Iniciativa científica de:

GECP lung cancer research

LUNG CANCER UPDATES

ASCO HIGHLIGHTS

31 MAYO - 4 JUNIO 2019

Con la colaboración de:

Bristol-Myers Squibb

illumina

Lilly

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Tratamiento neoadyuvante CPNM

Dr. Bartomeu Massutí

Día 1

Con la colaboración de:

Bristol-Myers Squibb
illumina
Lilly

Análisis interino Atezolizumab Neoadyuvante LCMC3

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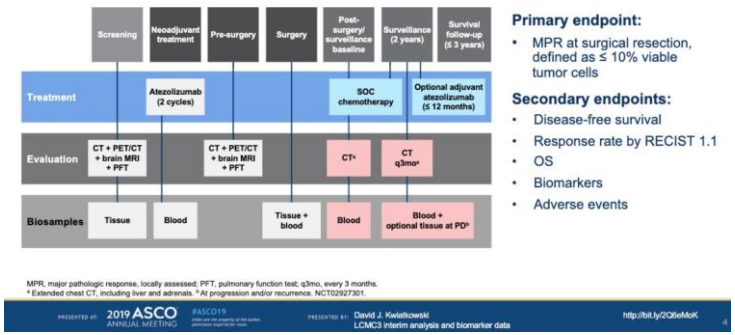
- EC Fase II Atezolizumab preoperatorio en estadios Ib, II, IIIA, IIIB
- Análisis de la Respuesta Patológica Mayor (futilidad)
- 101 p → 90 con CIR → 84 evaluables para RPM → 77 (se excluyen 7 EGFR y ALK)
- Eficacia: pCR 5%, MPR 19%

LCMC3 Study Design



Patient Demographics and Baseline Characteristics

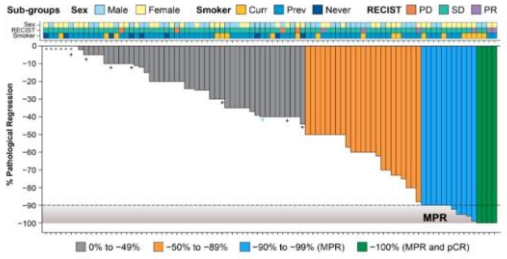
Baseline Characteristics	Safety Population N = 101
Age, median (range), years	65 (37-83)
Sex, male, n (%)	47 (47%)
Histology, n (%)	
Non-squamous / squamous	66 (65%) / 35 (35%)
Tobacco use history, n (%)	
Never	10 (10%)
Current / former	23 (23%) / 68 (68%)
Clinical stage at initial diagnosis, n (%)	
IB	11 (11%)
IIA / IIB	16 (16%) / 28 (28%)
IIIA / IIIB	39 (39%) / 7 (7%)

Baseline Characteristics (cont)	N = 101
PD-L1 IHC, SP142, n (%)[a]	
TC1/2/3 or IC1/2/3 (positive)	39 (51%)
TC0 and IC0 (negative)	38 (49%)
Unknown	24
PD-L1 IHC, 22C3, TPS, n (%)	
≥ 50%	23 (29%)
1%-49%	14 (18%)
< 1%	43 (54%)
Unknown	21
EGFR, n (%)	
Positive / negative	7 (10%) / 66 (90%)
Unknown	28
ALK, n (%)	
Positive / negative	1 (2%) / 45 (98%)
Unknown	55

IC, tumor-infiltrating immune cell; TC, tumor cell; TPS, tumor proportion score.
[a] TC1/2/3 or IC1/2/3 = PD-L1+ ≥ 1% on TC or IC; TC0 and IC0 = PD-L1+ < 1% on TC and IC.
PRESENTED AT: 2019 ASCO ANNUAL MEETING #ASCO19
PRESENTED BY: David J. Kwiatkowski
LCMC3 interim analysis and biomarker data
http://bit.ly/2Q6eMoK
5

- La respuesta patológica se correlaciona con reducción volumen
- No correlación con PD-L1 ni con TMB ni con secuenciación exoma (40 p)
- Continua reclutamiento (151/180)
- IMPower 030 en asociación a QT

