V SIMPOSIO GETHI | ONCOLOGÍA TRANSVERSAL AL SERVICIO DEL PACIENTE

Estudios con inmunoterapia en tumores infrecuentes

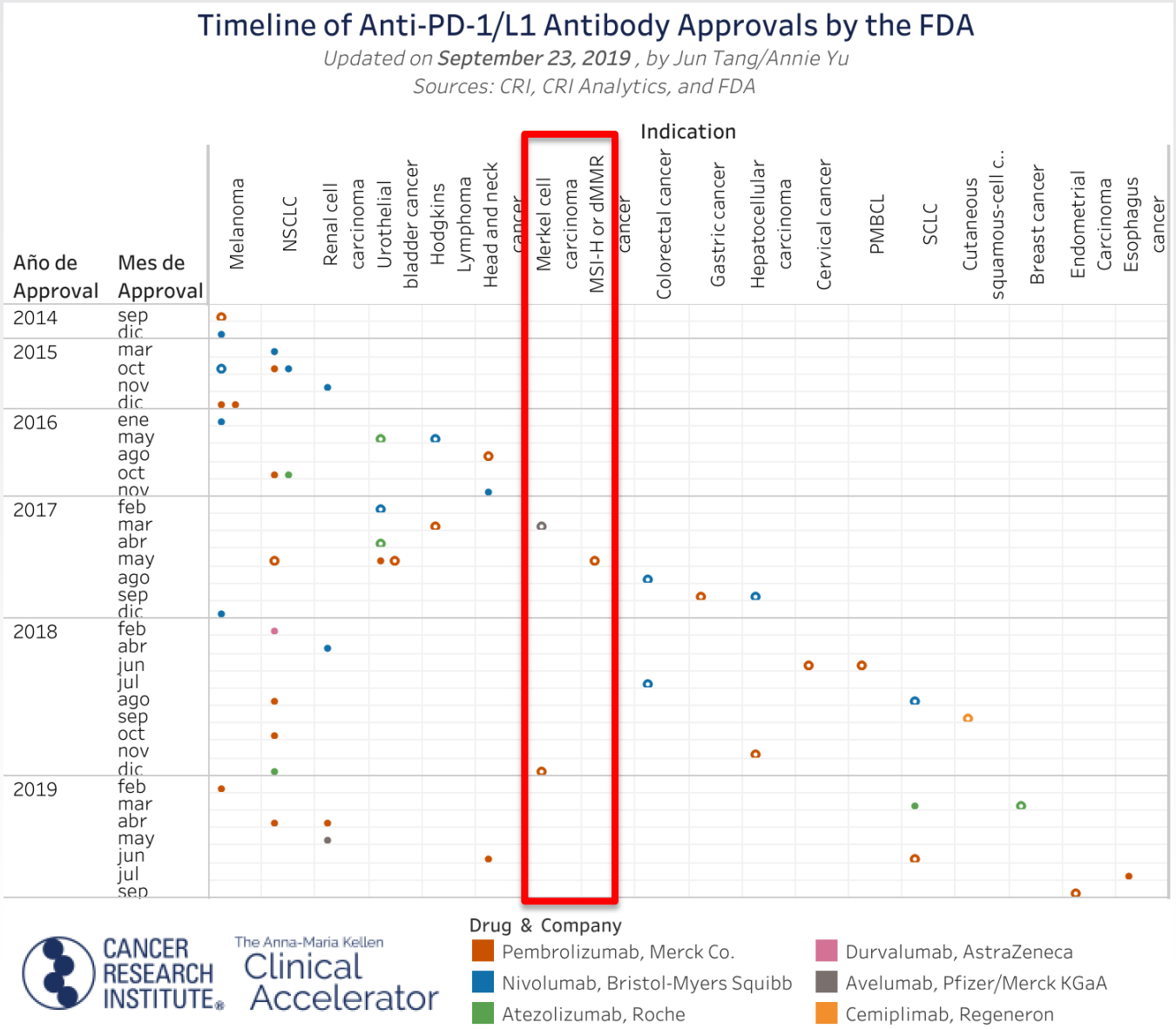
Resultados preliminares del estudio GETHI021

"Nivo-rare"

Hospital Universitario Fundación Alcorcón
SaludMadrid
Comunidad de Madrid

Xabier Mielgo Rubio, MD
Unidad de Oncología
Hospital Universitario Fundación Alcorcón

