

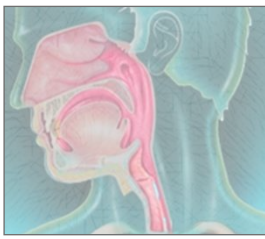
Traitements systémiques des carcinomes épidermoïdes de la tête et du cou

en cours et à venir

1^{ère} journée scientifique « Les cancers ORL »

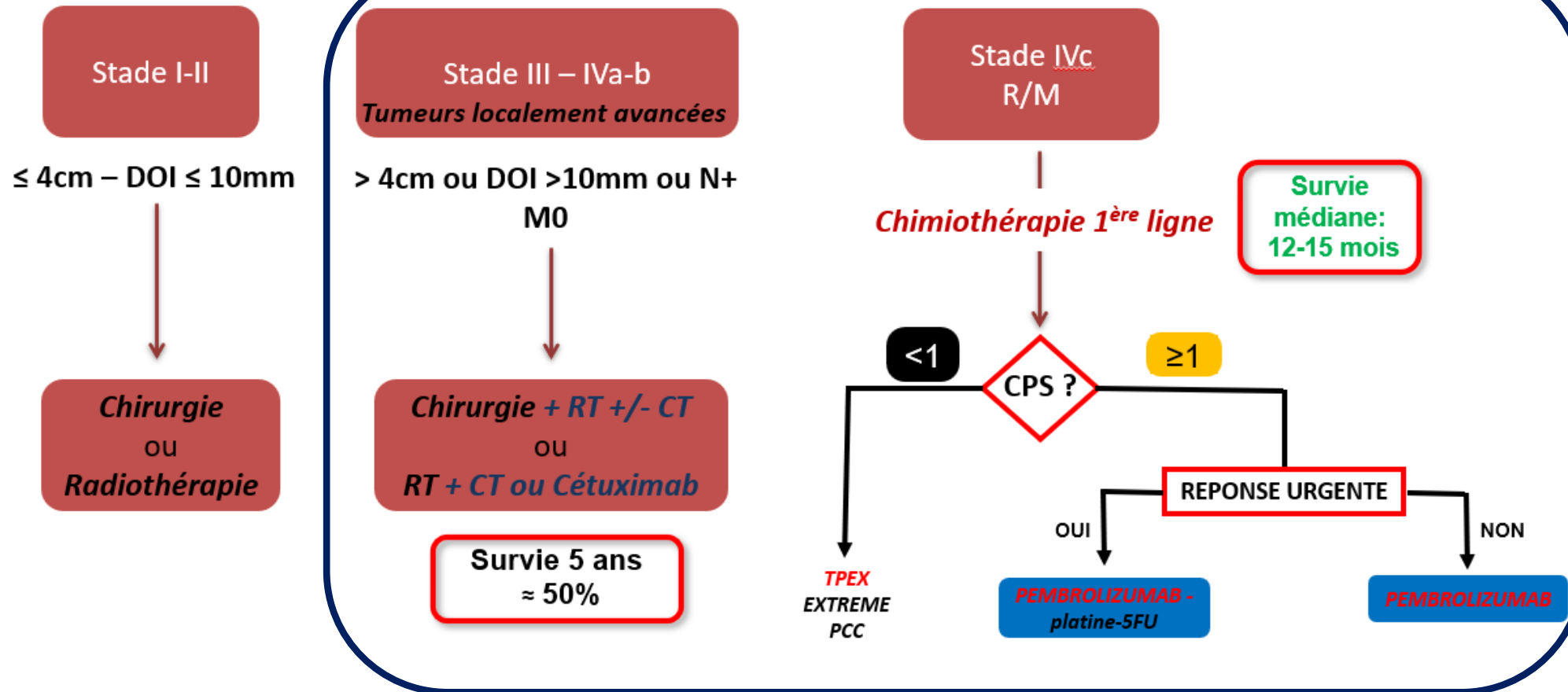


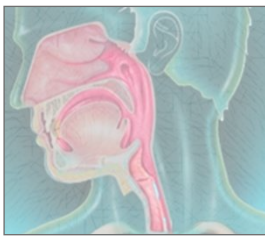
Dr Mickaël BURG Y



TRAITEMENTS STANDARDS ACTUELS


Stratégies en fonction du stade





Les agents thérapeutiques

Taxanes



sels de platine

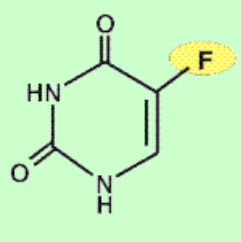
N[Pt](Cl)(Cl)N

CISPLATINE


N[Pt](Cl)(N1CCC1)N

CARBOPLATINE


5FU

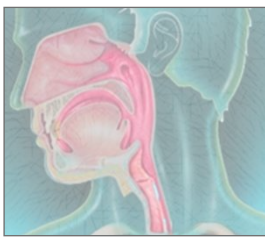


Cetuximab



Nivolumab/Pembrolizumab



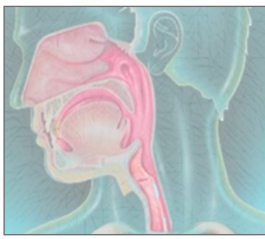


☐ LOCALEMENT AVANCEE

☐ RECIDIVANT / METASTATIQUE (R/M)

