AACR-NCI-EORTC Virtual International Conference on
MOLECULAR TARGETS AND CANCER THERAPEUTICS
October 7-10, 2021

Preliminary antitumor activity of MCLA-158, an IgG1 bispecific antibody targeting EGFR and LGR5, in advanced head and neck squamous cell carcinoma

Antoine Hollebecque*,[1] Irene Brana,[2] Lara Iglesias,[3] Caroline Even,[1] Shumei Kato,[4] Marc Díez García,[2] Mateo Bover,[3] Patricia Martin-Romano,[1] Rocio Garcia-Carbonero,[3] Guillen Argilés,[2] Josep Tabernero,[2] Rajan Khanna,[5] Viktoriya Stalbovskaya,[5] Jeroen Lammerts van Bueren,[5] Kees Bol,[5] Mohamed Bekkrada,[6] Andrew Joe,[5] Ernesto Wasserman,[5] Ezra E.W. Cohen[7]

1. Gustave Roussy Cancer Campus, Villejuif, France; 2. Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain; 3. Hospital Universitario 12 de Octubre, Imas12, Madrid, Spain; 4. UC San Diego Health, CA, US; 5. Merus NV, Utrecht, the Netherlands; 6. Oncology Therapeutic Development (OTD), Clichy, France; 7. Moores Cancer Center, UC San Diego Health, CA, US

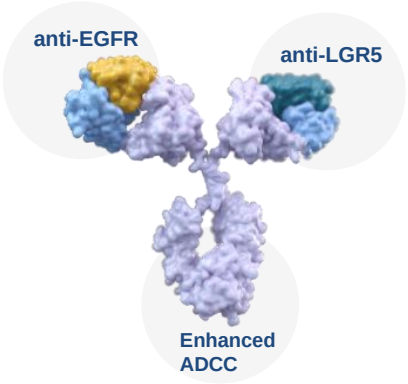
* Presenting author

MCLA-158 is a bispecific antibody targeting EGFR and LGR5

EGFR and WNT signaling are oncogenic and mitogenic drivers in several cancer types, including HNSCC

MCLA-158 is a first-in-class molecule with enhanced ADCC activity and high target affinity

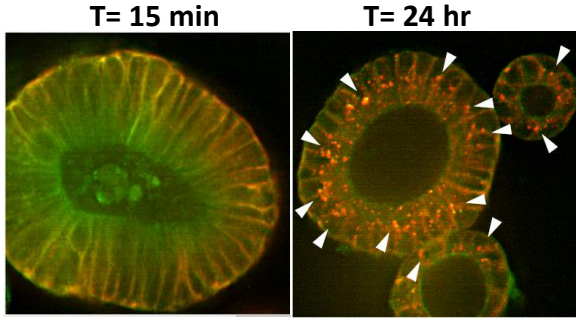
Blocks EGFR signaling, inducing potent growth inhibition



Significant MCLA-158-induced internalization of EGFR and LGR5 results in EGFR degradation[1]

MCLA-158 has potent antitumor activity in patient-derived HNSCC xenograft models[1]

Recurrent/metastatic HNSCC has a poor prognosis, with ~15% ORR and median OS ~8 months in 2nd line[2-4]



EGFR MCLA-158

High magnification images of P18T organoids shows that after 24h exposure, MCLA-158 (red) is localized intracellularly in speckle-like patterns and overall EGFR expression (green) is strongly reduced.

1. Argiles et al. J Clin Oncol. 39, no. 3_suppl (Jan 2021) Abst 62. 2. Cohen E et al. Lancet 2019;393:156-67
3. Ferris et al. N Engl J Med 2016;375:1856-67. 4. Larkins et al. Oncologist 2017; 22:873-78

Phase 1 Study: Cohort Expansion in HNSCC

Dose escalation is completed: No DLTs, RP2D established at 1500 mg Q2W based on safety, PK and predicted receptor occupancy.[1]
Cohort expansion is ongoing at the RP2D in solid tumor indications.

Inclusion criteria

- Prior standard therapy
- ECOG PS 0-1
- Measurable disease
- Baseline tumor biopsy

- Intravenous MCLA-158 1500 mg Q2W, 28-day cycle
- Until PD or toxicity
- Tumor assessment Q8W

Survival follow-up

(up to 1 year)

Objectives and Population

- **Primary objective:** safety and tolerability
- **Secondary objectives:** antitumor activity (RECIST 1.1 per investigator), PK and immunogenicity
- **Efficacy evaluable population:** opportunity for at least 1 post-baseline tumor assessment at the cut-off

Enrollment and Interim Analysis

- **Data cut-off date:** 09-Aug-2021
- **Enrollment:** 10 patients
- **Efficacy evaluable population**: 7 patients
  - 3 patients recently enrolled excluded (first dose <8 weeks from data cut-off date)