Checkpoint inhibitors en cáncer raro

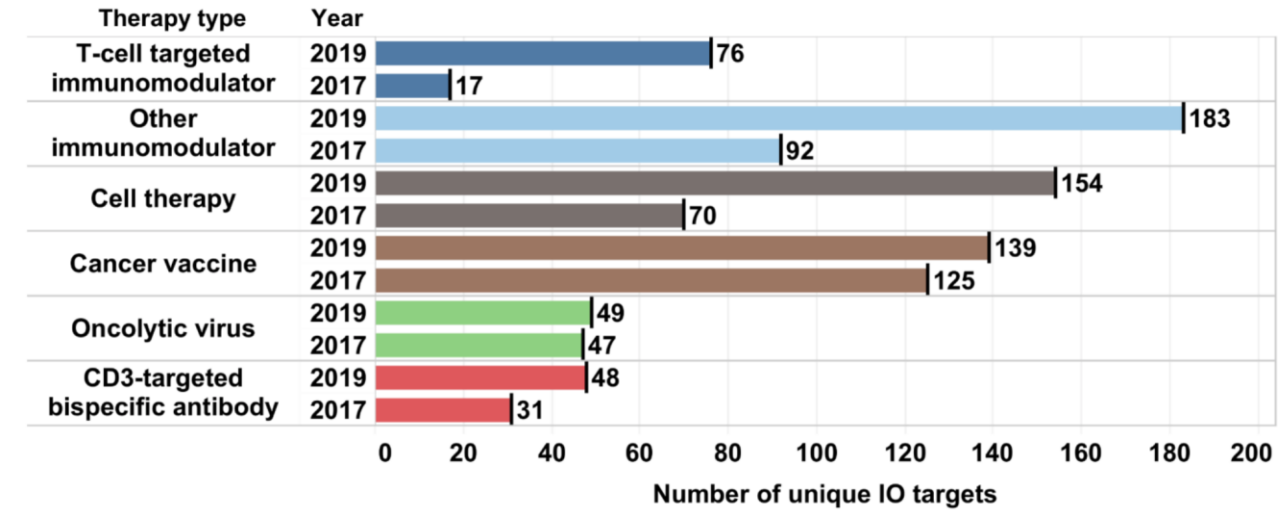


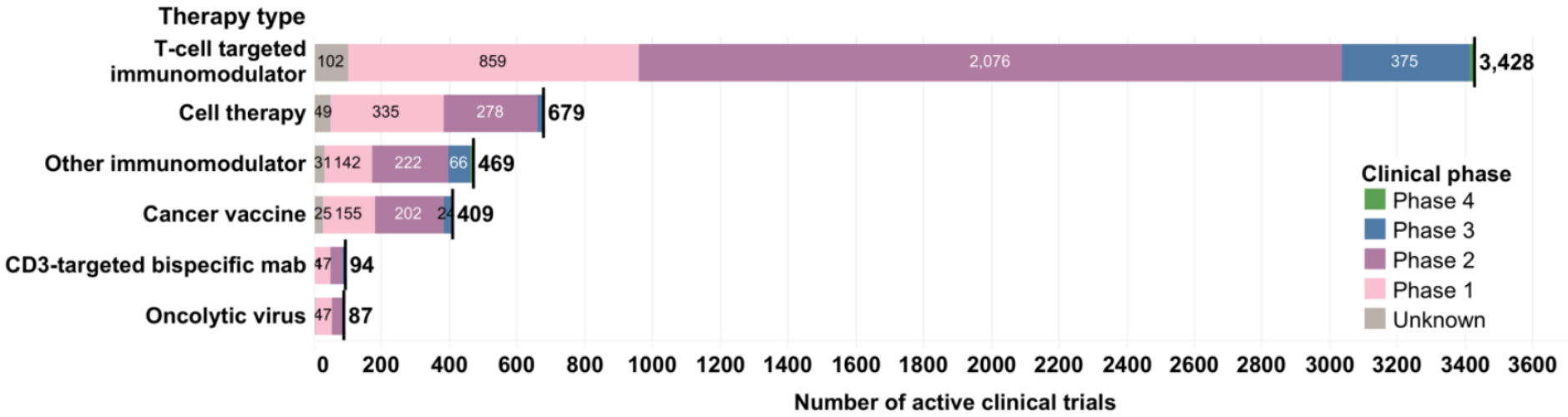
CANCER RESEARCH INSTITUTE

The Anna-Maria Kellen Clinical Accelerator

Yu, J. X. Et al. *Nat Rev. Drug. Discov 2019*

Ensayos clínicos con IO V SIMPOSIO GETH





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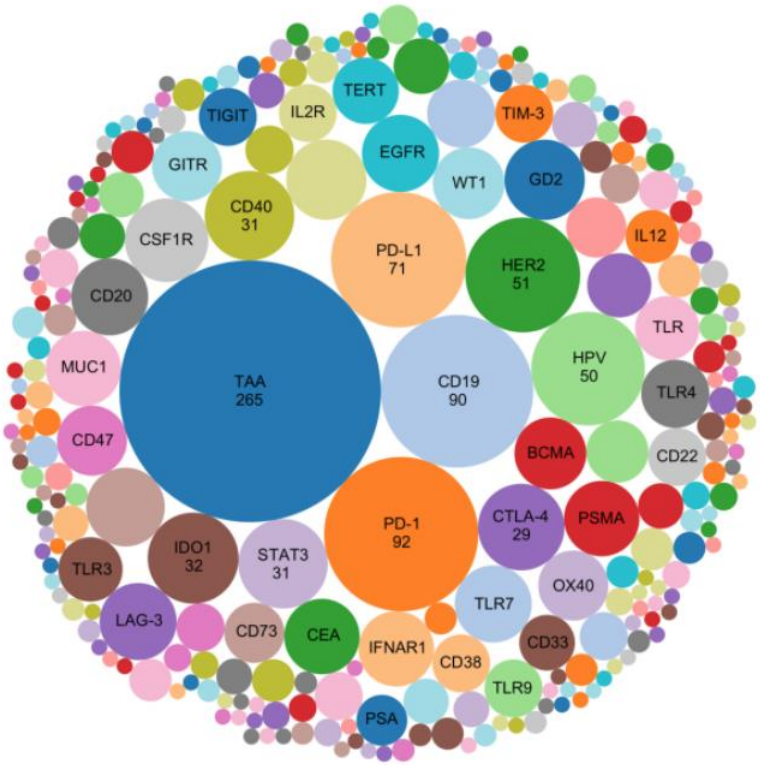
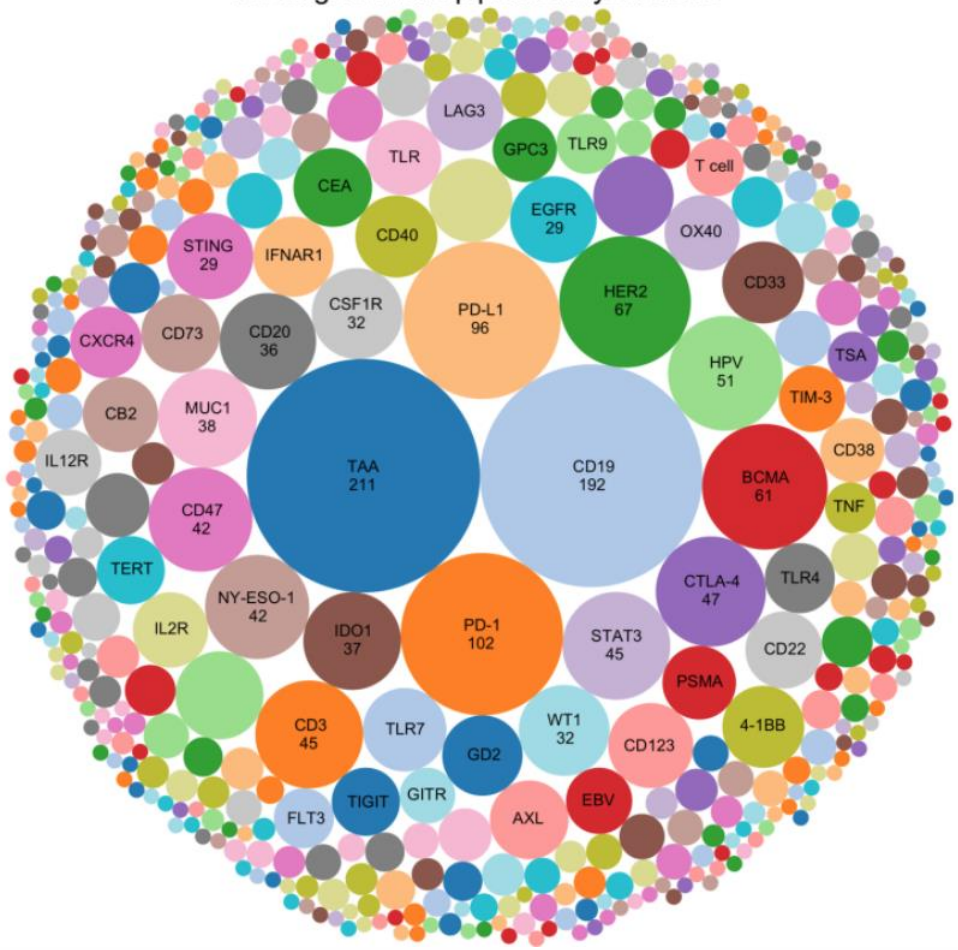
Target pipeline comparison V SIMPOSIO GETH

263 targets in the pipeline in year 2017



468 targets in the pipeline in year 2019



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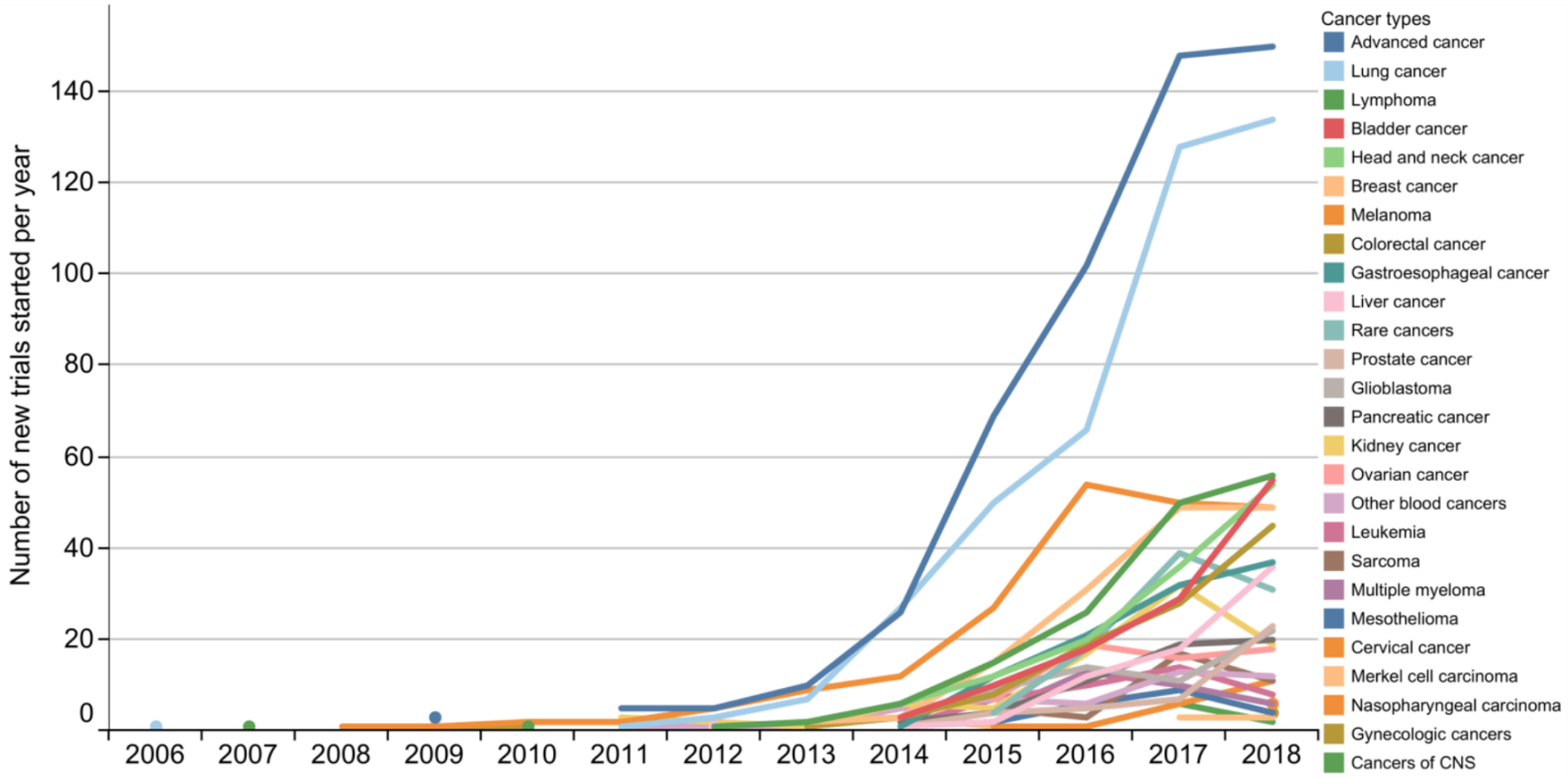
What about rare cancer?