➤ *TRAITEMENTS STANDARDS ACTUELS*

➤ *DEFIS ACTUELS – MOLECULES et STRATEGIES FUTURES*



TRAITEMENTS STANDARDS ACTUELS

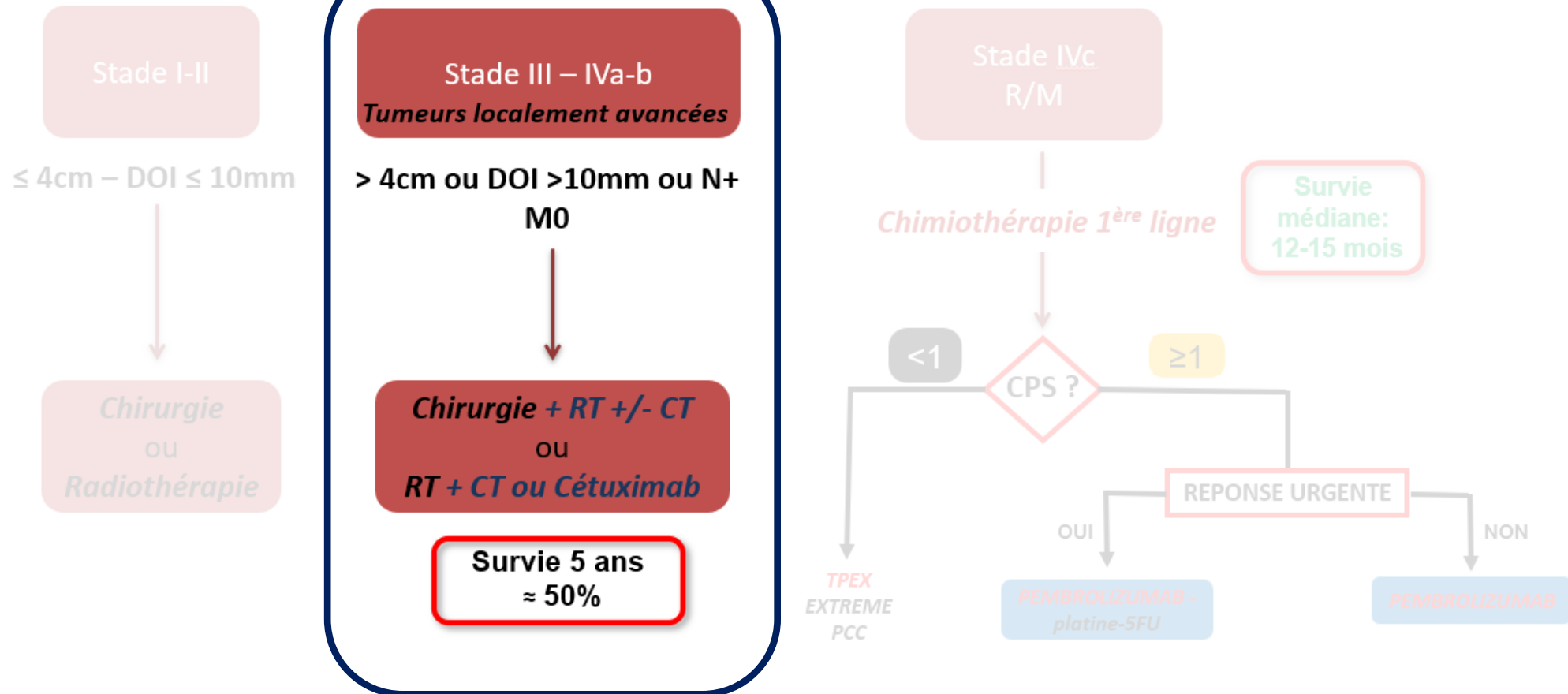
Stratégies en fonction du stade

LOCALEMENT AVANCEE

- Standards actuels
- Molécules et stratégies futures

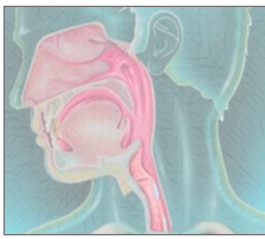
R/M

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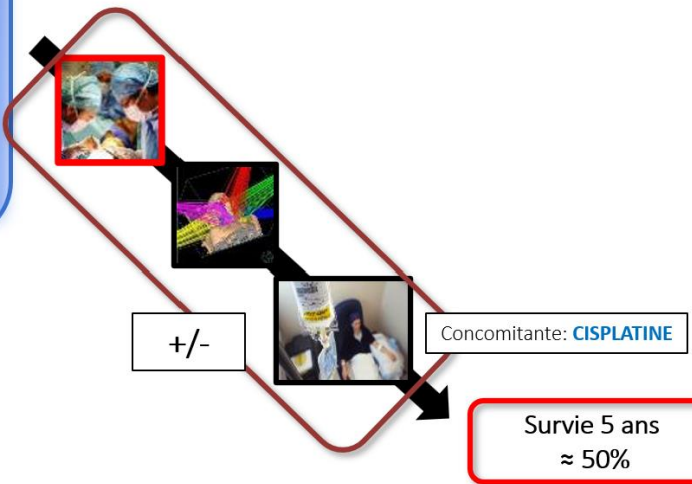
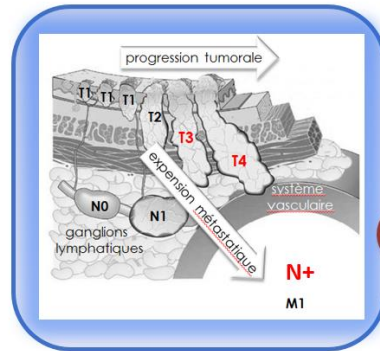


LOCALEMENT AVANCEE

TRAITEMENTS STANDARDS ACTUELS



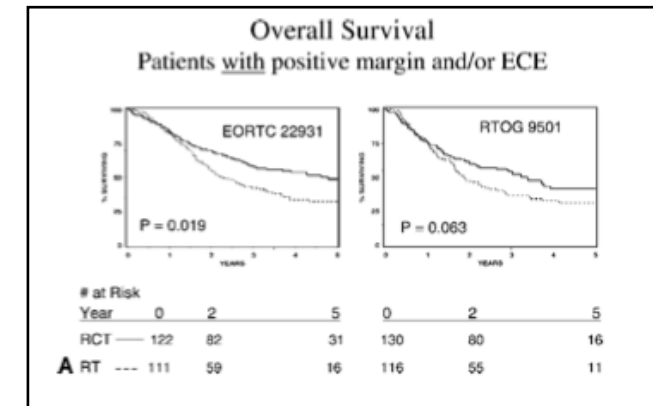
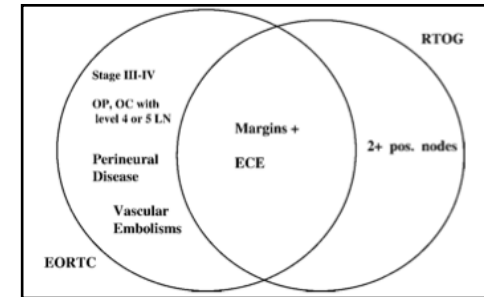
CHIRURGIE PREMIERE



Chimiothérapie concomitante si:
≥ R1 et/ou rupture capsulaire

DECES :
 Rechute LR : 40%
 Métastases : 30%
 2eme cancers : 10%
 Comorbidités : 20%

RT +/- CDDP 3W:
EORTC 22931
RTOG 9501



LOCALEMENT AVANCEE

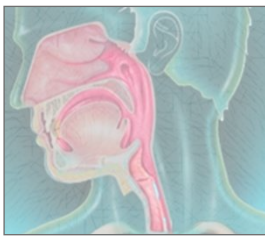
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R/M

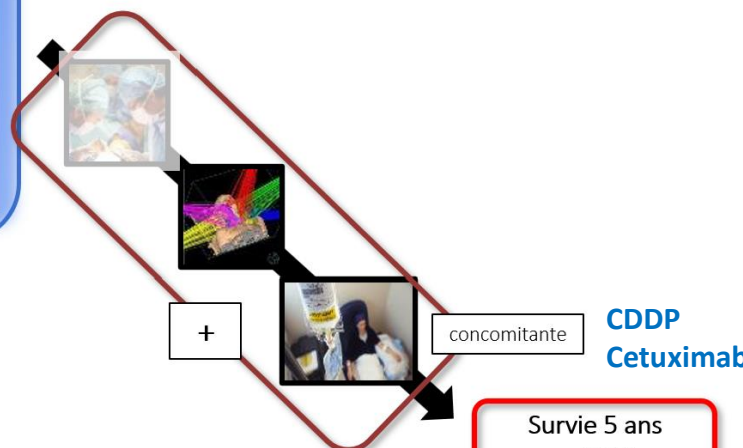
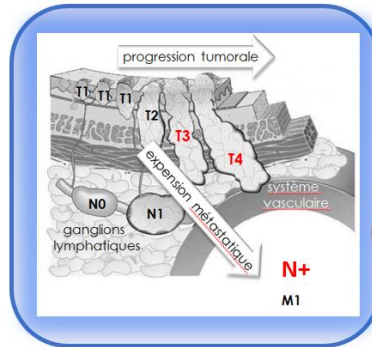
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LOCALEMENT AVANCEE

TRAITEMENTS STANDARDS ACTUELS



TUMEUR EN PLACE



Survie 5 ans
≈ 50%

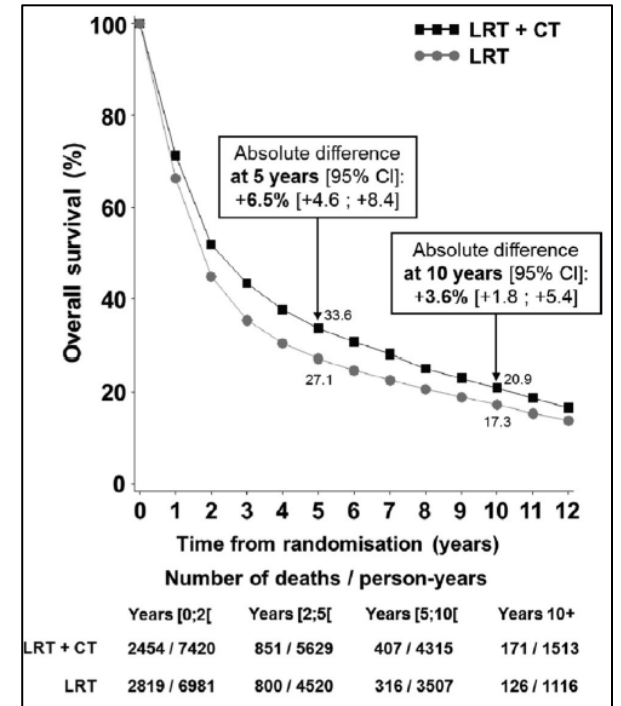
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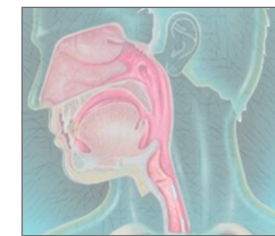
R/M

