Lenvatinib plus pembrolizumab in patients with advanced endometrial cancer: an interim analysis of a multicentre, open-label, single-arm, phase 2 trial

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Summary

Background Lenvatinib is a multikinase inhibitor of VEGFR1, VEGFR2, and VEGFR3, and other receptor tyrosine kinases. Pembrolizumab, an antibody targeting PD-1, has moderate efficacy in biomarker-unselected endometrial cancer. We aimed to assess the combination of lenvatinib plus pembrolizumab in patients with advanced endometrial carcinoma, after establishing the maximum tolerated dose in a phase 1b study.

Methods In this open-label, single-arm, phase 2 study done at 11 centres in the USA, eligible patients were aged 18 years or older and had metastatic endometrial cancer (unselected for microsatellite instability or PD-L1), had an

CÁNCER DE ENDOMETRIO

INTRODUCCIÓN

Tumor ginecológico más frecuente en los países desarrollados.

Sobrevida global: 95% en estadios iniciales, 69% en tumores localmente avanzados y del 16,8% con enfermedad a distancia a 5 años.

Edad media: 63 años.

Incidencia es de 8 tumores cada 100.000 mujeres y la mortalidad de 2 por 100.000 mujeres año.

6ta causa de muerte por cáncer entre las mujeres, en aumento.

FACTORES DE RIESGO: niveles elevados de estrógeno, por diabetes, obesidad, dieta rica en grasas, menarca temprana, menopausia tardía, sind. de Lynch, edad mayor de 55 años, tamoxifeno.

Mientras el 30% aproximadamente de los casos quirúrgicos tienen inestabilidad microsatelital, el 70% de las recaídas son estables.

TRATAMIENTOS

-1ERA LINEA DE ELECCIÓN: CARBOPLATINO/PACLITAXEL: TASA DE RTA 40 AL 62%, SG 13 A 29 MESES

DOXORRUBICINA+CISPLATINO/ CISPLATINO+PACLI+DOXO/ CARBO+PACLI+BEVA

-MONOTERAPIA EN PRIMERA LÍNEA RTA DE: 21 AL 36%/ SEGUNDA LÍNEA: 4 AL 27% (DOCETAXEL, PACLITAXEL, DOXO LIPOSOMAL,BEVACIZUMAB,

-2DA LÍNEA : PEMBROLIZUMAB (KEYNOTE 028) EN PACIENTES CON dMMR, TASA DE RTA 52%

NIVOLUMAB, PEMBROLIZUMAB + LENVATINIB, LAROTRECTINIB,

-KEYNOTE 028/158 TASA OBJETIVA 19.3% DE 83 PACIENTES 2 RTA COMPLETAS 14 RTAS PARCIALES, MEDIA DE RTA NO ALCANZADA.

-RIESGO BAJO E INTERMEDIO/PALIATIVO: MEDROXIPROGESTERONA, MEGESTROL, TAMOXIFENO

SYSTEMIC THERAPY FOR ENDOMETRIAL CARCINOMA

Adjuvant Treatment When Used for Uterine-Confined Disease
Preferred Regimens • Carboplatin/paclitaxel

Recurrent, Metastatic, Or High-Risk Disease[a,b]			
	Preferred Regimens	**Other Recommended Regimens**	**Useful In Certain Circumstances**
Systemic therapies[a,b]	• Carboplatin/paclitaxel (category 1 for carcinosarcoma)[1] • Carboplatin/paclitaxel/trastuzumab[c] (for stage III/IV or recurrent HER2-positive uterine serous carcinoma)[2]	• Carboplatin/docetaxel[d] • Cisplatin/doxorubicin[3] • Cisplatin/doxorubicin/paclitaxel[e,f,3] • Carboplatin/paclitaxel/bevacizumab[e,g,4] • Cisplatin • Carboplatin • Doxorubicin • Liposomal doxorubicin • Paclitaxel[5] • Albumin-bound paclitaxel[h] • Topotecan • Bevacizumab[g,i,6] • Temsirolimus[7] • Docetaxel[d] (category 2B) • Ifosfamide (for carcinosarcoma) • Ifosfamide/paclitaxel (for carcinosarcoma)[8] • Cisplatin/ifosfamide (for carcinosarcoma)	N/A
Biomarker-directed systemic therapy for second-line treatment	N/A	N/A	• Lenvatinib/pembrolizumab[j,k,9] • Pembrolizumab[l] (for TMB-H[10] or MSI-high [MSI-H]/MMR deficient [dMMR] tumors[m,11]) • Nivolumab[n,12] • Larotrectinib or entrectinib for *NTRK* gene fusion-positive tumors (category 2B)[e]

SYSTEMIC THERAPY FOR ENDOMETRIAL CARCINOMA

Recurrent, Metastatic, Or High-Risk Disease			
	Preferred Regimens	**Other Recommended Regimens**	**Useful In Certain Circumstances**