Supplementary Figure 3. The evolution of new trials started per year by different cancer types. Cancer types with approved PD-1/L1 mabs have shown either slow growth or decrease of new trials per year.

Yu, J. X. Et al. *Nat Rev. Drug. Discov 2019*

IO en tumores raros

Tipo tumor	Tratamiento	Promotor	Colaborador	Fase	Objetivo principal	N prevista	
Sólidos avanzados	Durvalumab + Tremelimumab	CCTG	AstraZeneca	II	ORR RECISTv1.1	160	NCT02879162
Sólidos avanzados	Durvalumab + Tremelimumab	Greenville Health System	AstraZeneca	II	iRECIST/Safety	50	NCT02938793
Sólidos avanzados	Nivolumab + Ipilimumab	NCI		II	ORR RECISTv1.1	707	NCT02834013
Tumores pediátricos del adulto	Nivolumab + Ipilimumab	GETHI	BMS	II	ORR RECISTv1.1	98	
Sólidos avanzados	Nivolumab + Ipilimumab	Olivia-Newton-John Cancer InstituteAustralia	BMS	II	Clinibal Benefit Rate	120	NCT0292393
Genitourinarios raros	Nivolumab + Ipilimumab	Danna-Farber Cancer Institute	BMS	II	ORR RECISTv1.1	57	NCT03333616
Sólidos avanzados	Cobimetinib + Atezolizumab	MD Anderson	Genentech	II	ORR RECISTv1.1	60	NCT03108131
Sólidos avanzados	Atezolizumab + Bevacizumab	MD Anderson	Genentech	II	ORR RECISTv1.1	160	NCT03074513
Sólidos avanzados	Pembrolizumab	MD Anderson	NCI	II	Non-progression rate RECISTv1.1	275	NCT02721732
Sólidos avanzados	Pembrolizumab	UNICANCER	NCI France	II	ORR RECISTv1.1	350	NCT03012620
Sólidos avanzados	Nivolumab	UNICANCER	NCI France	II	ORR RECISTv1.1	300	NCT03012581
Tumores raros SNC	Nivolumab	NCI		II	ORR/PFS-6	180	NCT03173950
Tumores pediátricos	Atezolizumab	NCI	Genentech	I/II	ORR RECISTv1.1	90	NCT02541604
Genitourinarios raros	Cabozantinib + Nivolumab + Ipilimumab	NCI		II	ORR RECISTv1.1	186	NCT03866382

S1609 DART: A Phase II Basket Trial of Dual Anti-CTLA-4 and Anti-PD-1 Blockade in Rare Tumors

Sandip Pravin Patel[1], Megan Othus[2], Young Kwang Chae[3], Frank Giles[3], Jourdain Hayward[4], Christine McLeod[4], Helen X. Chen[5], Elad Sharon[5], Edward Mayerson[2], Christopher W. Ryan[6], Melissa Plets[2], Charles David Blanke[6], Razelle Kurzrock[1]
[1]University of California San Diego; [2]SWOG Statistical Center, Seattle, WA; [3]Northwestern University; [4]SWOG Data Operations Center, Seattle, WA; [5]National Cancer Institute, Cancer Therapy Evaluation Program ; [6]Oregon Health & Science University

Introduction

Background:

- Immune checkpoint blockade targeting anti-CTLA-4 (ipilimumab) and anti-PD-1 (nivolumab) has revolutionized cancer therapy
- To date, majority of clinical trials and FDA approvals for these agents have been in more common cancer
- This trial evaluates the efficacy of ipilimumab plus nivolumab across rare tumors
  - First federally-funded basket study investigating immunotherapy across rare cancers

Study Design:

- 566 patients to-date
- Ipilimumab (ipi) 1mg/kg iv q6 weeks continuously with nivolumab (nivo) 240mg iv q2 weeks until disease progression, severe toxicity, or withdrawal of consent.
- Single-arm study with a Simon's two-stage design
-

Patient Population:

- ≥ 18 years old
- Incurable rare cancer
- RECIST-measurable disease
- Patients with well-controlled HIV and viral hepatitis are eligible.
- Exclusion criteria include history of severe autoimmune condition, solid organ transplant, or unstable brain metastasis.

Current status: As of May 13, 2019

- 566 patients have enrolled onto S1609 DART from 312 sites.
- 11 of the initial 37 cohorts progressed to the 2nd stage of the two-stage design.

Study Endpoints

Primary:

ORR by RECIST v1.1

Secondary:

-PFS, OS
-Toxicity
-Correlative studies

Schema

INCURABLE RARE CANCER

↓

Allocation to existing defined rare histologic cohort OR
Review by SCs for "Not otherwise categorized" cohort

↓

Ipilimumab 1mg/kg iv q6 weeks with nivolumab 240mg iv q2 weeks until PD, unacceptable toxicity, withdrawal of consent

Study Population

Status	#	COHORT NAME	TOTAL REGS.	REGS. LAST 12 Month	REGS. LAST 6 Month	REGS. LAST 3 Month	REGS. LAST 30 DAYS	REGS. LAST 7 DAYS	# of ACT. INSTs	# of CURR IRBs
Permanent Close	1	Epithelial tumors of nasal cavity, sinuses, nasopharynx	7	0	0	0	0	0	312	151
Permanent Close	2	Epithelial tumors of major salivary glands	31	1	0	0	0	0		
Permanent Close	3	Salivary gland type tumors of head and neck, lip, esophagus, stomach, trachea and lung, breast and other location	7	1	0	0	0	0		
Temporary Close	4	Undifferentiated carcinoma of gastrointestinal (GI) tract	7	5	0	0	0	0		
Permanent Close	5	Adenocarcinoma with variants of small intestine	25	0	0	0	0	0		
Permanent Close	6	Squamous cell carcinoma with variants of GI tract (stomach small intestine, colon, rectum, pancreas)	6	0	0	0	0	0		
Permanent Close	7	Fibromixoma and low grade mucinous adenocarcinoma (pseudomixoma peritonei) of the appendix and ovary	10	0	0	0	0	0		
Temporary Close	8	Rare Pancreatic tumors including acinar cell carcinoma, mucinous cystadenocarcinoma or serous cystadenocarcinoma	11	2	0	0	0	0		
Permanent Close	9	Intrahepatic cholangiocarcinoma	9	0	0	0	0	0		
Permanent Close	10	Extrahepatic cholangiocarcinoma and bile duct tumors	10	0	0	0	0	0		
Temporary Close	11	Sarcomatoid carcinoma of lung	7	4	4	1	0	0		
Temporary Close	12	Bronchoalveolar carcinoma lung (a.k.a. adenocarcinoma in situ, minimally invasive adenocarcinoma, lepidic predominant adenocarcinoma, or invasive mucinous adenocarcinoma)	6	2	0	0	0	0		
Permanent Close	13	Non-epithelial tumors of the ovary	25	0	0	0	0	0		
Permanent Close	14	Trophoblastic tumor	3	1	0	0	0	0		
Permanent Close	15	Transitional cell carcinoma other than that of the renal, pelvis, ureter, or bladder	1	0	0	0	0	0		
Permanent Close	16	Cell tumor of the testes and extragonadal germ tumors	17	7	6	3	0	0		
Open	17	Epithelial tumors of penis - squamous adenocarcinoma cell carcinoma with variants of penis	17	10	7	4	2	1		
Open	18	Squamous cell carcinoma variants of the genitourinary (GU) system	7	3	1	0	0	0		
Open	19	Spindle cell carcinoma of kidney, pelvis, ureter	3	0	0	0	0	0		
Permanent Close	20	Adenocarcinoma with variants of GU system (excluding prostate cancer)	9	0	0	0	0	0		
Open	21	Odontogenic malignant tumors	4	0	0	0	0	0		
Permanent Close	22	Endocrine carcinoma of pancreas and digestive tract	12	0	0	0	0	0		
Permanent Close	23	Neuroendocrine carcinoma including carcinoid of the lung	35	2	0	0	0	0		
Temporary Close	24	Pheochromocytoma, malignant	7	2	0	0	0	0		
Permanent Close	25	Paraganglioma	6	3	0	0	0	0		
Temporary Close	26	Carcinomas of pituitary gland, thyroid gland parathyroid gland and adrenal cortex	14	0	0	0	0	0		
Open	27	Desmoid tumors	11	1	1	0	0	0		
Permanent Close	28	Peripheral nerve sheath tumors and NF1-related tumors	9	0	0	0	0	0		
Permanent Close	29	Malignant giant cell tumors	3	1	1	1	0	0		
Permanent Close	30	Chordoma	11	3	0	0	0	0		
Permanent Close	31	Adrenal cortical tumors	21	8	0	0	0	0		
Permanent Close	32	Tumor of unknown primary (Cancer of Unknown Primary; CuP)	21	0	0	0	0	0		
Permanent Close	33	Not Otherwise Categorized (NOC) Rare Tumors, after discussion with Study Chairs	127	9	0	0	0	0		
Permanent Close	34	Adenoid cystic carcinoma	27	1	0	0	0	0		
Temporary Close	35	Vulvar cancer	9	0	0	0	0	0		
Temporary Close	36	MetaPLASTIC carcinoma (of the breast)	19	12	10	3	0	0		
Permanent Close	37	Gastrointestinal stromal tumor (GIST)	12	0	0	0	0	0		
		TOTAL	566	78	30	12	2	1		