- Standards actuels
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Pignon J-P MACH-NC Collaborative Group. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): An update on **107 randomized trials and 19,805 patients**, on behalf of MACH-NC Group. Radiother Oncol. 2021

MOLECULES et STRATEGIES FUTURES



LOCALEMENT AVANCEE

- *Standards actuels*
- *Molécules et stratégies futures*

R/M

- *Standards actuels*
- *Molécules et stratégies futures*



Nouvelles molécules

Nouvelles stratégies thérapeutiques ?

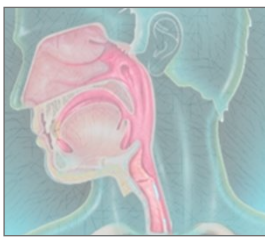
Nouvelles associations ?



**INNOVATION
THERAPEUTIQUE**

LOCALEMENT AVANCEE

NOUVELLES STRATEGIES THERAPEUTIQUES ?



Pembrolizumab néoadjuvant et adjuvant : KN-689

LOCALEMENT AVANCEE


- Standards actuels
- Molécules et stratégies futures

R/M

- Standards actuels
- Molécules et stratégies futures

Dual primary end
1) Major patholo
within resecte
nodes)
2) Event-free su

Resectable non –
metastatic
squamous cell
carcinoma of the
head and neck

 MERCK

**Merck's KEYTRUDA[®]
(pembrolizumab) Met Primary
Endpoint of Event-Free Survival
(EFS) as Perioperative Treatment
Regimen in Patients With Resected,
Locally Advanced Head and Neck
Squamous Cell Carcinoma**

KEYNOTE-689 is the first Phase 3 trial to demonstrate statistically significant and clinically meaningful improvement in EFS in the intent-to-treat population in the neoadjuvant and adjuvant setting for an anti-PD-1 therapy in earlier stages of head and neck squamous cell carcinoma

October 08, 2024 06:45 AM Eastern Daylight Time

Adjuvant treatment

High risk
Pembrolizumab 200 mg/3 weeks
(15 Cycles)
Radiotherapy + cisplatin

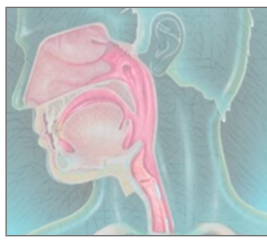
Low risk
Pembrolizumab 200 mg/3 weeks
(15 Cycles)
Radiotherapy

High risk
Radiotherapy + cisplatin

Low risk
radiotherapy

LOCALEMENT AVANCEE

NOUVELLES STRATEGIES THERAPEUTIQUES ?



DEESCALADE THERAPEUTIQUE – place de l'immunochimiothérapie néoadjuvante

pCR: most effective combination in HNSCC

➤ **TPF: 13.4%** 124 patients Zhong L ping et al J Clin Oncol. 2013

➤ **Single-agent PD-1 inhibitor: non rapporté**

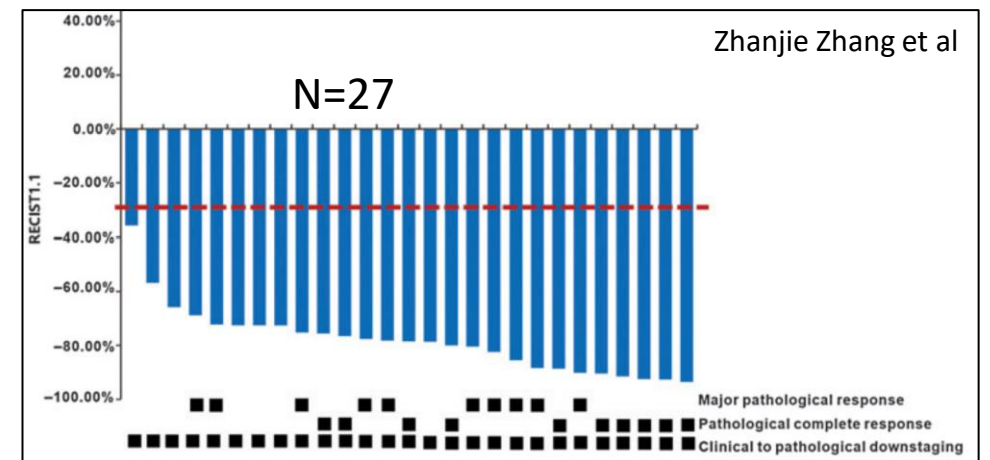
➤ **Immuno-chimiothérapie: 35% - 42%**

PD 0% - 14% (1 seul étude)

MPR 44-100%

Wise-Draper Clin Cancer Res 2022
Uppaluri Clin Cancer Res 2020
JD Schoenfeld JAMA Oncol 2020
LP Zhong J Clin Oncol 2013
Z Zhang Clin Cancer Res 2022

Neoadjuvant ICT for the Treatment of Locally Advanced HNSCC: Phase 2 Clinical Trial



LOCALEMENT AVANCEE

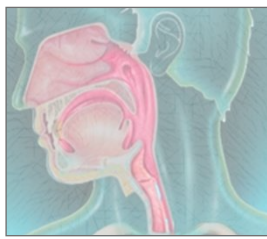
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R/M

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LOCALEMENT AVANCEE

NOUVELLES STRATEGIES THERAPEUTIQUES ?



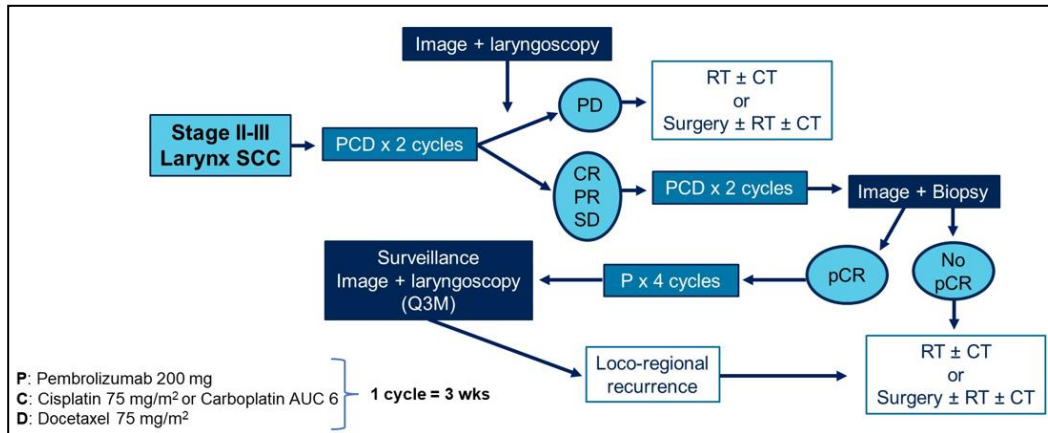
DEESCALADE THERAPEUTIQUE – place de l'immunochimiothérapie néoadjuvante

LOCALEMENT AVANCEE

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R/M

- Standards actuels
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Immuno-Chemotherapy as single treatment modality for Larynx Preservation (ICoLP)

23 patients évaluable
(T3: 54.2%, N1:16.7%)

pCR	N (%)
Yes	18 (78.3%)
No	4 (17.4%)
Equivocal	1 (4.3%)

Immuno-CT only: 47.8% (11/23 pts)
= no gastrostomy tube or tracheostomy

5 pCR durable > 1y

MOLECULES et STRATEGIES FUTURES



LOCALEMENT AVANCEE

- *Standards actuels*
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R/M

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Nouvelles stratégies thérapeutiques ?