Hormone therapy[o]	• Medroxyprogesterone acetate/tamoxifen (alternating)
	• Megestrol acetate/tamoxifen (alternating)
	• Progestational agents
	  ▸ Medroxyprogesterone acetate
	  ▸ Megestrol acetate
	  ▸ Levonorgestrel intrauterine device (IUD) (for select fertility-sparing cases)
	• Aromatase inhibitors
	• Tamoxifen
	• Fulvestrant
		• Everolimus/letrozole (for endometrioid histology)	N/A

LENVATINIB MÁS PEMBROLIZUMAB

Análisis interino de estudio FASE 2, multicéntrico, abierto, una rama de tratamiento.

INCLUSIÓN: MAYORES DE 18 AÑOS, CÁNCER DE ENDOMETRIO METASTÁSICO MEDIBLE POR irRECIST,NO HAYAN RECIBIDO MÁS DE 2 LÍNEAS, EXPECTATIVA DE VIDA DE MÁS DE 12 SEMANAS, ECOG: 0 a , BUENA FUNCIÓN RENAL, HEPÁTICA, HTA CONTROLADA CON O SIN MEDICAMENTOS

EXCLUSIÓN: TTO PREVIO CON ANTI PDL1/PD1 O LENVATINIB

OBJETIVO PRIMARIO: TASA DE RESPUESTA OBJETIVA A LA SEMANA 24

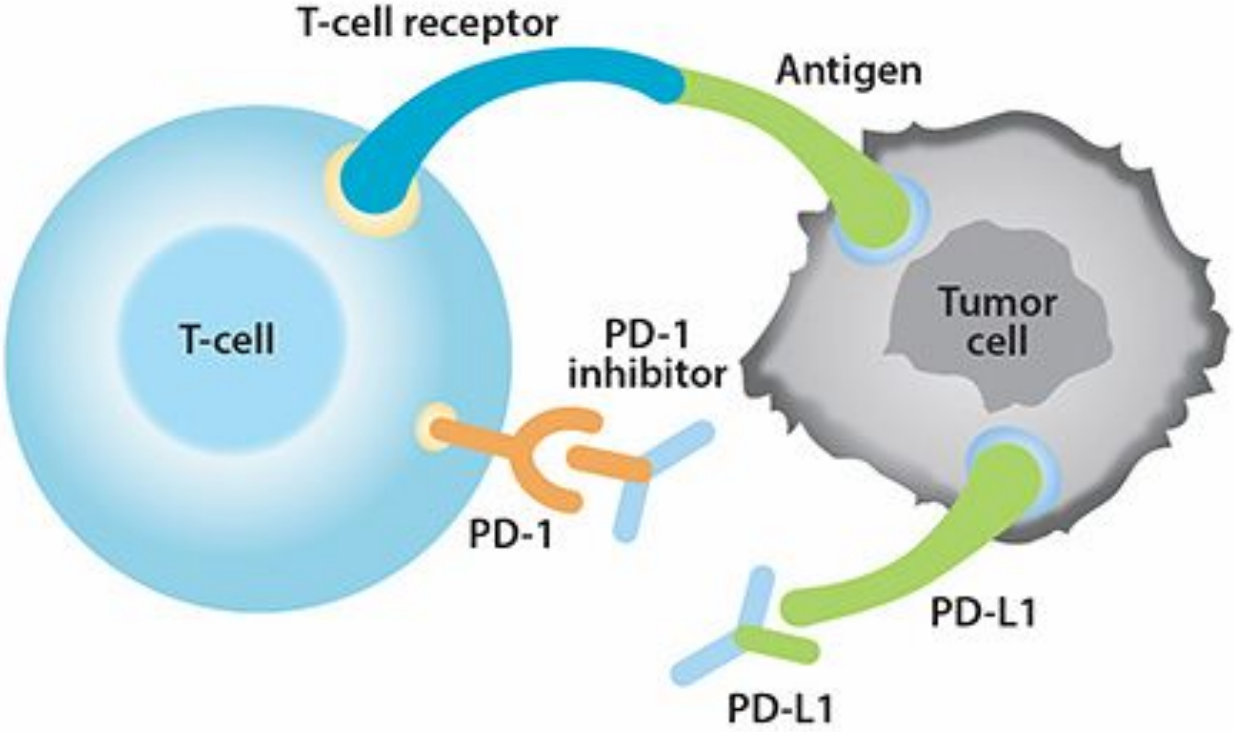
SE RECLUTARON 53 PACIENTES DESDE SEPTIEMBRE 2015 A JULIO DE 2017