Statistical Design

- **Two Stage Design:**
  - 87% power with a one-sided alpha of 13% in each subtype
    - Primary Endpoint = ORR [CR+PR], null = 5%, alternative = 30%
  - Cohort deemed positive if 2 or more responses out of 16
  - First stage: 6 eligible patients per histologic subtype
    - If no response is observed, accrual to that histologic subtype will be permanently closed.
    - If ≥ 1 response, enroll additional 10 patients

Group participation and number of sites

- 566 patients accrued from 312 sites
- Neuroendocrine cohort with 2/3 of accruals from community sites

Translational Medicine

- With CIMACS (PI: Wistuba):
  - WES; RNAseq.
  - Tumor Mutational Burden
  - Immune Cell Profiling
  - Germline variants
  - PD-L1 IHC (Neogenomics)
  - cfDNA analyses (Circulogene)
  - Proteomics (Biodesix)
- Create a TCGA for rare tumors with clinical annotation

References

Latest cohort and accrual information available at: http://www.swogstat.org/accrual/dart.htm

CT.gov ID: NCT02834013

Acknowledgements

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SWOG Leading cancer research. Together. NIH NATIONAL CANCER INSTITUTE UC San Diego

Patel SP et al. ASCO 2019
DOI: 10.1200/JCO.2019.37.15_suppl.TPS2658

Response Type	All Patients (n=33)	High grade (n=19)	Low/Intermediate grade (n=14)
Complete Response (CR)	1 (3%)	1 (5%)	0
Partial Response (PR)	7 (21%)	7 (37%)	0
Stable Disease (SD)>6months	2 (6%)	0	2 (14%)
SD	11 (33%)	3 (17%)	8 (57%)
Progressive Disease (PD)	12 (36%)	8 (42%)	4 (29%)
CR+PR	8 (24%)	8 (42%)	0
CR+PR+SD>6mo	10 (30%)	8 (42%)	2 (14%)

Best Response Summary in 33 Patients with Neuroendocrine Cancer

Patel SP. AACR 2019
DOI: 10.1158/1538-7445.AM2019-CT039

Results of a Phase II Study of Nivolumab and Ipilimumab in Advanced Bladder Cancer of Variant Histologies

Bradley A McGregor MD[1]; Matthew Campbell MD[2], Wanling Xie MS[1], Arlene Siefker-Radtke MD[2], Amishi Shah MD[2], Aradhana Venkatesan MD[2], Lauren Nguyen[1]
Kerry L Kilbridge MD[1], Glenn Bubley MD[3], Guru Sonpavde MD[1], Rana McKay MD[4], Toni K. Choueiri MD[1]
[1]Dana-Farber Cancer Institute, Boston, Massachusetts, [2]MD Anderson Cancer Center, Houston, Texas [3]Beth Israel Deaconess Medical Center, Boston Massachusetts, [4]University of California San Diego, San Diego, California

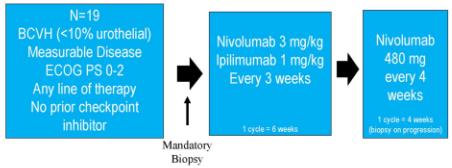
BACKGROUND

- While urothelial carcinoma is the most common malignancy of the bladder and upper tract, non-urothelial histologies account for approximately 10% of bladder and upper tract tumors [1]
- Patients with bladder cancer of variant histologies (BCVH) such as squamous and small cell carcinoma, adenocarcinoma have poorer outcomes[2,3]
- The optimal management of this heterogeneous group of patients has not been clearly defined given paucity of data to guide clinical decision making
- Nivolumab and Ipilimumab has demonstrated safety and efficacy in urothelial carcinoma and other solid malignancies[4]
- Lower dose ipilimumab with higher dose nivolumab has been studied in renal cell carcinoma with favorable toxicity profile[5]

OBJECTIVES

- Multicenter open-label single arm phase II trial to determine the overall response rate of Nivolumab and Ipilimumab in patients with BCVH (NCT03333616)

METHODS



- **Primary Endpoints**
  - Overall Response Rate
- **Secondary Endpoint**
  - Duration of Response
  - Progression Free Survival
  - Overall Survival
  - Toxicity
- **Correlative Endpoints**
  - PDL-1 expression (≥1% tumor cell membrane staining)
  - Total exonic mutation burden
  - Neoantigen Load

- 19 patients with BCVH enrolled 4/2018-1/2019 from 4 US sites

Table 1: Patient characteristics (N=19)

Age (median, range)	61	36-80
	N	%
Sex		
Female	5	26.3
Male	14	73.7
Primary disease site		
Bladder	15	78.9
Renal Pelvis	1	5.3
Ureter	1	5.3
Urethra	2	10.5
Prior Treatment		
No	6	31.6
Yes *	13	68.4
N Stage at initial diagnosis		
N0	9	47.4
N+	6	31.5
Unknown	4	21.1
M Stage at initial diagnosis		
M0	9	47.4
M1	6	31.6
Unknown	4	21.1

*platinum-based chemotherapy in 12 patients

Figure 1: Distribution of Subtypes

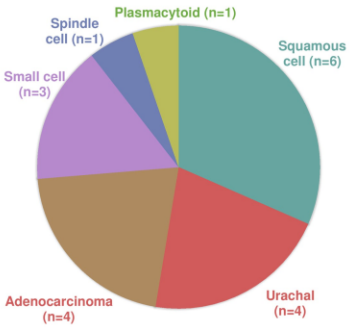


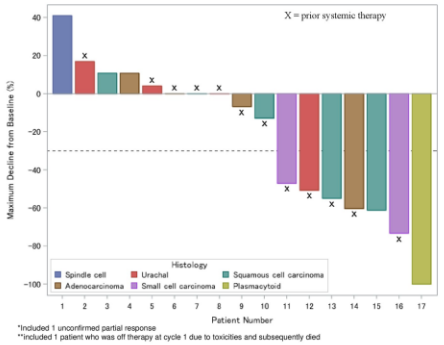
Table 2: Breakdown of Overall Response Rate (ORR)

	N	%
Complete Response (CR)	1	5.3
Partial Response (PR)*	6	31.6
Stable Disease	4	21
Progressive Disease**	8	42.1
ORR (CR+PR)	7	37 (80%CI: 22-54)
CR+PR+SD	11	58% (80%CI: 41-74)

* 1 unconfirmed PR
** 2 patients not evaluable (1 patient withdrew before imaging due to toxicities, 1 patient with clinical progression and no scans).
+ CR

	PD	SD	PR/CR	ORR %
Adenocarcinoma	3	0	1	25
Urachal	1	2	1	25
Squamous Cell	2	2	2	33
Small Cell	1	0	2	66
Spindle Cell	1	0	0	0
Plasmacytoid	0	0	1+	100
Prior Systemic Therapy	4	4	5	38
No prior systemic therapy	4	0	2	33

Figure 2. Maximum Tumor Response



*Included 1 unconfirmed partial response
**included 1 patient who was off therapy at cycle 1 due to toxicities and subsequently died

