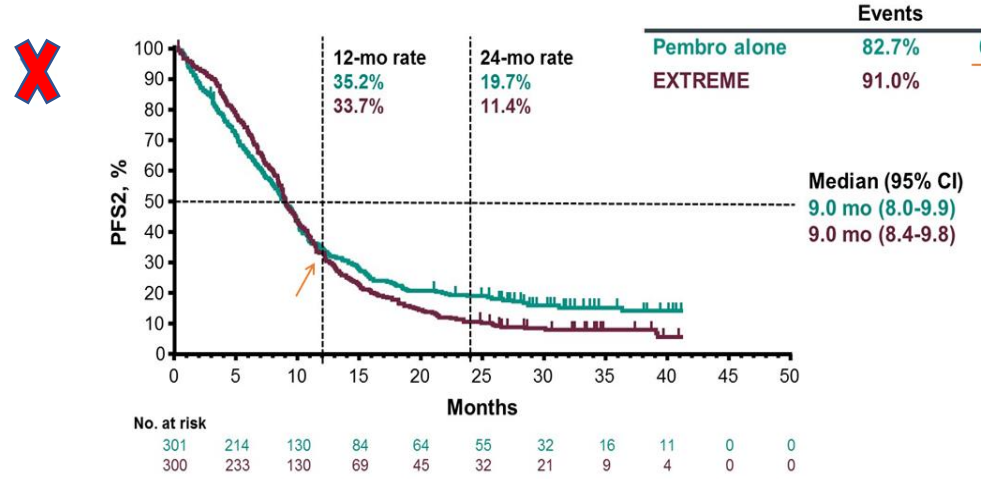
KEYTRUDA® (pembrolizumab)

# Pembrolizumab mono PFS2




## PFS2: Initially Randomized, Pembro vs EXTREME, Total Population

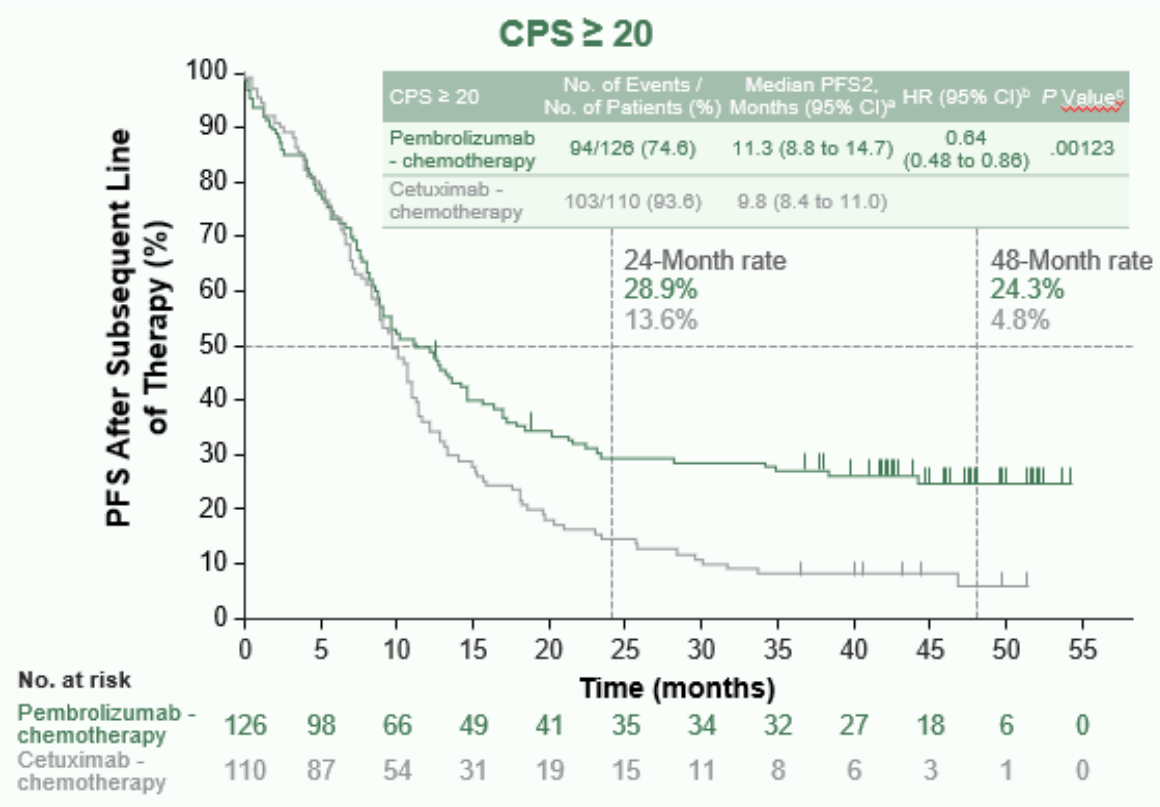



- PFS2 analysis involved patients in the ITT population (Pembro vs EXTREME)

Data cutoff: February 25, 2019 (final analysis).

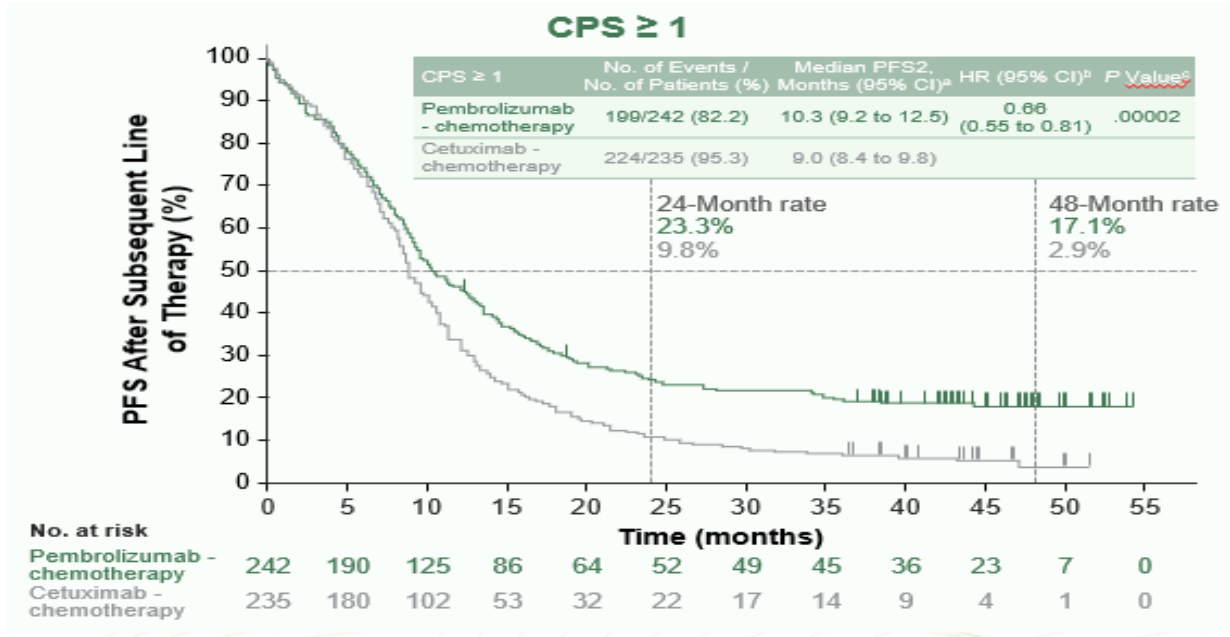
# Pembrolizumab combo PFS2

## CPS ≥ 20



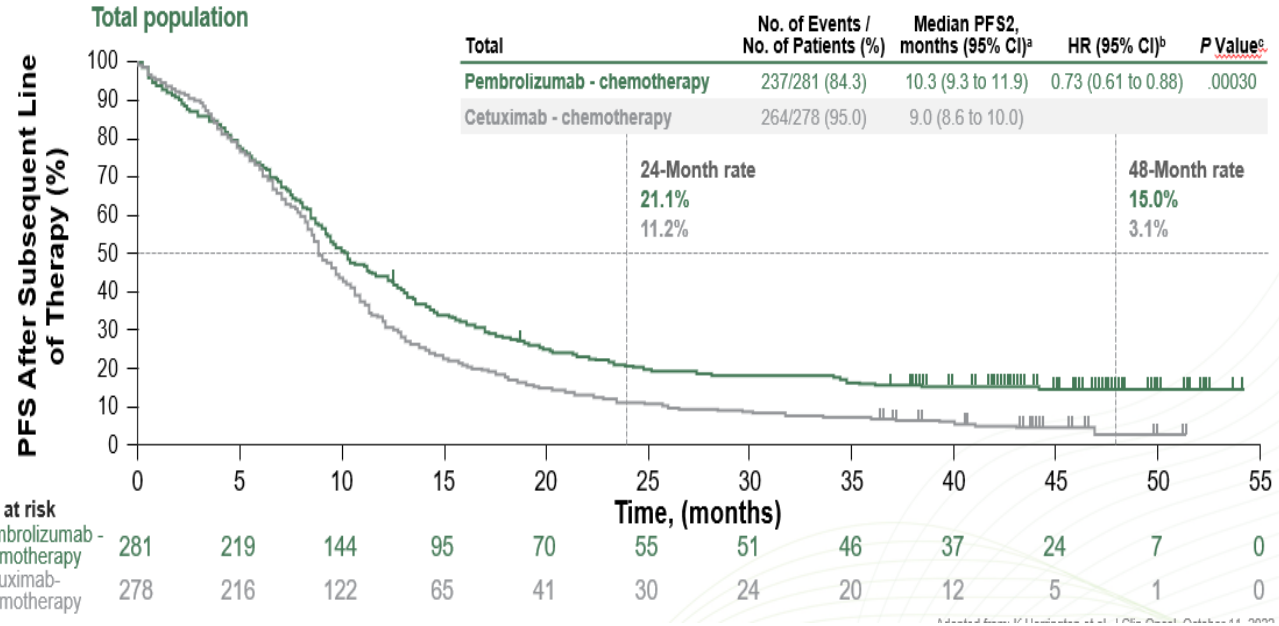

| CPS ≥ 20 | No. of Events / No. of Patients (%) | Median PFS2, Months (95% CI)[a] | HR (95% CI)[b] | *P* Value[c] |
|---|---|---|---|---|
| Pembrolizumab - chemotherapy | 94/126 (74.6) | 11.3 (8.8 to 14.7) | 0.64 (0.48 to 0.86) | .00123 |
| Cetuximab - chemotherapy | 103/110 (93.6) | 9.8 (8.4 to 11.0) | | |

## CPS ≥ 1




| CPS ≥ 1 | No. of Events / No. of Patients (%) | Median PFS2, Months (95% CI)[a] | HR (95% CI)[b] | *P* Value[c] |
|---|---|---|---|---|
| Pembrolizumab - chemotherapy | 199/242 (82.2) | 10.3 (9.2 to 12.5) | 0.66 (0.55 to 0.81) | .00002 |
| Cetuximab - chemotherapy | 224/235 (95.3) | 9.0 (8.4 to 9.8) | | |

## Total population



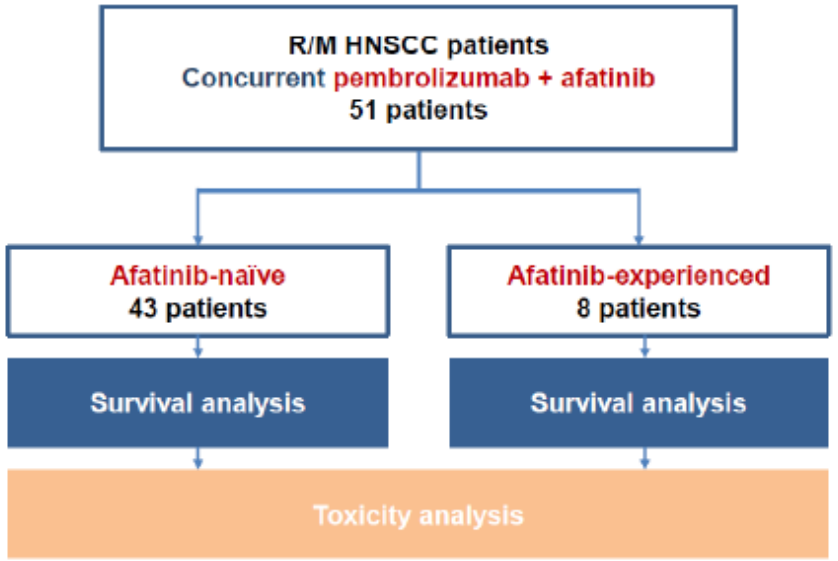

| Total | No. of Events / No. of Patients (%) | Median PFS2, months (95% CI)[a] | HR (95% CI)[b] | *P* Value[c] |
|---|---|---|---|---|
| Pembrolizumab - chemotherapy | 237/281 (84.3) | 10.3 (9.3 to 11.9) | 0.73 (0.61 to 0.88) | .00030 |
| Cetuximab - chemotherapy | 264/278 (95.0) | 9.0 (8.6 to 10.0) | | |

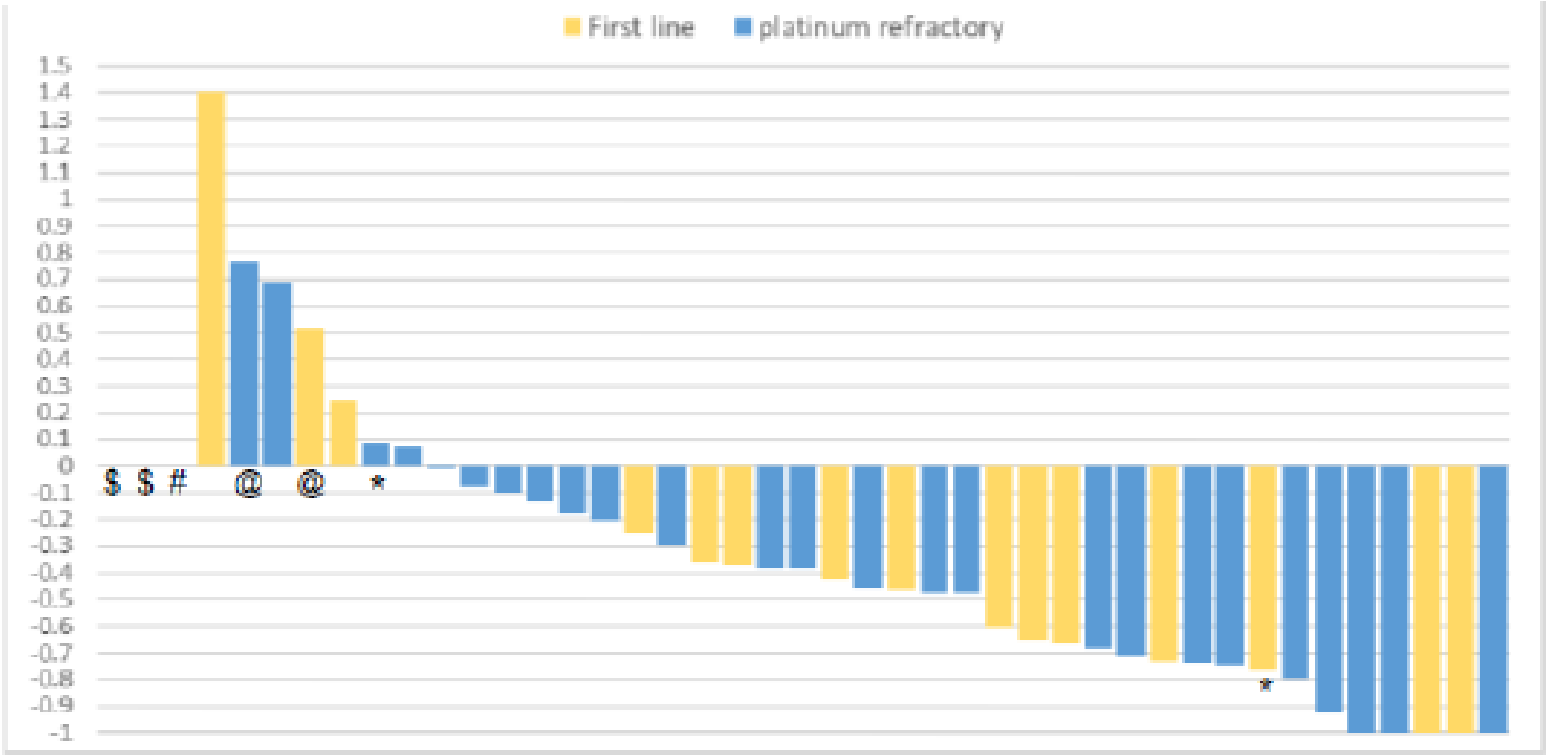
# 1062P
# Pembrolizumab and afatinib for recurrent or metastatic head and neck squamous cell carcinoma

