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PERSONALIZED TREATMENT ACCORDING TO GERIATRIC ASSESSMENT IN 1ST LINE RECURRENT AND/OR METASTATIC (R/M) HEAD AND NECK SQUAMOUS CELL CANCER (HNSCC) PATIENTS AGED 70 OR OVER.

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DISCLOSURE SLIDE

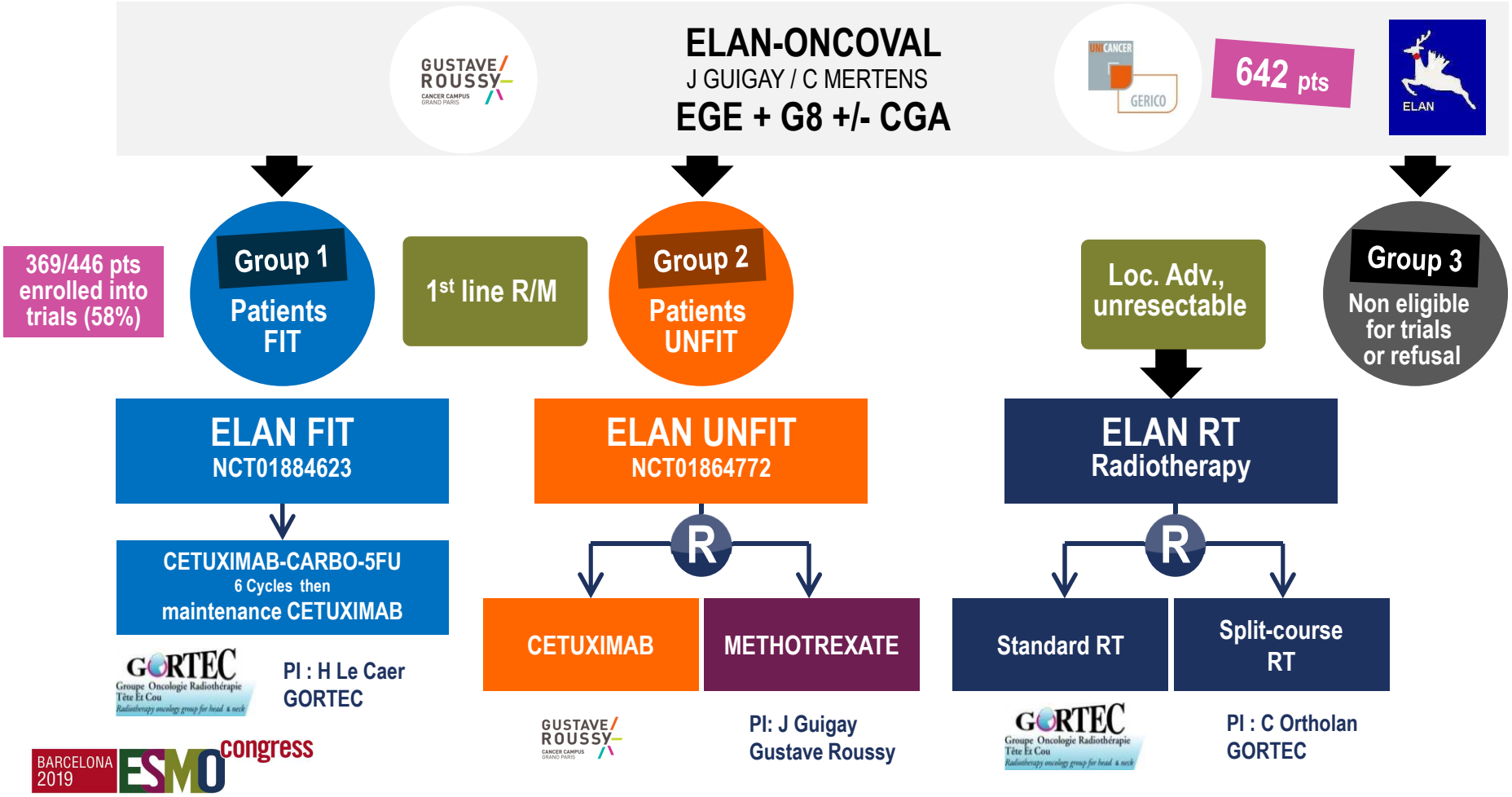
ELAN program:
Funding from INCa PAIR, Ligue Contre le Cancer, Sandoz, GEMLUC-GEFLUC, Centre Hospitalier Princesse Grâce de Monaco
Merck KGaA : cetuximab for ELAN-UNFIT

J Guigay:
Advisory board member for Astra Zeneca, BMS, Innate Pharma, Merck KGaA, Nanobiotix

ELAN TRIALS

Background

- Challenges in treating patients aged 70 years and older with HNSCC are to maximise the treatment benefit/risk ratio and manage tumour related symptoms
- No standard systemic treatment has been validated to date
- Ten years ago, GERICO-GORTEC groups developed **ELAN**, a french large prospective clinical program, to improve the management of elderly HNSCC patients and set:
  - > The Elan Geriatric Evaluation (EGE) is an adapted geriatric evaluation that is feasible for use in daily practice. ELAN ONCOVAL study showed that EGE is more suitable than G8 for HNSCC patients (ESMO 2017, ASCO 2019).
  - > New standards of care for this patient population: RT in Locally advanced (phase III ELAN RT), 1st line systemic treatment for R/M (ELAN FIT and ELAN UNFIT trials)
  - > We report here the results of ELAN **FIT** and **UNFIT** trials dedicated to elderly R/M HNSCC pts