Pathological Regression in Intended Surgery Population (n = 90)



Nivolumab vs Nivolumab+Ipilimumab
EC NEOSTAR

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- 44 pacientes
- Estadíos I-IIIA N2u
- Objetivos: IO+IO incrementa MPR; induce respuesta inmune (CD8, TILs)
- Diseño Simon 2 estratos (15 + 6 p). Objetivo ≥ 6 MPR

Patient demographics and treatment

		Overall n = 44	N n = 23	NI n = 21
Age at randomization, Mean (SD)		65.6 (8.3)	66.1 (8.5)	65.0 (8.3)
Gender	Male	28 (64%)	15 (65%)	13 (62%)
Race	White	37 (84%)	21 (91%)	16 (76%)
Smoking status	Never smoker	8 (18%)	5 (22%)	3 (14%)
	Former/current smoker	36 (82%)	18 (78%)	18 (86%)
Stage (AJCC7th)	Stage IA	8 (18%)	4 (17%)	4 (19%)
	Stage IB	15 (34%)	7 (30%)	8 (38%)
	Stage IIA	7 (16%)	2 (9%)	5 (24%)
	Stage IIB	5 (11%)	5 (22%)	0 (0%)
	Stage IIIA	9 (20%)	5 (22%)	4 (19%)
Histology	Squamous cell	17 (39%)	10 (43%)	7 (33%)
	Adenosquamous	1 (2%)	0 (0%)	1 (5%)
	Adenocarcinoma	26 (59%)	13 (57%)	13 (62%)
Invasive Med staging	43	43 (98%)	22 (96%)	21 (100%)

	Overall n = 44	N n = 23	NI n = 21
Neoadjuvant therapy			
Completed	41 (93%)	22 (96%)	19 (90%)
Not completed	3 (7%)	1 (4%)*	2 (10%)**
Surgery			
Underwent surgery	39 (89%)	22 (96%)*	17 (81%)*
No surgery	5 (11%)	1 (4%)	4 (19%)
Adjuvant therapy			
Platinum chemotherapy	22 (50%)	13 (57%)	9 (43%)
Postoperative radiation	9 (20%)	3 (13%)	6 (29%)

* Grade 3 hypoxia after 1 dose
** Grade 3 diarrhea after 1 dose; grade 2 pneumonitis after 2 doses
* 1 patient in each arm underwent surgery off trial

Median time to surgery was 31 days (range 21-87)
8 (22%) operations were delayed beyond 42 days
Sepesi et al. WCLC 2019

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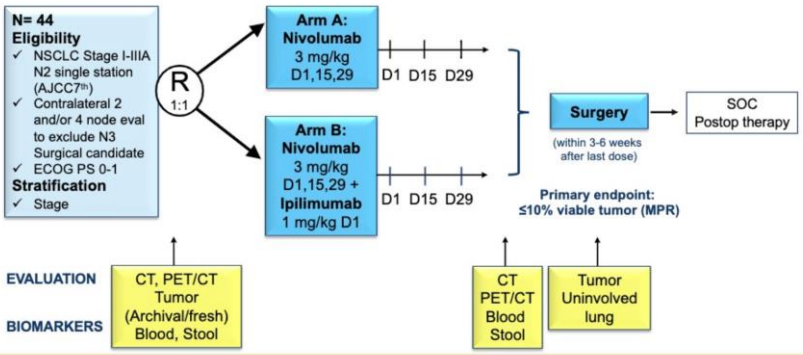
NEOSTAR: phase II study of induction checkpoint blockade for untreated stage I-IIIA NSCLC amenable for surgical resection