FREE

H-F Kao, R-L Hong

*Annals of Oncology*, Volume 29, Issue suppl_8, October 2018, mdy287.018,
https://doi.org/10.1093/annonc/mdy287.018
**Published:** 23 October 2018




**ORR: 58.8%**
**Tumor size decrease: 74.4%**

$ not evaluable
# diagnosed as clinical PD, no image follow-up
* new lesion, diagnosed as PD
@ measured by physical examination

Professor Hong

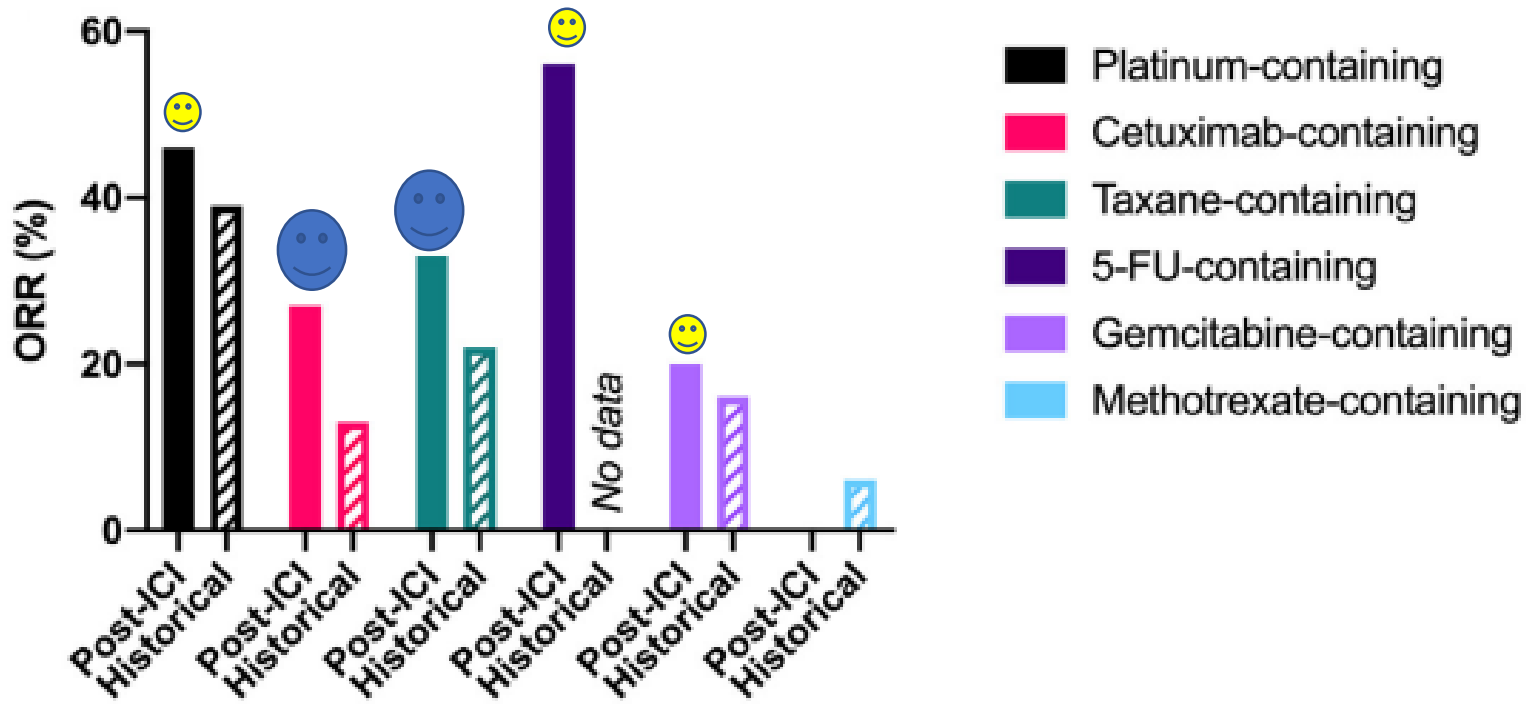
Kao et al. *ESMO*. 2019

Contents lists available at ScienceDirect

Oral Oncology

journal homepage: www.elsevier.com/locate/oraloncology

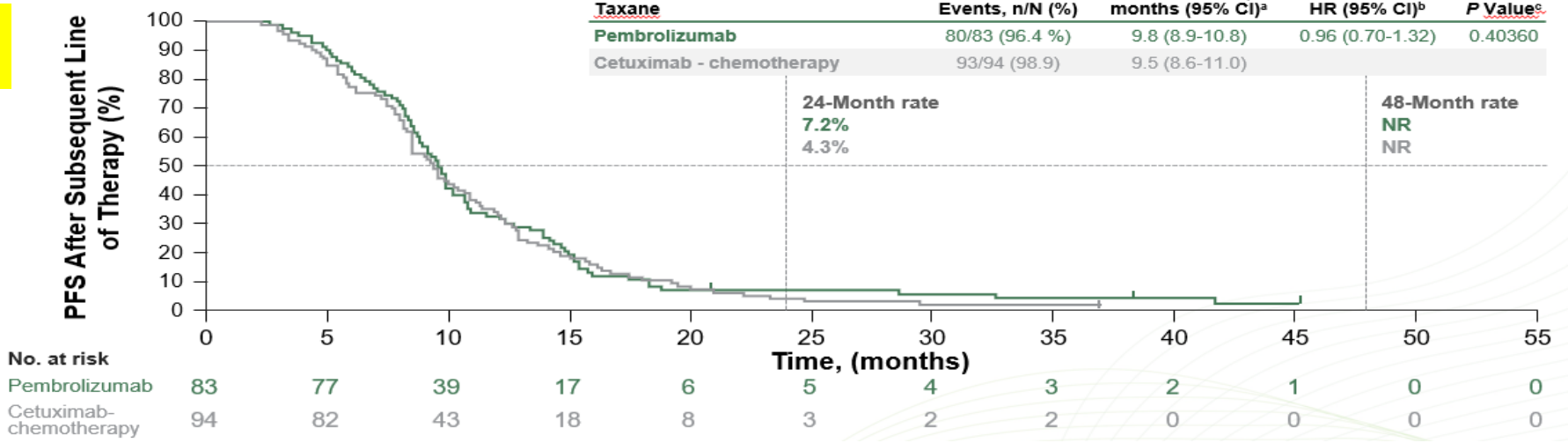
# Chemotherapy after immune checkpoint blockade in patients with recurrent, metastatic squamous cell carcinoma of the head and neck




Oral Oncology 105 (2020)

Pembro Mono

## Kaplan-Meier estimates of PFS on subsequent line of therapy **Pembro alone** *vs* **cetuximab + chemo** in patients who received **taxane-based chemo** as next line of therapy

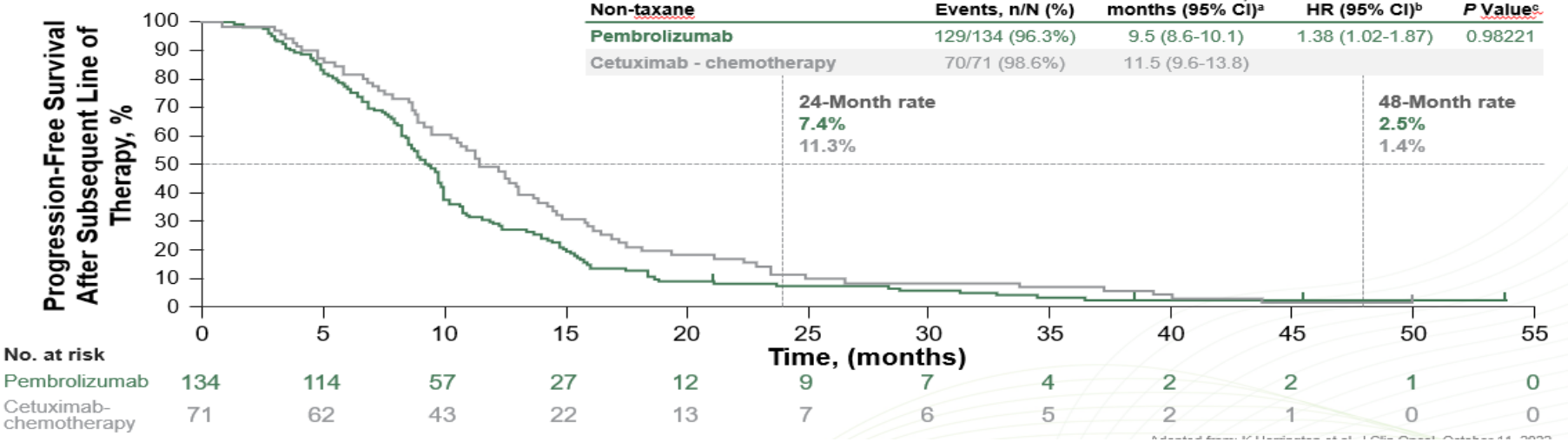



| Taxane | Events, n/N (%) | Median PFS2, months (95% CI)[a] | HR (95% CI)[b] | *P* Value[c] |
|---|---|---|---|---|
| Pembrolizumab | 80/83 (96.4 %) | 9.8 (8.9-10.8) | 0.96 (0.70-1.32) | 0.40360 |
| Cetuximab - chemotherapy | 93/94 (98.9) | 9.5 (8.6-11.0) | | |

| | 24-Month rate | 48-Month rate |
|---|---|---|
| Pembrolizumab | 7.2% | NR |
| Cetuximab - chemotherapy | 4.3% | NR |

| No. at risk | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Pembrolizumab | 83 | 77 | 39 | 17 | 6 | 5 | 4 | 3 | 2 | 1 | 0 | 0 |
| Cetuximab-chemotherapy | 94 | 82 | 43 | 18 | 8 | 3 | 2 | 2 | 0 | 0 | 0 | 0 |

## Kaplan-Meier estimates of PFS on subsequent line of therapy **Pembro alone** *vs* **cetuximab + chemo** in patients who received **non-taxane-based chemo** as next line of therapy




| Non-taxane | Events, n/N (%) | Median PFS2, months (95% CI)[a] | HR (95% CI)[b] | *P* Value[c] |
|---|---|---|---|---|
| Pembrolizumab | 129/134 (96.3%) | 9.5 (8.6-10.1) | 1.38 (1.02-1.87) | 0.98221 |
| Cetuximab - chemotherapy | 70/71 (98.6%) | 11.5 (9.6-13.8) | | |

| | 24-Month rate | 48-Month rate |
|---|---|---|
| Pembrolizumab | 7.4% | 2.5% |
| Cetuximab - chemotherapy | 11.3% | 1.4% |

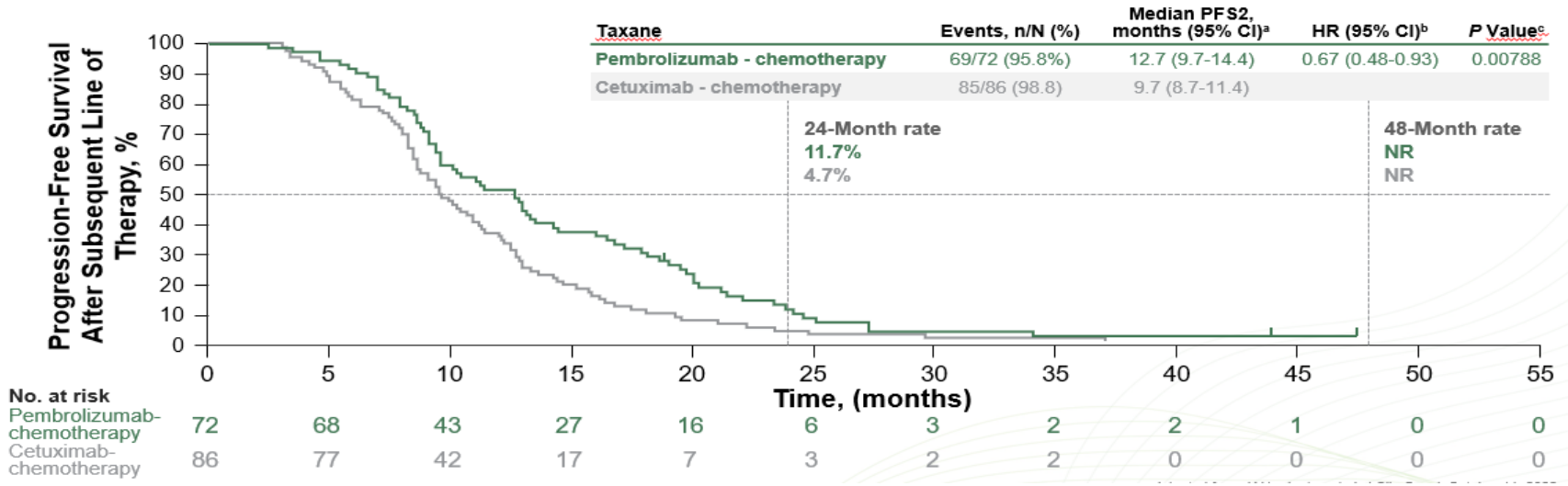
| No. at risk | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Pembrolizumab | 134 | 114 | 57 | 27 | 12 | 9 | 7 | 4 | 2 | 2 | 1 | 0 |
| Cetuximab-chemotherapy | 71 | 62 | 43 | 22 | 13 | 7 | 6 | 5 | 2 | 1 | 0 | 0 |

Pembro Combo

Pembro +任何C/T都好

Cetuximab + taxotere沒比較好

Kaplan-Meier estimates of PFS on subsequent line of therapy **pembro + chemo** *vs* **cetuximab + chemo** in patients who received **taxane-based chemo** as next line of therapy

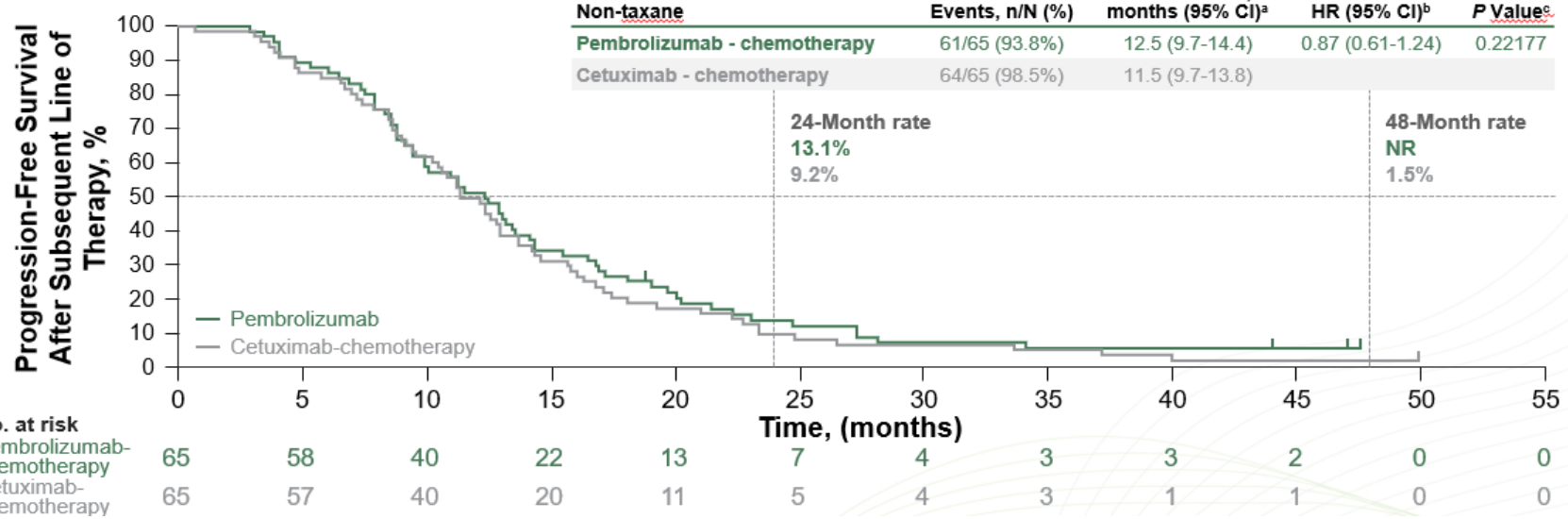



| Taxane | Events, n/N (%) | Median PFS2, months (95% CI)[a] | HR (95% CI)[b] | *P* Value[c] |
|---|---|---|---|---|
| Pembrolizumab - chemotherapy | 69/72 (95.8%) | 12.7 (9.7-14.4) | 0.67 (0.48-0.93) | 0.00788 |
| Cetuximab - chemotherapy | 85/86 (98.8) | 9.7 (8.7-11.4) | | |

| | 24-Month rate | 48-Month rate |
|---|---|---|
| | 11.7% | NR |
| | 4.7% | NR |

| No. at risk | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Pembrolizumab-chemotherapy | 72 | 68 | 43 | 27 | 16 | 6 | 3 | 2 | 2 | 1 | 0 | 0 |
| Cetuximab-chemotherapy | 86 | 77 | 42 | 17 | 7 | 3 | 2 | 2 | 0 | 0 | 0 | 0 |