ELAN-ONCOVAL
J GUIGAY / C MERTENS
EGE + G8 +/- CGA
642 pts
369/446 pts enrolled into trials (58%)
Group 1
Patients FIT
1st line R/M
Group 2
Patients UNFIT
Loc. Adv., unresectable
Group 3
Non eligible for trials or refusal
ELAN FIT
NCT01884623
CETUXIMAB-CARBO-5FU
6 Cycles then
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ELAN RT
Radiotherapy
R
Standard RT
Split-course RT
PI : C Ortholan
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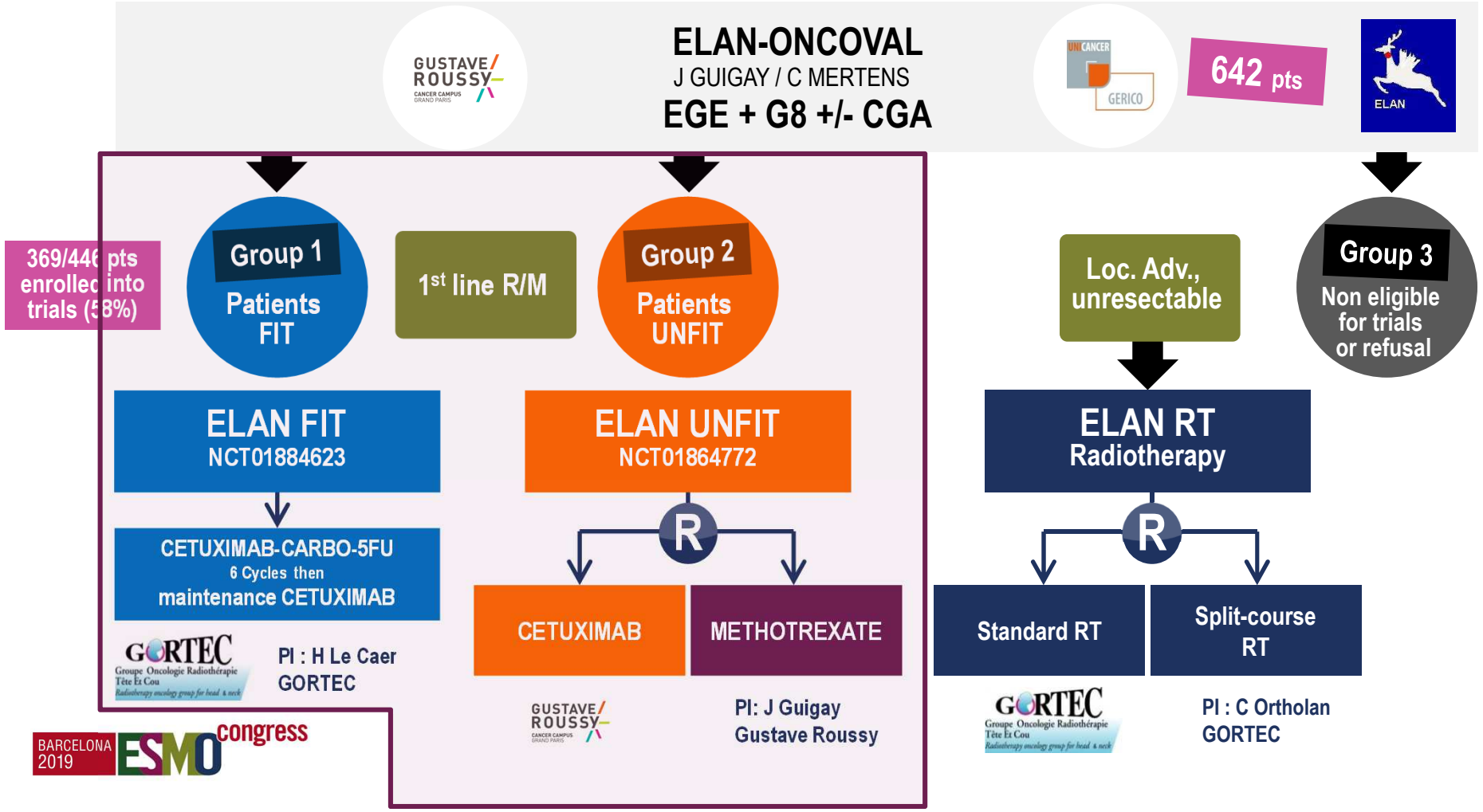
ELAN-FIT & UNFIT TRIALS

Methodology

- Patients aged 70 years and older with R/M HNSCC enrolled in the ELAN-ONCOVAL study were classified as fit or unfit according to the ELAN geriatric evaluation (EGE) with optional Comprehensive Geriatric Assessment.

- **Fit patients** were eligible for enrolment in the 2-stage **phase II ELAN-FIT trial** (NCT01884623) testing the standard **cetuximab-carboplatin-5FU (EXTREME) combination**

- **Unfit patients** could enter the randomized **phase III ELAN-UNFIT trial** (NCT01864772) comparing monotherapy with cetuximab 500 mg/m2 every 2 weeks to methotrexate 40 mg/m2 weekly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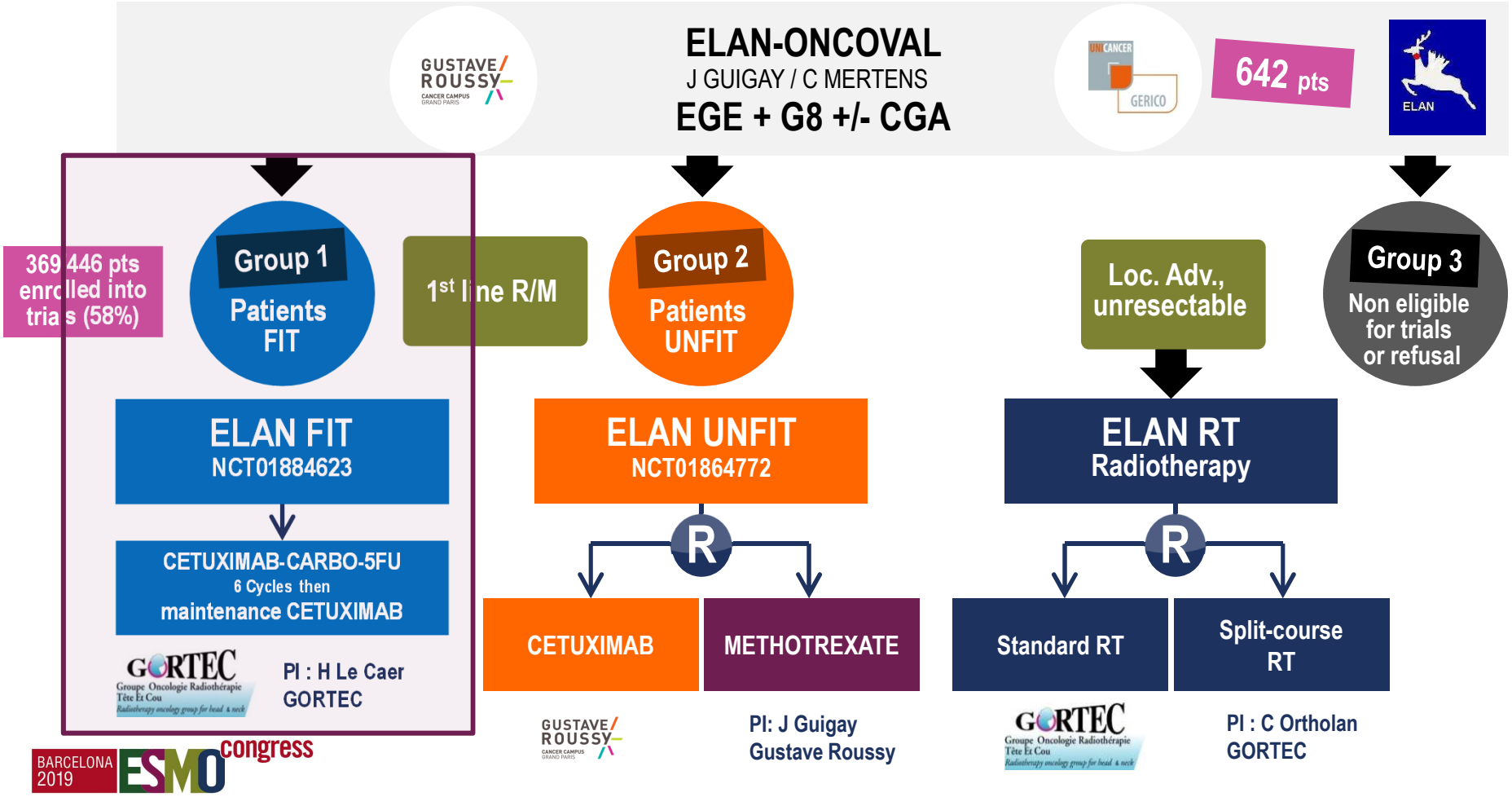
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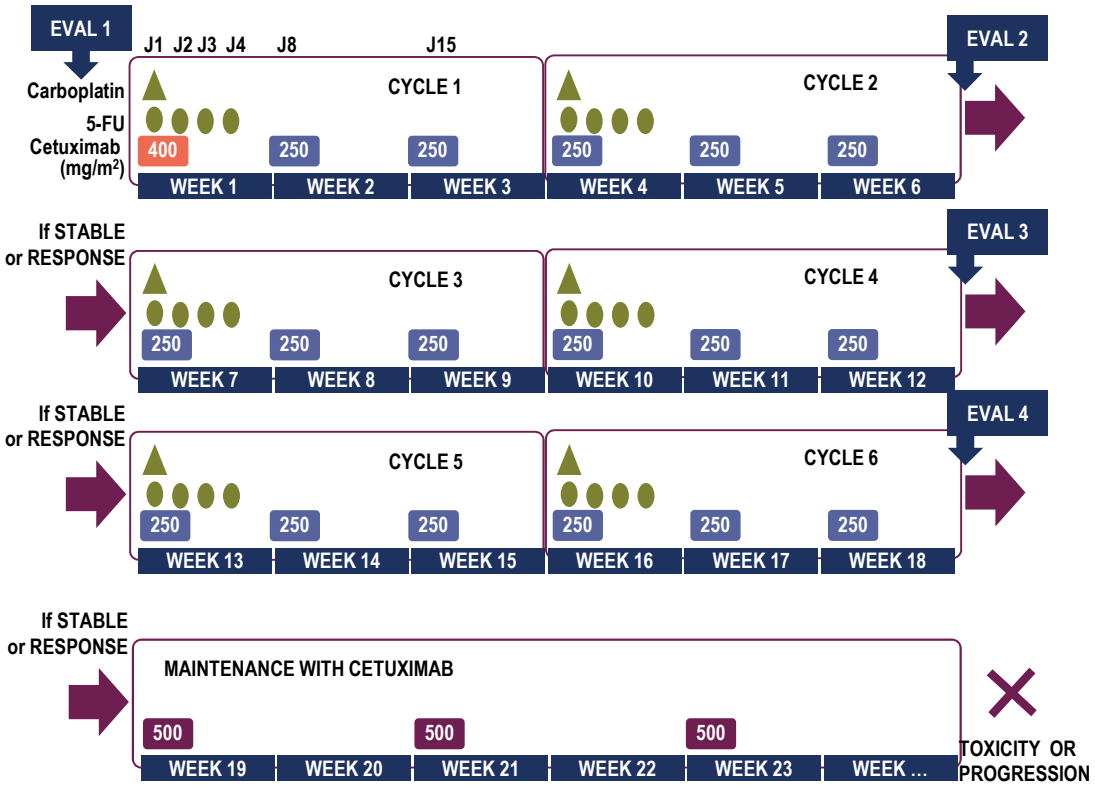
ELAN-FIT: DESIGN