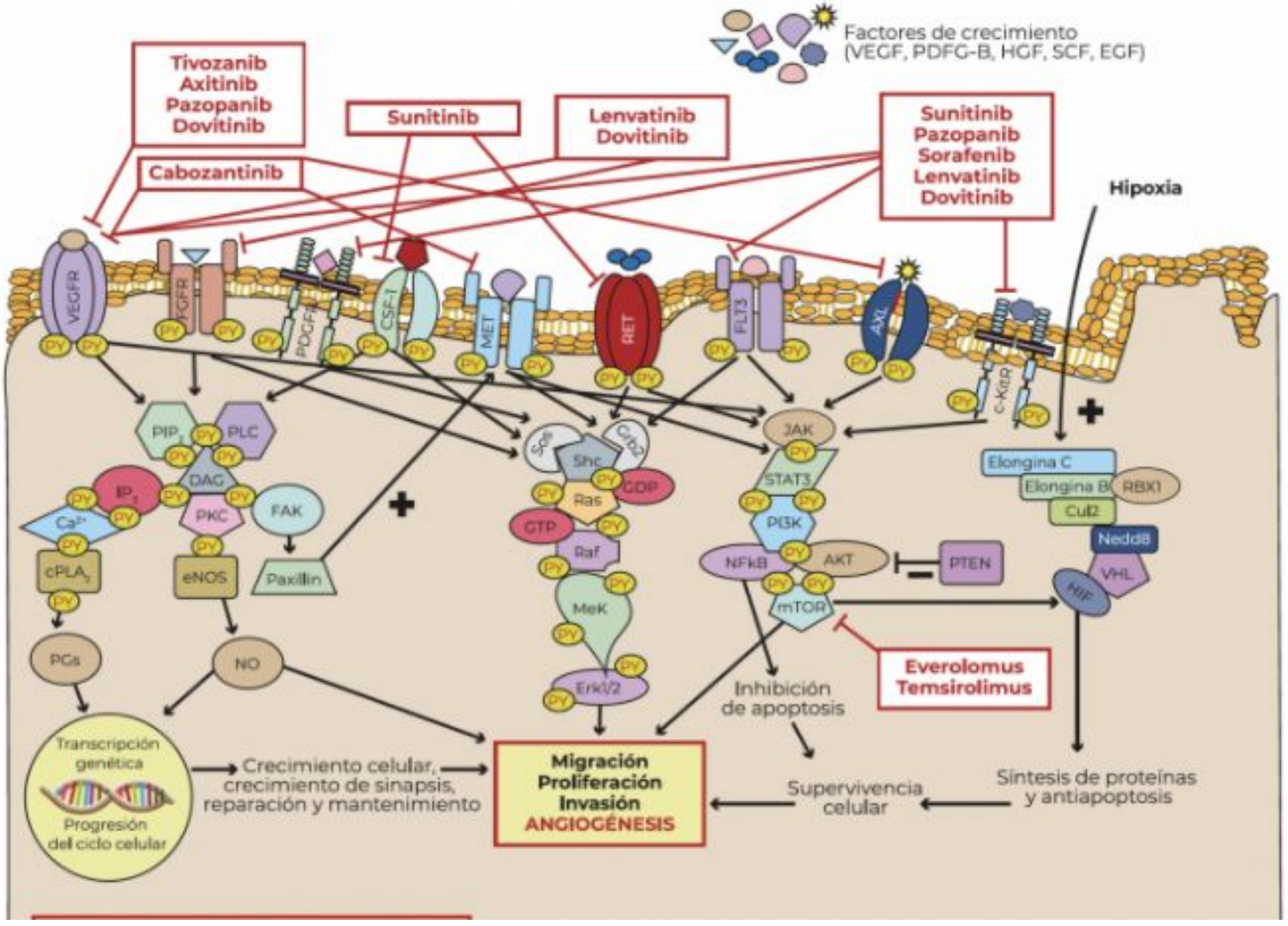
ON GOING

RESULTADOS INMADUROS

PEMBROLIZUMAB: 200 MG EV CADA 21 DÍAS (anti PD-1)

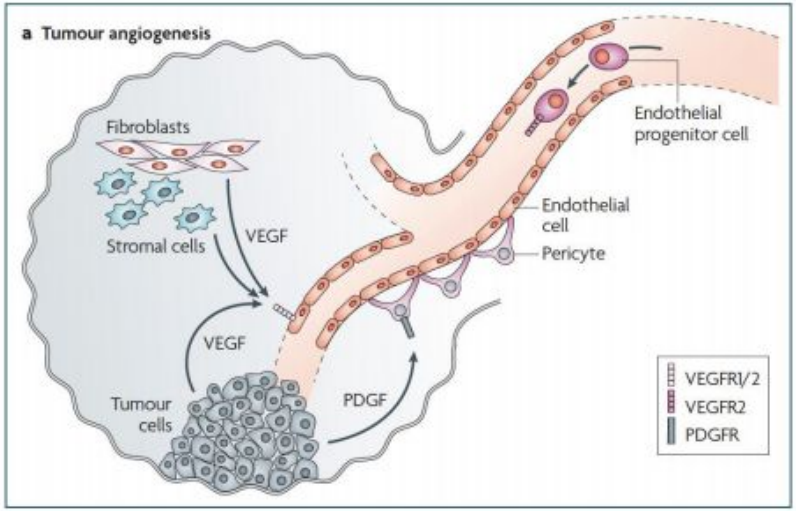
LENVATINIB 20 MG DÍA (inhibidor oral multiquinasa VEGFR1–3, FGFR1–4, PDGFRα y de oncogenes RET y KIT.