Kaplan-Meier estimates of PFS on subsequent line of therapy **pembro + chemo** *vs* **cetuximab + chemo** in patients who received **non–taxane-based chemo** as next line of therapy




| Non-taxane | Events, n/N (%) | Median PFS2, months (95% CI)[a] | HR (95% CI)[b] | *P* Value[c] |
|---|---|---|---|---|
| Pembrolizumab - chemotherapy | 61/65 (93.8%) | 12.5 (9.7-14.4) | 0.87 (0.61-1.24) | 0.22177 |
| Cetuximab - chemotherapy | 64/65 (98.5%) | 11.5 (9.7-13.8) | | |

| | 24-Month rate | 48-Month rate |
|---|---|---|
| | 13.1% | NR |
| | 9.2% | 1.5% |

| No. at risk | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Pembrolizumab-chemotherapy | 65 | 58 | 40 | 22 | 13 | 7 | 4 | 3 | 3 | 2 | 0 | 0 |
| Cetuximab-chemotherapy | 65 | 57 | 40 | 20 | 11 | 5 | 4 | 3 | 1 | 1 | 0 | 0 |

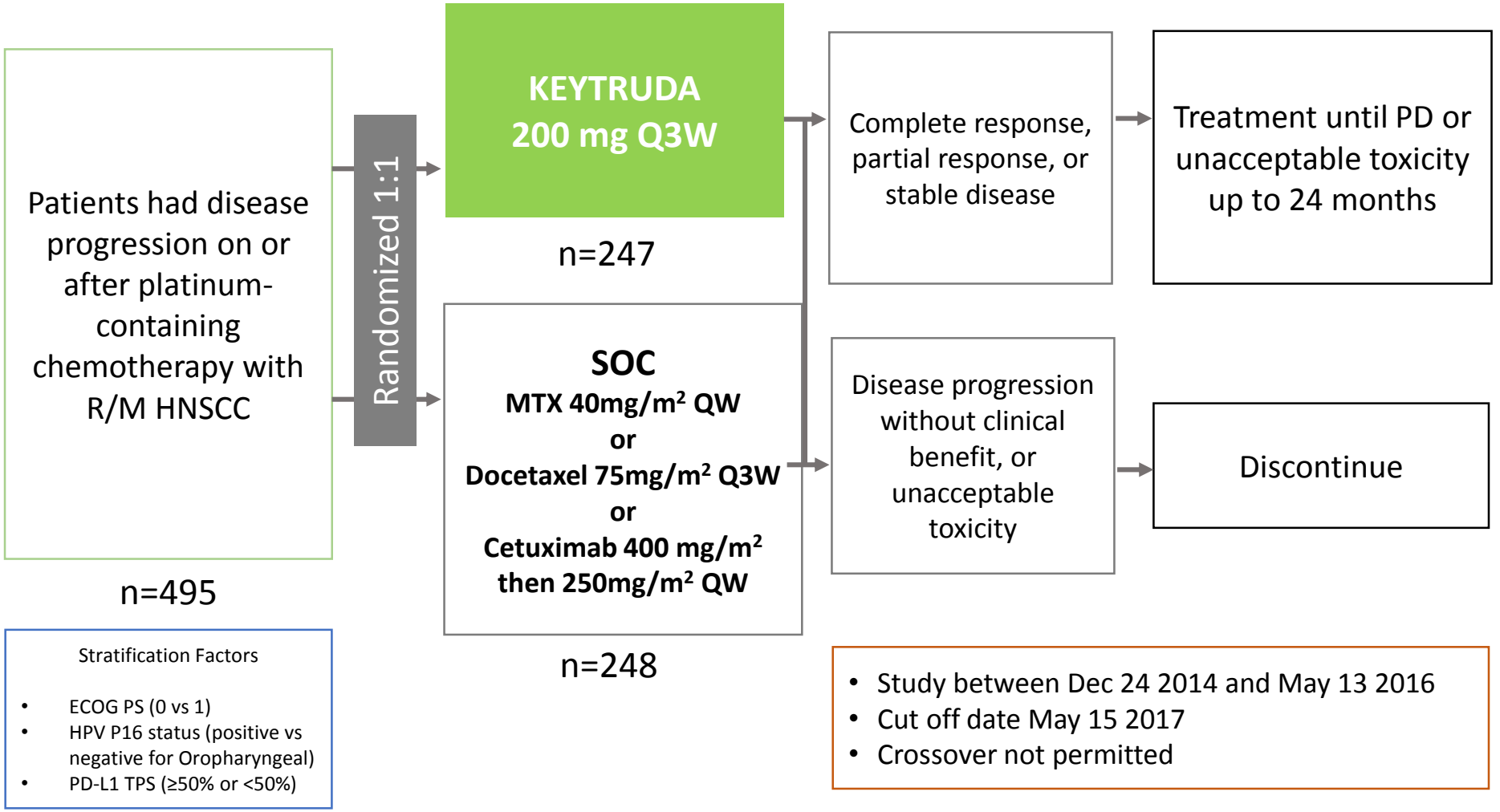
# Sequencing strategies for immunotherapy

- **Pembro monotherapy**
  - High CPS
  - Low burden of disease
  - Greater DoR for responders
  - Better AE provide
  - Convenience
  - Patient preference

- **Pembro + Chemotherapy**
  - Negative +/- Low CPS
  - Improved ORR/PFS
  - Bulky disease
  - Symptomatic
  - R/M in high dose XRT field

Often overlapping choice for clinicians/patients

# KEYNOTE-040: multicenter, open-label, randomized controlled phase 3 study

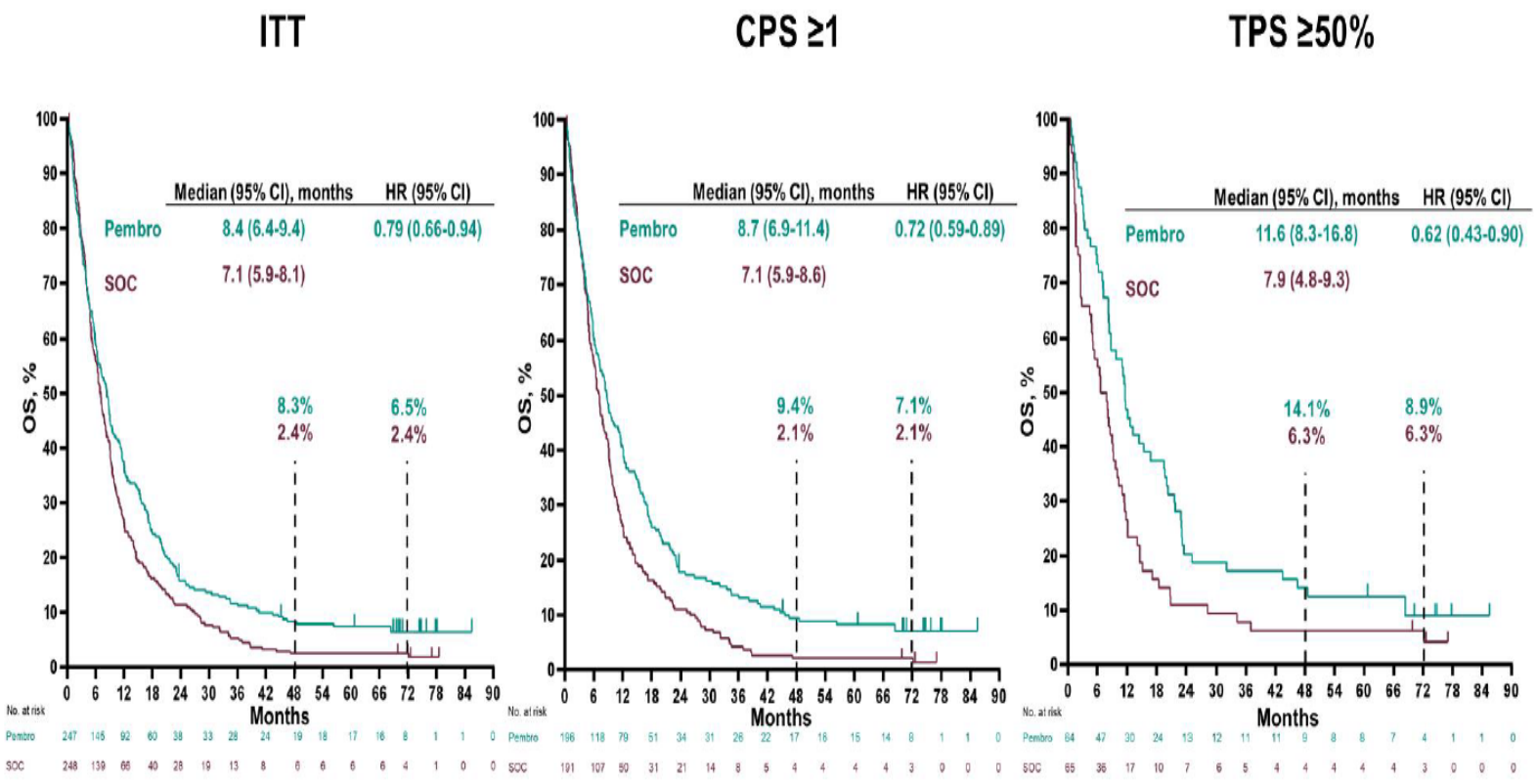



SOC: Standard of card; MTX: Methotrexate; ECOG PS: Eastern Cooperative Oncology Group Performance Status; PD: Disease progression; PD-L1: Programmed cell death protein ligand 1; TPS: Tumor proportion score; HPV: Human Papillomavirus

Ezra Cohen, et al. Lancet Vol. 393:156-67; January 12, 2019

# Overall Survival

6 ys-OS




| | Pembro n = 247 | SOC n = 248 |
|---|---|---|
| **ORR, % (95% CI)** | 15.4 (11.1-20.5) | 8.9 (5.6-13.1) |
| **Best objective Response** | | |
| CR | 14 (5.7) | 1 (0.4) |
| PR | 24 (9.7) | 21 (8.5) |
| SD | 54 (21.9) | 67 (27.0) |
| PD | 109 (44.1) | 97 (39.1) |
| Non-CR/Non-PD | 1 (0.4) | 1 (0.4) |
| NE | 3 (1.2) | 6 (2.4) |
| NA | 42 (17.0) | 55 (22.2) |

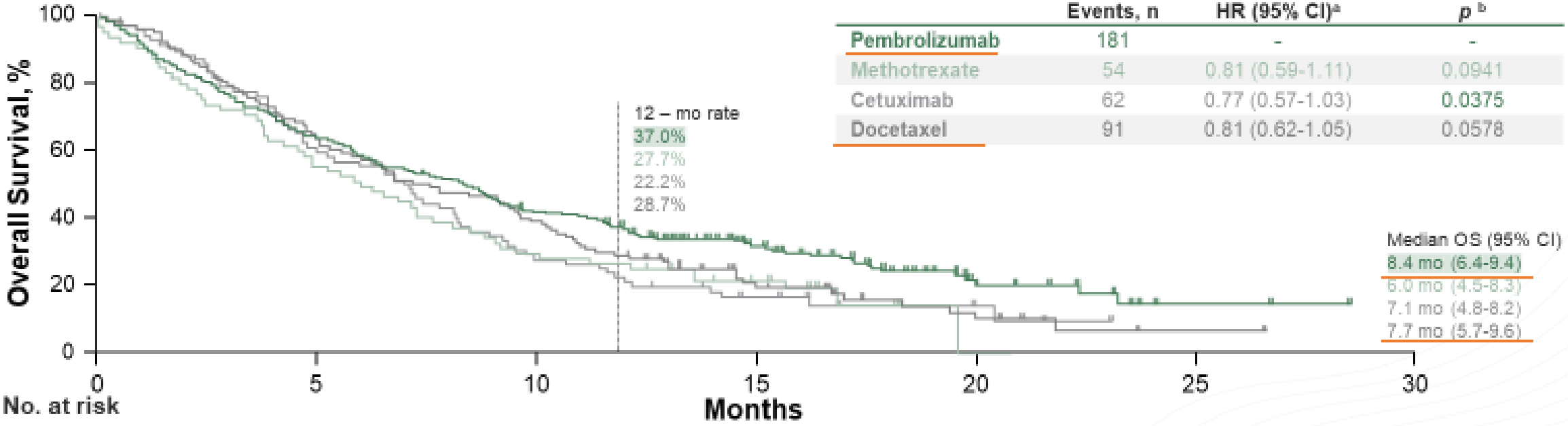
Values are n (%) unless otherwise specified.
Data cutoff date February 3, 2022.

Data cutoff date February 3, 2022.