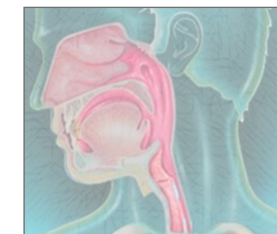
Nouvelles associations ?



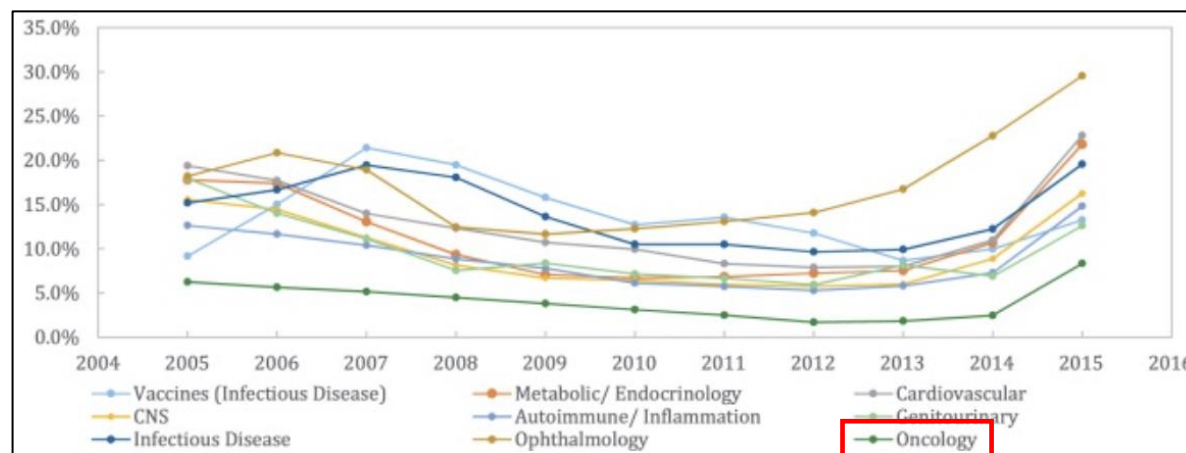
**INNOVATION
THERAPEUTIQUE**

RECIDIVANT / METASTATIQUE

Clinical Trials



NOUVELLES MOLECULES



Probability of success (POS) of a clinical trial

2012: 1,7 %
2014: 2.5%
2015: 8.3%

Oncology: 3.4% success rate

Median duration for oncology trials (Phases 1 - 3): **13 years**

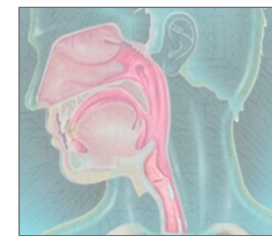
All indications (industry)								
	Phase 1 to Phase 2		Phase 2 to Phase 3			Phase 3 to Approval		Overall
	POS		POS	POS		POS		POS, %
	1,2, %		2,3, %	2,APP, %		3,APP, %		
Therapeutic group	Total paths	(SE, %)	Total paths	(SE, %)	(SE, %)	Total paths	(SE, %)	(SE, %)
Oncology	17 368	57.6	6533	32.7	6.7	1236	35.5	3.4

- LOCALEMENT AVANCEE
 - Standards actuels
 - Molécules et stratégies futures

- R/M
 - Standards actuels
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RECIDIVANT / METASTATIQUE

NOUVELLES MOLECULES



☐ LOCALEMENT AVANCEE

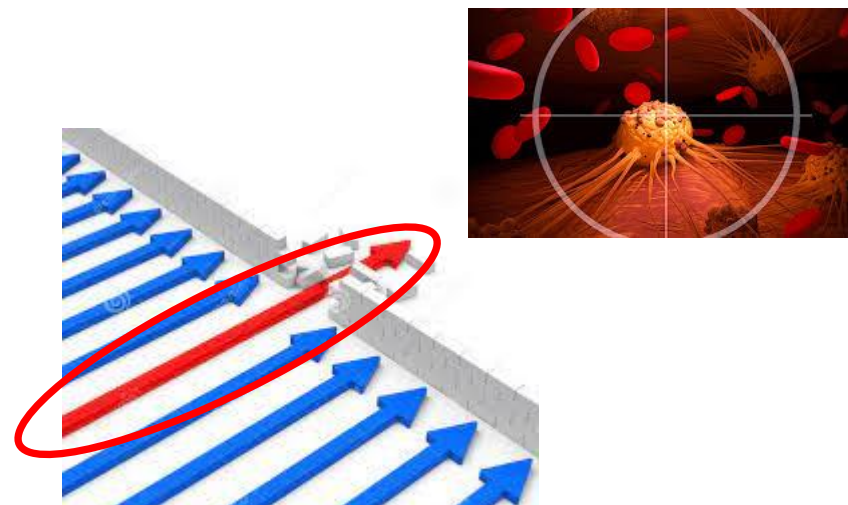
- Standards actuels
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☐ R/M

- Standards actuels
- Molécules et stratégies futures



366 Antineoplastic and immunomodulating agents
(ATC code L01)



Cisplatine

1980

Cetuximab

2008

Nivolumab/Pembrolizumab

2016-2017

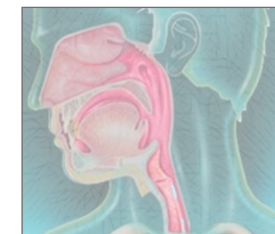
CETEC: 40 ans d'innovation thérapeutique...

Place **marginale** de la génétique dans les CETEC

- Amplification HER 2 <1%
- Fusion NTRK et RET <3%
- HRAS: 4%
- Activation PIK3CA: 30-35% - **échec des essais cliniques**

RECIDIVANT / METASTATIQUE

NOUVELLES MOLECULES



LOCALEMENT AVANCEE

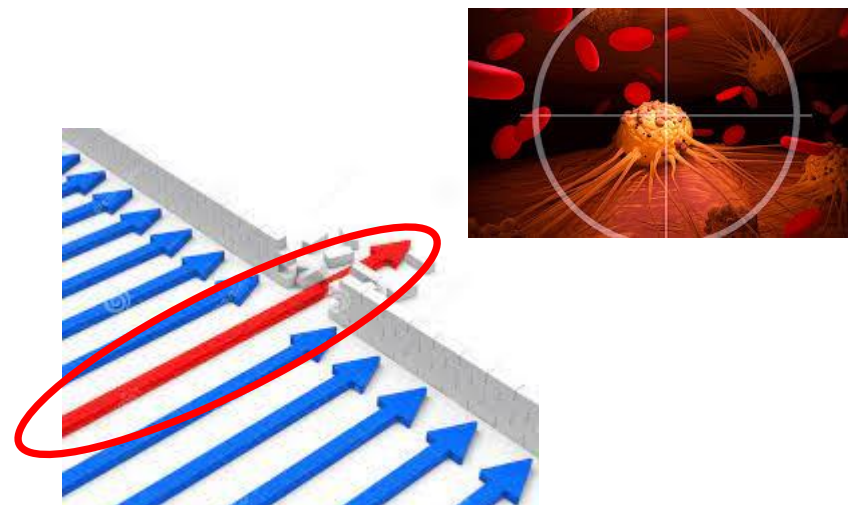
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R/M