- **KEY ELIGIBILITY CRITERIA**
  - > FIT elderly R/M HNSCC not suitable for locoregional treatment
  - > Age 70 years or more
  - > PS 0-1
  - > Creatinine clearance >60 mL/min
  - > No Anti-EGFR for 1 year
- **EXTREME regimen**
  - > 6 cycles Q3W
  - > CARBOPLATIN = AUC 5 IV
  - > 5FU = 4000 mg/m2 96h continuous infusion
  - > CETUXIMAB = 400 mg/m2 (loading dose), then 250 mg/m^2 IV weekly
  - > GCSF and EPO support



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ELAN-FIT: METHODS

- Phase II **single-arm trial, in 2 steps**, based on **Bryant et Day design combining efficacy and toxicity endpoints**
  - Efficacy: **Objective response rate (ORR) at 12 weeks**
    - Hypothesis: inacceptable rate 15%, promising rate 35%
  - Toxicity: **grade ≥ 4 adverse event (AE) or loss of autonomy** (ADL decrease ≥ 2 points) one month after end of chemotherapy (skin rash grade 4 was counted only if it leads to cetuximab definitive stop)
    - Hypothesis: inacceptable rate 40%, promising rate 25%
- Required number of patients: **78 patients**
- **First step among 37 patients**: continue to 2nd step if ≥ 7 patients with Objective Response and ≤ 13 patients with grade ≥ 4 AE or ADL decrease ≥ 2 points
- **Second step among 78 patients: treatment promising if ≥ 18 patients with Objective Response and ≤ 25 patients with grade ≥ 4 AE or ADL decrease ≥ 2 points**
- Type I error for ORR = 0.05; type I error for toxicity=0.08, power=89%

ELAN-FIT

Characteristics, ITT Population

85 enrolled from september 2013 to june 2018, 7 ineligible, 78 analyzed. Median FU = 30 months

	N (N=78)	%
Gender		
Male	66	85
Female	12	15
Performance status (OMS)		
0	31	40
1	47	60
Age (years)		
≥ 80	14	18
Median [min ; max]	75 [70 ; 89]	

Primary Site	N (N=78)	%
Oropharynx	30	38
Oral cavity	17	22
Hypopharynx	9	12
Larynx	18	23
Other	4	5

Evolution type	N (N=78)	%
Loco-regional recurrence alone	36	46
Metastasis alone	23	29
Both	19	25

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ELAN-FIT: RESULTS ON MAIN ENDPOINT

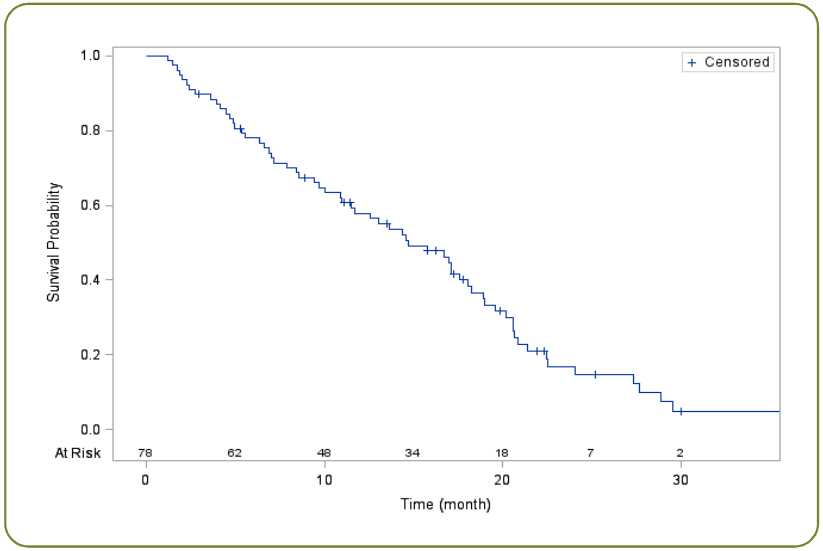
- Efficacy: RECIST Criteria, Central review at W12:
  - ✓ **ORR (CR +PR) at W12 = 40 %** (31/78 pts) (CI 95%=29%; 51%)
  - ✓ Stable Disease = 35% (27/78 pts)
  - ✓ Progression or deaths = 23% (18/78 pts)