# KEYNOTE-040: Pembrolizumab versus methotrexate, docetaxel, or cetuximab for recurrent or metastatic head-and-neck squamous cell carcinoma[1]

## Post Hoc Analyses of Treatment Options From the Phase 3 KEYNOTE-040 Trial

### Overall Survival by SOC Treatment




| | Events, n | HR (95% CI)[a] | p [b] |
|---|---|---|---|
| Pembrolizumab | 181 | - | - |
| Methotrexate | 54 | 0.81 (0.59-1.11) | 0.0941 |
| Cetuximab | 62 | 0.77 (0.57-1.03) | 0.0375 |
| Docetaxel | 91 | 0.81 (0.62-1.05) | 0.0578 |

Median OS (95% CI)
8.4 mo (6.4-9.4)
6.0 mo (4.5-8.3)
7.1 mo (4.8-8.2)
7.7 mo (5.7-9.6)

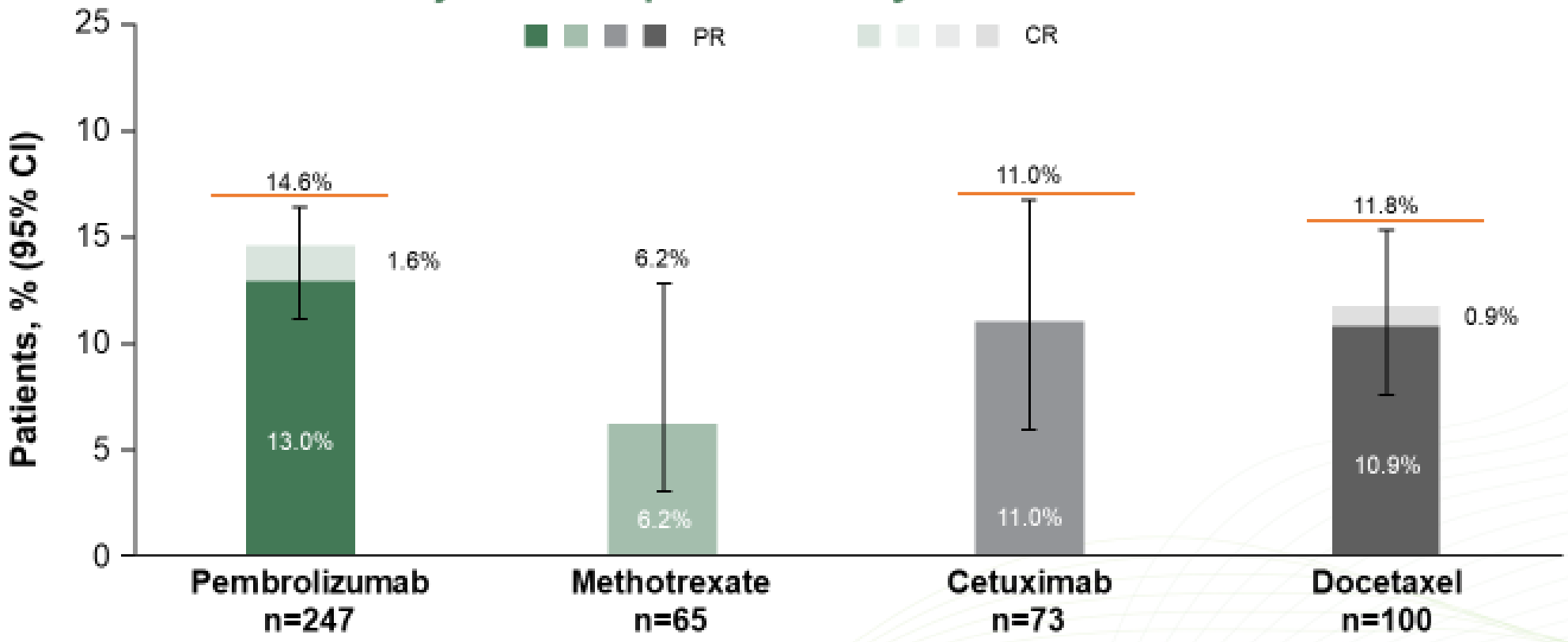
Data cutoff date: May 15, 2017
ECOG, Eastern Cooperative Oncology Group; HPV, human papillomavirus; HR, hazard ratio; OS, overall survival; PD-L1, programmed death ligand 1; PS, performance status; SOC, standard of care.
[a] HR for pembrolizumab versus SOC, from product-limit (Kaplan-Meier) method for censored data. CI based on Cox regression model with treatment as a covariate stratified by ECOG PS, HPV status, and PD-L1 status.
[b] One-sided P value based on log-rank test.
1. C. Le Tourneau et al. Presented at ESMO. 2018

KEYTRUDA® (pembrolizumab)

# KEYNOTE-040: Pembrolizumab versus methotrexate, docetaxel, or cetuximab for recurrent or metastatic head-and-neck squamous cell carcinoma[1]

Post Hoc Analyses of Treatment Options From the Phase 3 KEYNOTE-040 Trial

## Objective Response Rate by SOC Treatment




Data cutoff: May 15, 2017
CR, complete response; PR, partial response; SOC, standard of care.
1. C. Le Tourneau et al. Presented at ESMO. 2018

KEYTRUDA® (pembrolizumab)

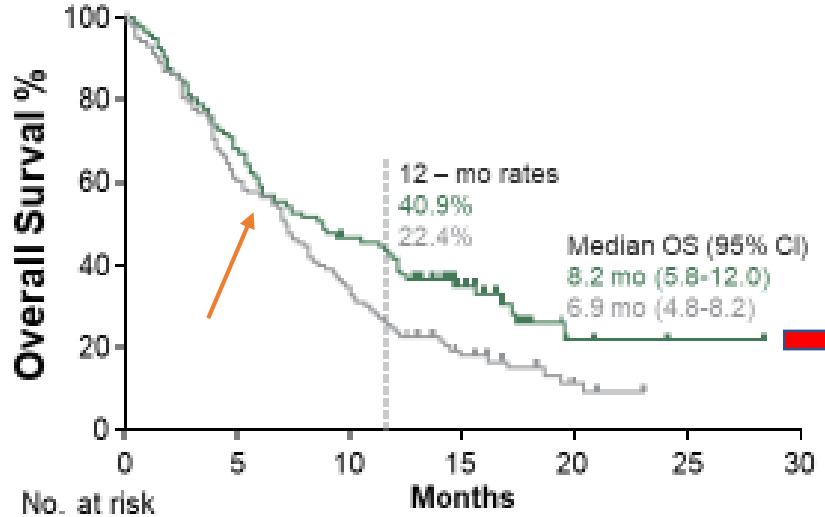
# KEYNOTE-040: Pembrolizumab versus methotrexate, docetaxel, or cetuximab for recurrent or metastatic head-and-neck squamous cell carcinoma[1]

## Post Hoc Analyses of Treatment Options From the Phase 3 KEYNOTE-040 Trial

### Overall Survival by Prior Cetuximab Use[a]

#### No Prior Cetuximab

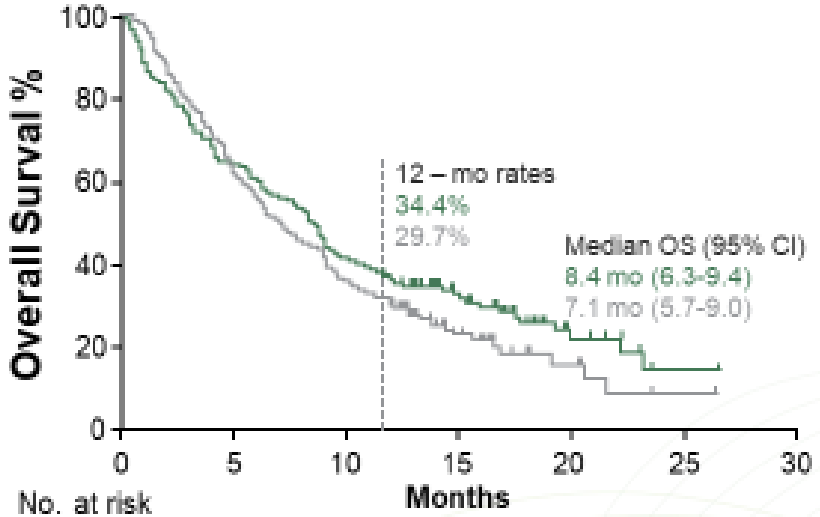
| | Events, n | HR (95% CI) | p |
|---|---|---|---|
| Pembrolizumab | 72 | 0.78[b] (0.56 - 1.07) | 0.0618[c] |
| Chemotherapy | 94 | - | - |




| No. at risk | | | | | | | |
|---|---|---|---|---|---|---|---|
| | 102 | 58 | 44 | 18 | 4 | 1 | 0 |
| | 108 | 64 | 34 | 14 | 4 | 0 | 0 |

#### With Prior Cetuximab

| | Events, n | HR (95% CI) | p |
|---|---|---|---|
| Pembrolizumab | 109 | 0.89[b] (0.56 - 1.07) | 0.1915[c] |
| Chemotherapy | 113 | - | - |




| No. at risk | | | | | | | |
|---|---|---|---|---|---|---|---|
| | 145 | 92 | 59 | 30 | 10 | 1 | 0 |
| | 140 | 87 | 48 | 20 | 6 | 1 | 0 |

There was a trend toward **improved OS** with pembrolizumab versus SOC in patients who did not previously receive cetuximab, though this may represent a less heavily pretreated population.

Data cutoff: May 15, 2017

ECOG, Eastern Cooperative Oncology Group; HPV, human papillomavirus; HR, hazard ratio; OS, overall survival; PD-L1, programmed death ligand-1; PS, performance status.

a HR (95% CI) of OS adjusted for sex, prior line of therapy, current disease metastasis, current disease overall stage, nodal involvement, and sum of target lesion size stratified by ECOG PS (0 vs 1), HPV status (positive vs negative), and PD-L1 status (strongly positive, not strongly positive) was 0.82 (0.59-1.15; P = 0.129) for no prior cetuximab and 0.87 (0.66-1.14; P = 0.152) for prior cetuximab.

b HR for pembrolizumab versus chemotherapy, from product-limit (Kaplan-Meier) method for censored data. CI based on Cox regression model with treatment as a covariate stratified by ECOG PS, HPV status, and PD-L1 status.

C One-sided P value based on log-rank test.

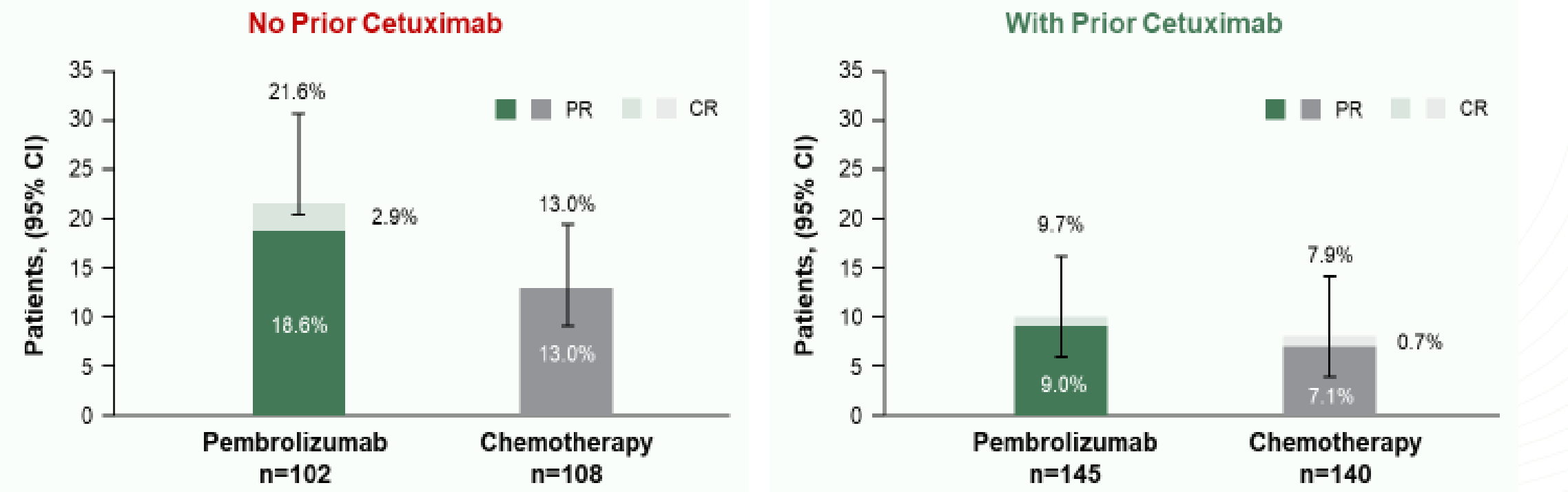
1. C. Le Tourneau et al. Presented at ESMO. 2018

KEYTRUDA® (pembrolizumab)

# KEYNOTE-040: Pembrolizumab versus methotrexate, docetaxel, or cetuximab for recurrent or metastatic head-and-neck squamous cell carcinoma[1]

Post Hoc Analyses of Treatment Options From the Phase 3 KEYNOTE-040 Trial

## Objective Response Rate by Prior Centuximab Use




There was a trend toward **improved ORR** with pembrolizumab versus SOC in patients **who did not previously receive cetuximab**, though this may represent a less heavily pretreated population.

Data cutoff date: May 15, 2017
CR, complete response; PR, partial response
1. C. Le Tourneau et al. Presented at ESMO. 2018

KEYTRUDA® (pembrolizumab)

# Outline

Case 1: 1 line combination

Case 2

Case 3

# Case sharing: M/68

- 201409, Squamous cell carcinoma of oral tongue, left tongue border,pT1N1M0, stage III.
- 20140911  Wide excision of tongue carcinoma +neck dissection, left (level I,II,III,IV) and CCRT with cisplatin.
- Dysphagia for 6+ months. Suspected hypopharyngeal tumor  by regular OPD check up.
- Admission

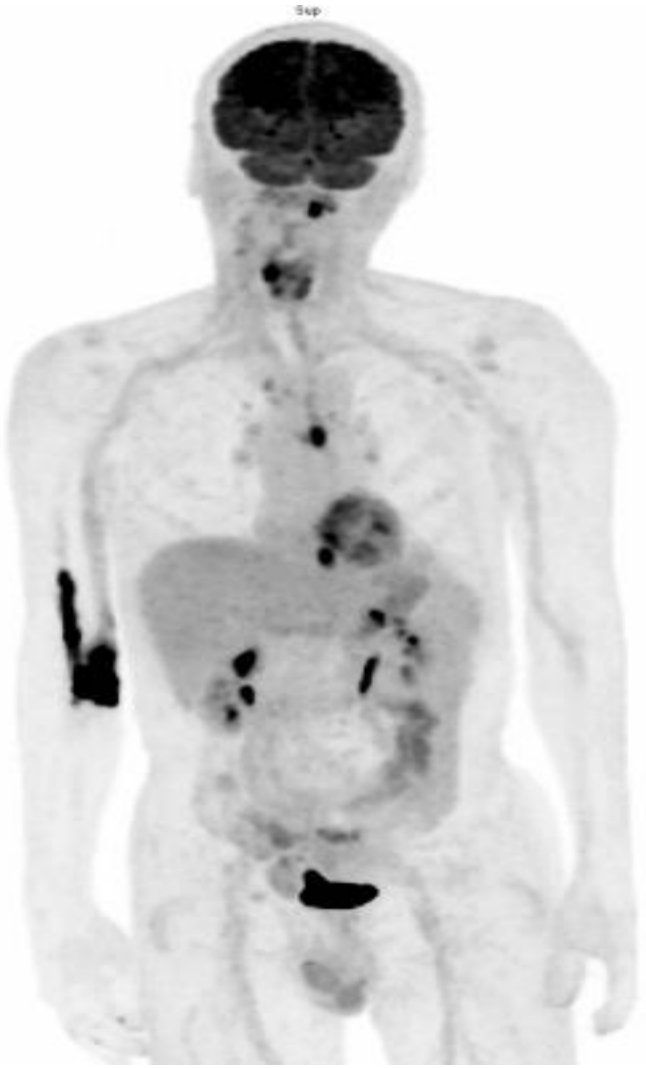
20210121

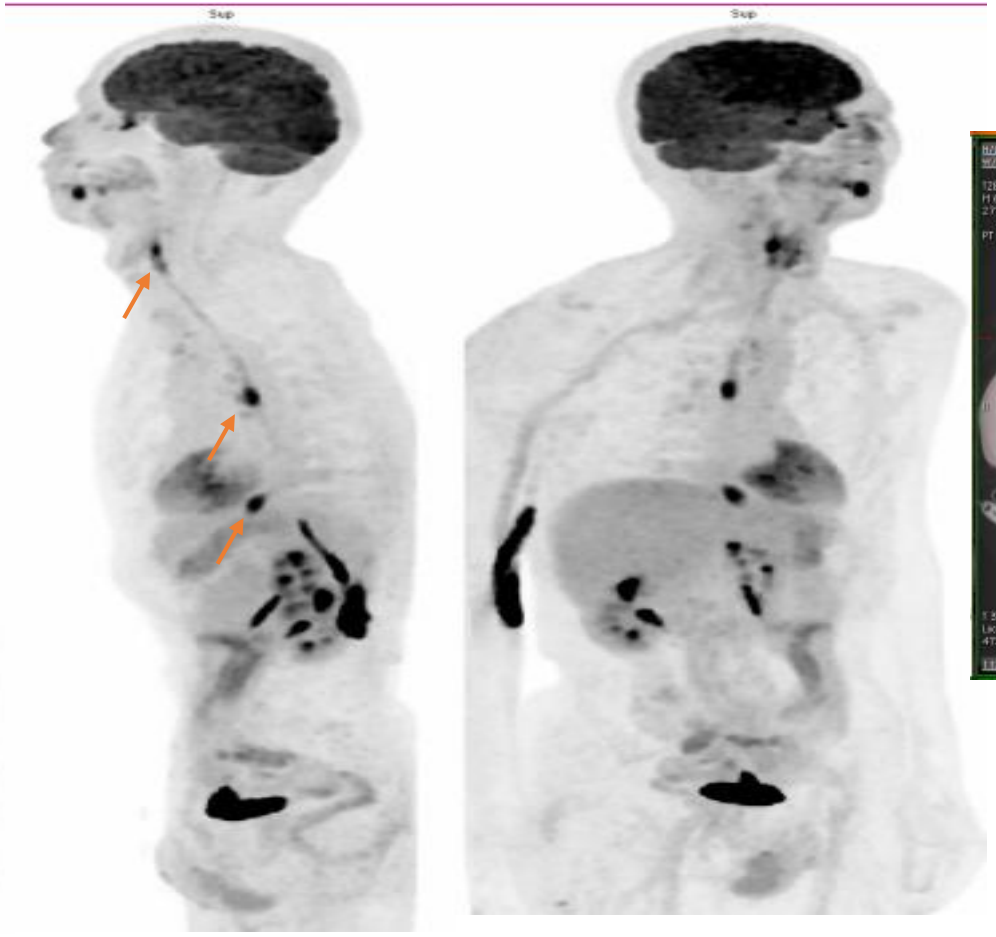
主治醫師 : 李日清
手術前診斷 : r/o hypopharnyx cancer
手術名稱 : biopsy
病理器官 : Mucosa, site?
病程摘要 :
病理診斷 : Squamous cell carcinoma, moderately differentiated.
報告內容 :
Mucosa, site?, biopsy --- Squamous cell carcinoma, moderately differentiated.