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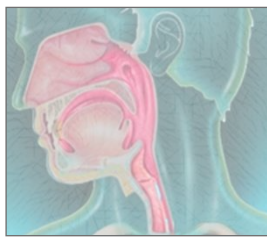
366 Antineoplastic and immunomodulating agents
(ATC code L01)



Uniquement **ESSAI PHASE III** pour confirmation de l'efficacité d'un traitement justifiant son AMM et son remboursement

LOCALEMENT AVANCEE

IMPORTANCE DES ESSAIS PHASE III



DEBIO1143 + Radiothérapie-Cisplatine

Phase II du DEBIO1143 randomisée en double aveugle en association à la RCT avec Cisplatine haute dose dans les CETEC LA à haut risque

LOCALEMENT AVANCEE

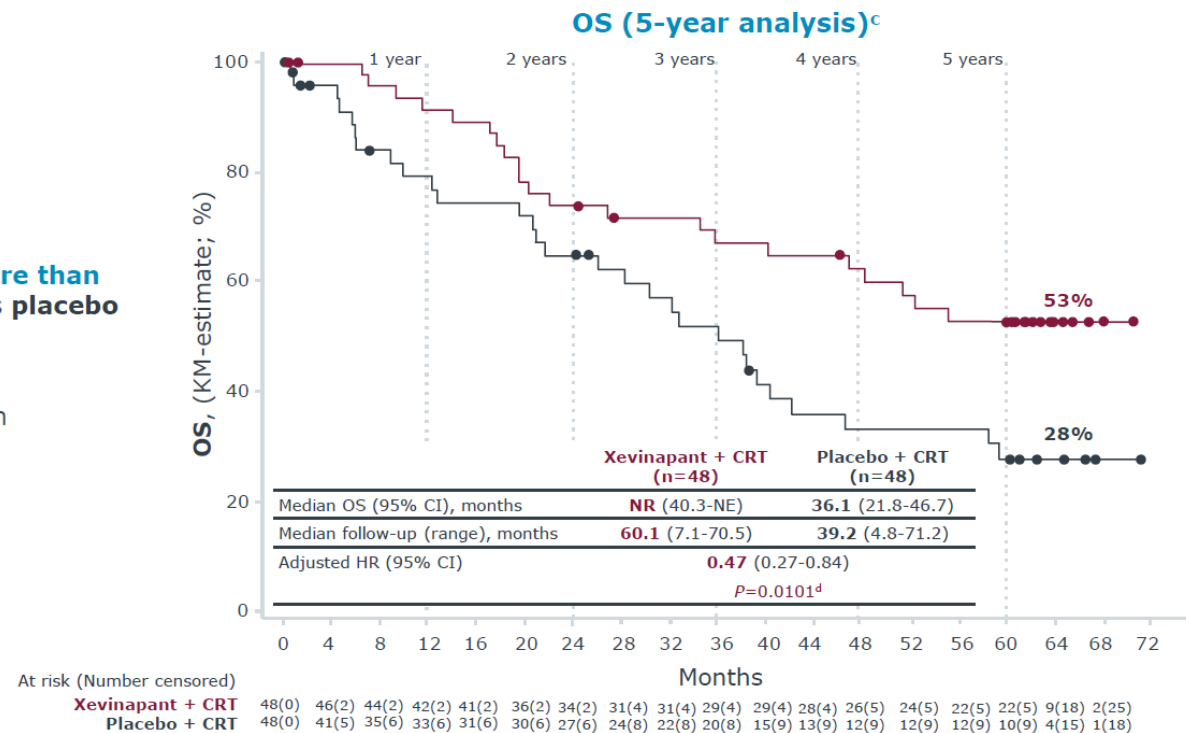
- Standards actuels
- Molécules et stratégies futures

R/M

- Standards actuels
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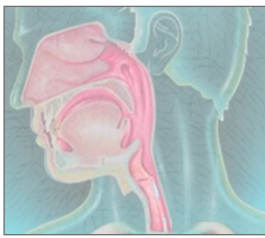
- The risk of death was more than halved with **xevinapant** vs placebo

- Median OS prolonged with **xevinapant** vs placebo



LOCALEMENT AVANCEE

IMPORTANCE DES ESSAIS PHASE III



DEBIO1143 + Radiothérapie-Cisplatine

Etude phase 3 TrilynX ?

LOCALEMENT AVANCEE

- Standards actuels
- Molécules et stratégies futures

R/M

- Standards actuels
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24 JUN 2024 | DARMSTADT, GERMANY

MERCK

Not intended for UK-, US- or Canada-based media

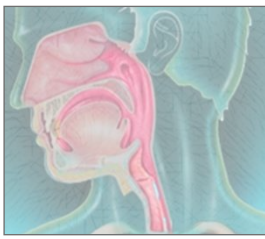
Merck, a leading science and technology company, today announced the discontinuation of the Phase III randomized TrilynX study evaluating xevinapant plus chemoradiotherapy (CRT) in patients with unresected locally advanced squamous cell carcinoma of the head and neck (LA SCCHN). The decision follows a pre-planned interim analysis performed by the study's Independent Data Monitoring Committee, which found that the trial would be unlikely to meet its primary objective of prolonging event-free survival. Top-line safety data were overall compatible with the chemo-radio sensitizing properties of xevinapant. The company will conduct an in-depth review of the data and will share the results in a peer-reviewed forum.

LA SCCHN has proven to be a difficult-to-treat form of cancer. CRT has remained the standard of care for decades, despite multiple studies designed to improve outcomes with new treatment approaches, including multiple immunotherapy trials.

"We sincerely thank the patients, caregivers and clinical investigators who participated in this trial," said Danny Bar-Zohar, Global Head of Research & Development and Chief Medical Officer for the Healthcare business sector of Merck. "While we are disappointed by these results, we remain steadfast in our commitment to develop transformative medicines within our oncology portfolio for areas of high unmet need."

Given the totality of the data, the company decided to also stop the Phase III clinical trial X-Ray Vision (xevinapant plus radiotherapy, compared to placebo plus radiotherapy) in patients who underwent resection of locally advanced head and neck cancer.

Merck is working to develop and deliver new treatment options that exploit the vulnerabilities of tumor cells. The company is exploring modalities including antibody drug conjugates (ADCs) and DNA damage response (DDR) inhibitors, across multiple tumor types, including many that have proven difficult to treat where there are significant unmet needs for patients. The company's support for the head and neck cancer community remains steadfast with Erbitux[®], approved in combination with radiotherapy for the initial treatment of locally advanced SCCHN, and which continues to be studied in more than 200 active clinical trials, including at least 15 Phase III studies.