Figure 3: Kaplan Meier Estimate of Progression Free Survival

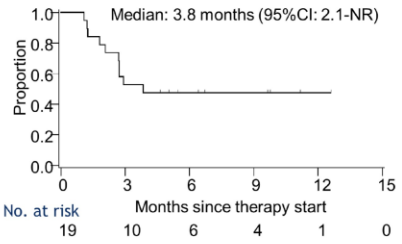


Table 3. Treatment Related Adverse Events*

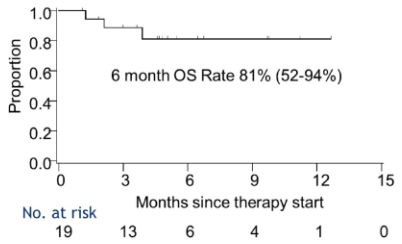
	Toxicity grade CTCAE v4.0					Total	
	1	2	3	4	5	N	%
Fatigue	6	2				8	42
Rash maculo-papular	6	1				7	37
Hypothyroidism	3	2				5	26
Lipase increased	2	1	2			5	26
Pruritus	3	1				4	21
Hyperthyroidism	2	1				3	16
Diarrhea	2		1			3	16
Adrenal Insufficiency		2				2	11
Serum amylase increased	1	1				2	11
Hyponatremia				1		1	5
Colitis			1			1	5
Generalized muscle weakness			1			1	5
Encephalitis					1	1	5
Seizure				1		1	5

*>10% or any grade ≥3

Treatment Summary

- Median cycles of therapy received: 4
  - Range 1-11 cycles
- 9 patients remain on therapy
  - Median number of cycles for patients still on therapy is 7
- 10 patients discontinued therapy
  - 8 for progressive disease
  - 1 for unacceptable toxicities
  - 1 treatment related death
- 5 patients (26%) required high dose steroids (≥40 mg prednisone or equivalent) for irAE

Figure 4: Kaplan Meier Estimate of Overall Survival



CONCLUSIONS

- Nivolumab and ipilimumab has clinical activity in BCVH with ORR 37%
- As with prior experience, regimen is well tolerated with a manageable toxicity profile
- Correlative work exploring biomarkers of response and resistance is ongoing
- Cohorts exploring adrenocortical carcinoma, treatment refractory germ cell tumors, penile carcinoma and non-adenocarcinoma of the prostate have nearly finished accrual
- An additional cohort exploring activity in any genitourinary malignancy with neuroendocrine differentiation will soon open to accrual

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BRADLEY_MCGREGOR@DFCI.HARVARD.EDU
Twitter: BradMcG04
TONI_CHOUEIRI@DFCI.HARVARD.EDU
Twitter: @DrChoueiri

McGregor BA et al. ASCO 2019
DOI: 10.1200/JCO.2019.37.15_suppl.4518

Safety and interim results from a phase II, single-arm study of atezolizumab and bevacizumab in Merkel cell carcinoma (MCC).

Results:

11 pts enrolled. Median age was 70 (range:57-84), (7) 63% were male, and 7 (63%) had been treated with curative intent. Five (45%) pts had received platinum/etoposide (2 in the neo-adjuvant setting and 3 in first-line). Median follow-up is 9.7 months (range:2.8-15.9). Adverse events (AEs) that occurred in > 1 pt: hypertension (7), proteinuria (3), fatigue (2), peripheral edema (2), epistaxis (2), and transaminitis (2). Grade 3 AEs: hypertension (2), proteinuria (1), and auto-immune hepatitis (1); all manageable. Only 1 subject discontinued treatment due to toxicity (auto-immune hepatitis). There were no grade > 3 AEs. Objective response occurred in 7 (64%) pts, including 3 (27%) complete responses (CR). One partial response was unconfirmed (patient discontinued treatment after 1 dose of atezo/bev due to grade 3 hepatitis). 4 pts remain on treatment (1 pt with CR withdrew consent for further therapy and has not recurred). Median PFS is 6.3 months (95% CI:4.5-NA).

Conclusions:

Atezo + bev was well tolerated in MCC pts. Safety was consistent with that of the individual agents. Activity is encouraging with 64% ORR (27% CR rate) and mPFS of 6.3 months. Clinical trial information: NCT03074513

Ferraroto R et al. ASCO 2019
DOI: 10.1200/JCO.2019.37.15_suppl.e21006

Nivo-rare Trial

A multicenter phase 2 study of nivolumab combined with ipilimumab in patients with pediatric solid tumors presenting in adulthood

Promotor:

GETHI (Grupo Español de Tumores Huérfanos e Infrecuentes)

Coordinadores:

Xabier Mielgo Rubio

Jesús García-Donas

Fundamento y justificación

- Los tumores pediátricos del adulto que aparecen en la edad adulta son un grupo hetereogéneo de tumores que comparten algunas características como una baja incidencia, la falta de opciones terapéuticas y un pronóstico probre.

- Los tumores pediátricos generalmente se originan a partir de células que pueden presentar antígenos distintos a los presentes en las células de tejidos maduros, y éstos podrían actuar como diana para el sistema inmune si éste es estimulado adecuadamente. De esta manera, los *checkpoint inhibitors* podrían tener actividad relevante en estos tumores.

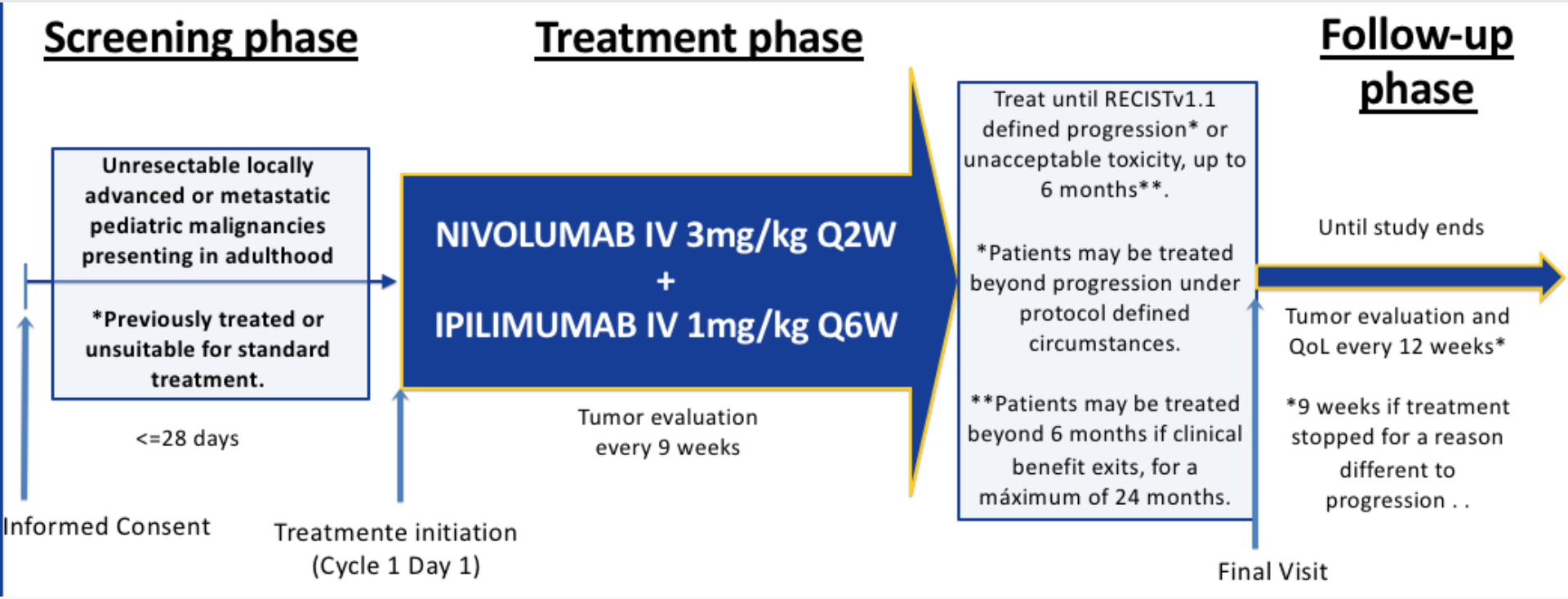
- Hemos diseñado el primer ensayo clínico fase II de nivolumab e ipilimumab en este ámbito.

- A continuación presentamos los resultados de la primera fase preplaneada del estudio con los 30 primeros pacientes evaluables.