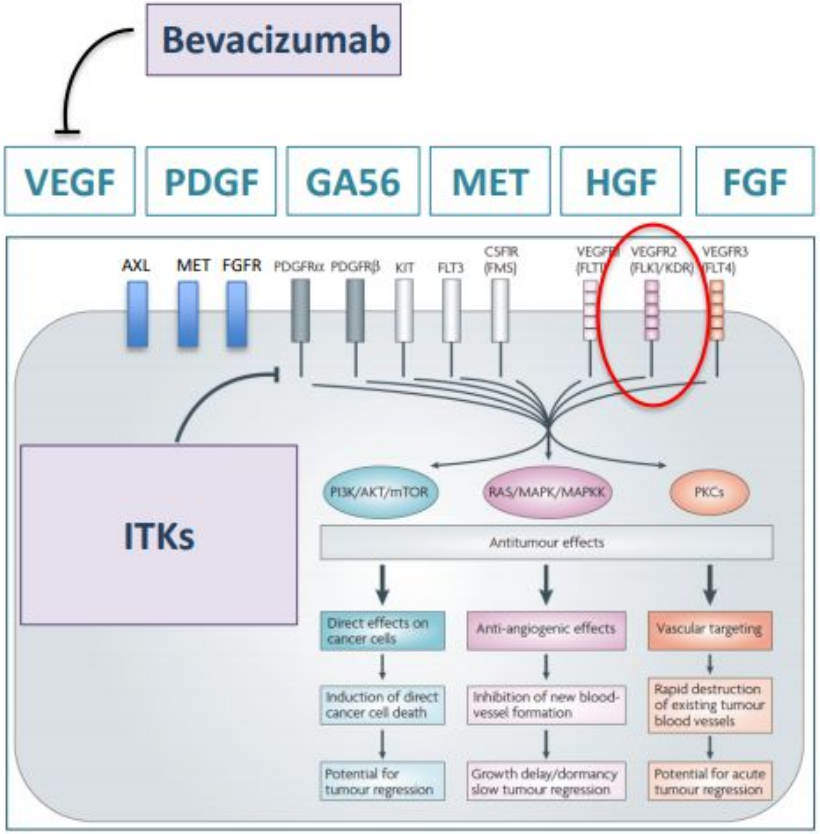

T-cell receptor
Antigen
T-cell
PD-1
inhibitor
Tumor
cell
PD-1
PD-L1
PD-L1


Factores de crecimiento
(VEGF, PDFG-B, HGF, SCF, EGF)
Tivozanib
Axitinib
Pazopanib
Dovitinib
Cabozantinib
Sunitinib
Lenvatinib
Dovitinib
Sunitinib
Pazopanib
Sorafenib
Lenvatinib
Dovitinib
Hipoxia
VEGFR
FGFR
PDGFR
CSF-1
MET
RET
FLT3
AXL
c-KitR
PIP2
PLC
DAG
IP3
Ca2+
PKC
FAK
cPLA2
eNOS
Paxillin
PGs
NO
Sos
Grb2
Shc
Ras
GDP
GTP
Raf
MeK
Erk1/2
JAK
STAT3
PI3K
NFkB
AKT
PTEN
mTOR
Elongina C
Elongina B
RBX1
Cul2
Nedd8
VHL
HIF
Everolomus
Temsirolimus
Inhibición
de apoptosis
Síntesis de proteínas
y antiapoptosis
Supervivencia
celular
Transcripción
genética
Progresión
del ciclo celular
Crecimiento celular,
crecimiento de sinapsis,
reparación y mantenimiento
Migración
Proliferación
Invasión
ANGIOGÉNESIS

TKIs

➢ Mecanismo de acción





TKIs

Mecanismo de acción

Target	Sunitinib	Pazopanib	Tivozanib	Axitinib	Cabozantinib	Lenvatinib
VEGFR1	x	x	x	x		x
VEGFR2	x	x	x	x	x	x
VEGFR3	x	x	x	x		x
c-KIT	x	x	x		x	x
PDGFRα	x	x				x
PDGFRβ	x	x				
CSF1R	x					
FLT3	x				x	
RET	x				x	x
b-Raf						
c-Raf						
MET					x	
AXL					x	
ROS					x	
TYRO3					x	
MER					x	
TRKB					x	
TIE-2					x	
FGFR1-4						x

DATO IMPORTANTE

EN UN MODELO DE RATONES LENVATINIB SUSTANCIALMENTE DISMINUYO LA POBLACION DE MACRÓFAGOS ASOCIADOS AL TUMOR Y ELEVÓ EL NÚMERO DE CÉLULAS T CD8, LO QUE AUMENTÓ LA ACTIVIDAD ANTITUMORAL DEL ANTI PD1.