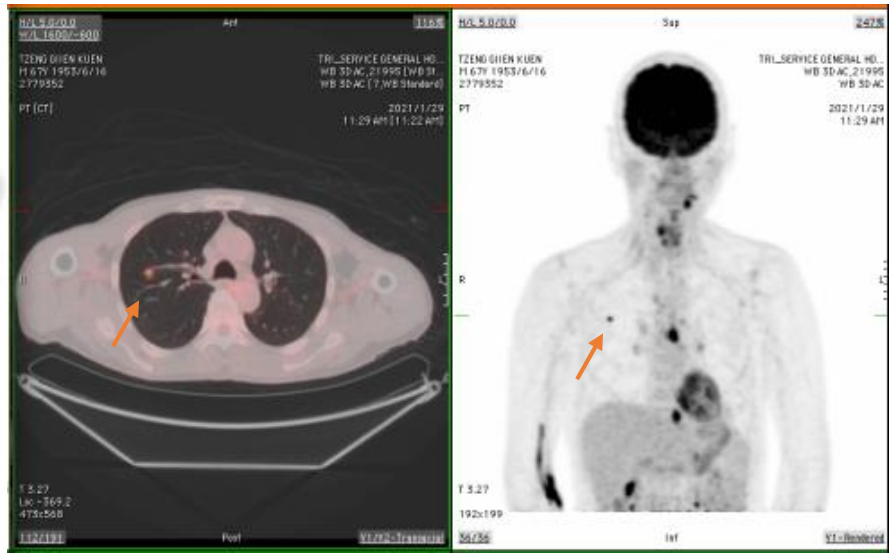
##########
Immunohistochemical stains: "A"
P16: negative for tumor cells.
P53: overexpressed for tumor cells.
Ki-67: increased proliferative index.
##########

20210129 PET

1. hypopharynx (right  pyriform sinus, SUVmax.: 9.8).
2. mid-thoracic  (SUVmax.: 9.6) and lower-thoracic esophagus (SUVmax.: 10). Few nodal lesions in the pre-&  sub-carinal regions (SUVmax.: 4).
3. right upper lung on the delayed imaging (delayed SUVmax.: 6.4).

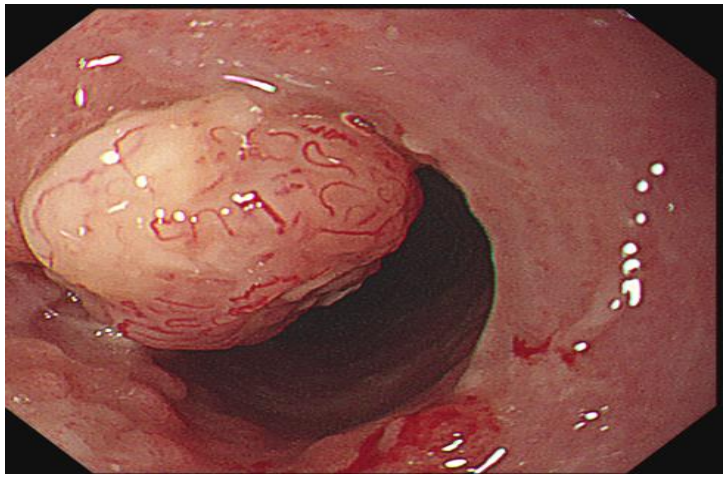


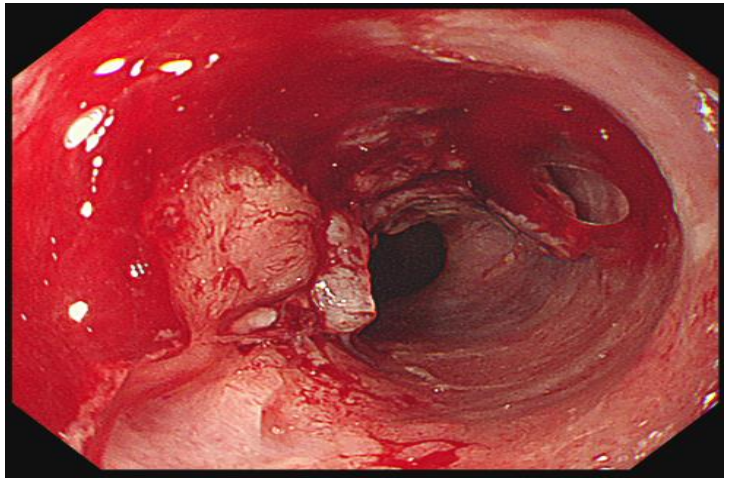




20210201 PES:

1. Highly suspected esophageal cancers,
   M3 and L/3





手術前診斷 : One protruding mass wih uneven surface at th 27 cm from the incisor (biopsy C)
手術名稱 : biopsy
病理器官 : Esophagus, 27 cm from the incisior "C"
病程摘要 :
病理診斷 : Squamous cell carcinoma, moderately differentiated.
報告內容 :
Esophagus, 27 cm from the incisior "C", biopsy --- Squamous cell carcinoma, moderately differentiated.

########################################
Immunohistochemical stains: "A"
CK: positive for tumor cells.
p40: positive for tumor cells.
p16: negative for tumor cells.
p53: no overexpression.
Ki-67: proliferative index, 50%.
########################################

手術前診斷 : One volcano-like tumor 1.5 cm in size at the 39 cm from the incisor (biopy B)
手術名稱 : biopsy
病理器官 : Esophagus, 39 cm from the incisior "B"
病程摘要 :
病理診斷 : Squamous cell carcinoma, moderately differentiated.
報告內容 :
Esophagus, 39 cm from the incisior "B", biopsy --- Squamous cell carcinoma, moderately differentiated.

- 2021/02/03 Micro-laryngeal surgery

手術前診斷 : Hypopharyngeal tumor, bilateral
手術名稱 : operation?
病理器官 : Hypopharynx, "R't anterior"
病程摘要 :
病理診斷 : Squamous cell carcinoma, moderately differentiated.
報告內容 :
1. Hypopharynx, "R't anterior", operation? --- Squamous cell carcinoma, moderately differentiated.
2. Hypopharynx, "R't posterior", ditto --- Squamous cell carcinoma in situ at least, see description.
1. Hypopharynx, "L't anterior", ditto --- Microinvasive squamous cell carcinoma.

##########################################
Immunohistochemical stains:
"A" "R't anterior"
CK: positive for tumor cells.
P16: percentage 15%, intensity 1+.
P53: no overexpression.
##########################################

# Active Problem

- Squamous cell carcinoma, moderately differentiated of hypopharynx, T1N0M1 (suspected lung metastases)
- Squamous cell carcinoma of esophagus, M/3, L/3 with sub-carinal lymph node involvement, T1N1M0-1 (suspected lung metastases).

# Active Problem

- Squamous cell carcinoma, moderately differentiated of hypopharynx, T1N0M1 (suspected lung metastases)
- Squamous cell carcinoma of esophagus, M/3, L/3 with sub-carinal lymph node involvement, T1N1M0-1 (suspected lung metastases).

**Plan to do:**

1. Refused lung mass surgery
2. 22C3: TPS:20%, CPS 25% (hypopharynx tissue)

# Medication treatment ?

(1) Pembrolizumab (KN048, mono)

(2) Pembrolizumab + PF regimen (KNO48, combo) (KN590, IO combo)

(3) Extreme regimen (Erbitux+PF)

(4) PF regimen (KN590, control)

(5) Neoadjuvant CCRT with PF regimen, then to evaluate surgery or adjuvant C/T

# Medication treatment ?

**(1) Pembrolizumab (KN048, mono)**

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(3) Extreme regimen (Erbitux+PF)

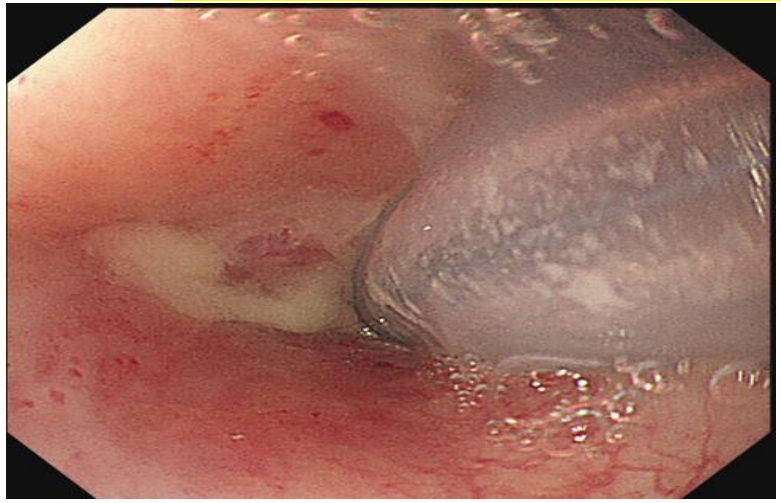
(4) PF regimen (KN590, control)

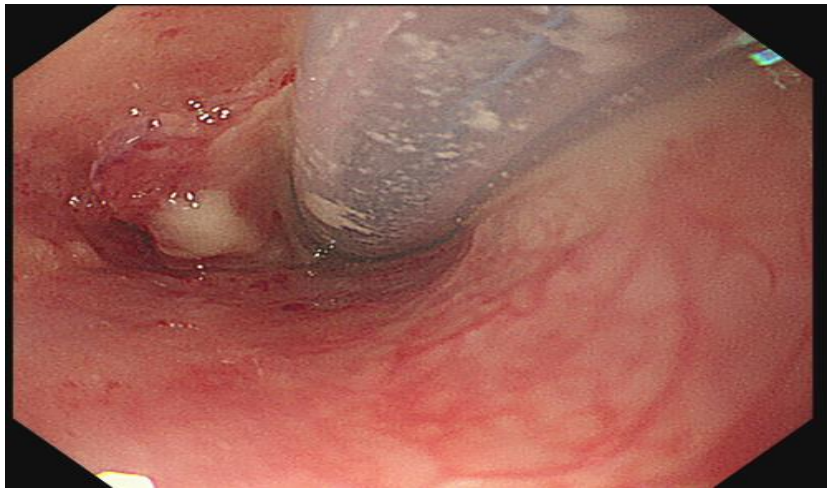
(5) Neoadjuvant CCRT with PF regimen, then to evaluate surgery or adjuvant C/T

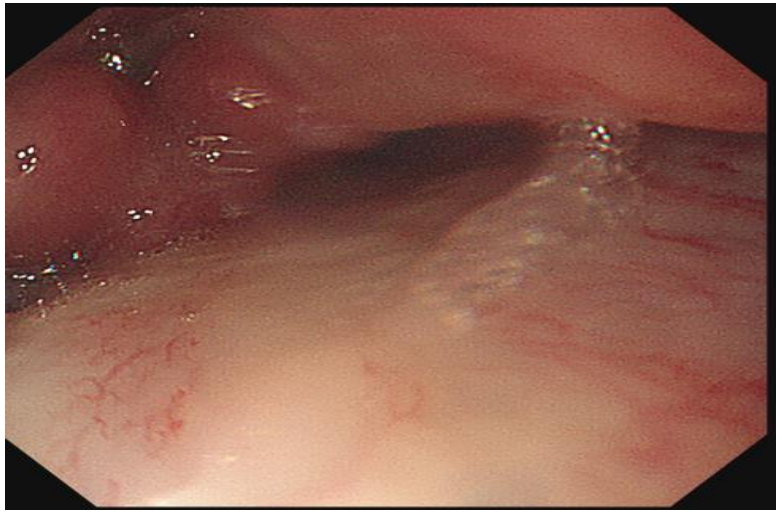
20211220 PES

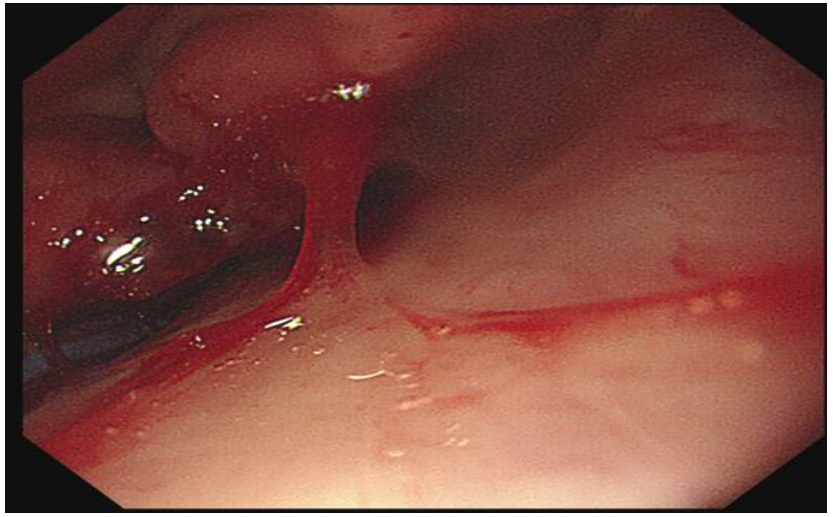
Irregular mucosal lesion over the hypopharyngeal region (biopsy).
Marked  stricture over the hypopharyneal region, the scope could not pass through it.