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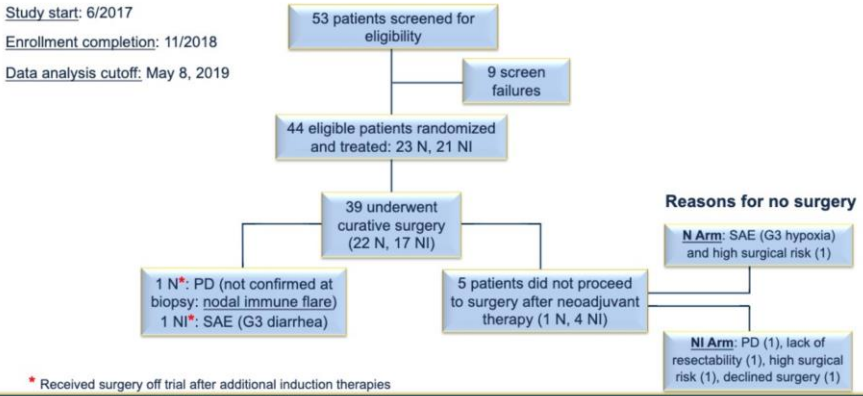
Patient recruitment and disposition



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Nivolumab vs Nivolumab+Ipilimumab
EC NEOSTAR

- Correlación RECIST-MPR
- Posibilidad de fenómeno “flare” en PET ganglionar mediastínico en situación de respuesta
- Incremento EAs para combinación pero no diferencias en G3-4
- Complicaciones cirugía: 31% (IO); 14% (IO-IO)
- Expresión PD-L1 se asocia con respuesta RECIST y con MPR

Treatment-related adverse events (TRAEs), surgical complications and follow up

Grade 1-2 TRAE*

N (23)	n	n/23 (%)	NI (21)	n	n/21 (%)
Fatigue	8	35%	Rash acneiform	11	52%
Rash acneiform	6	26%	Fatigue	7	33%
Anemia	3	13%	Nausea	7	33%
Hyponatremia	3	13%	Cough	6	29%
Diarrhea	2	9%	Diarrhea	6	29%
Increased Alanine Aminotransferase	2	9%	Chills	3	14%
Flu like symptoms	2	9%	Anemia	2	10%
Headache	2	9%	Dyspnea	2	10%
Hypomagnesemia	2	9%	Hyperthyroidism	2	10%
Pruritus	2	9%	Pruritus	2	10%
			Vomiting	2	10%

* The maximum grade of TRAE from a patient is considered

Grade 3-5 TRAE

N (23)	n	n/23 (%)	NI (21)	n	n/21 (%)
Hypermagnesemia (G3)	1	4%	Diarrhea (G3)	1	4%
Hypoxia (G3)	1	4%	Hyponatremia (G3)	1	4%
Pneumonia (G3)*	1	4%			
Pneumonitis (G5)*	1	4%			

* From the same patient

Surgical complications

N (23)	n	n/23 (%)	NI (21)	n	n/21 (%)
Air Leak	5	22%	Air Leak	3	14%
Bronchopleural fistulas*	2	9%			
Empyema*	1	4%			
Pneumonia*	1	4%			
Pneumonitis*	1	4%			

* From the same patient

Median follow-up time after randomization: 8.4 months
Arm A: 1 pt (IIB) died of steroid-treated pneumonitis 4.1 months after randomization
Arm B: 1 pt (IIIA) had PD 2 months after randomization, and died of disease 17 months after randomization

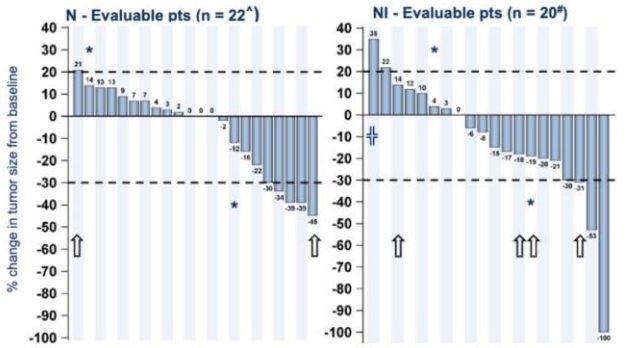
Radiographic responses (RECIST)