	Lenvatinib plus pembrolizumab group (n=53)
Mean age, years (SD)	64 (8)
Race	
White	44 (83%)
Black	2 (4%)
Other	7 (13%)
ECOG performance status	
0	20 (38%)
1	33 (62%)
Histological subtypes	
Endometrioid adenocarcinoma	
FIGO grade 1	5 (9%)
FIGO grade 2	11 (21%)
FIGO grade 3	6 (11%)
Serous adenocarcinoma	20 (38%)
Clear cell adenocarcinoma	2 (4%)
Other adenocarcinomas or adenocarcinoma not otherwise specified	9 (17%)
Previous surgical tumour debulking	53 (100%)
Number of previous systemic therapies	
One	23 (43%)
Two	23 (43%)
Three or more	7 (13%)
Previous chemotherapy	
Platinum-based doublet therapy	52 (98%)
Platinum monotherapy	1 (2%)
Taxane monotherapy	1 (2%)
Doxorubicin or liposomal doxorubicin	12 (23%)
Other cytotoxic chemotherapy	4 (8%)
Previous hormonal therapy	6 (11%)
Previous bevacizumab	3 (6%)

(Table 1 continues on next page)

	Lenvatinib plus pembrolizumab group (n=53)
(Table 1 continues from previous page)	
Previous radiotherapy	30 (57%)
PD-L1 status	
Positive	13 (25%)
Negative	11 (21%)
Unknown	29 (55%)
Microsatellite status	
High microsatellite instability	4 (8%)
Microsatellite stable	45 (85%)
Unknown	4 (8%)

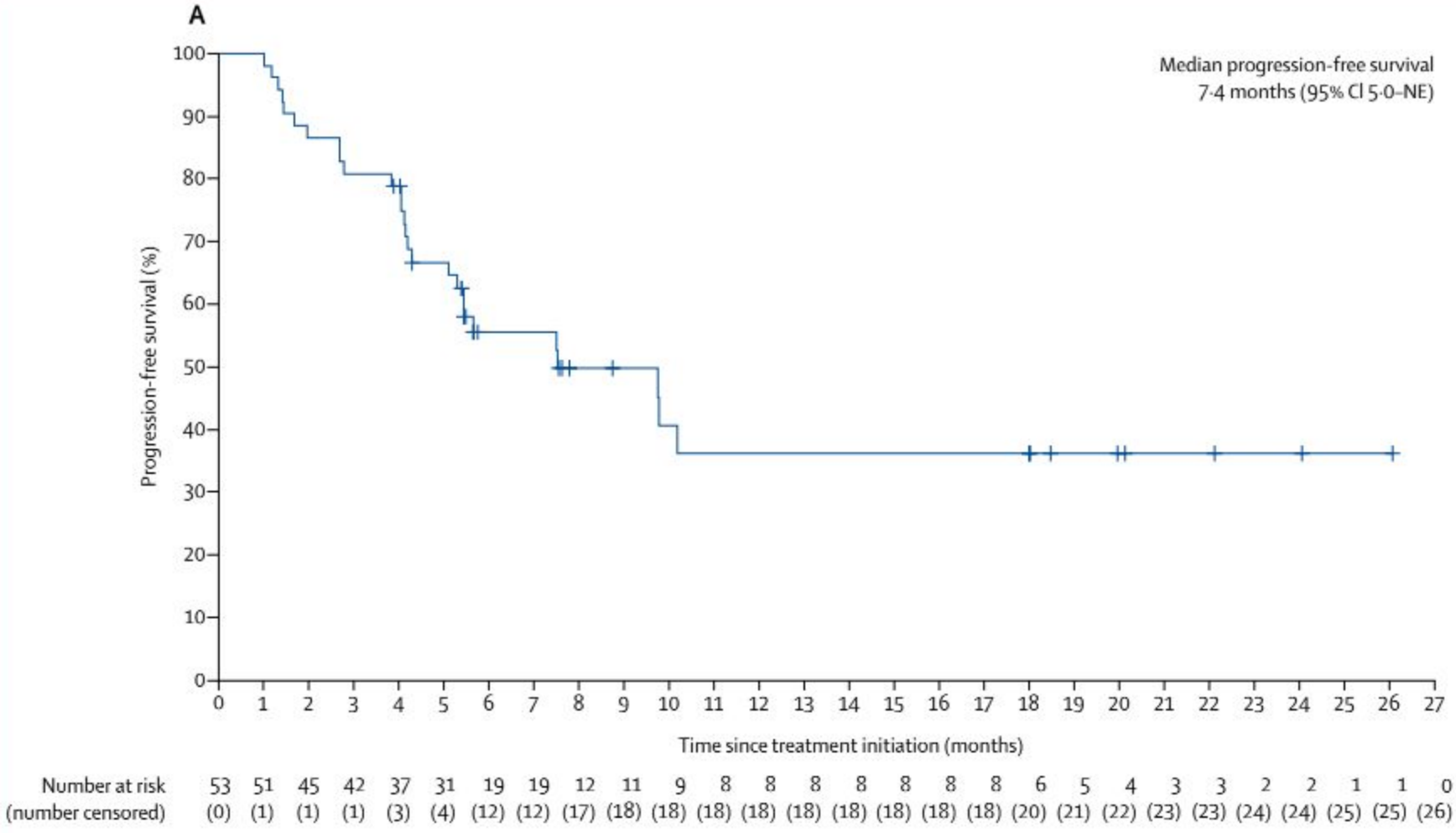
Data are n (%), unless otherwise specified. ECOG=Eastern Cooperative Oncology Group. FIGO=International Federation of Gynecology and Obstetrics.