- Toxicity: **less than 25 Pts** had a grade ≥ 4 or decrease of ADL ≥ 2 points or reaction leading to stop cetuximab

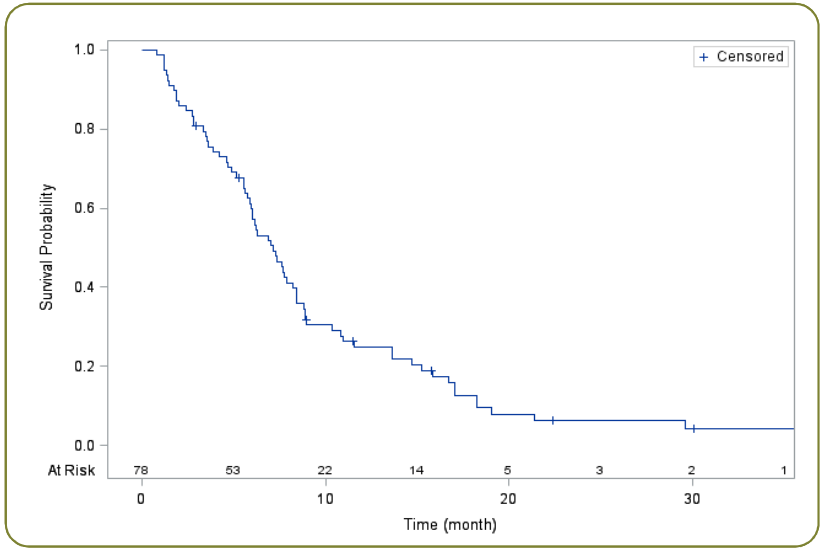
- **The study reached the main endpoint** with promising rates of efficacy and safety

ELAN-FIT: SURVIVAL

- **Median OS = 14.7 m [95% CI : 11.0 ; 18.1]**
- 1y OS = 57.9% [95% CI : 46.6% ; 68.4%]



- **Median PFS = 7.2 m [95% CI : 5.9 ; 8.4]**
- 1y PFS = 24.9% [95% CI : 16.5% ; 35.8%]



ELAN-FIT: SAFETY

Adverse events (AEs) during CT phase

Maximal grade of AEs	N	%
% patients with no AE or AE grade 1-2	14	18%
% patients with AEs grade 3	45	58%
% patients with AEs grade 4	19	24%
% patients with AEs grade 5	0	0%

- 4 patients with decrease of ADL ≥ 2 points.
- 4 patients received only one dose of cetuximab following hypersentivity reaction

AE grade 4 : 19 patients (24%) → **24 patients (31%) with grade ≥ 4 or decrease of ADL ≥ 2 points or reaction leading to stop cetuximab.**

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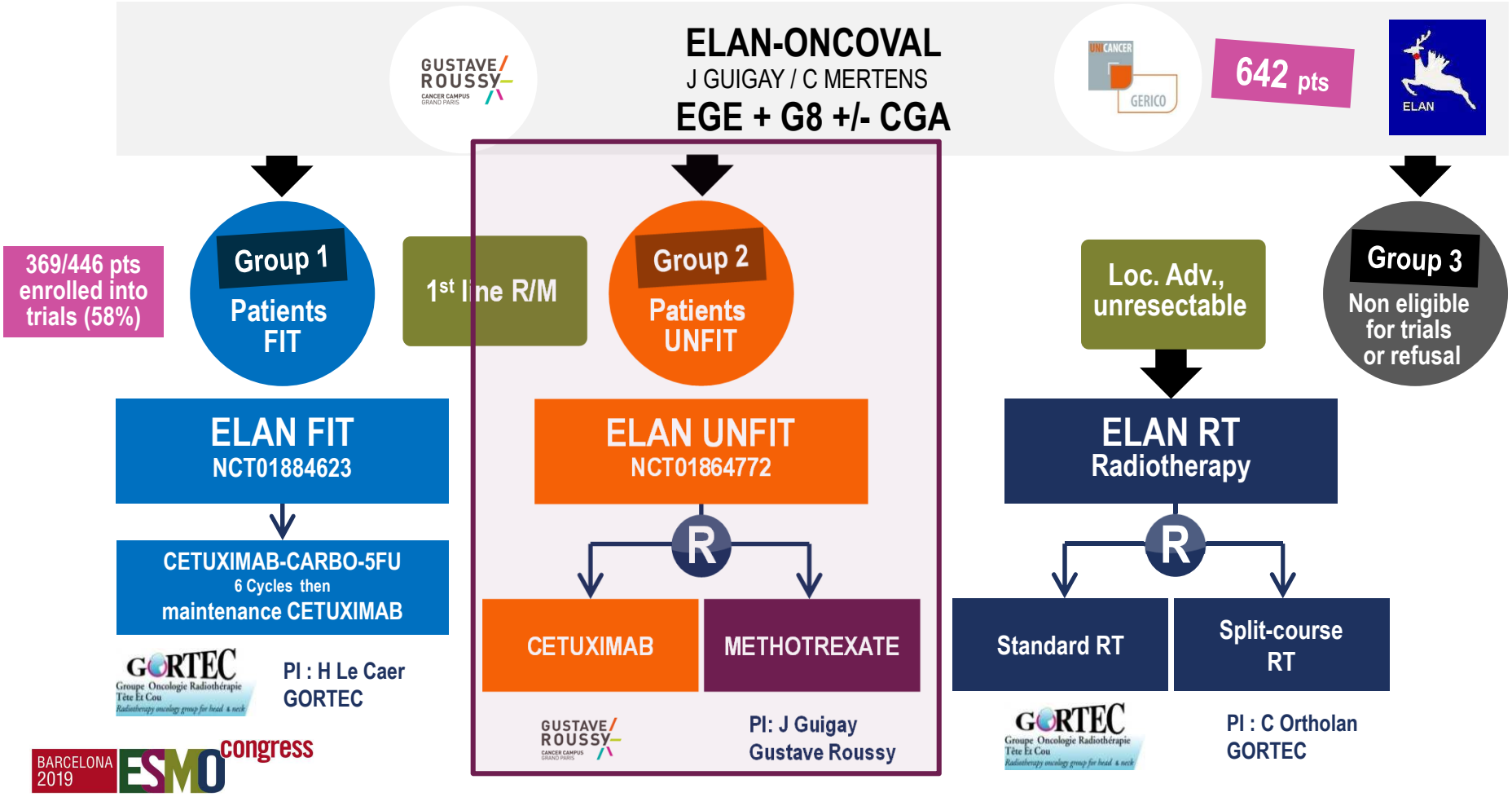
ELAN-FIT: MOST FREQUENT AES GRADE ≥ 3

