ΑΝΟΣΟΘΕΡΑΠΕΙΑ, ΣΥΝΔΥΑΣΜΟΙ ΑΝΟΣΟΘΕΡΑΠΕΙΑΣ ΚΑΙ ΣΥΝΔΥΑΣΜΟΙ ΜΕ ΧΗΜΕΙΟΘΕΡΑΠΕΙΑ

Novel Approaches with IO

Δημήτριος Βαλούκας
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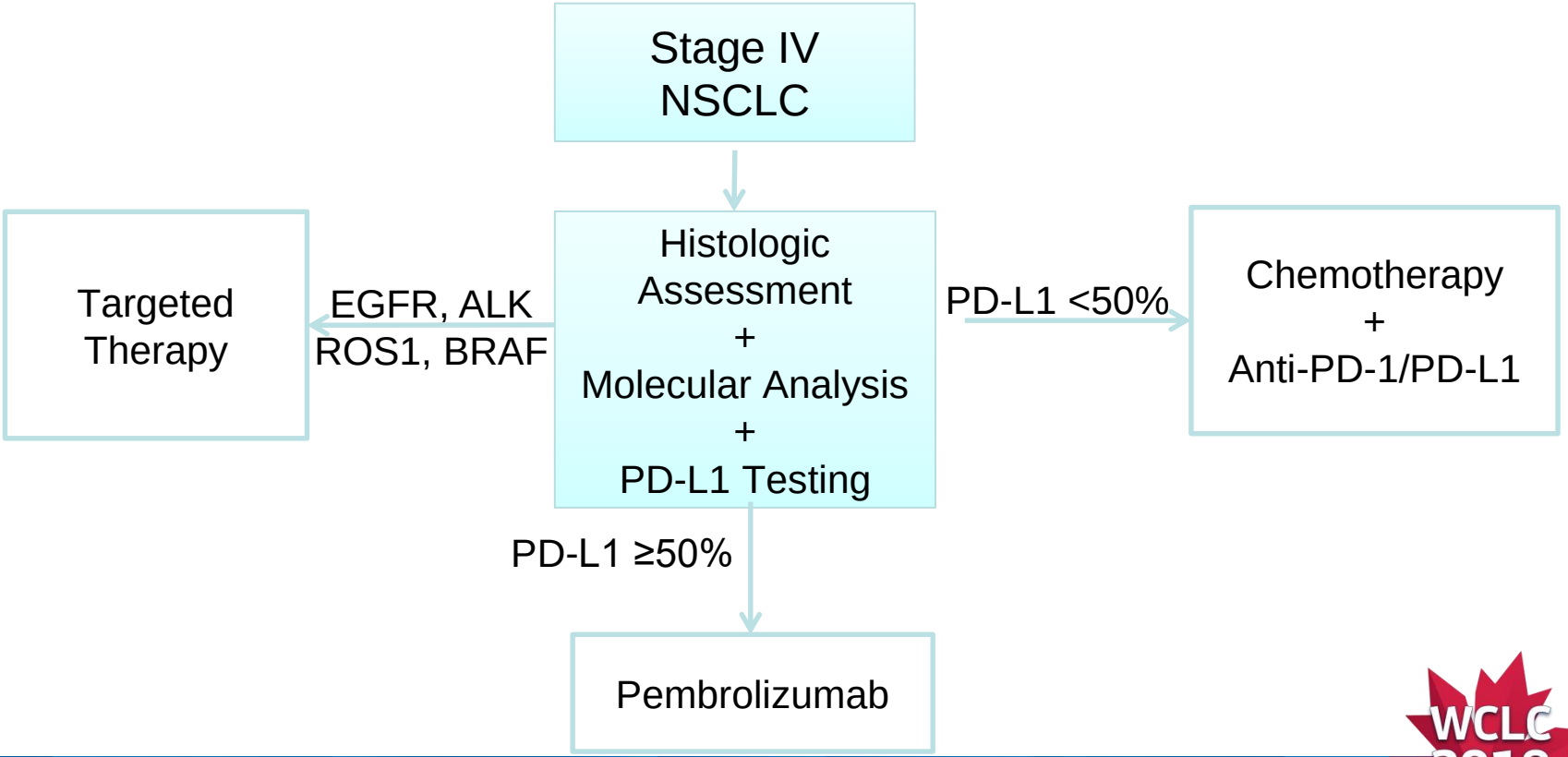
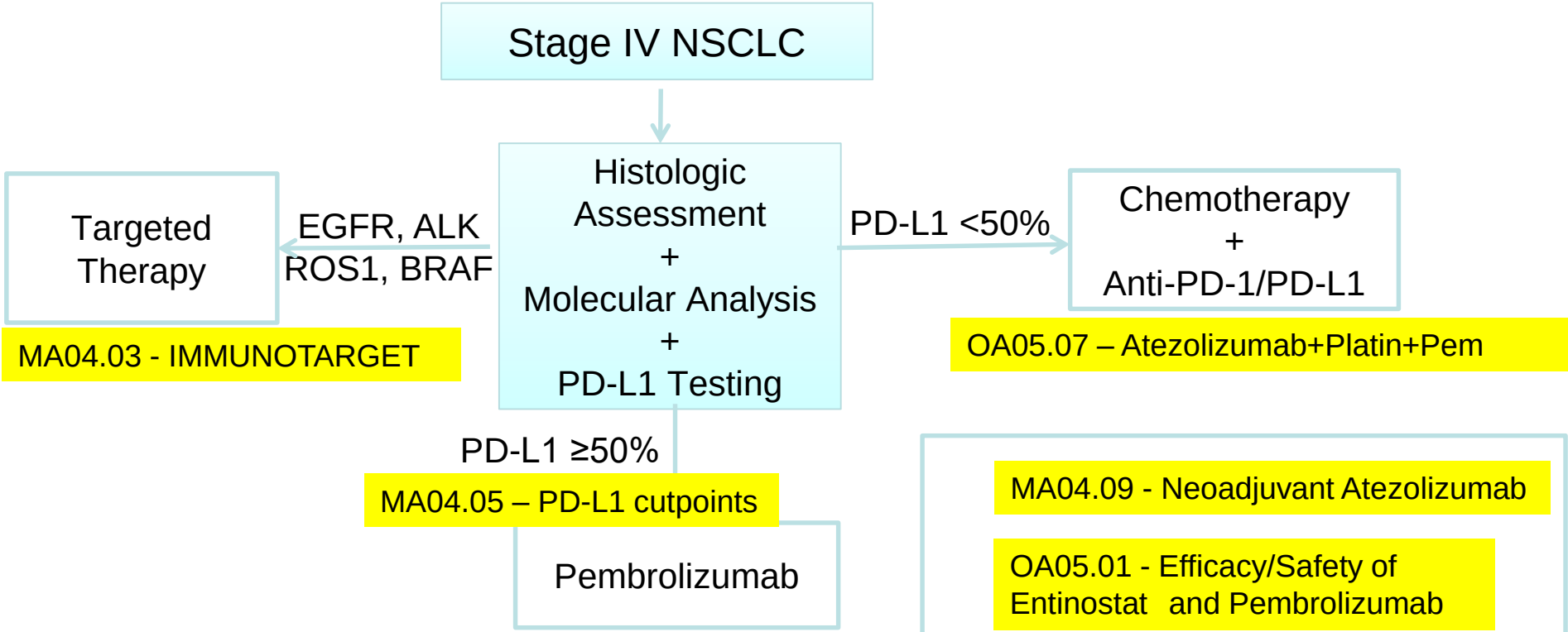
Παθ.Ογκολογική Κλινική Α.Π.Θ.
ΓΝ «Παπαγεωργίου»