1. Argiles et al. J Clin Oncol. 39, no. 3_suppl (Jan 2021) Abst 62

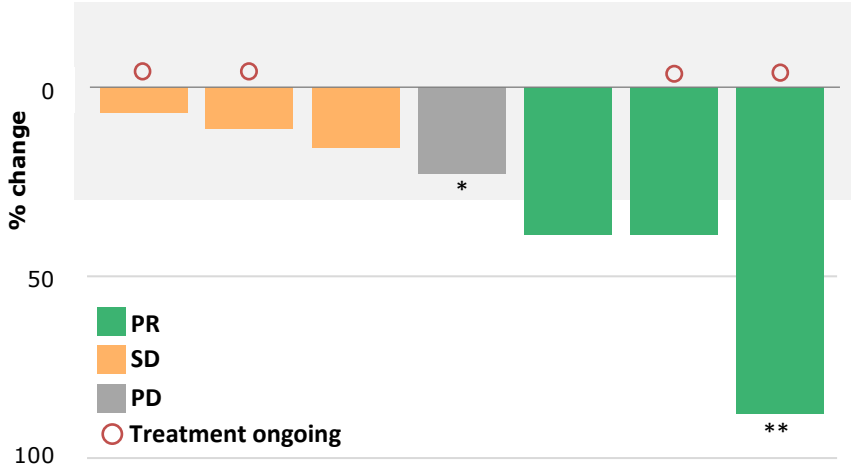
HNSCC population characteristics, prior treatment and disposition

BASELINE CHARACTERISTICS	HNSCC N=10
Age (years), median (range)	65 (50-77)
Male / female	9 (90%) / 1 (10%)
ECOG PS 0 / 1	4 (40%) / 6 (60%)
Squamous cell carcinoma histology	10 (100%)
Tumor location	
▪ Larynx / tongue	4 (40%) / 3 (30%)
▪ Oropharynx / hypopharynx	1 (10%) / 1 (10%)
▪ Unknown primary	1 (10%)
EGFR H-score, median (range) (n=5)	140 (50-300)
EGFR IHC score 2+ / 3+ (n=5)	1 (20%) / 4 (80%)

PRIOR TREATMENT AND DISPOSITION	HNSCC N=10
N lines prior therapy, median (range)	2 (1-3)
▪ Platinum-based chemotherapy	10 (100%)
▪ PD-(L)1 inhibitor	9 (90%)
▪ Cetuximab	0%
MCLA-158: treatment ongoing	7 (70%)
Reason for discontinuation	
▪ Disease progression	3 (30%)
MCLA-158: N cycles initiated	
▪ Median (range)	4 (1 – 8)

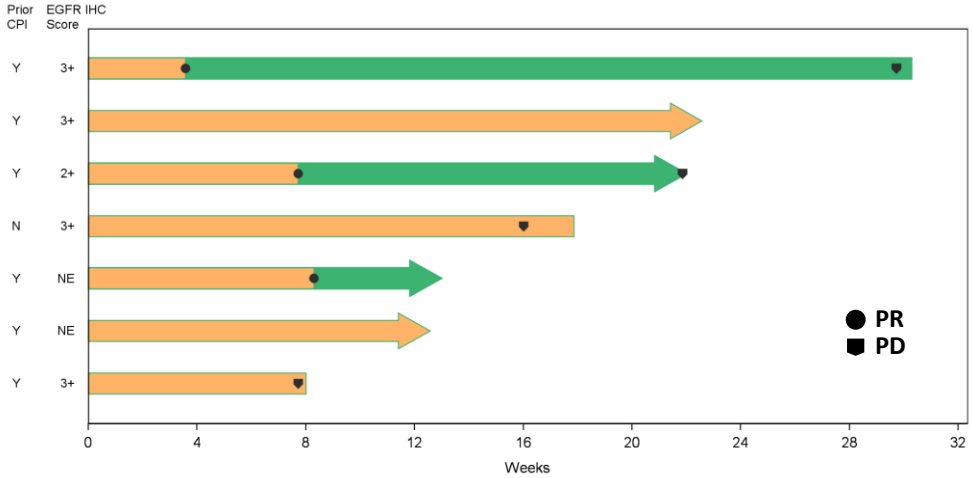
MCLA-158 Interim Efficacy Analysis in HNSCC

Best % change in target lesions from baseline



* Best response of PD due to progression in non-target lesions and a new lesion
** Unconfirmed PR at data cut-off date; CR reported after the data cut-off date