	Total		Gd 3	Gd 4	Gd 5
AE term	N	%	N	N	N
Leukopenia	22	28%	18	4	-
Neutropenia	20	26%	15	5	-
Thrombopenia	15	19%	13	2	-
Mcositis	13	17%	12	1	-
Anemia	12	15%	9	3	-
Fatigue	11	14%	11	-	-
Rash acneiform	10	13%	10	-	-
Magnesium disorder	9	12%	4	5	-
Natremia disorder	9	12%	7	2	-
Potassium disorder	8	10%	7	1	-
Infection	7	9%	4	3	-
Diarrhea	5	6%	5	-	-
Gamma GT increase	5	6%	4	1	-
Decrease of general status	4	5%	3	1	-

- Median number of CT cycles delivered = 5
- 56% patients started maintenance. Median duration was 3 months

ELAN-FIT: COMPLIANCE

- During CT phase: 30 pts received the planned 6 cycles; Patients received a median of **5 cycles** de 5FU and/or carboplatin ,
- Main reason to delay CT was hematological toxicity
- Main reasons to stop CT before end of CT phase were: Toxicity: 11 patients, Decrease of PS: 10 patients; Progression : 9 patients; Refusal : 6 patients
- 4 patients received only one dose of cetuximab following hypersentivity reaction
- **56% patients started maintenance**. Median duration was 3 months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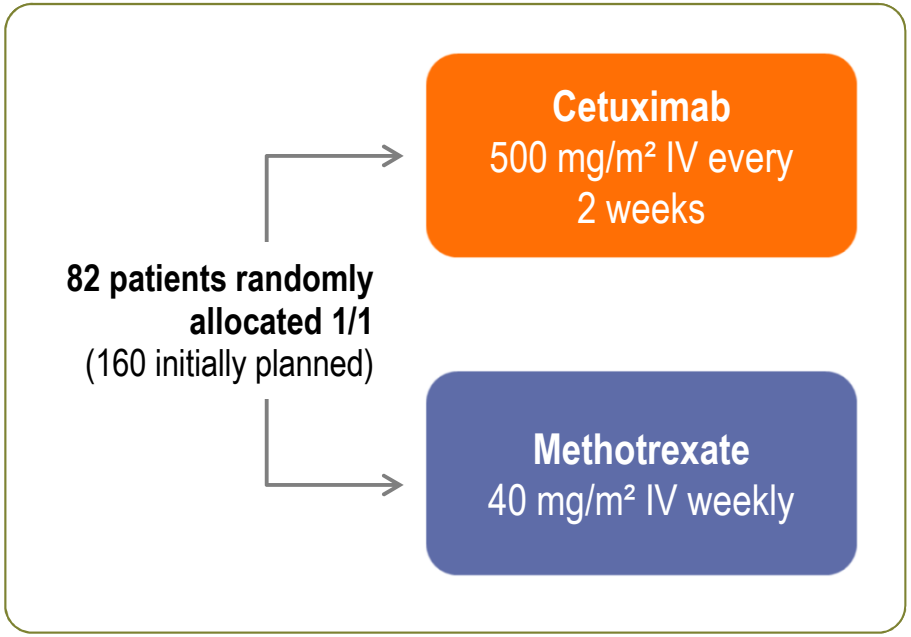
ELAN-UNFIT DESIGN

Main endpoint: Failure free survival

- **KEY ELIGIBILITY CRITERIA**
  - > Unfit elderly R/M HNSCC not suitable for locoregional treatment
  - > Age 70 years or more
  - > PS 0-2
  - > Creatinine clearance > or = 50 mL/min
  - > First line for R/M HNSCC
  - > No previous Anti-EGFR except during RT stopped more than 1 year before

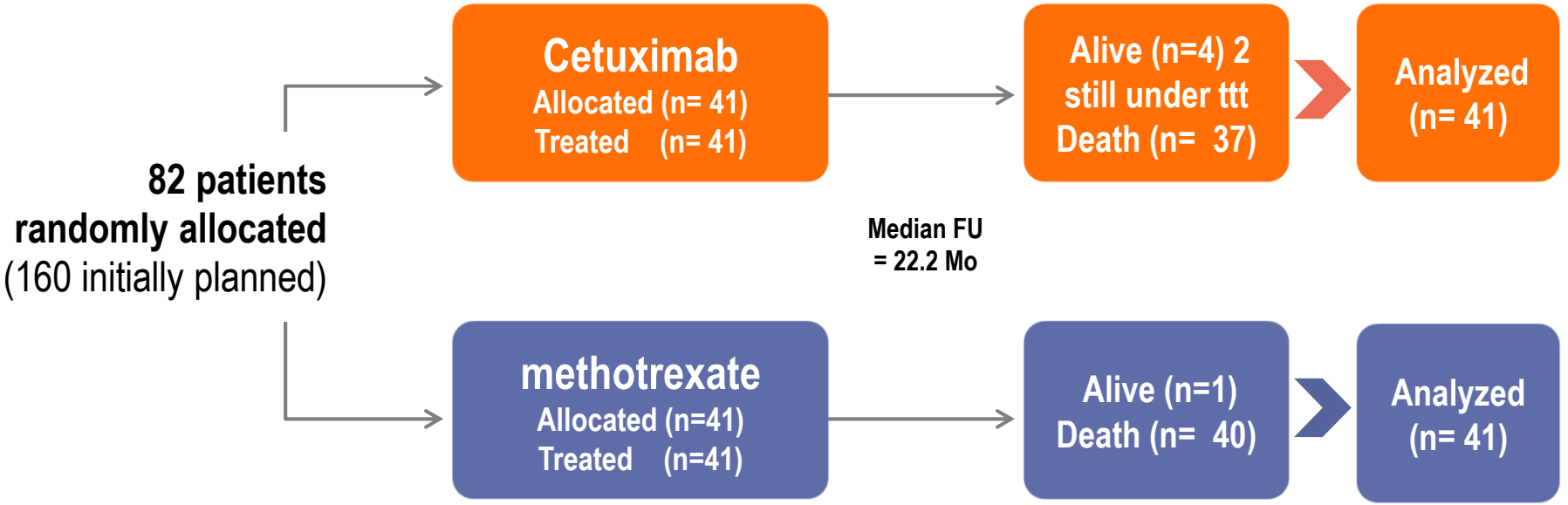


***Minimization** criteria:*
PS: 0-1 vs 2 ; Comorbidity Charlson score ≤ 2 vs ≥ 3 ; Albuminemia: > 34 g/L vs ≤ 34 g/L ; Type of evolution: locoregional progression vs metastatic evolution ; Geriatrician consultation done before inclusion (yes vs no)