Pembrolizumab 200 mg, tri-weekly 202103-202112



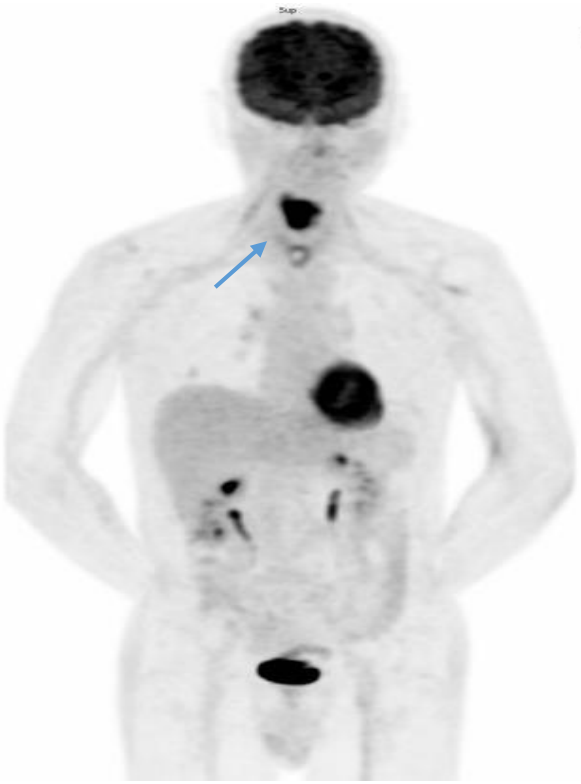


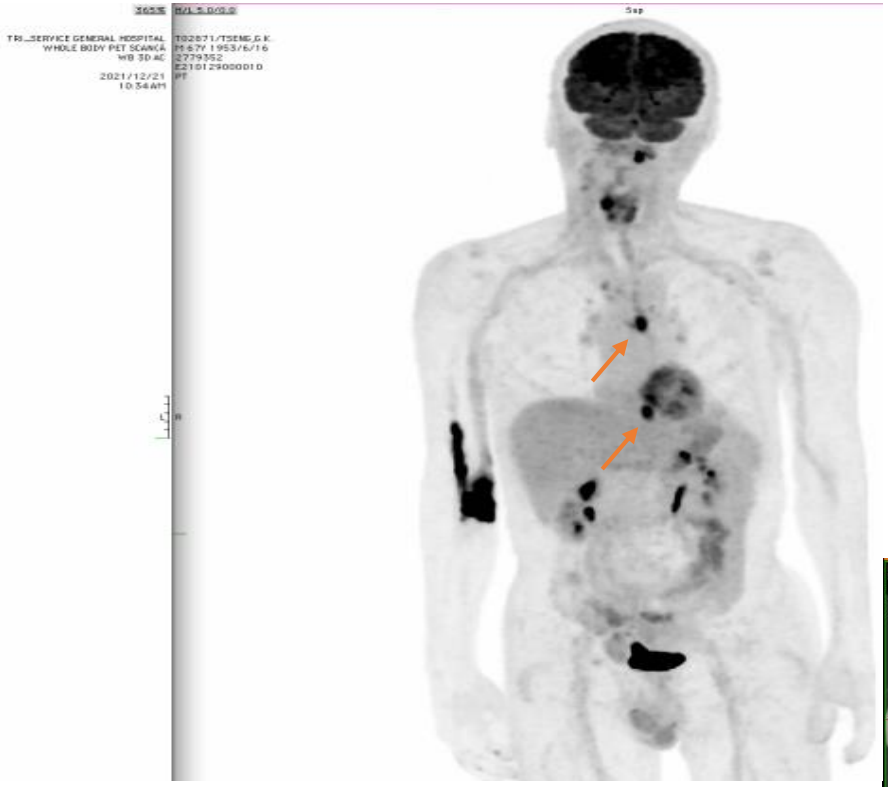


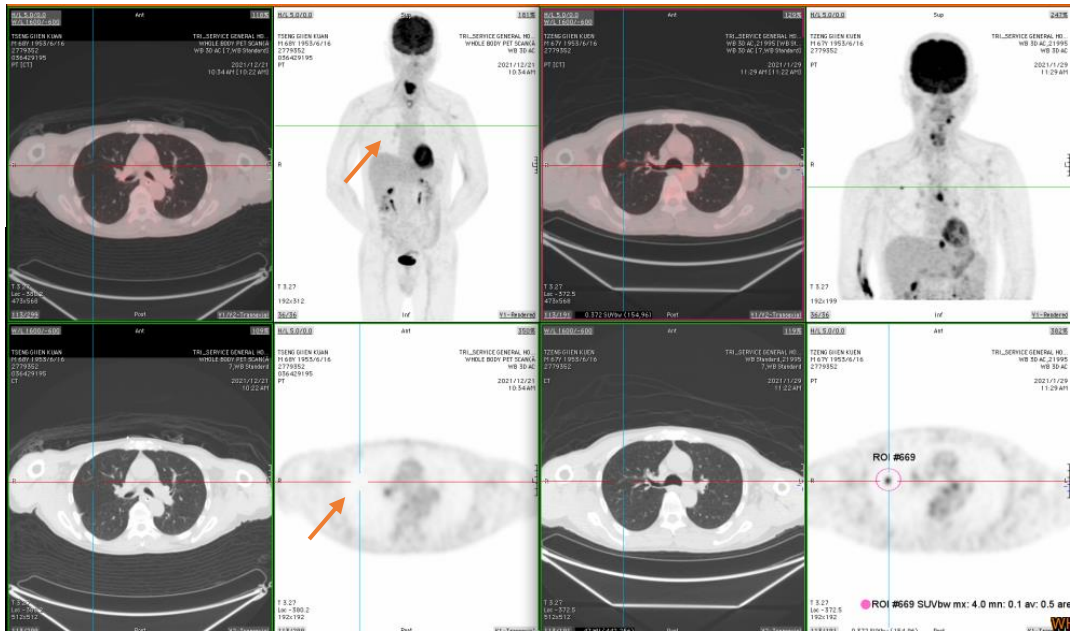


20211221 PET

Progressive interval change at the hypopharynx with soft tissue swelling and nearly total occlusion of upper air way (SUVmax.= 13.0, prior= 6.4)







20211230

```
手術名稱 : total laryngectomy
病理器官 : Larynx
病程摘要 :
病理診斷 : Squamous cell carcinoma, poorly differentiated, invading muscle layer.
報告內容 :
1. Larynx, total laryngectomy --- Squamous cell carcinoma,
poorly differentiated, invading muscle layer.
2. Lateral cutting ends and base, ditto --- Free of tumor
invasion.
3. Epiglottis, ditto --- Tumor involvement.
4. Thyroid cartilage, ditto --- Free of tumor invasion.
5. Cricoid cartilage, ditto --- Free of tumor invasion.
6. Hyoid bone, ditto --- Free of tumor invasion.
7. Adjacent muscle, neck, ditto --- Free of tumor invasion.
8. Lymphovascular space invasion ---- Identified.
9. Perineural invasion --- Identified.
10. AJCC pathological staging --- pT2Nx (correlate with clinical
M), stage II at least.

##########################################
Immunohistochemical stains: "C"
P40: positive for tumor cells.
P16: positive for tumor cells.
CD34: highlighting vessels.
S-100: highlighting nerve bundles.
##########################################
```

*. Squamous cell carcinoma, moderately differentiated of hypopharyngeal, pT2NxM0, stage II s/p total laryngectomy + neck dissection + tracheostomy + submental flap on 2021/12/24, post chemotherapy with Cisplatin + 5-FU .

# Medication treatment ?

## Self-reflection

(1) Pembrolizumab (KN048, mono)

(2) Pembrolizumab + PF regimen (KNO48, combo) (KN590, IO combo)

(3) Extreme regimen (Erbitux+PF)

(4) PF regimen (KN590, control)

(5) Neoadjuvant CCRT with PF regimen, then to evaluate surgery or adjuvant C/T

# Medication treatment ?

## Self-reflection

(1) Pembrolizumab (KN048, mono)

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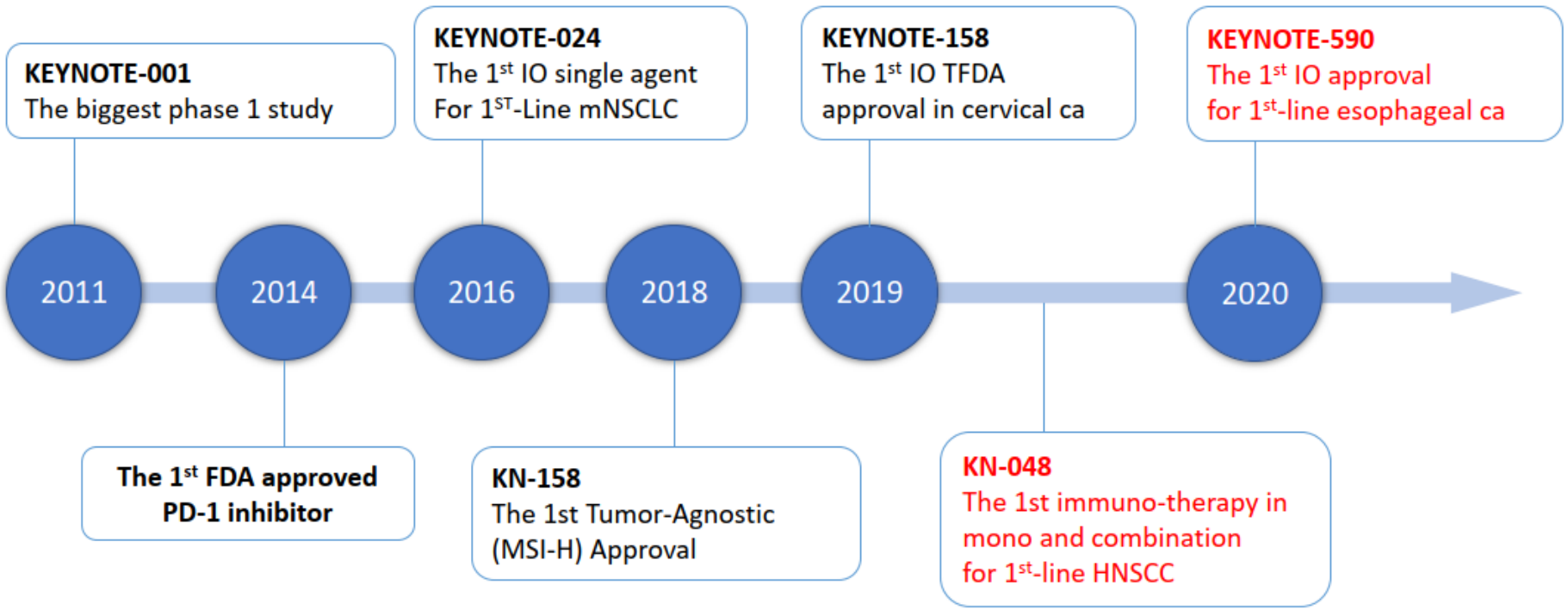
(3) Extreme regimen (Erbitux+PF)

(4) PF regimen (KN590, control)

(5) Neoadjuvant CCRT with PF regimen, then to evaluate surgery or adjuvant C/T

# Pembrolizumab leads in immuno-oncology since 2011



# Outline

Case 1: 1 line combination

Case 2: 1 line mono

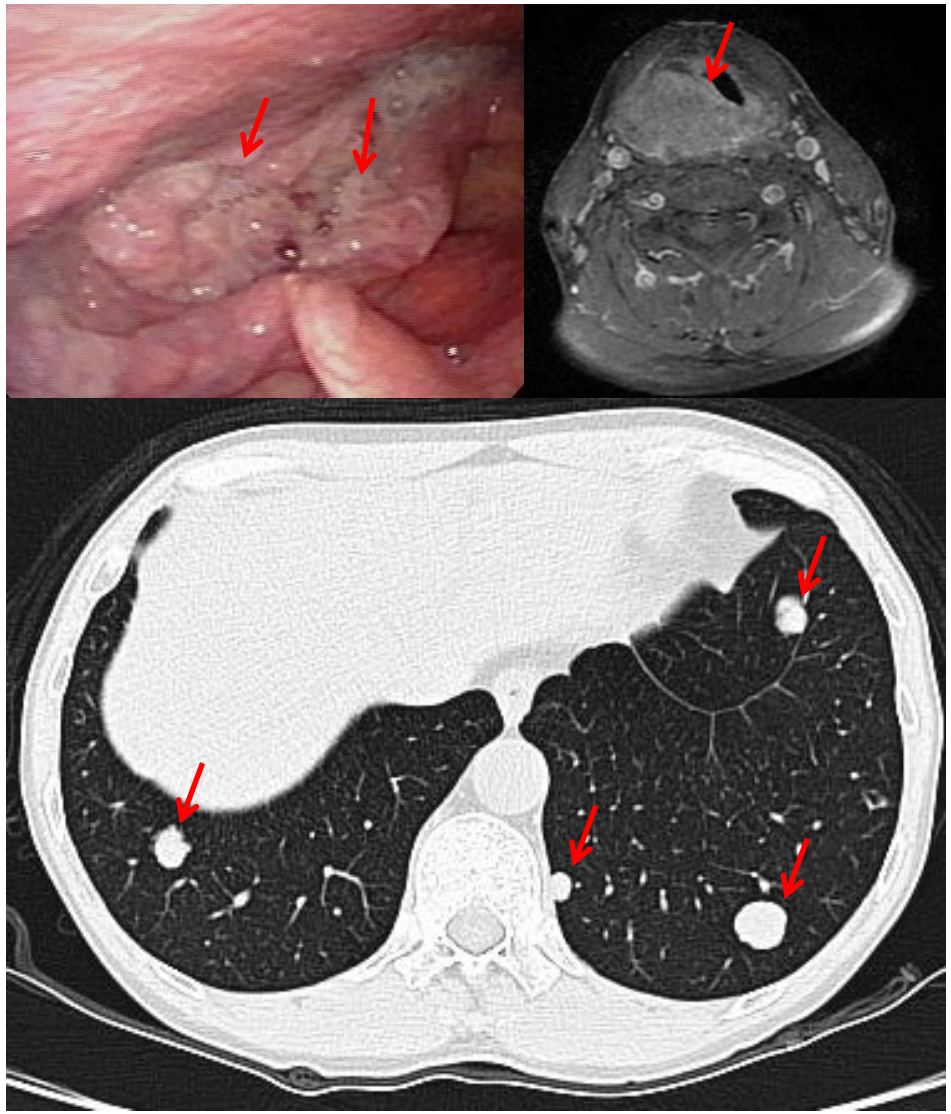
Case 3

# M/52

- palpable mass over right neck since 2018.01. The difficulty in swallowing was also noted.
- to XX醫院,neck sonography 20180307: one mass 2.5*1.7 cm at right supra-thyroid. chest X ray 20180314: suspected lung cancer. This time, admitted for lung cancer survey.

- History of **smoking, alcohol, betel nut**
- **賣臭豆腐**

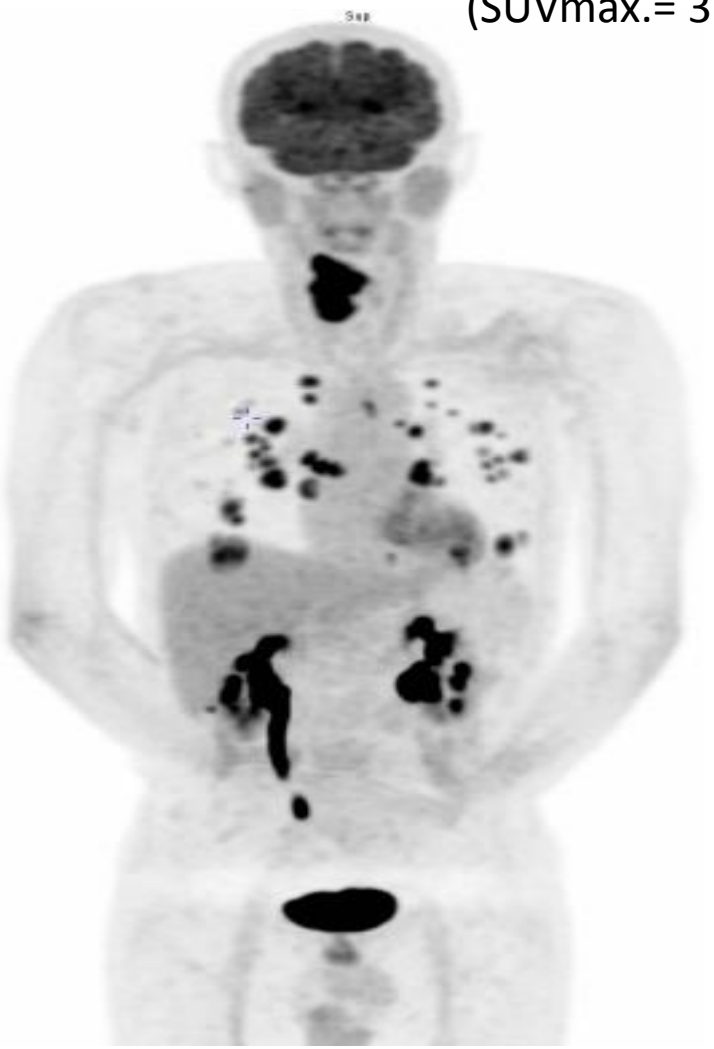
2018.3 initial diagnosis: ADCC of hypopharynx with lung metastasis, cT4aN0M1