Stage IV NSCLC
Histologic Assessment + Molecular Analysis + PD-L1 Testing
EGFR, ALK ROS1, BRAF
Targeted Therapy
PD-L1 <50%
Chemotherapy + Anti-PD-1/PD-L1
PD-L1 ≥50%
Pembrolizumab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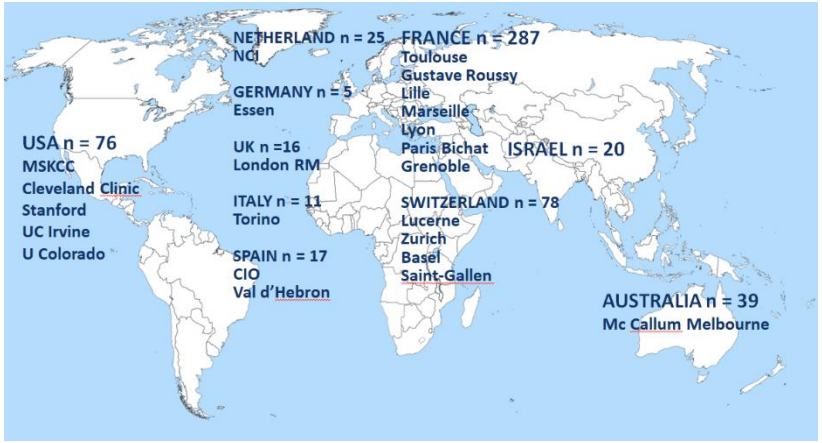
PD-L1 ≥50%
MA04.05 – PD-L1 cutpoints
Pembrolizumab
MA04.09 - Neoadjuvant Atezolizumab
OA05.01 - Efficacy/Safety of Entinostat and Pembrolizumab