Table 1: **Baseline characteristics of the per-protocol population**

	Investigator review (n=53)	Independent review (n=53)
Objective response at week 24	21 (39·6%; 26·5–54·0)	24 (45·3%; 31·6–59·6)
Objective response at data cutoff	21 (39·6%; 26·5–54·0)	25 (47·2%; 33·3–61·4)
Best overall response		
Complete response	1 (1·9%)	3 (5·7%)
Partial response	20 (37·7%)	22 (41·5%)
Stable disease	25 (47·2%)	19 (35·8%)
Progressive disease	4 (7·5%)	5 (9·4%)
Unknown or not assessable	3 (5·7%)	4 (7·5%)
Median duration of response, months		
Median (95% CI)	NE (7·4–NE)	NE (5·8–NE)
Range*	1·2–23·4	1·2–23·4
IQR	7·4–NE	NE–NE
Proportion with responses ≥6 months	12 (83·0%; 55·9–94·2)	11 (79·3%; 48·5–92·9)
Proportion with responses ≥12 months	7 (64·5%; 32·8–84·2)	8 (79·3%; 48·5–92·9)
Median time to response, months (95% CI; IQR)	2·7 (1·3–2·8; 1·3–2·8)	2·6 (1·4–2·8; 1·4–3·7)

Data are n (%; 95% CI) or n (%), unless otherwise specified. NE=not estimable (because of an insufficient number of events at the data cutoff to estimate the median or upper limits of the 95% CI). *Some patients had ongoing responses.

Table 2: **Tumour responses as assessed by investigators or independent reviewers**


A
Median progression-free survival
7·4 months (95% CI 5·0–NE)
Progression-free survival (%)
100
90
80
70
60
50
40
30
20
10
0
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27
Time since treatment initiation (months)
Number at risk 53 51 45 42 37 31 19 19 12 11 9 8 8 8 8 8 8 8 6 5 4 3 3 2 2 1 1 0
(number censored) (0) (1) (1) (1) (3) (4) (12) (12) (17) (18) (18) (18) (18) (18) (18) (18) (18) (18) (20) (21) (22) (23) (23) (24) (24) (25) (25) (26)