Response (RECIST)	Overall n = 44	N n = 23	NI n = 21
	n (%)	n (%)	n (%)
CR	1 (2%)	0 (0%)	1 (5%)
PR	8 (18%)	5 (22%)	3 (14%)
SD	28 (64%)	15 (65%)	13 (62%)
PD	6 (14%)	3 (13%)	3 (14%)
Not evaluable	1 (2%)	0 (0%)	1 (5%)#

received one dose NI complicated by TRAE

ORR (CR+PR): 20% (9/44)

ORR by Arm:
N: 22% (5/23)
NI: 19% (4/21)



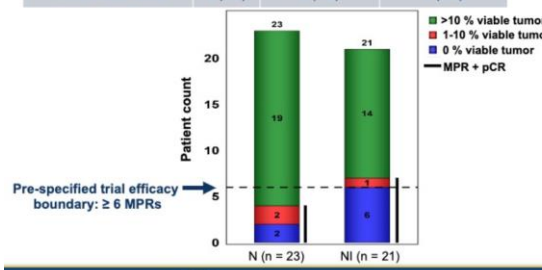
^solid lesion < 1 cm (considered SD)
#1 not evaluable: received one dose of NI complicated by TRAE; surgery off trial

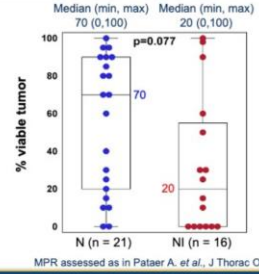
⇧ no surgery on trial * Overall PD due to new lesions; ⫩ SD with cavitation, wall thickness increase/inflammation

Primary endpoint: MPR rate
NI meets the pre-specified trial efficacy boundary

Overall ITT Resected + not resected*	Total n = 44	N n = 23	NI n = 21
MPR + pCR	11 (25%)	4 (17%) (95% CI:5%,39%)	7 (33%) (95% CI:15%,57%)
0% viable tumor (pCR)	8 (18%)	2 (9%)	6 (29%)
1-10% viable tumor	3 (7%)	2 (9%)	1 (5%)

Evaluable* Resected on trial	Total n = 37	N n = 21	NI n = 16
MPR + pCR	11 (30%)	4 (19%)	7 (44%)
0% viable tumor (pCR)	8 (22%)	2 (10%)	6 (38%)
1-10% viable tumor	3 (8%)	2 (10%)	1 (6%)