Immunotherapy for NSCLC with Oncogenic Driver Mutations: New Results from the Global IMMUNOTARGET Registry

Oliver Gautschi1, Alexander Drilon2, Julie Milia3, Amelie Lusque3, Laurent Mhanna3, Bob Li2, Joshua K. Sabari4, Alexis B. Cortot5, Benjamin Besse6, Laura Mezquita6, Ben J. Solomon7, Alesha A. Thai8, Sebastien Couraud9, Remi Veillon10, Céline Mascaux11, Fabrice Barlesi12, Michael Van Den Heuvel13, Robert D. Schouten14, Heather A. Wakelee15, Angela Mah15, D. Ross Camidge16, Terry L. Ng17, Nir Peled18, Yosef Lilach19, Sanjay Popat20, Sai-Hong I. Ou21, Viola Zhu22, Vamsidhar Velcheti23, Alessandra Curioni Fontecedro24, Dilara Akhoundova24, Martin Früh25, Gerard Zalcman26, Valerie Gounant26, Silvia Novello27, Paolo Bironzo27, Enriqueta Felip28, Alex Martinez-Marti29, Denis Moro-Sibilot30, Rafael Rosell31, Niki Karachaliou32, Martin Schuler33, Martin Wiesweg33, Joachim Diebold34, Julien Mazieres3;

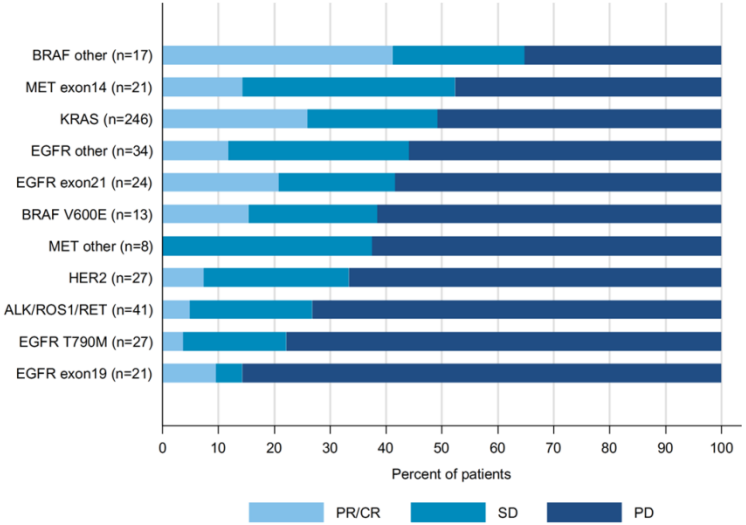
/Switzerland



- World-wide retrospective registry of anti-PD-1/PD-L1 therapy by patient genotype
- Most data is from 2nd/3rd line therapy with single-agent

WCLC 2018

Molecular subtypes sorted by best response (RECIST1.1)