Diseño y métodos

- Ensayo clínico fase II, multicéntrico, abierto de un solo brazo, llevado a cabo en 15 centros del GETHI
- **Objetivos:** evaluar la eficacia y seguridad de la combinación de nivolumab e ipilimumab en pacientes adultos (>=18 años) con tumores pediátricos metastásicos o localmente avanzados que hayan progresado a tratamiento estándar o no sean candidatos al mismo.
- **Esquema de tratamiento:** nivolumab 3mg/kg IV q2sem + ipilimumab 1mg/kg IV q6sem durante 6 meses o hasta progresión/toxicidad inaceptable, hasta un máximo de 24 meses.
- **Objetivo principal:** tasa de respuesta global (TRG) de acuerdo a criterios RECISTv1.1
- Objetivos secundarios: SLP, SG, TCE, toxicidad, calidad de vida

Esquema



- PS ≤ 2
- Treated and controlled CNS metastasis accepted

Diseño estadístico

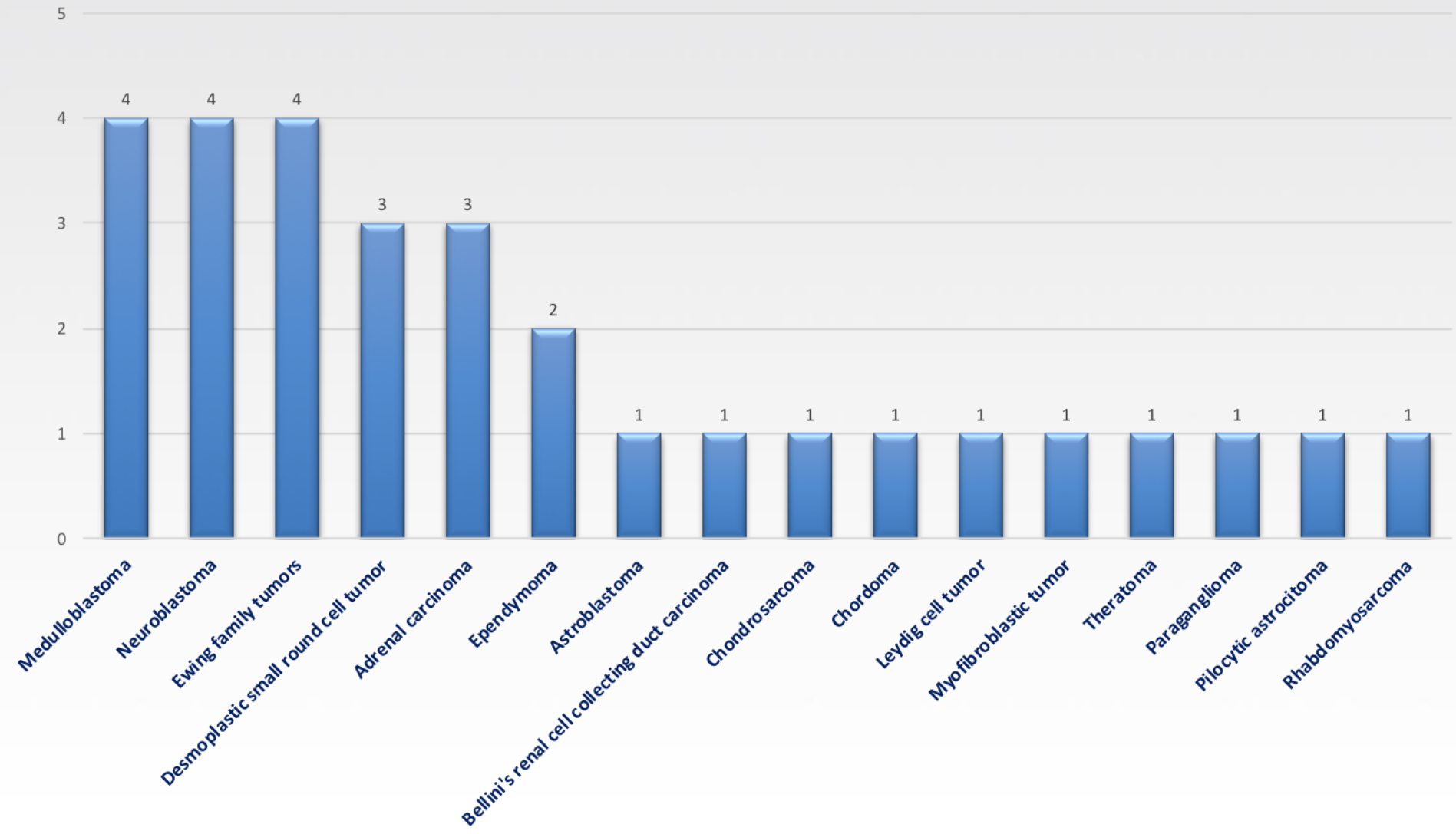
- **Hipótesis: H_a ORR > 20% (RECIST v1.1)**
  - Nivo + Ipi tienen actividad en los tumores pediátricos del adulto avanzados

- **Diseño óptimo de Simon con 2 etapas**
  - 1ª etapa: 30 pacientes. $H_0 \leq 10\%$
    - Si ≤3 pacientes responden → FIN del estudio
  - 2ª etapa: hasta 89 pacientes. $H_0 \leq 20\%$
    - Si 14 respuestas el estudio será positivo
    - Error tipo I=0,05. Potencia del 80%.

Características basales de los pacientes

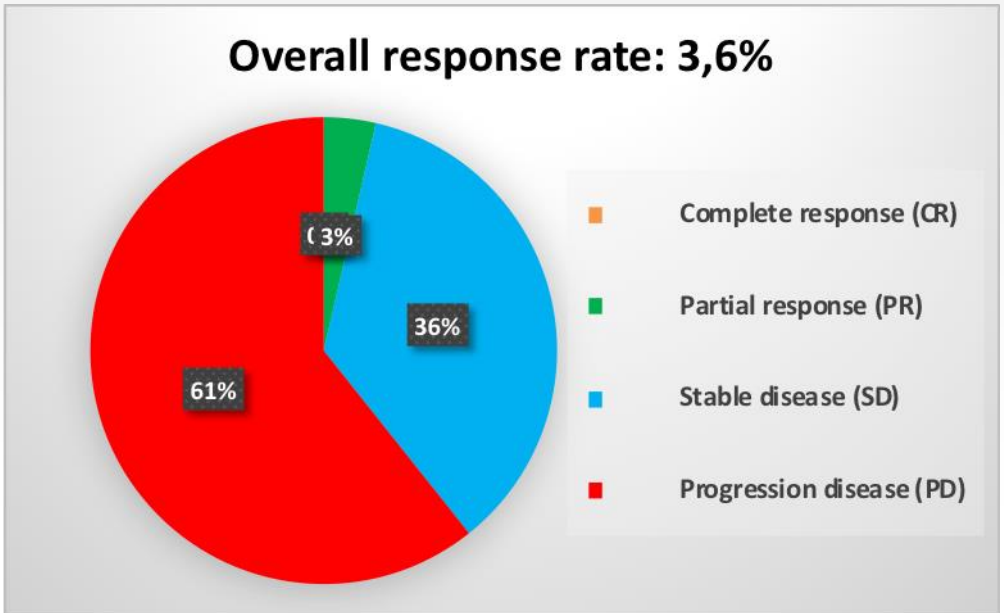
AGE ---- mean, range	43 (20-75)
SEX ---- N. (%)	
Male	20 (66,7%)
Female	10 (33,3%)
RACE ---- N. (%)	
Caucasian	29 (96,7%)
EXTENSION OF TUMOR ---- N. (%)	
Metastatic	23 (76,7%)
Not metastatic	7 (23,3%)
PREVIOUS RT ---- N. (%)	
Yes	9 (30%)
PREVIOUS SYSTEMIC TX ---- N. (%)	
Yes	27 (90%)
No. PREVIOUS TX LINES ---- mean, range	3 (1-9)
BEST RESPONSE TO PREVIOUS TX --- N. (%)	
Complete Response (CR)	3 (10%)
Partial Response (PR)	6 (20%)
Stable Disease (SD)	5 (16,6%)
Progression Disease (PD)	10 (33,3%)
Unknown	6 (20%)
ECOG PS	
PS 0	9 (30%)
PS 1	18 (60%)
PS 2	3 (10%)