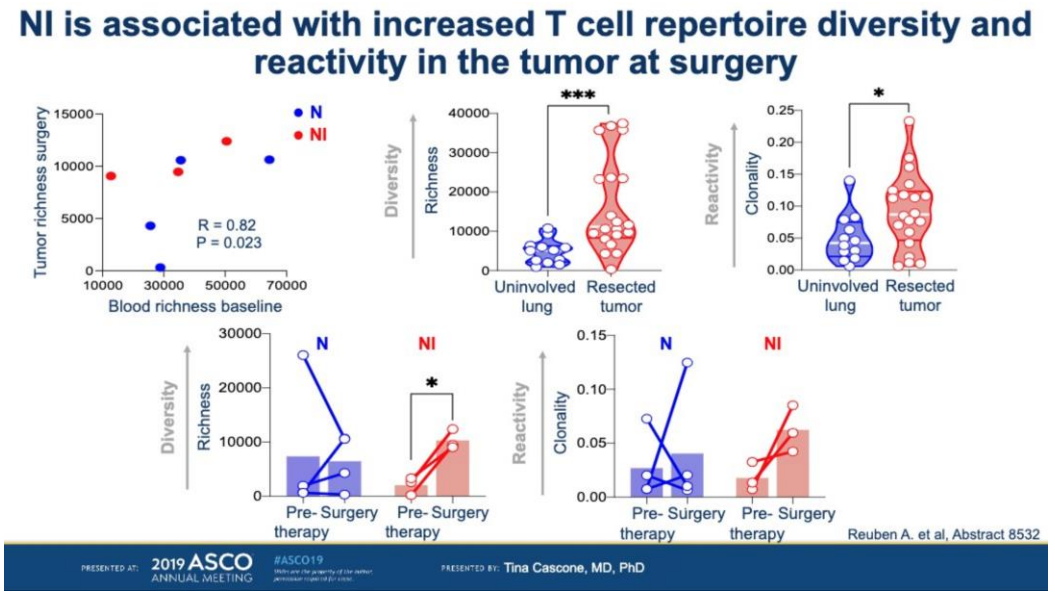


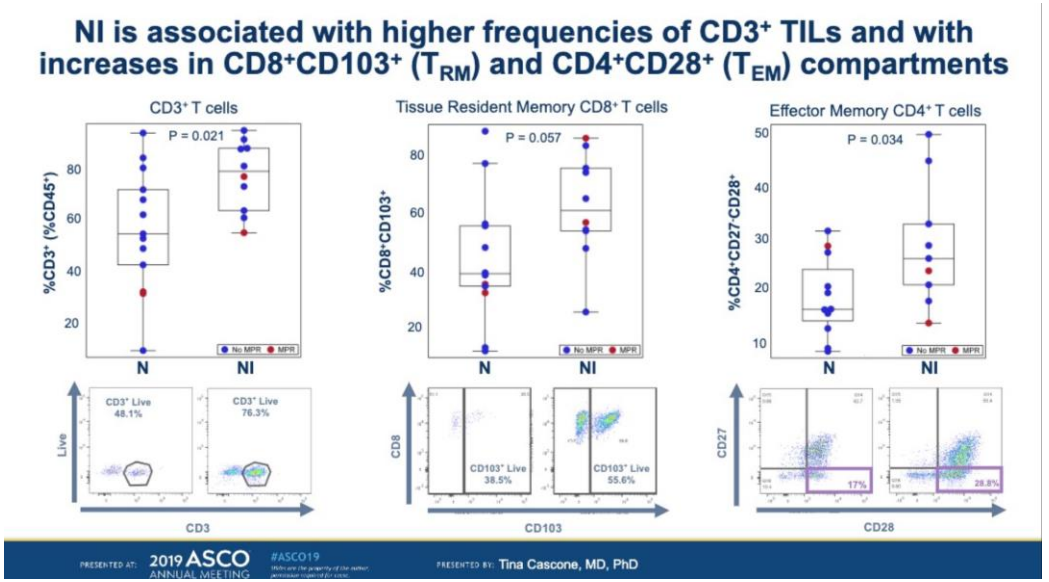


MPR assessed as in Pataer A. *et al.*, J Thorac Oncol 2012

Nivolumab vs Nivolumab+Ipilimumab
EC NEOSTAR

- Potencial creciente del tratamiento neoadyuvante con inmunoterapia (baja tasa de progresión, alta tasa resección)
- Relevancia de la RPM
- Combinaciones superiores a IO agente único
- Tolerancia favorable
- Posibilidad de investigación translacional dinámica
- Posibilidad individualización tratamiento/Biomarcadores
- Tratamiento postoperatorio no definido
- Seguimiento corto





Situación actual de Inmunoterapia adyuvante en CPNM

Summary of Neoadjuvant Immunotherapy Studies

	N resected	Stage	Drug(s)	Cycles	MPR	RECIST ORR
LCMC3	84	IB-IIIB	Atezo	2	18% (10-28)	7%
NEOSTAR						
Arm A	23	IA-IIIA	Nivo	3	17% (5-39)	22%
Arm B	21	IA-IIIA	Nivo/Ipi	3	33% (15-57)	19%
Forde et al[1]	20	IB-IIIA	Nivo	2	45% (23-68)	10%
Historical Control						
Chaft et al[2]	41	IB-IIIA	Cisplatin/Docetaxel/Bev	4	27% (15-43)	45%
Immunotherapy + chemotherapy						
NADIM[3]	30	IIIA	Nivo/Carbo/Paclitaxel	3	80% (61-92)	70%
Shu et al.[4]	11	IB-IIIA	Atezo/Carbo/Nab-Paclitaxel	2	64% (32-88)	73%

[1]Forde et al. *NEJM* 2018 [2]Chaft et al. *JTO* 2013 [3]Provencio et al. WCLC 2018 #OA01.05 [4]Shu et al. ASCO 2018 #8532