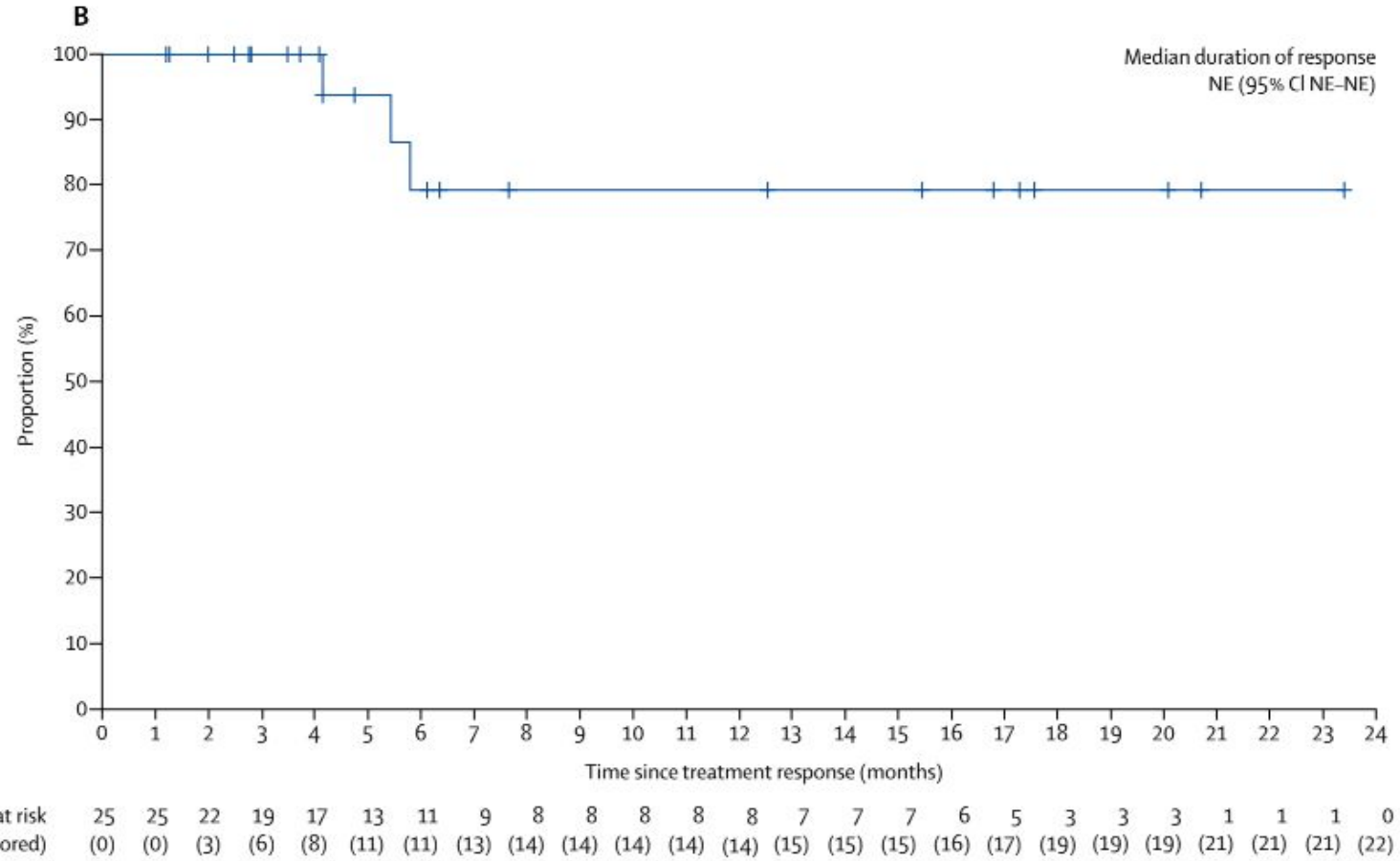


***Figure 2*: Progression-free survival (A) and duration of response (B)**

In (A), progression-free survival was assessed by investigators in the per-protocol population (n=53), whereas in (B), duration of response was assessed by independent reviewers in responders only (n=25). Both investigators and independent reviewers used the immune-related Response Evaluation Criteria In Solid Tumors in their assessments. NE=not estimable.