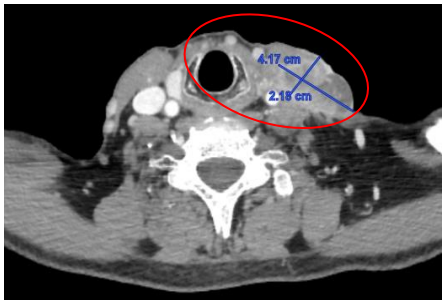
Time to response and duration of exposure

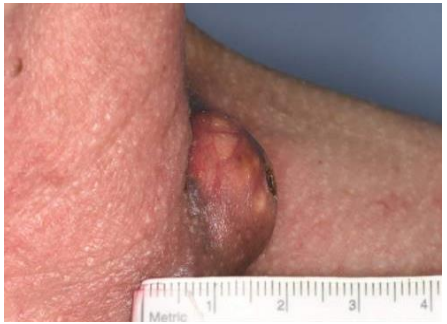


Duration of exposure is defined as the time between the first dose and the last exposure date, where the last exposure date is the date of the last infusion + 13 days.
CPI, checkpoint inhibitor; IHC immunohistochemistry

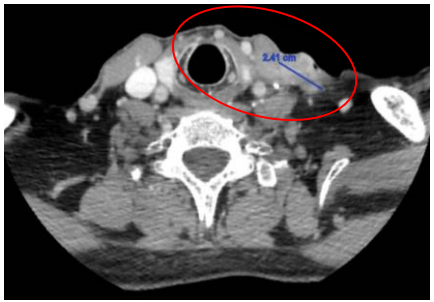
Clinical response to MCLA-158 in HNSCC

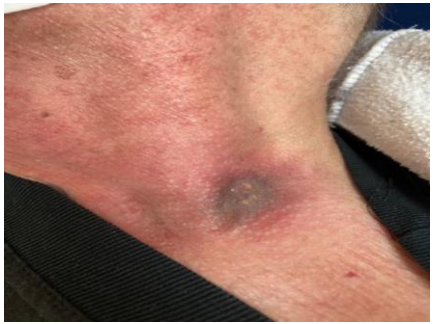
Baseline





Cycle 3





67-year-old male patient

Lesion location: larynx

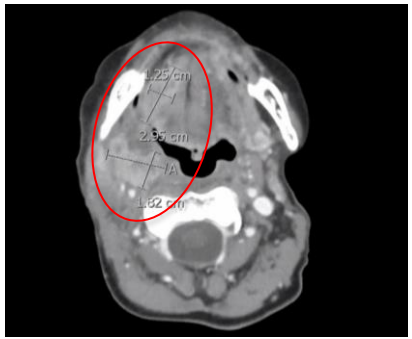
MCLA-158 cycles: 6+

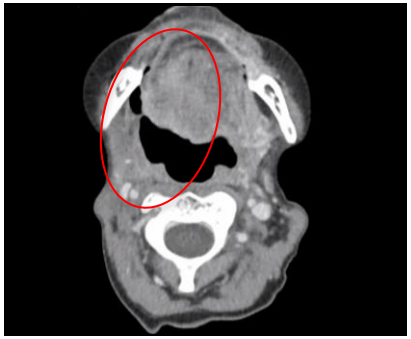
Best response: PRc (-41%)

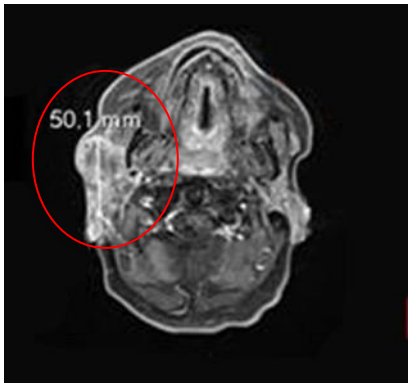
Prior treatment: platinum + paclitaxel + durvalumab

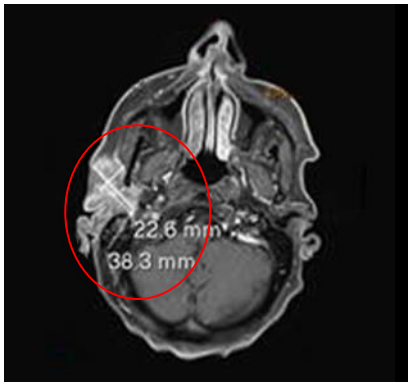
Clinical response to MCLA-158 in HNSCC

Baseline | **Cycle 4**









59-year-old female patient

Lesion location: tongue

MCLA-158 cycles: 4+

Best response: PR (-88%; CR reported after data cut-off)

Prior treatment: RT → pembrolizumab + platinum + 5-FU

67-year-old male patient

Lesion location: oropharynx

MCLA-158 cycles: 8

Best response: PRc (-40%)