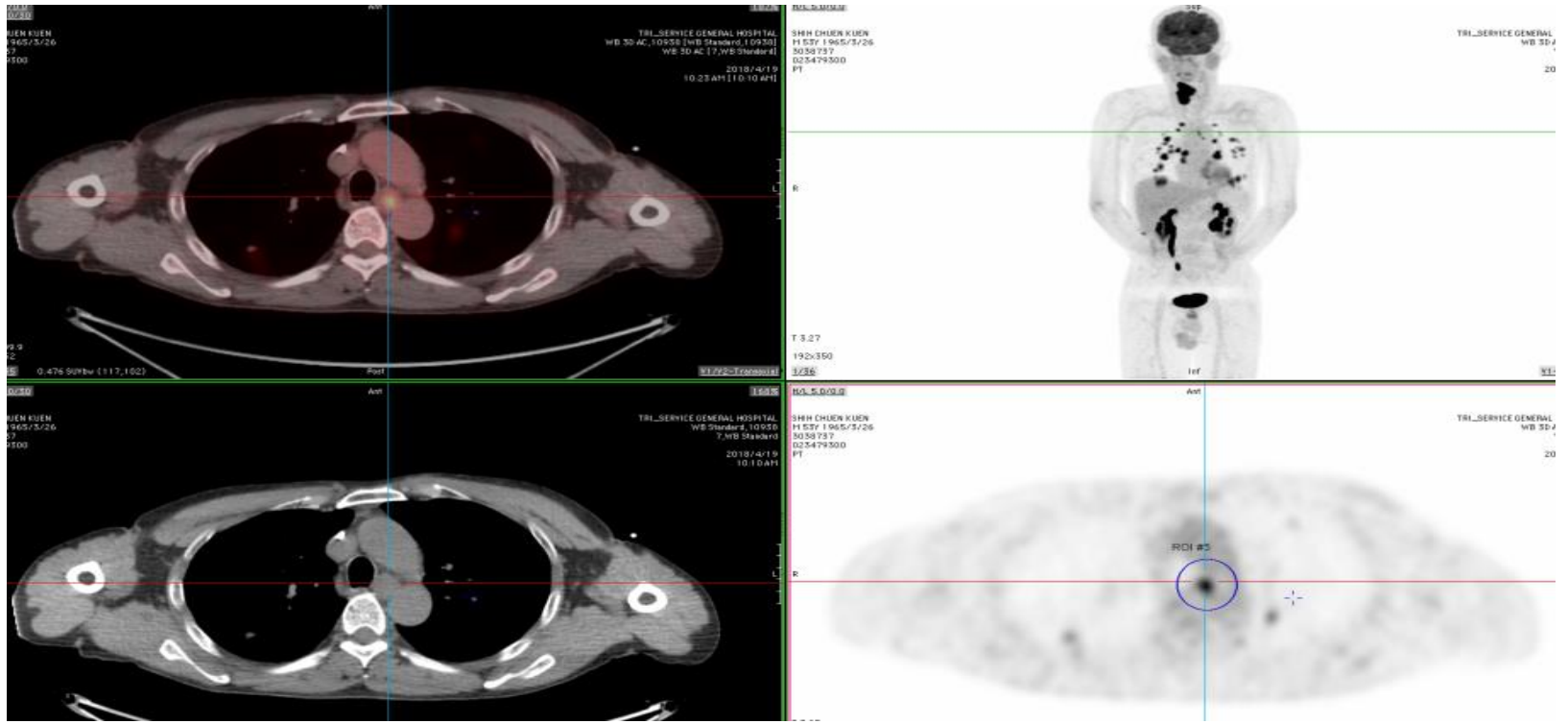


Adenoid cystic carcinoma of right hypopharynx

20180419

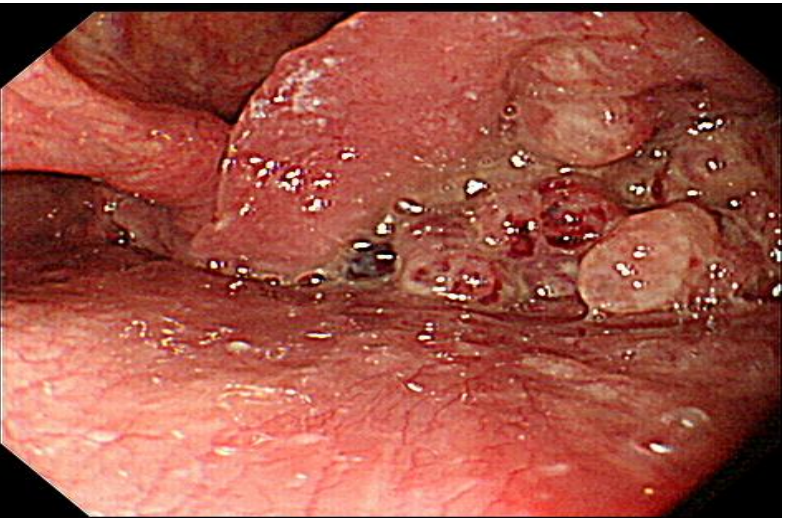
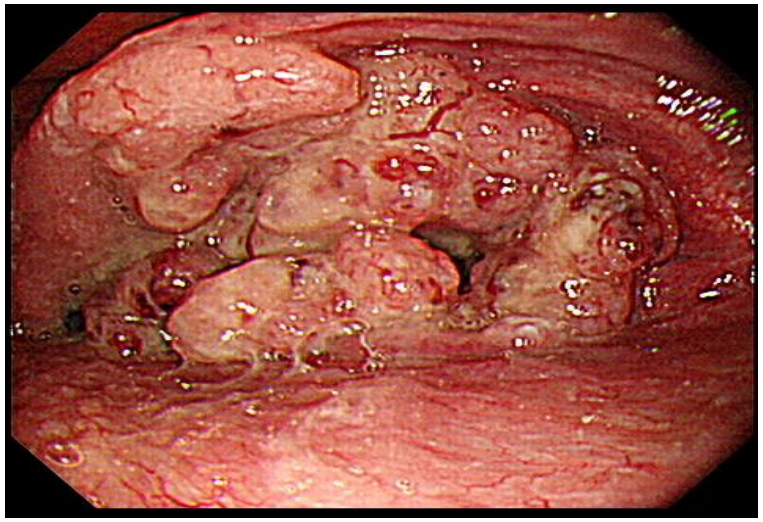
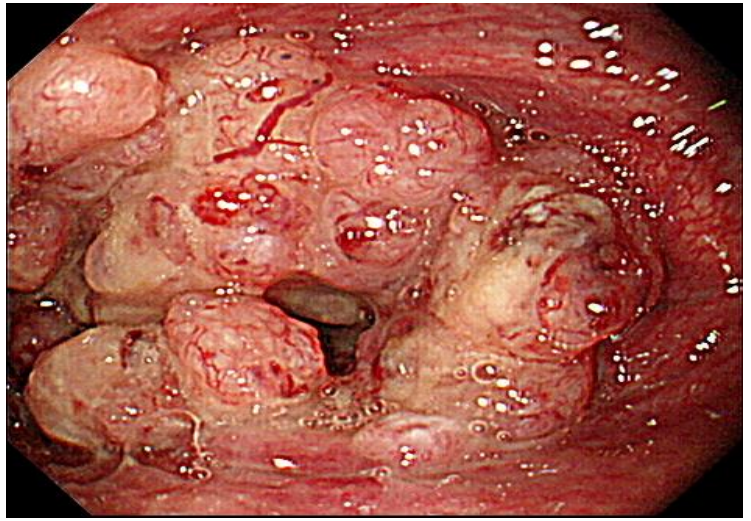
1. mass over the right neck level II/III with hypopharynx, thyroid cartilage and thyroid involvement (SUVmax.= 11.6, size= 6.1 cm) (T4a).
2. Moderate FDG-avidity over esophagus at T5 level (SUVmax.= 4.9).
3. multiple nodules in RUL (SUVmax.= 8.1, size= 1.7 cm), RML (SUVmax.= 7.3, size= 1.5 cm), RLL (SUVmax.= 3.7 cm), LUL (SUVmax.= 5.7, size= 1.5 cm)and LLL (SUVmax.= 9.2, size= 2.1 cm) (M1).





A ulceration mass  from 30 cm to 20 cm, U/3 (biopsy)

20180417

手術前診斷 : A ulceration mass  from 30 cm to 20 cm, U/3 (biopsy)
手術名稱 : biopsy
病理器官 : Esophagus, U/3
病程摘要 :
病理診斷 : Squamous cell carcinoma, moderately differentiated.
報告內容 :
Esophagus, U/3, biopsy --- Squamous cell carcinoma, moderately differentiated.

##################################################
Immunohistochemical stains: "A"
CK: positive for tumor cells.
P40: positive for tumor cells.
Her2/neu: negative staining.
##################################################

# Active Problem

- Adenoid cystic carcinoma of right hypopharynx, cT4aN0M1, stage IVC with multiple lung metastasis
- Squamous cell carcinoma of (from 30 cm to 20 cm), U/3, T2N0M0-1 (suspected lung metastases)

# Medication treatment ?

(1) Pembrolizumab (KN048, mono)

(2) Pembrolizumab + PF regimen (KNO48, combo) (KN590, IO combo)

(3) Extreme regimen (Erbitux+PF)

(4) PF regimen (KN590, control)

# Medication treatment ?

(1) Pembrolizumab (KN048, mono)

(2) Pembrolizumab + PF regimen (KNO48, combo) (KN590, IO combo)

(3) Extreme regimen (Erbitux+PF)

**(4) PF regimen (KN590, control)**

# post CCRT with PF (20180421, 20180501, 20180509,20180717, 20180730)

**Final Diagnosis:** 1. Adenoid cystic carcinoma of the hypopharynx, cT4aN0M1, stage IVC, with partial airway compression and lung metastasis, s/p CCRT 2. Squamous cell carcinoma, moderately differentiated, of the esophagus, 20-30 cm, cT2N0M0

**RT goal:** Curative

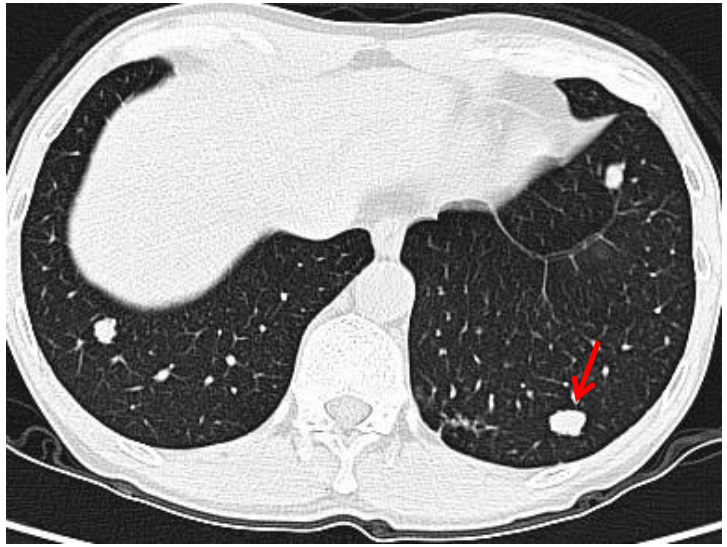
**Combination with chemotherapy:** CCRT

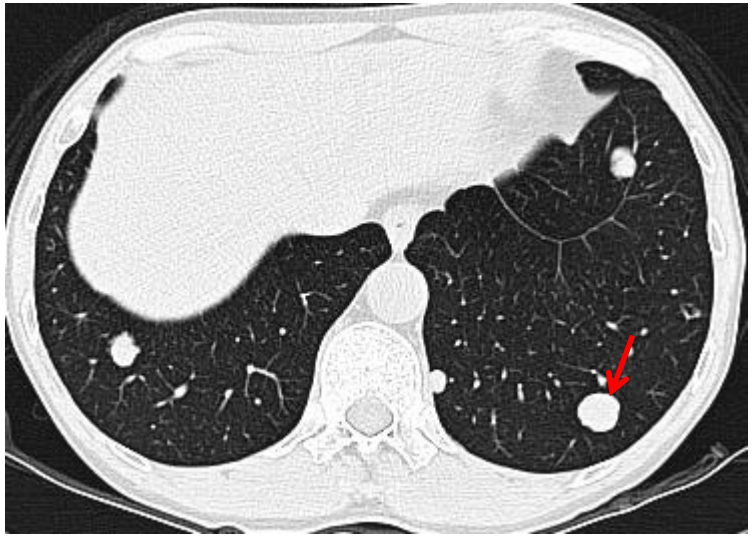
**RT treatment course:**

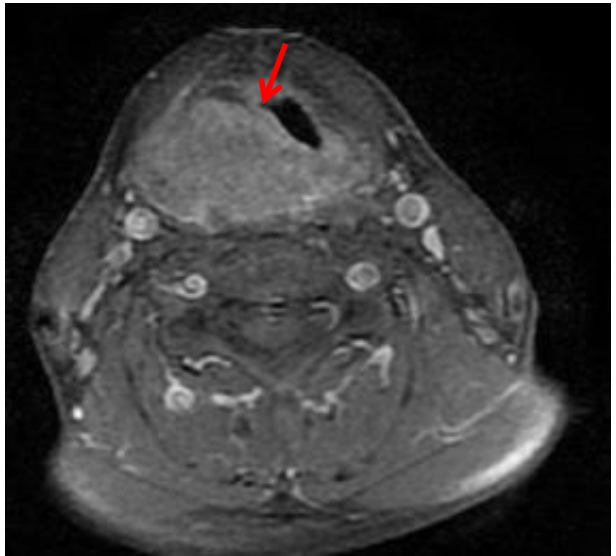
| Target | Target sites | Technique | Dose per fraction(cGy) | No. of fractions | Total dose:P.D./N.D.(cGy) | Starting/Termination Data | Total tx. datys |
|---|---|---|---|---|---|---|---|
| T | Hypopharyngeal tumor | IMRT<br>6MV photon | 205.4 | 35.0 | P:7000.0<br>N:7189.0 | S:107/05/04<br>T:107/06/22 | 48 |
| N | High risk nodal areas | IMRT<br>6MV photon | 171.4 | 35.0 | P:6000.0<br>N:5999.0 | S:107/05/04<br>T:107/06/22 | 48 |
| N | Low risk nodal areas | IMRT<br>6MV photon | 154.2 | 35.0 | P:5400.0<br>N:5397.0 | S:107/05/04<br>T:107/06/22 | 48 |
| | | | | | P:<br>N: | S:<br>T: | |
| PTV1=Gross tumor; PTV 2=High risk lymphatic drainage area; PTV 3=Low risk lymphatic drainage area | | | | | | | |
| Interruption of treatment day during RT. **P.D. : Prescribed dose ; N.D. : Nominal dose** | | | | | | | |

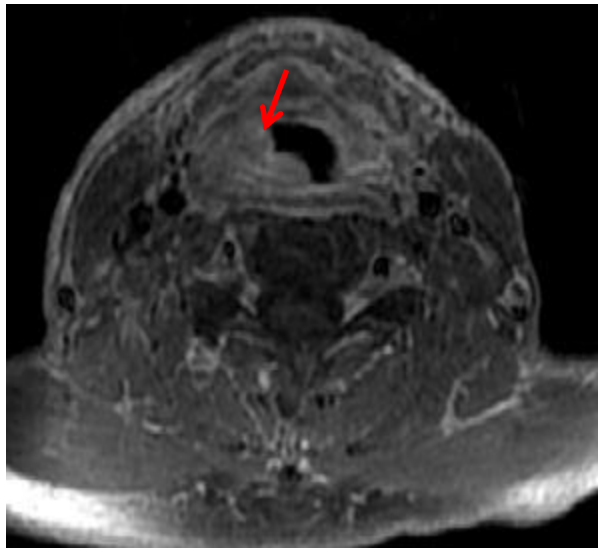
**Post-radiotherapy assessment and comments:**
1.Acute Radiation Toxicity: Radiation Laryngitis (Gr.3)
2.Response at Completion of RT: Other
3.Comments: The patient has completed CCRT and he tolerated well. RT OPD FU was advised.