ELAN-UNFIT : METHODS

- **Phase III randomized** trial comparing cetuximab 500 mg/m² every 2 weeks versus weekly methotrexate 40 mg/m².
- **Primary endpoint: failure-free survival (FFS),** defined as time from randomization to the first event among **progression** (according to RECIST), **treatment stop** (whatever the cause), **ADL decrease ≥ 2 points** or **death** (whatever the cause)
- Assuming 2-sided 5% level of statistical significance, observing 151 failures will provide 80% power to detect a **FFS hazard ratio (HR) of 0.625 corresponding to a median FFS improvement of 1.5-month** from 2.5 months expected with methotrexate to 4 months expected with cetuximab.
- 151 failures were expected out of **164 patients** (82 per arm)
- One interim futility analysis planned when around 50% of failures were observed
- The trial enrolment was **stopped for futility** after this interim analysis done in **June 2018 based on 79 failures and 81 patients**

ELAN-UNFIT: DISPOSITION OF RANDOMIZED PATIENTS



- Median FU: time from randomization to date of death or date of last follow-up if the patient was alive

ELAN-UNFIT

Characteristics, ITT Population

	Cetuximab n=41	Methotrexate n=41
Male	29 (70%)	31 (76%)
Female	12 (29%)	10 (24%)
Age (years)		
Mean (std)	78.8 (5.4)	79.3 (5.3)
Median [range]	78 [70-90]	79 [71-91]
>= 80 years	17 (41%)	20 (49%)
PS ECOG		
0	3 (7%)	1 (2%)
1	21 (51%)	22 (54%)
2	17 (41%)	18 (44%)
Frailty		
Median number of geriatric frailties by EGE (range)	2 [0-5]	3 [0-4]
Comprehensive geriatric assessment (CGA)	26 (63%)	22 (55%)

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Disease characteristics at initial diagnosis: by randomized treatment

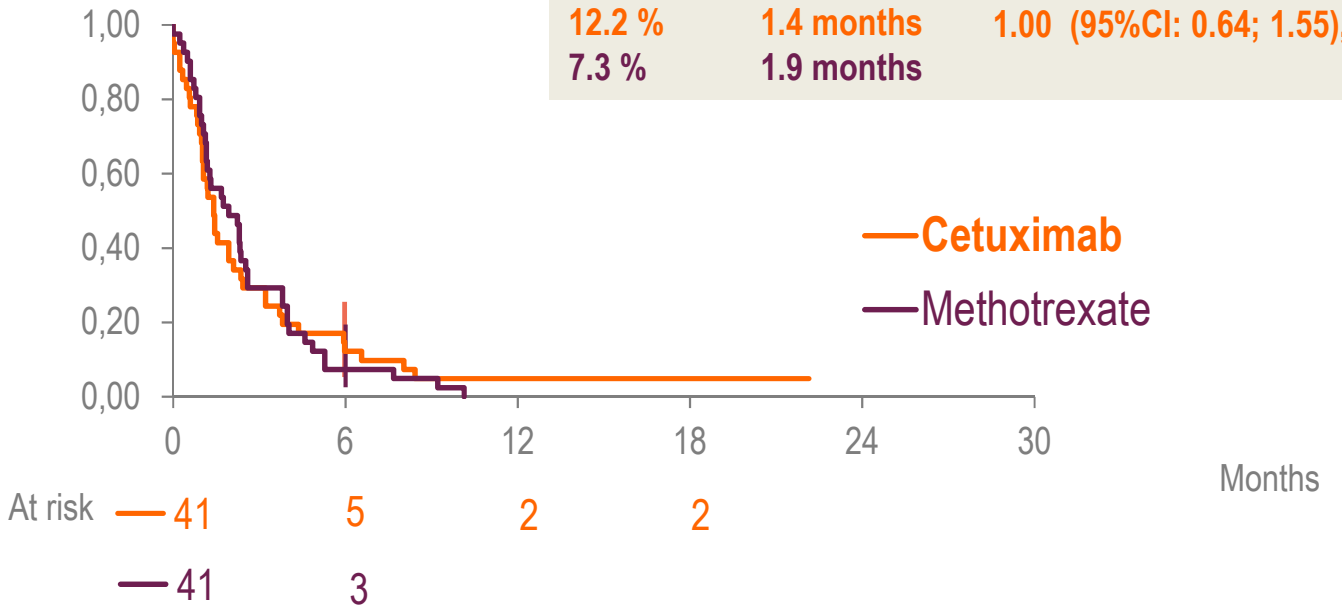
	Cetuximab n=41	Methotrexate n=41
Initial location		
Oropharynx	15 (37%)	15 (37%)
Oral cavity	13 (32%)	17 (41%)
Hypopharynx	6 (15%)	4 (10%)
Larynx	6 (15%)	4 (10%)
Other	1 (2%) (lip)	1 (2%) (nodes alone and M1)

	Cetuximab n=41	Methotrexate n=41
Evolution type		
Loco-regional recurrence alone	21 (51%)	24 (59%)
Metastasis alone	10 (24%)	10 (24%)
Both	9 (22%)	7 (17%)
Advanced primary larynx cancer without metastasis	1 (2%)	0

ELAN-UNFIT: RESULTS

Failure-free survival

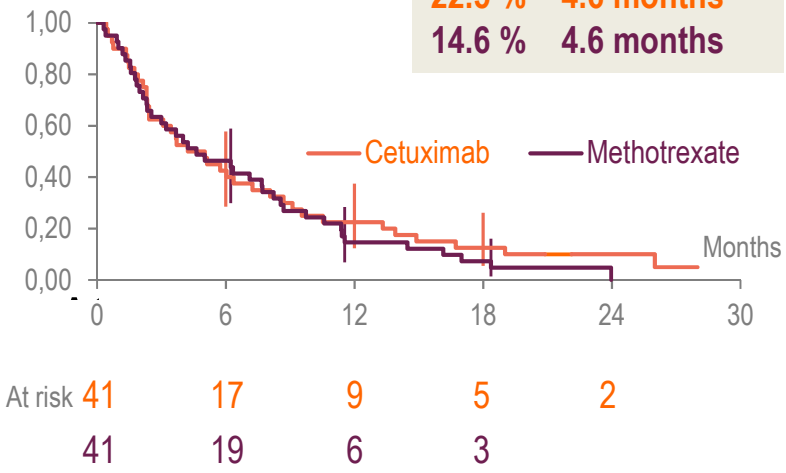
6 months	Median FFS	HR
12.2 %	1.4 months	1.00 (95%CI: 0.64; 1.55), p-value=0.995
7.3 %	1.9 months	