TRAITEMENTS STANDARDS ACTUELS

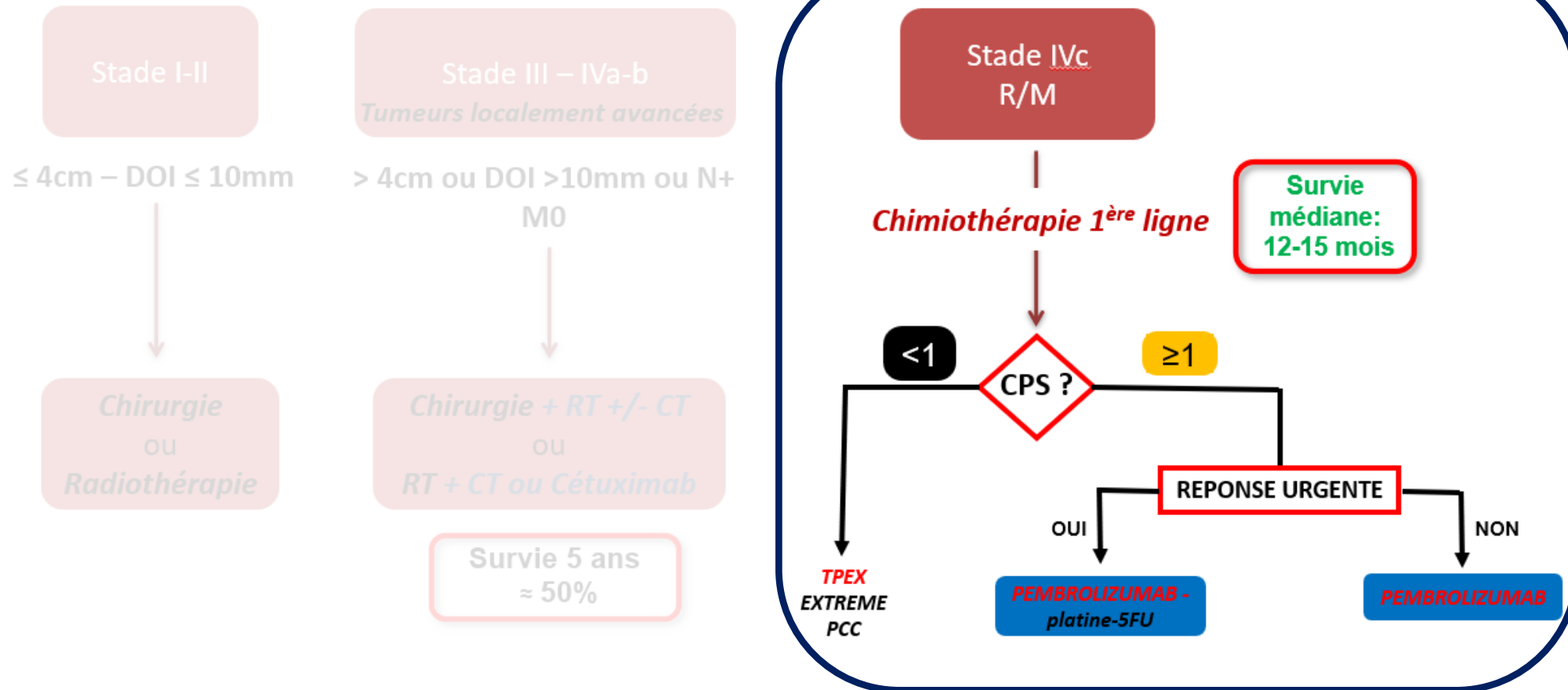
Stratégies en fonction du stade

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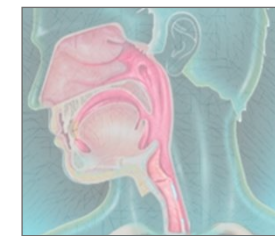
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RECIDIVANT / METASTATIQUE



TRAITEMENTS STANDARDS ACTUELS

Pembrolizumab
vs Pembrolizumab+Chimiothérapie
vs EXTREME

1ère ligne R/M
Keynote 048

LOCALEMENT AVANCEE

- Standards actuels
- Molécules et stratégies futures

R/M

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- Molécules et stratégies futures

Principaux critères d'inclusion

- CE de l'oropharynx, cavité orale, hypopharynx, ou larynx
- Stade R/M incurable par traitements localisés
- ECOG PS 0 ou 1
- Evaluation tissulaire du statut PD-L1
- Statut p16 pour les oropharynx

Facteurs de stratification

- Expression de PD-L1 (TPS ≥ 50% vs <50%)
- Statut p16 pour les oropharynx (positif vs négatif)
- ECOG performance status (0 vs 1)

Pembrolizumab (P)
35 cycles

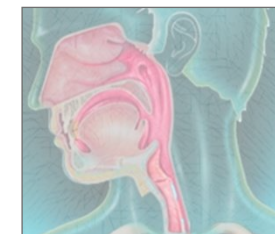
Pembrolizumab (P)
+
Platine - 5FU (C) X6

PMB
35 cycles

EXTREME X6

Cetuximab
250 mg/m²
hebdo

RECIDIVANT / METASTATIQUE



TRAITEMENTS STANDARDS ACTUELS

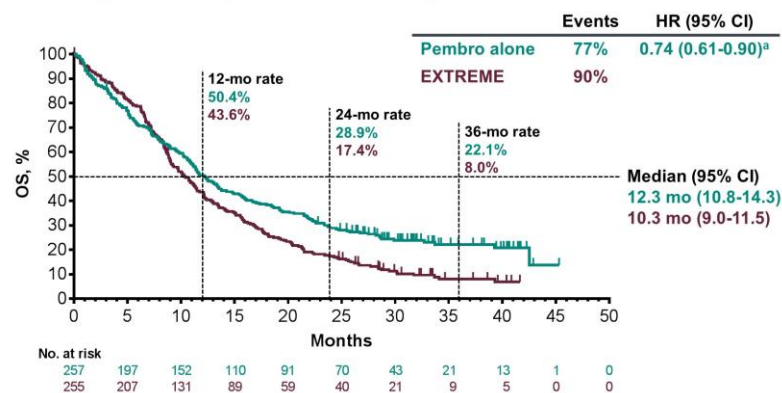
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R/M

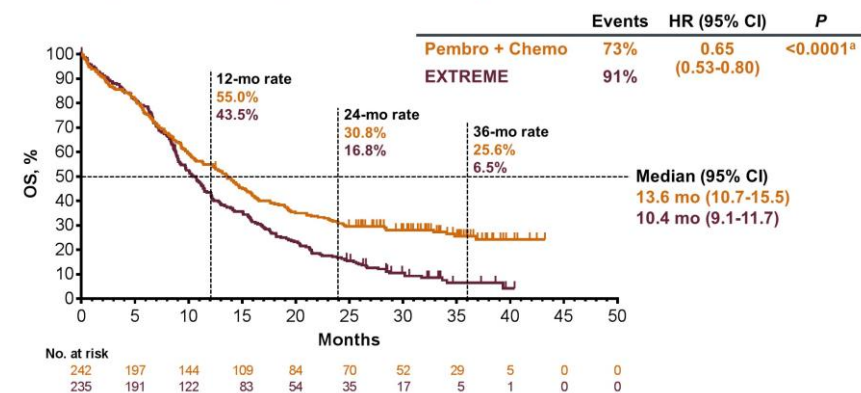
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OS, P vs E, CPS ≥1 Population



^aAt IA2 (data cutoff date: Jun 13, 2018); HR 0.78 (95% CI 0.64-0.96).
 EA (data cutoff date: Feb 25, 2019).

OS, P+C vs E, CPS ≥1 Population

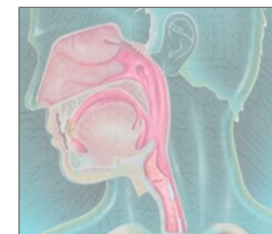


^aStatistically significant at the superiority threshold of P = 0.0026.
 EA (data cutoff date: Feb 25, 2019).