2018.07:
s/p CCRT with PF: lung mild progression, hypopharynx PR









# Next Medication treatment ?

(1) Pembrolizumab (KN048, mono)

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(3) Extreme regimen (Erbitux+PF)

(4) PF regimen (KN590, control)

(5) Pembrolizumab+ platinum+ taxanes

# Next Medication treatment ?

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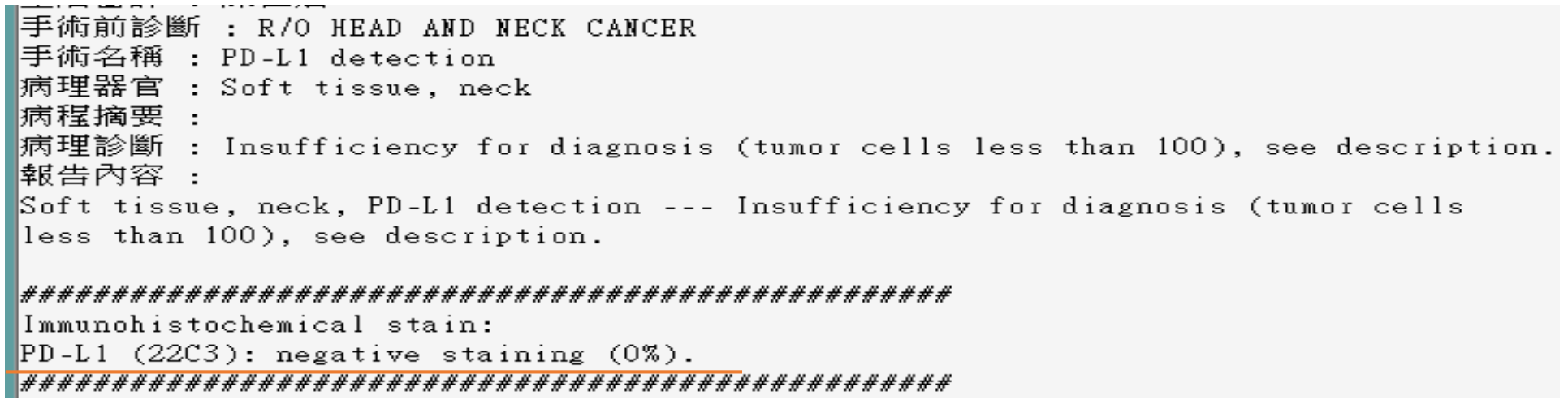

手術前診斷 : R/O HEAD AND NECK CANCER
手術名稱 : PD-L1 detection
病理器官 : Soft tissue, neck
病程摘要 :
病理診斷 : Insufficiency for diagnosis (tumor cells less than 100), see description.
報告內容 :
Soft tissue, neck, PD-L1 detection --- Insufficiency for diagnosis (tumor cells less than 100), see description.

##################################################
Immunohistochemical stain:
PD-L1 (22C3): negative staining (0%).
##################################################

經濟OK

# Next Medication treatment ?

(1) Pembrolizumab (KN048, mono)

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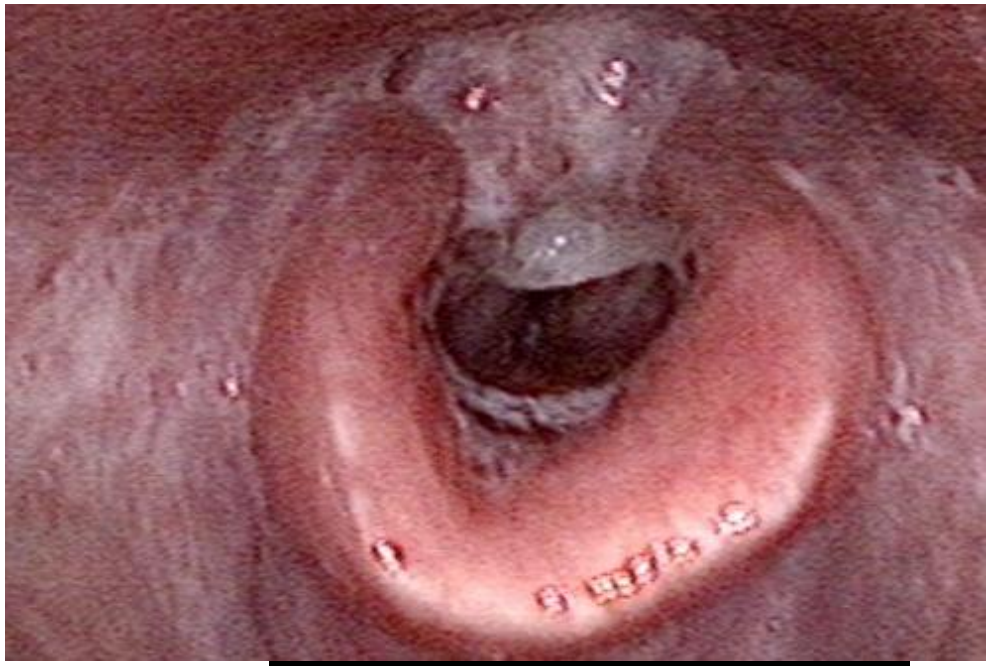
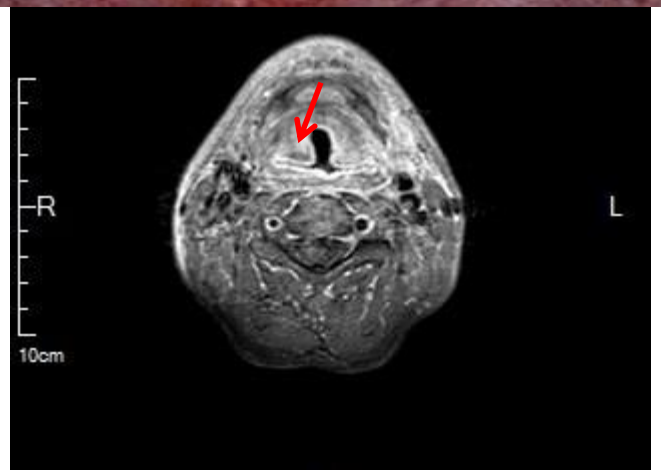
Soft tissue, neck, PD-L1 detection --- Insufficiency for diagnosis (tumor cells less than 100), see description.

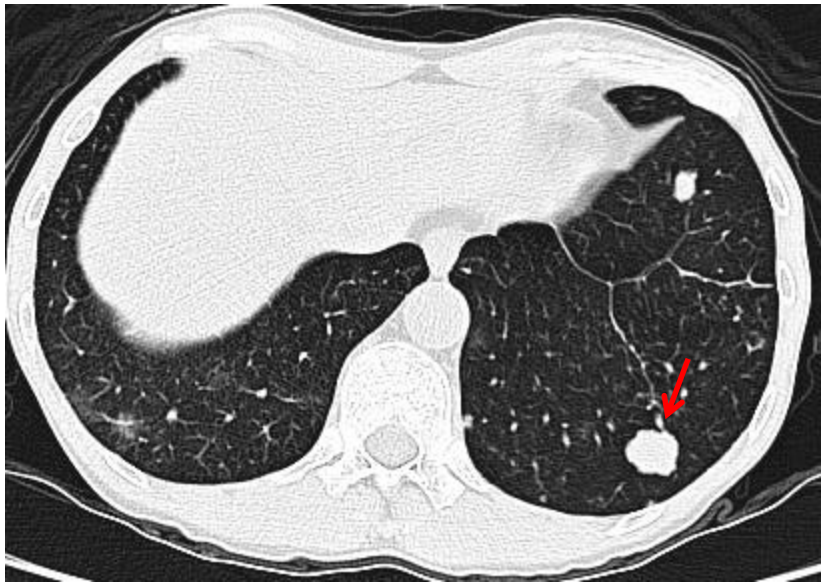
##################################################
Immunohistochemical stain:
PD-L1 (22C3): negative staining (0%).
##################################################

shift to Pembrolizumab, tri-weekly, Carboplatin + Paclitaxel, d1,d8,tri-weekly (20180828,20180925, 20181015, 20181107)

2018.12:
lung mild progression (stable), hypopharynx nearly CR



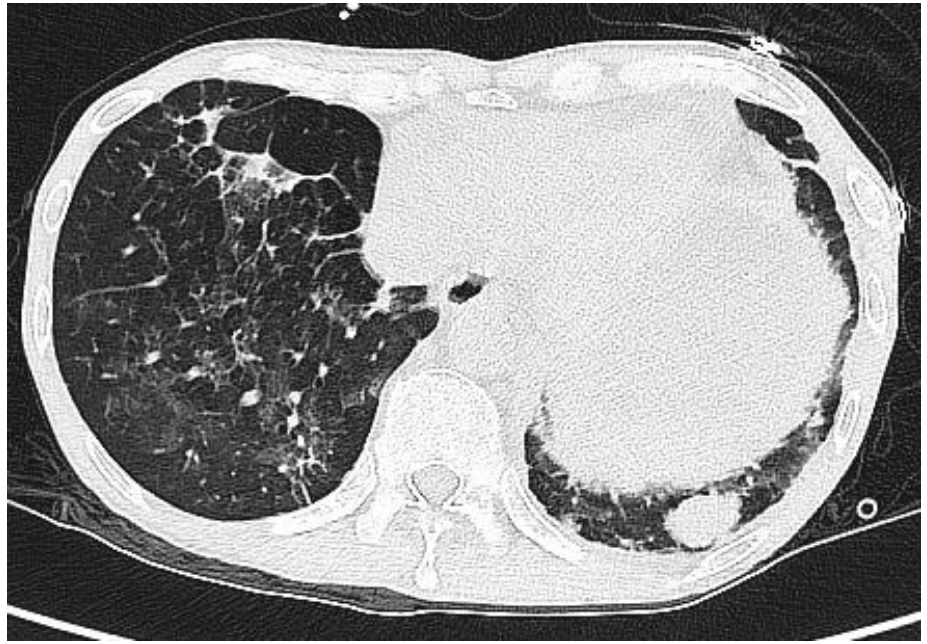


shift to Pembrolizumab, tri-weekly, + Carboplatin + Paclitaxel, d1,d8,tri-weekly (20180828,20180925, 20181015, 20181107), pembrolizumab + Paclitaxel (20190108, 20190319), pembrolizumab + Docetaxel (20190430, 20190618), pembrolizumab (20190710)

Pembrolizumab+-(platinum+ taxanes): 12months

201908 lung metastasis progression



201908 Aspiration pneumonia with acute respiratory failure, hospice care

# Medication treatment ?

**Self-reflection**

(1) Pembrolizumab (KN048, mono)

(2) Pembrolizumab + PF regimen (KNO48, combo) (KN590, IO combo)

(3) Extreme regimen (Erbitux+PF)

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# Medication treatment ?

**Self-reflection**

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(3) Extreme regimen (Erbitux+PF)

(4) PF regimen (KN590, control)

# Take home message

Case 1: 1 line combination

Case 2: 1 line mono

Case 3: Adenoid cystic carcinoma, lung or pleural metastases

# NCCN Guidelines Version 1.2023 Very Advanced Head and Neck Cancer

## PRINCIPLES OF SYSTEMIC THERAPY FOR NON-NASOPHARYNGEAL CANCERS

(Oral Cavity [including mucosal lip],Oropharynx,Hypopharynx,Glottic Larynx,Supraglottic Larynx,Ethmoid Sinus,Maxillary Sinus, and Occult Primary)

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

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

#### Preferred Regimens

**First-Line[c]**

- **Pembrolizumab/platinum (cisplatin or carboplatin)/5-FU** (category 1)[c,30]
- **Pembrolizumab (for tumors that express PD-L1 with CPS ≥ 1)**[c,30] (category 1)

**Subsequent-Line (if not previously used)**

- Nivolumab[31] (if disease progression on or after platinum therapy) (category 1)
- **Pembrolizumab**[32-34] (if disease progression on or after platinum therapy) (category 1)

#### Other Recommended Regimens (First-and Subsequent-Line)

**Combination Regimens**

- Cetuximab/platinum(cisplatin orcarboplatin)/5-FU35 (category 1)
- Cisplatin/cetuximab[36]
- Cisplatin or carboplatin/docetaxel[37] or paclitaxel[38]
- Cisplatin/5-FU[35,39]
- Cisplatin or carboplatin/docetaxel/cetuximab[40]
- Cisplatin or carboplatin/paclitaxel/cetuximab[41]
- Pembrolizumab/platinum(cisplatin or carboplatin) /docetaxel[30,37]
- Pembrolizumab/platinum(cisplatin or carboplatin) /paclitaxel (category 2B)[30,38]

**Single Agents**

- Cisplatin[35,42]
- Carboplatin[43]
- Paclitaxel[44]
- Docetaxel[45,46]
- 5-FU[42]
- Methotrexate[35,47]
- Cetuximab[40,48]
- Capecitabine [50]
- Afatinib[51] (subsequent-line only, if disease progression on or after platinum therapy) (category 2B)

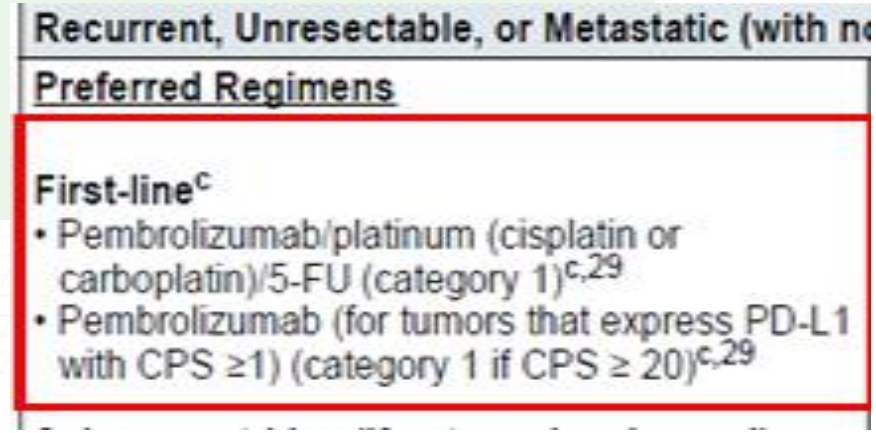
#### Useful in Certain Circumstances (First- and Subsequent-Line)

- Squamous cell carcinoma
  - Cetuximab/nivolumab[52]
  - Cetuximab/pembrolizumab (category 2B)[53]
- For select ethmoid/maxillary sinus cancers (ie, small cell, SNEC, high-grade olfactory esthesioneuroblastoma, SNUC with neuroendocrine features):
  - Cisplatin/etoposide or carboplatin/etoposide[14]
  - Cyclophosphamide/doxorubicin/ vincristine (category 2B)[15]
- Pembrolizumab(for MSI-H,dMMR,or TMB-H [≥10 mut/Mb]tumors)[54]
- Cisplatin/pemetrexed (for PS 0-1) (category 2B)[55]
- Gemcitabine/paclitaxel (category 2B)[56]

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

Note: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.





# ASCO Guideline 2022 Update

| Recommendations | Type | Evidence Quality | Strength of recommendation |
|---|---|---|---|
| PD-L1 immunohistochemistry testing **should be performed** in patients with recurrent or metastatic HNSCC | Evidence based, benefits outweigh harms | High | Strong |
| PD-L1 combined positive score **(CPS) ≥ 1 should be interpreted** as positive and correlates with a clinical benefit to PD-1 inhibitors | Evidence based, benefits outweigh harms | High | Strong |
| **Pembrolizumab monotherapy** or **pembrolizumab, platinum, and fluorouracil should be offered as first-line** treatment for patients with recurrent or metastatic HNSCC with a **CPS ≥ 1** | Evidence based, benefits outweigh harms | High | Strong |
| **Pembrolizumab, platinum, and fluorouracil may be offered as first-line** treatment for patients with recurrent or metastatic HNSCC with a **CPS < 1** | Evidence based, benefits outweigh harms | Moderate | Strong |

Strength of recommendation - Strong:
- In recommendations for an intervention, the desirable effects of an intervention outweigh its undesirable effects.
- In recommendations against an intervention, the undesirable effects of an intervention outweigh its desirable effects.
- All or almost all informed people would make the recommended choice for or against an intervention.

Quality of evidence
**High:** We are very confident that the true effect lies close to that of the estimate of the effect.
**Moderate:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Please refer to the complete guideline to view the most recent and complete version

PD-L1, programmed death ligand-1; CPS, combined positive score; HNSCC: head and neck squamous cell carcinoma

E Yilmaz et al. J Clin Oncol. 2022 Dec 15

KEYTRUDA® (pembrolizumab)