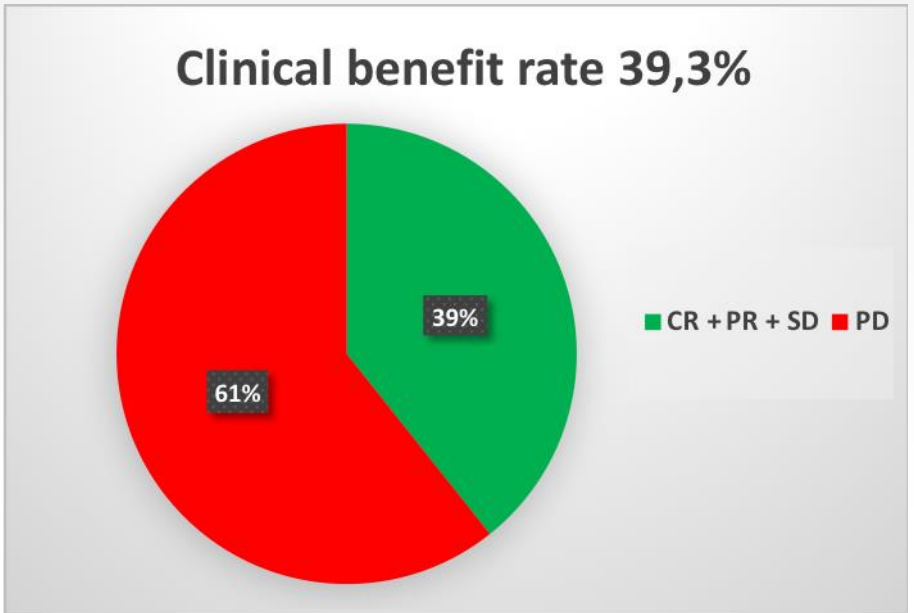
Tipos histológicos



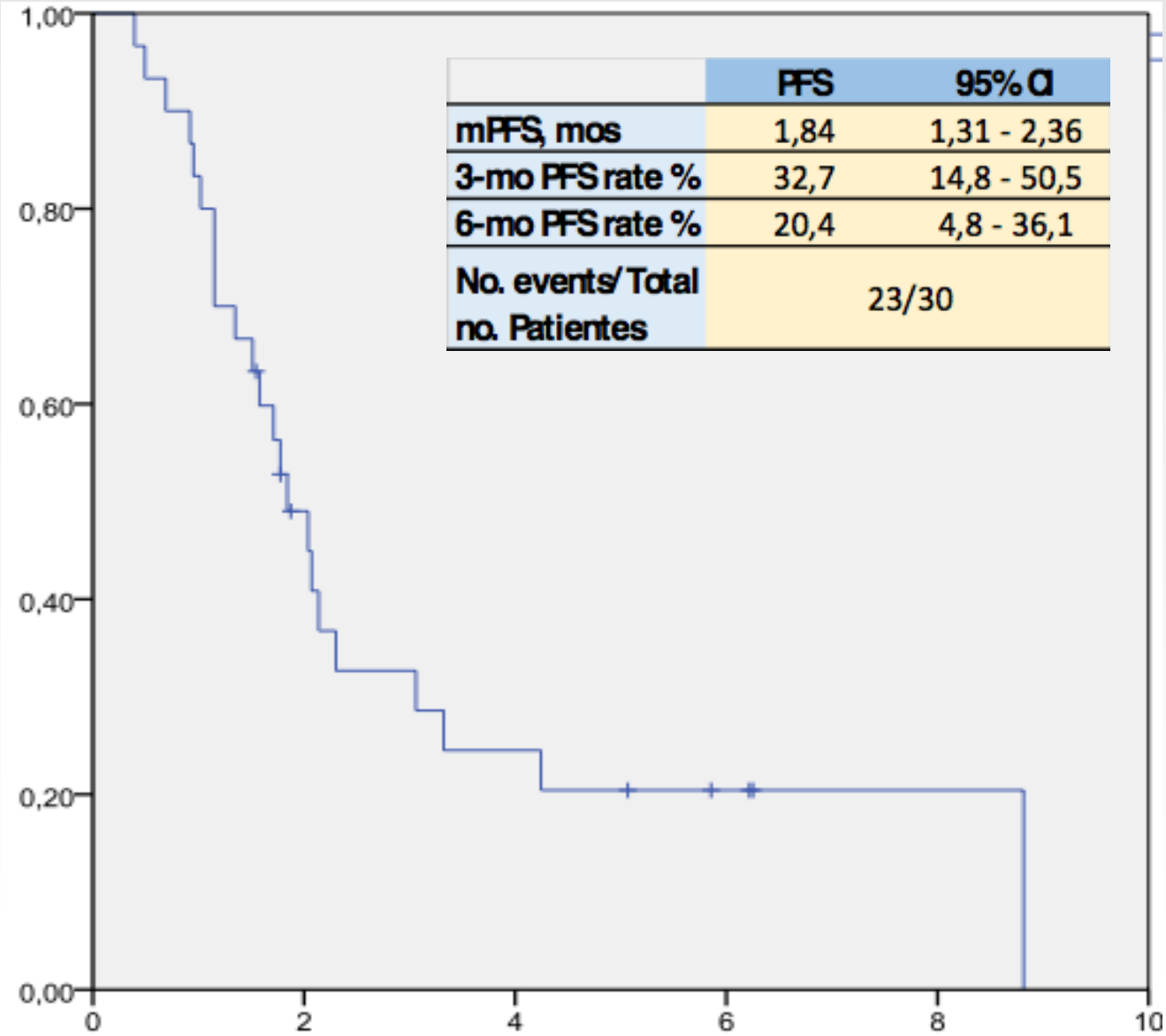
Resultados: TRG y TCE

Best overall response ---- no. (%) (valid %)	
Complete response (CR)	0
Partial response (PR)	1 (3,3%) , (3,6%)
Stable disease (SD)	10 (33,3%) , (35,7%)
Progression disease (PD)	17 (56,7%) , (60,7%)
No evaluated	2 (6,7%)
Overall response ---- no. (%)	
CR + PR	1 (3,6%)
Clinical benefit ---- no. (%)	
CR + PR + SD	11 (39,3%)



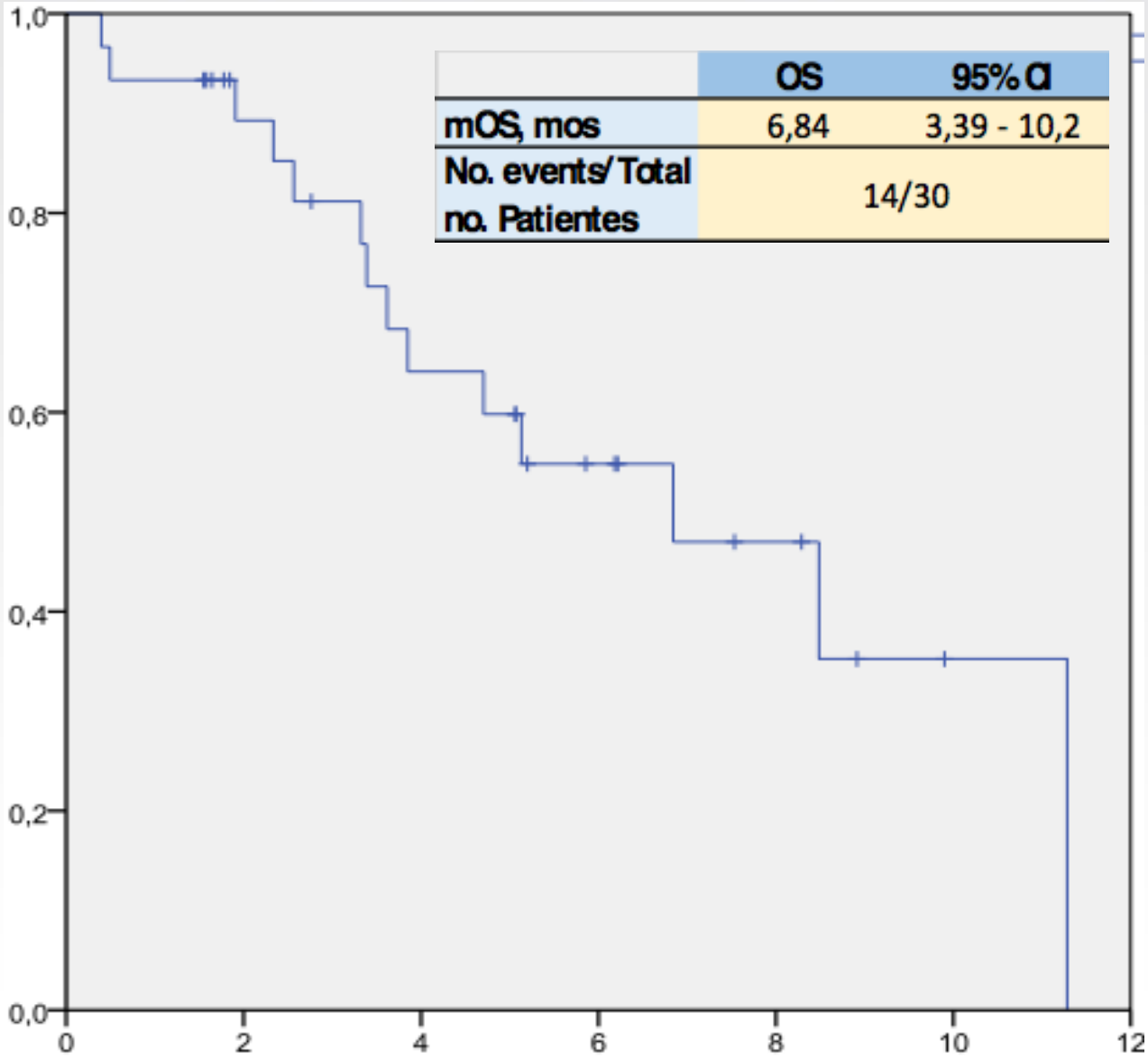


Resultados: SLP



	PFS	95% CI
mPFS, mos	1,84	1,31 - 2,36
3-mo PFS rate %	32,7	14,8 - 50,5
6-mo PFS rate %	20,4	4,8 - 36,1
No. events/ Total no. Patientes	23/30	