RECIDIVANT / METASTATIQUE

MOLECULES/STRATEGIES FUTURES

DEFIS

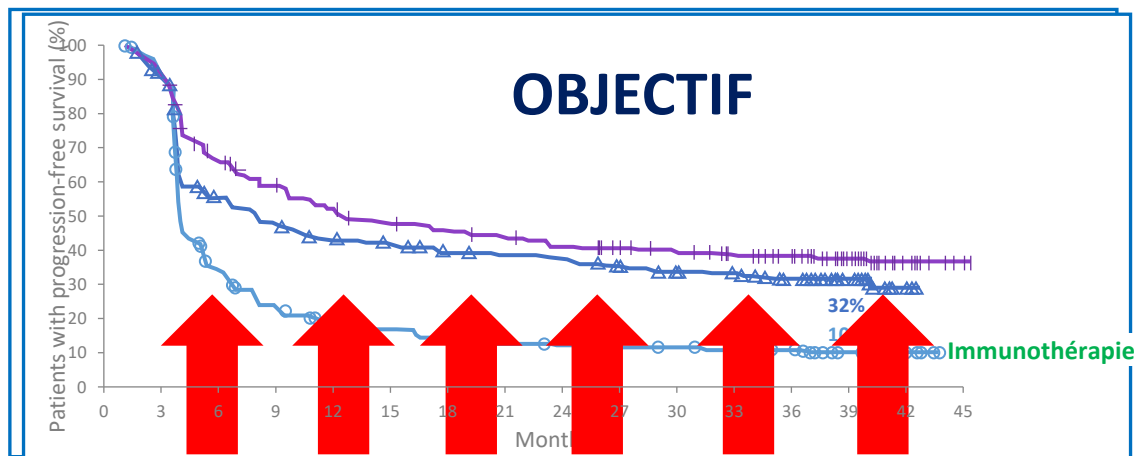


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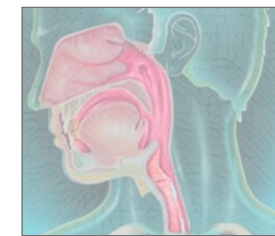
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Immunothérapie + ? +/- chimiothérapie

MOLECULES et STRATEGIES FUTURES



Nouvelles stratégies thérapeutiques ?

Nouvelles associations ?



**INNOVATION
THERAPEUTIQUE**

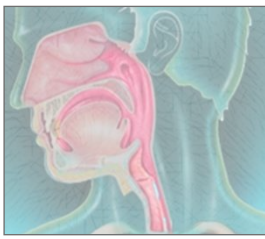
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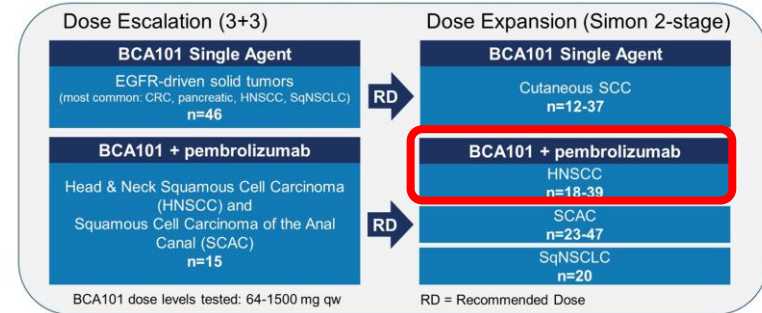
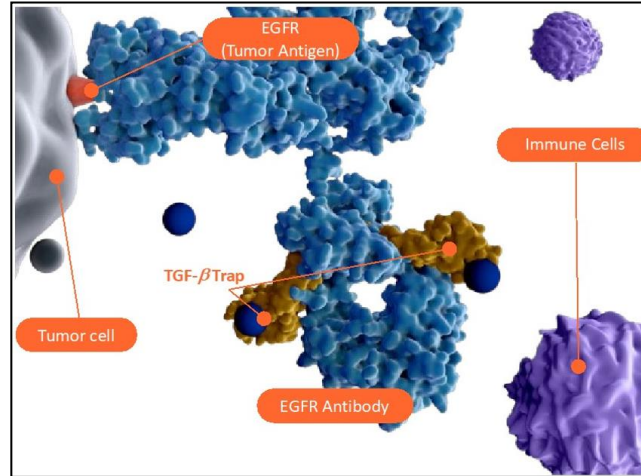
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RECIDIVANT / METASTATIQUE



NOUVELLES MOLECULES

BCA101 inhibiteur bispécifique EGFR/TGFβ
+ Pembrolizumab Phase 1/1b



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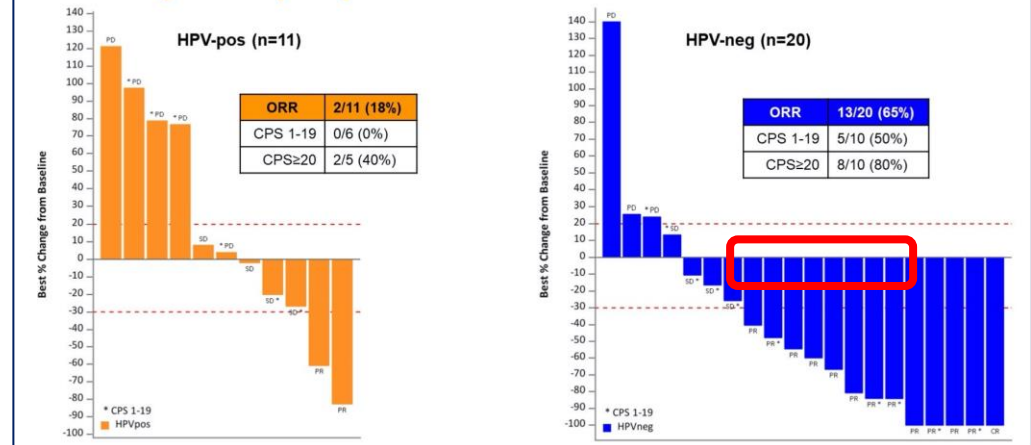
Population

- R/M HNSCC
- Oral cavity, oropharynx, hypopharynx & larynx
- HPV (p16) testing required for oropharyngeal cancer
- CPS≥1
- No prior systemic therapy in R/M setting**

Simon 2-stage (H0 vs. HA, 19% vs. 38%)

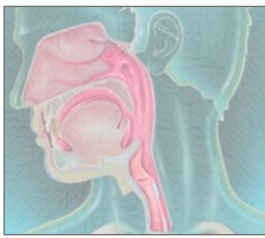
- Stage 1: 18 evaluable pts, ≥4 responses required to proceed to stage 2
- Stage 2: Additional 21 patients (total n=39), 11 responses required to warrant further assessment in larger cohort

Preliminary Efficacy – by HPV status



	mPFS	Range
HPV-neg (n=12)	Not reached	1.3-14.6+

RECIDIVANT / METASTATIQUE



NOUVELLES MOLECULES

MRG003 Anticorps conjugué anti-EGFR Phase 2

LOCALEMENT AVANCEE

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- Standards actuels
- Molécules et stratégies futures