Prior treatment: platinum (neoadj) → pembrolizumab

MCLA-158 Safety Profile at RP2D

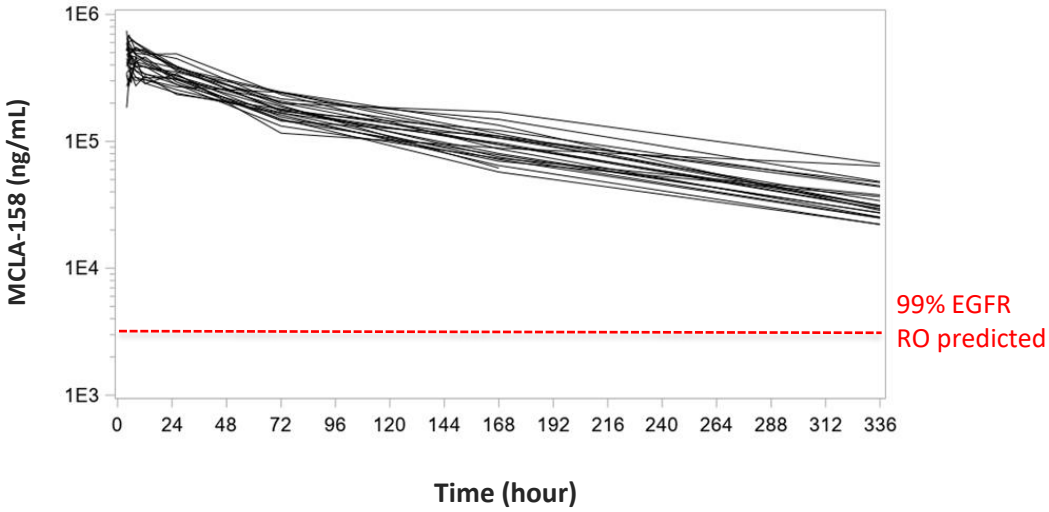
Preferred Term	Irrespective of Causality		Suspected Related	
	All Grades	Grades 3-5	All Grades	Grades 3-5
N patients with ≥1 AE	**27 (93%)**	**13 (45%)**	**27 (93%)**	**5 (17%)**
Rash	10 (35%)	0	10 (35%)	0
Asthenia	9 (31%)	1 (3%)	3 (10%)	1 (3%)
Hypotension	8 (28%)	1 (3%)	8 (28%)	1 (3%)
Nausea	8 (28%)	1 (3%)	5 (17%)	0
Decreased appetite	7 (24%)	1 (3%)	0	0
Dermatitis acneiform	6 (21%)	1 (3%)	5 (17%)	1 (3%)
Dyspnea	6 (21%)	2 (7%)	5 (17%)	2 (7%)
Erythema	5 (17%)	0	5 (17%)	0
Vomiting	5 (17%)	1 (3%)	3 (10%)	0
Chest pain	4 (14%)	0	1 (3%)	0
Dysphagia	4 (14%)	1 (3%)	0	0
Hypomagnesaemia	4 (14%)	1 (3%)	2 (7%)	1 (3%)
Pruritus	4 (14%)	0	4 (14%)	0
Pyrexia	4 (14%)	0	2 (7%)	0
Chills	3 (10%)	0	3 (10%)	0
Constipation	3 (10%)	0	0	0
Diarrhea	3 (10%)	0	1 (3%)	0
Rash pustular	3 (10%)	0	3 (10%)	0
Skin toxicity	3 (10%)	0	3 (10%)	0

- Safety profile is based on 29 patients with solid tumors treated at 1500 mg Q2W
- Most frequent AEs were infusion-related reactions[1]
  - 72% any grade, 7% grade ≥3
  - Time to onset: first infusion for all patients
  - Manageable with prophylaxis/ prolonged infusion
- Mild to moderate skin toxicity (3% severe events)
- No treatment-related grade 4 or 5 AEs
- No patients discontinued due to toxicity

[1] Composite term including all AEs considered by the investigator as an IRR during 24h post-infusion

PK and immunogenicity

Individual MCLA-158 serum concentration vs time curves for patients treated at the RP2D (n=23)



At 1500 mg MCLA-158 Q2W:

- Mean terminal half-life was 112h
- >99% EGFR receptor occupancy (RO) predicted for the entire dosing interval
- No relevant anti-MCLA-158 antibody (ADA) activity was observed in samples up to Cycle 7

Conclusions

- MCLA-158 was observed to have **substantial and promising antitumor activity** in the first 7 patients with HNSCC previously treated with both platinum-based chemotherapy and checkpoint inhibitors
  - 3 patients with partial responses per RECIST 1.1 by investigator review
  - Tumor shrinkage in most patients
- MCLA-158 was observed to be well tolerated with a **manageable safety profile**
- Exploration of MCLA-158 in HNSCC is continuing and is planned in **other tumor indications**