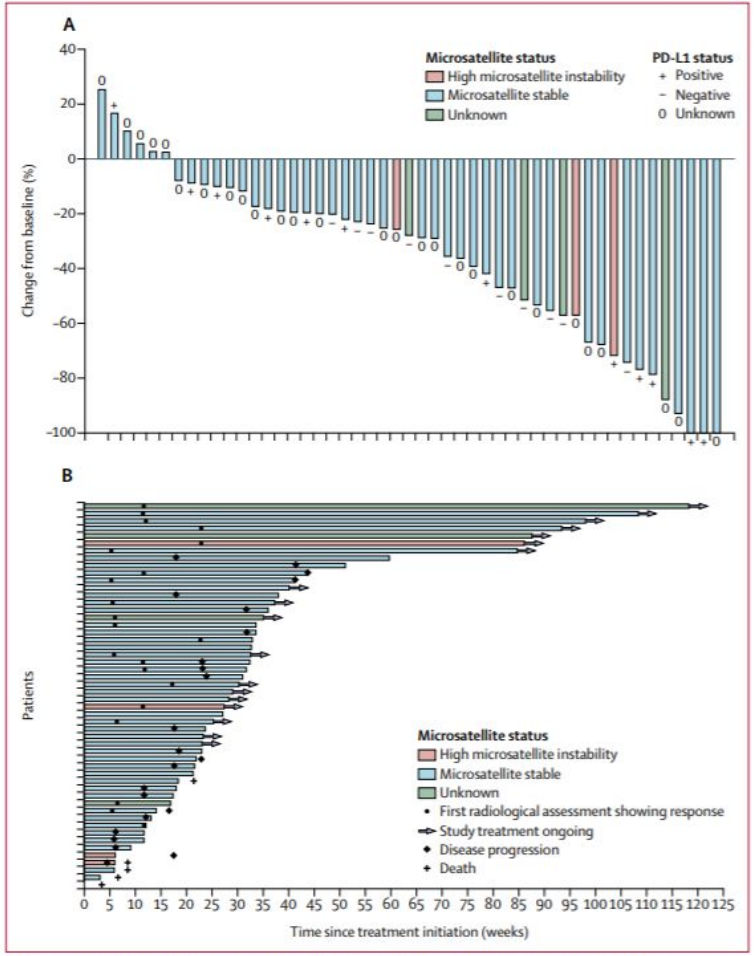


Figure 1: **Maximum percentage change in sum of diameters of target lesions from baseline (A), and time on treatment (B)**

In (A), only patients with available tumour assessments at data cutoff are shown. Changes in tumour size were judged by investigators according to the immune-related Response Evaluation Criteria In Solid Tumors. In (B), all patients in the per-protocol population (n=53) are shown.

	Grade 1–2	Grade 3*
Any treatment-related adverse event	13 (25%)	36 (68%)
Serious treatment-related adverse events	2 (4%)	13 (25%)
Fatigue	26 (49%)	3 (6%)
Hypothyroidism	25 (47%)	0
Diarrhoea	23 (43%)	4 (8%)
Decreased appetite	21 (40%)	0
Nausea	20 (38%)	0
Stomatitis	18 (34%)	0
Weight loss	15 (28%)	0
Arthralgia	14 (26%)	0
Palmar–plantar erythrodysesthesia syndrome	14 (26%)	3 (6%)
Hypertension	13 (25%)	18 (34%)
Vomiting	13 (25%)	0
Headache	12 (23%)	0
Proteinuria	12 (23%)	1 (2%)
Dysphonia	10 (19%)	0
Dry mouth	9 (17%)	0
Dry skin	7 (13%)	0
Abdominal pain	6 (11%)	0
Constipation	6 (11%)	0
Hypomagnesaemia	6 (11%)	0
Oral pain	6 (11%)	1 (2%)
Dehydration	5 (9%)	1 (2%)
Increased aspartate aminotransferase	4 (8%)	1 (2%)
Anaemia	3 (6%)	1 (2%)
Hyponatraemia	2 (4%)	2 (4%)
Increased lipase	2 (4%)	1 (2%)
Increased alanine aminotransferase	2 (4%)	1 (2%)
Prolonged electrocardiogram QT interval	2 (4%)	1 (2%)
Hypokalaemia	1 (2%)	1 (2%)
Acute kidney injury	0	2 (4%)
Pulmonary embolism	0	2 (4%)
Syncope	0	2 (4%)
Adrenal insufficiency	0	1 (2%)
Cardiac failure	0	1 (2%)
Colitis	0	1 (2%)
Dysarthria	0	1 (2%)
Hypertensive encephalopathy	0	1 (2%)
Ischaemic colitis	0	1 (2%)
Neutropenia	0	1 (2%)
Pancreatitis	0	1 (2%)
Retinal vein occlusion	0	1 (2%)
Small intestinal obstruction	0	1 (2%)
Upper abdominal pain	0	1 (2%)

Data are n (%). Overall n=53. Grade 1 or 2 treatment-related adverse events occurring in at least 10% of the population and all grade 3 treatment-related adverse events are shown. Adverse events were graded according to the CommonTerminology Criteria for Adverse Events (version 4.03). *No grade 4 treatment-related adverse events were reported, and one grade 5 event (intracranial haemorrhage) was reported.

Table 3: **Treatment-related adverse events in the per-protocol population**

CONCLUSIONES

IMPORTANTE BENEFICIO EN PACIENTE CON LÍNEAS PREVIAS Y EN PACIENTES CON ESTABILIDAD MICROSATELITAL

-A LAS 24 SEMANAS 21 PACIENTES LOGRARON LA RESPUESTA OBJETIVA, SEG 13.3 MESES

-SOBREVIDA MEDIA DE LP 7.4 MESES (CON LÍNEAS PREVIAS DE TTO)

-DURACIÓN MEDIA DE RESPUESTA AUN NO ALCANZADA

-18 PACIENTES (34%) AÚN RECIBEN MEDICACIÓN

-35 PACIENTES (66%) DESCONTINUARON POR RAM (MAYOR % DE HIPOTIROIDISMO)

-UNA MUERTE POR HEMORRAGIA INTRACRANEAL

-IMPORTANTE BENEFICIO PARA PACIENTES CON ESTABILIDAD MICROSATELITAL

-TOXICIDAD ACEPTABLE Y MANEJABLE

-ESTUDIO FASE 3: LENVATINIB MÁS PEMBRO VS DOXORRUBICINA O PACLITAXEL EN RECLUTAMIENTO