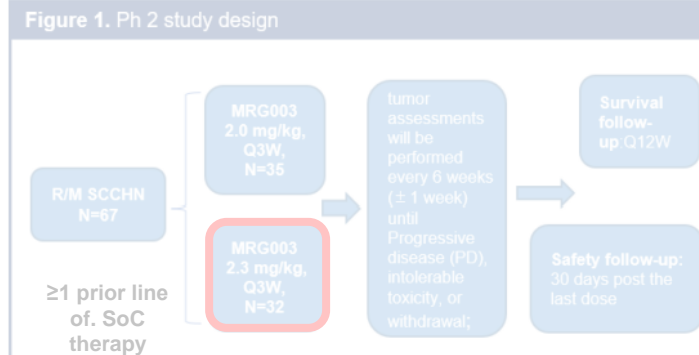
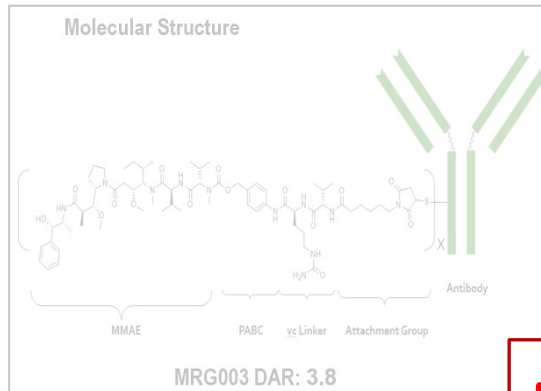
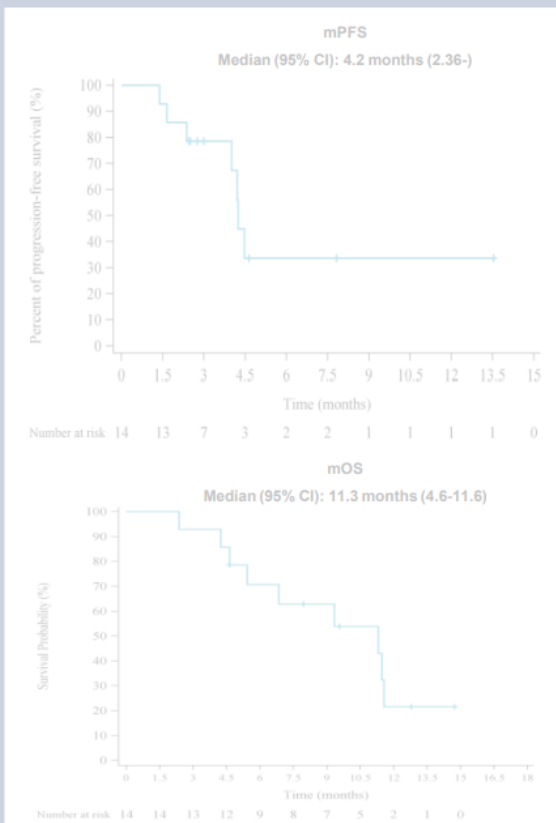
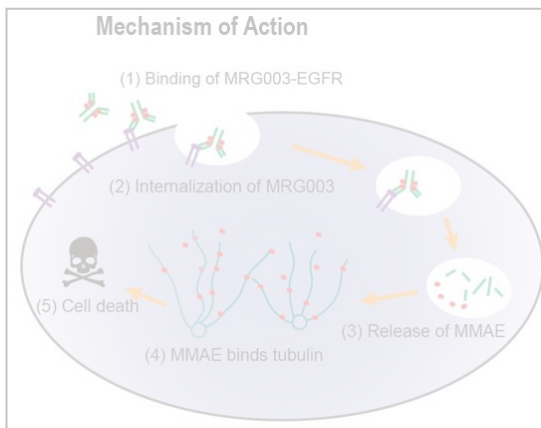


Figure 2. Kaplan-Meier estimates of mPFS and mOS in Ph2



Phase III en cours



CR	1
PR	5
SD	6
PD	2
NE	0
ORR	43%
DCR	86%

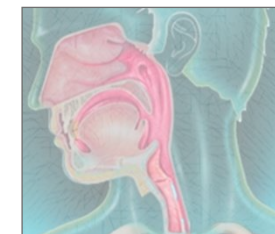
Table 2. Common TRAEs (PT) ≥ 20%

TRAE	Total (n=67) n (%)
Pruritus	17 (25.4)
Constipation	16 (23.9)
Anemia	14 (20.9)

≥G3 TRAEs ≥ 2%

TRAE	Total (n=67)
White blood cell count decreased	4 (6.0)
Anemia	3 (4.5)
Vomiting	2 (3.0)
Anorexia	2 (3.0)
Hypokalemia	2 (3.0)
Nausea	2 (3.0)

RECIDIVANT / METASTATIQUE



NOUVELLES MOLECULES

IMMUNE CHECKPOINT

LAG3 inhibitor or soluble version

TIM3 inhibitor

TIGIT inhibitor

phase I/II

LOCALEMENT AVANCEE

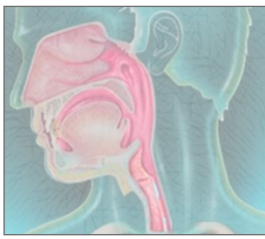
- Standards actuels
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R/M

- Standards actuels
- Molécules et stratégies futures

Essai	Traitement	Phase	No pts	Statut
NCT01968109	Relatlimab(LAG3i) +/- Nivolumab	I/IIa	1499	Tumeurs solides Recrutement terminé
TACTI-002 (NCT03625323) DeSpeville ASCO 2023	EftilagimodAlpha (LAG3) + Pembrolizumab	II	39/ 189	ORR 30%(CR 14%) mOS 8.7m 1-yr OS 46% CPS> 20 :ORR 60%. mOS15m 1-yr OS73% TACTI-003 phase III en cours
NCT05287113 Cohen ASCO 2023 Hamid ASCO 2023	3-bras: INCAGN02385(LAG3i) +INCAGNO2390 (TIM3i) +PD-L1i (retifanlimab) vs LAG3i+PDL1i vs PDL1i	rII	162	En cours Primary Endpoint : PFS
SKYSCRAPER-09 TIGIT (Cohen 2021 ESMO) NCT04665843	Atezolizumab+ tiragolumab vs Atezolizumab+ placebo	rII	120	First-line R/M HNSCC Primary endpoint ORR Recrutement en cours

RECIDIVANT / METASTATIQUE



NOUVELLES MOLECULES

Ac BISPECIFIQUES *phase I/II*

Essai	Traitement	Phase	No pts	Résultats
EGFR & TGF-beta: BCA101 (Hanna ASCO 2023) (NCT04429542)	BCA101 + Pembro	I-IB	39	1 ^{ère} ligne R/M CPS>1%: ORR 48% (1CR), mPFS4.8m. HPV+ ORR 65%.
MCLA-158 (Petosemtamab) (Cohen AACR 2023)	Anti-EGFR et anti-LGR5	II		2 ^{ème} ligne+ R/M : ORR 37% mOS 11,5m.
MCLA-158 + Pembrolizumab (NCT03526835)	Petosemtamab + Pembrolizumab	II	45	1 ^{ère} ligne R/M HNSCC PDL-1 positifs ORR : 67%

LOCALEMENT AVANCEE

- Standards actuels
- Molécules et stratégies futures

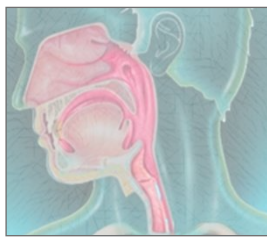
R/M

- Standards actuels
- Molécules et stratégies futures

RECIDIVANT / METASTATIQUE

NOUVELLES MOLECULES

Ac CONJUGUES (ADC) phase I/II



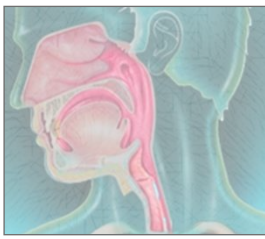
LOCALEMENT AVANCEE

- Standards actuels
- Molécules et stratégies futures

R/M

- Standards actuels
- Molécules et stratégies futures

Essai	Traitement	Phase	No pts	Résultats
Enfortumab Vedotin	ADC : anti-nectin-4 Conjugué au MMAE	II	39	ORR : 11/39 (28%)
Tisotumab Vedotin	ADC : anti-TF	II	40	ORR: 13/40 (32%)
MRG003 (NCT04868162) Xue ESMO 2023	ADC : anti-EGFR Mab conjugué au MMAE	II	67	≥ 2 ^{ème} ligne R/M 2,3 mg/kg : ORR 43% DCR 86% mPFS 4,2 Mo mOS 11,3 Mo Phase III vs MTX/Cetux. En cours
MRG003 + Pucotenlimab Ruan ASCO ASCO 2024	Pucotenlimab : Anti-PD-1	I-II	33	MRG003 RP2D : 2.0 mg/kg ORR phase I : 53.8% ORR phase II : 71.4%



En attendant...

LOCALEMENT AVANCEE

- *Standards actuels*
- *Molécules et stratégies futures*

R/M

- *Standards actuels*
- *Molécules et stratégies futures*



STANDARDS FIGES

- ***CETEC LA: >10 ans***
- ***CETEC R/M: >5 ans***