ELAN-UNFIT: RESULTS

Overall survival

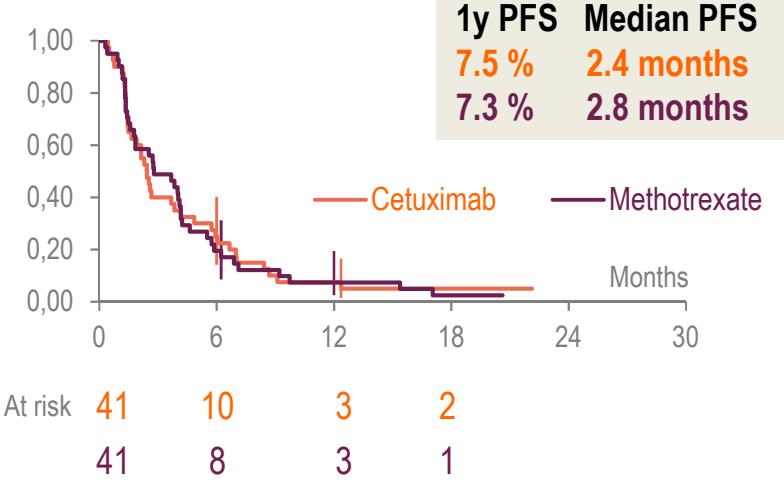
1y OS	Median OS
22.5 %	4.6 months
14.6 %	4.6 months



HR = 0.87 (95% CI: 0.55; 1.36) p-value=0.54

Progression-free survival

1y PFS	Median PFS
7.5 %	2.4 months
7.3 %	2.8 months



HR = 1.00 (95%CI: 0.64; 1.56), p-value=0.99

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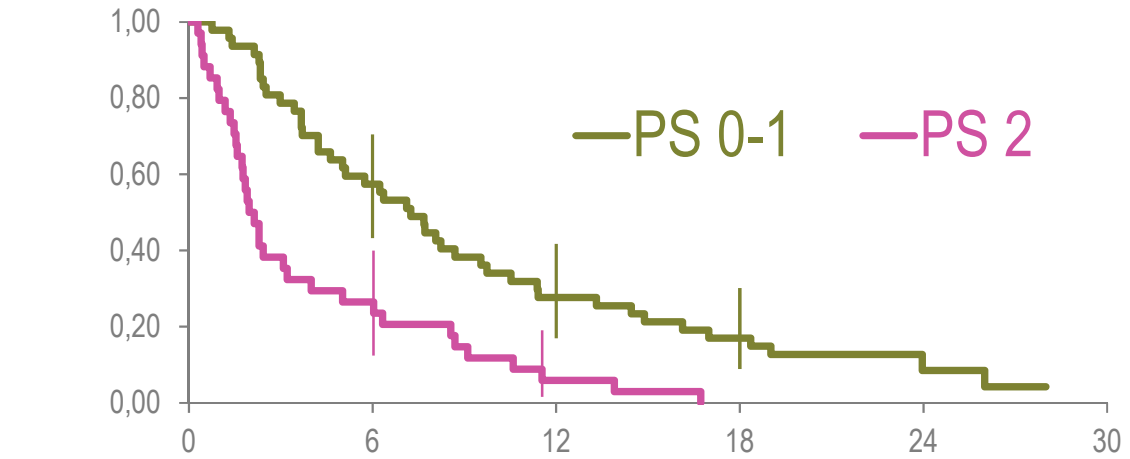
ELAN-UNFIT

Prognostic analysis of minimization factors on OS

	Deaths/pts	Median OS (in months)	12-month OS rate	Log rank p value
Charlson score ≤ 2 (n=68)	64/68	5.0	19.4%	
Charlson score ≥ 3 (n=14)	13/14	3.8	14.3%	0.97
PS 0-1 (n=47)	43/47	7.3	27.7%	
PS 2 (n=35)	34/35	2.1	5.9%	<0.0001
Albuminemia: > 34 g/L (n=60)	55/60	5.7	23.7%	
Albuminemia: ≤ 34 g/L (n=22)	22/22	2.2	4.6%	0.0014
Locoregional progression alone (n=46)	42/46	7.1	15.6%	
Metastatic evolution (n=36)	35/36	2.8	8.3%	0.018
CGA not done (n=33)	29/33	4.8	21.9%	
CGA done (n=49)	48/49	4.2	16.3%	0.64