Resultados: SG



	OS	95% CI
mOS, mos	6,84	3,39 - 10,2
No. events/ Total no. Patientes	14/30	

Toxicidad

AEs	N	%
Any grade AEs	12	40%
Grade 1-2 AEs	11	36,70%
Grade 3-4 AEs	4	13%
Fatal AEs	0	0%

AEs	Any Grade	Grade 1-2	Grade 3-4
Hypertransaminasemia	3 (10%)	2 (6,7%)	1 (3,3%)
Asthenia	3 (10%)	3 (10%)	0
Renal inssuficiency	2 (6,7%)	1 (3,3%)	1 (3,3%)
Anorexia	2 (6,7%)	2 (6,7%)	0
Arthralgia	2 (6,7%)	2 (6,7%)	0
Diarrhea	2 (6,7%)	2 (6,7%)	0
Conjunctuvitis	1 (3,3%)	1 (3,3%)	0
Constipation	1 (3,3%)	1 (3,3%)	0
Erythema	1 (3,3%)	1 (3,3%)	0
Fever	1 (3,3%)	0	1 (3,3%)
Hyperglucemia	1 (3,3%)	0	1 (3,3%)
Infusion reaction	1 (3,3%)	1 (3,3%)	0
Nausea	1 (3,3%)	1 (3,3%)	0
Pruritus	1 (3,3%)	1 (3,3%)	0
Vomiting	1 (3,3%)	1 (3,3%)	0
Dysgeusia	1 (3,3%)	1 (3,3%)	0

Conclusiones

- La combinación de nivolumab e ipilimumab ha mostrado beneficio clínico significativo en este tipo de tumores infrecuentes con escasas opciones terapéuticas
- El perfil de toxicidad es bueno y concordante a los estudios previos con la combinación de nivolumab e ipilimumab sin presentar nuevas toxcidades no esperadas.

Estudio negativo

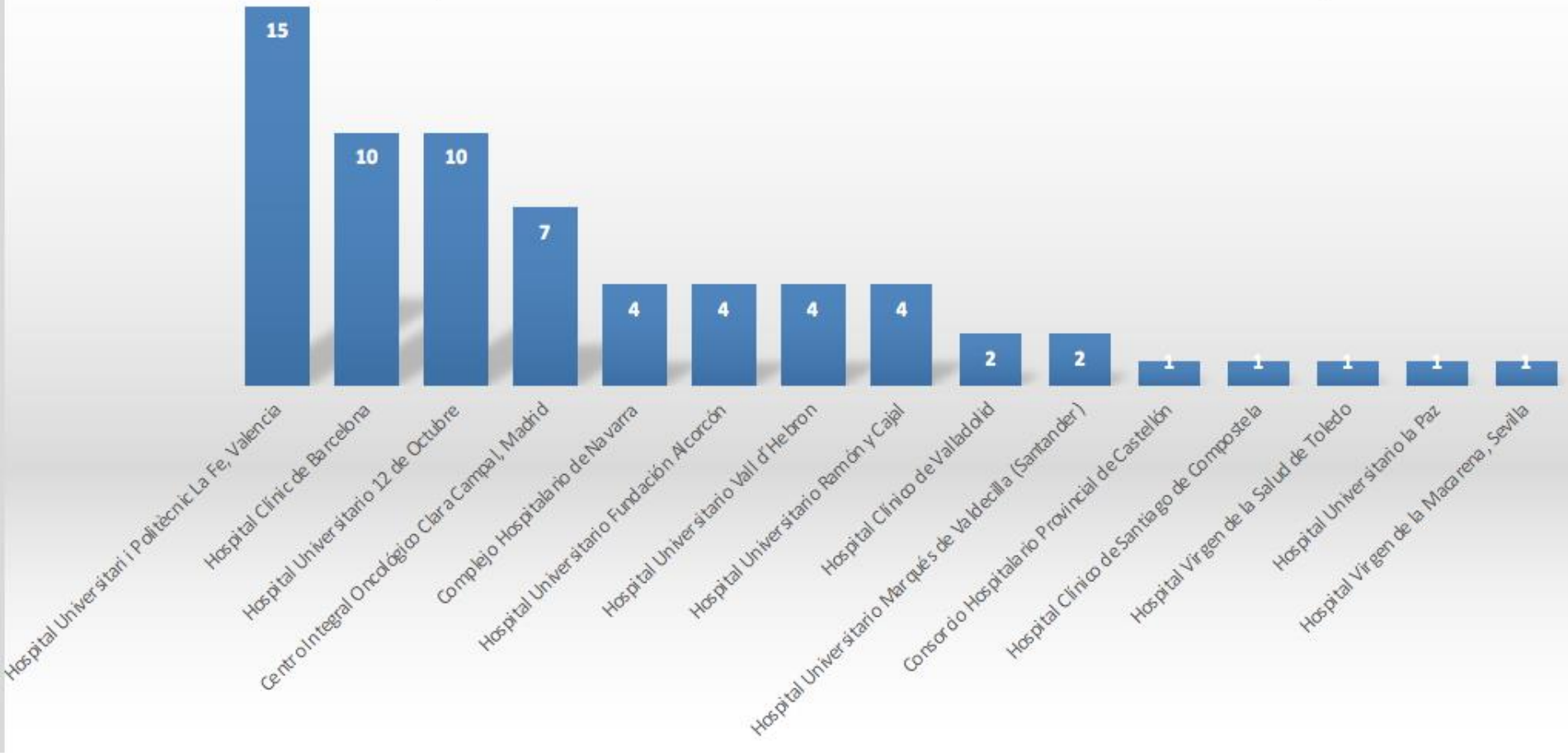
Enmienda relevante al protocolo

Enmienda al protocolo

- Cambio de objetivo principal: **TCE**
- Diseño
  - **Hipótesis: H_a TCE > 39,3% (RECIST v1.1: EE + RP + RC)**
  - **Diseño óptimo de Simon con 2 etapas**
    - 1ª etapa: 20 pacientes. $H_0 \leq 23\%$
      - Si ≤5 pacientes responden o se estabilizan ➜ FIN del estudio
    - 2ª etapa: hasta 69 pacientes. $H_0 \leq 39,3\%$
      - Error tipo I=0,05. Potencia del 80%.


RITMO DE RECLUTAMIENTO
80
70
60
50
40
30
20
10
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 28 29
2
5
11
16
21
26
32
32
34
35
37
38
40
43
46
48
50
50
55
56
56
60
61
63
63
63
63
66
67
Series1
Series2

Reclutamiento por centros



Estudio translacional

- Biomarcadores dependientes del tumor
  - PD-L1
  - TILs
  - Neoepítopos tumorales (WES DNA tumoral)
  - Multiplex microambiente tumoral
- Biomarcadores dependientes del paciente
  - Línea germinal
    - SNPs
    - lncRNA
  - Dinámicos
    - pAKT
    - mRNA-IL2

Agradecimientos

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Grupo Español de Tumores Huérfanos e Infrecuentes

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thank you
danke
рахмат
謝謝
ngiyabonga
teşekkür ederim
gracias
Баярлалаа
спасибо
faafetai lava
mersi
barka
welalin
tack
spas
dank je
kiitos
dankie
vinaka
спасибі
blagodaram
misaotra
matondo
paldies
grazzi
mahalo
tapadh leat
хвала
asante
manana
obrigada
tenki
murakoze
nanni
nandri
dhanyavad
mauruuru
koszonom
hvala
gracie
bayarlalaa
bedankt
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kop khun krap
taiku
obrigado
mèsi
didi madloba
najis tuke
ありがとう
tanemirt
grazie
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takk
dakujem
trugarez
kam sah hamnida
rahmat
terima kasih
rahmet
diolch
dhanyavadagalu
shukriya
merce
мерси
তোমাকে ধন্যবাদ
감사합니다
xiexie
ευχαριστώ
merci
eskerrik asko