ELAN-UNFIT: RESULTS

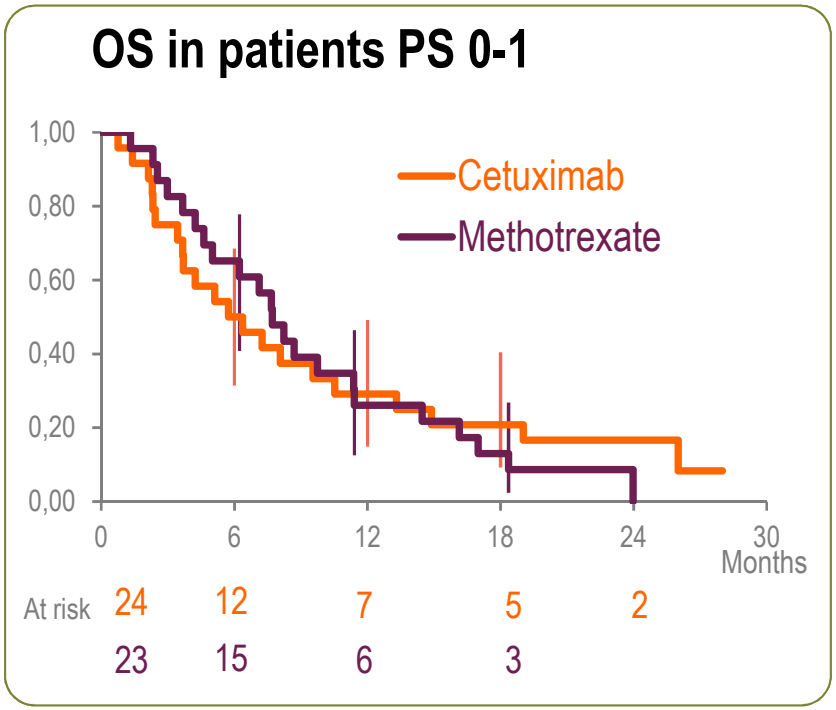
OS according to performance status

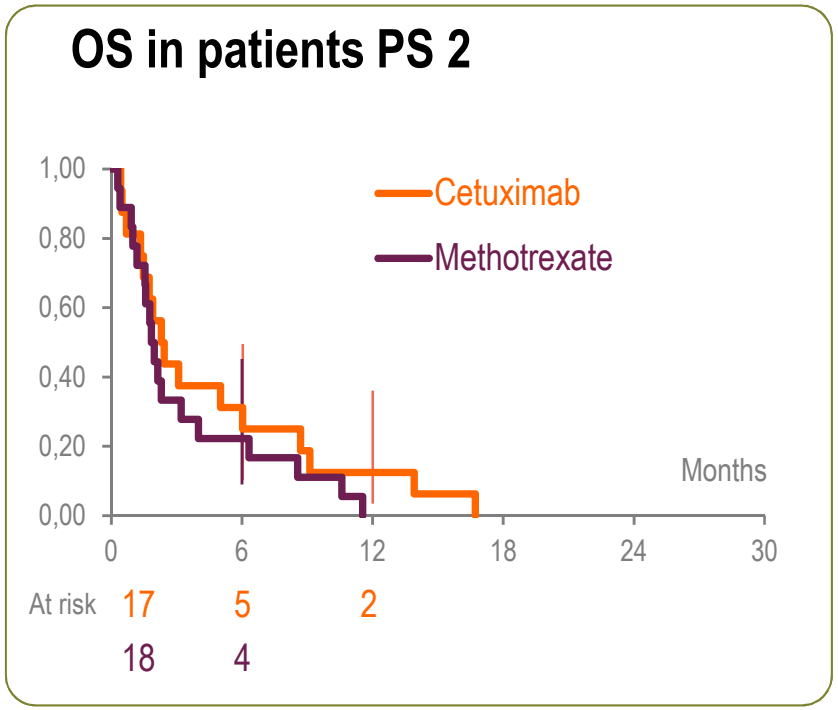


	1y OS	Median OS
PS 0-1	27.7 %	7.3 months
PS 2	5.9 %	2.1 months

At risk					
PS 0-1	47	27	13	8	2
PS 2	35	9	2		

ELAN-UNFIT: RESULTS





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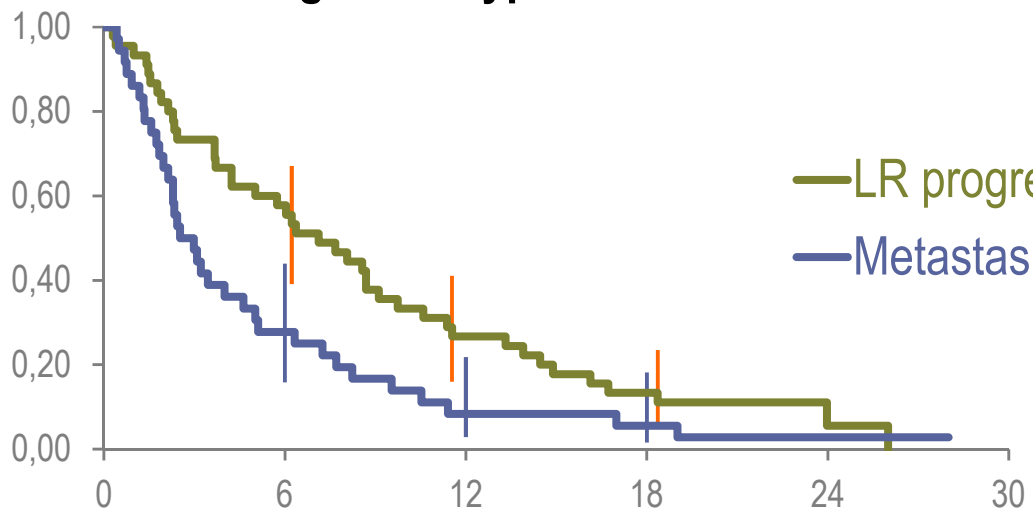
PS 0-1 (n=47) OS HR =0.93 (0.51;1.72) - PS 2 (n=35) OS HR = 0.71 (0.35;1.44)
Interaction p value = 0.60

ELAN-UNFIT: RESULTS

OS according to the type of evolution



1y OS	Median OS
15.6 %	7.1 months
8.3 %	2.8 months

ELAN-UNFIT: RESULTS

Objective Response Rate (ORR)

	Cetuximab arm	Methotrexate arm	p	PS 0-1	PS 2
Objective response rate	12.2% (95%CI=4.1%-26.2%)	14.6% (95%CI=5.6%-29.2%)	0.75	13%	14%

ELAN-UNFIT: RESULTS

Summary of adverse events

	Cetuximab N=41		Methotrexate N=41	
	N	%	N	%
At least one AE, whatever the grade	41	100%	41	100%
At least one AE of grade ≥ 2	38	93%	39	95%
At least one AE of grade ≥ 3	26	63%	30	73%
At least one AE of grade ≥ 4	11	27%	9	22%
AE of grade 5	5	12%	2	5%

	Pts PS ECOG 0-1 (n=47) (2 arms together)	Pts PS ECOG 2 (n=35) (2 arms together)
At least one AE of grade >=4	13%	40%

- The rate of patients with at least one AE of grade >=3 was not significantly different between the 2 arms (p=0.34)

ELAN-UNFIT: MOST FREQUENT AES GRADE ≥ 3

	Cetuximab N=41	Methotrexate N=41
AE term		
Leukopenia		
Neutropenia		
Thrombopenia		
Mucositis		
Anemia		
Fatigue		
Rash acneiform		
Magnesium disorder		
Natremia disorder		
Potassium disorder		
Infection		
Diarrhea		

UPDATE IN PROGRESS

ELAN FIT & UNFIT TRIALS: MAIN RESULTS

	ELAN FIT trial	ELAN UNFIT trial N=82			
	Carbo-5FU-cetux (n=78)	CX arm (n=41)	MTX arm (n=41)	Pts PS ECOG 0-1 (n=47) (2 arms together)	Pts PS ECOG 2 (n=35) (2 arms together)
Adverse events ≥ grade 4	24%	27%	22%	13%	40%
Objective response rate	At W12 : 40% (central review)	12%	15%	13%	14%
OS median (months)	**14.7** (95%CI=11.0-18.1)	**4.6** (95%CI=2.4-7.3)	**4.6** (95%CI=2.3-7.7)	**7.3** (95%CI=4.6-9.6)	**2.1** (95%CI=1.5-3.2)
1-year OS rate	**57.9%** (95%CI=46.6%-68.4%)	**22.5%** (95%CI=12.3%-37.5%)	**14.6%** (95%CI=6.9%-28.4%)	**27.7%** (95%CI=16.9%-41.8%)	**5.9%** (95%CI=1.6%-19.1%)
PFS median (months)	**7.2** (95%CI=5.9-8.4)	**2.4** (95%CI=1.5-3.8)	**2.8** (95%CI=1.6-4.2)	**3.8** (95%CI=2.6-5.5)	**1.5** (95%CI=1.2-2.3)
1-year PFS rate	**24.9%** (95%CI=16.5%-35.8%)	**7.5%** (95%CI=2.6%-19.9%)	**7.3%** (95%CI=2.5%-19.4%)	**12.8%** (95%CI=6.0%-25.2%)	**0%**

CONCLUSION

- Elderly patients aged 70 years and older, with R/M HNSCC, classified **fit** by adapted geriatric evaluation, were able to receive carboplatin-based EXTREME regimen that provided benefit similar to that observed in younger patients.

- Elderly patients with R/M HNSCC, classified **unfit** by geriatric assessment, showed less benefit from systemic treatment with either cetuximab or methotrexate. Those with poorer ECOG performance status (PS 2) derived no benefit from systemic therapy.

- New therapeutic options such as immunotherapy with checkpoint inhibitors should be explored for ECOG 0-1 unfit elderly patients

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