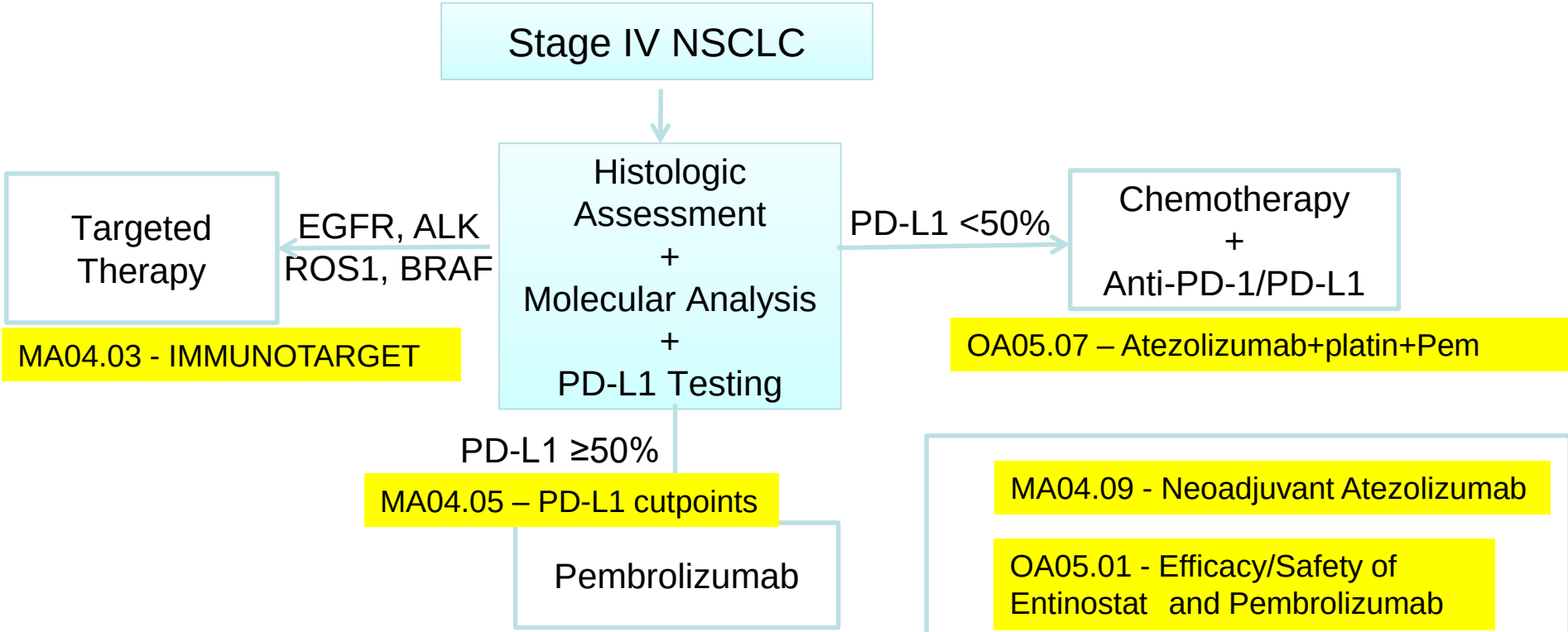


	PD	SD	PR/CR
BRAF other (n=17)	6 (35.3%)	4 (23.5%)	7 (41.2%)
MET exon14 (n=21)	10 (47.6%)	8 (38.1%)	3 (14.3%)
KRAS (n=246)	125 (50.8%)	57 (23.2%)	64 (26.0%)
EGFR other (n=34)	19 (55.9%)	11 (32.4%)	4 (11.8%)
EGFR exon21 (n=24)	14 (58.3%)	5 (20.8%)	5 (20.8%)
BRAF V600E (n=13)	8 (61.5%)	3 (23.1%)	2 (15.4%)
MET other (n=8)	5 (62.5%)	3 (37.5%)	0 (0.0%)
HER2 (n=27)	18 (66.7%)	7 (25.9%)	2 (7.4%)
ALK/ROS1/RET (n=41)	30 (73.2%)	9 (22.0%)	2 (4.9%)
EGFR T790M (n=27)	21 (77.8%)	5 (18.5%)	1 (3.7%)
EGFR exon19 (n=21)	18 (85.7%)	1 (4.8%)	2 (9.5%)

IMMUNOTARGET key messages

- **ICI response rate and disease control rate were higher in $BRAF^{non600}$/KRAS subgroups compared with ALK/ROS1/RET and $EGFR^{del19}$**

- **PD-L1 status may have some predictive value in mutant EGFR. Better predictive molecular markers are needed**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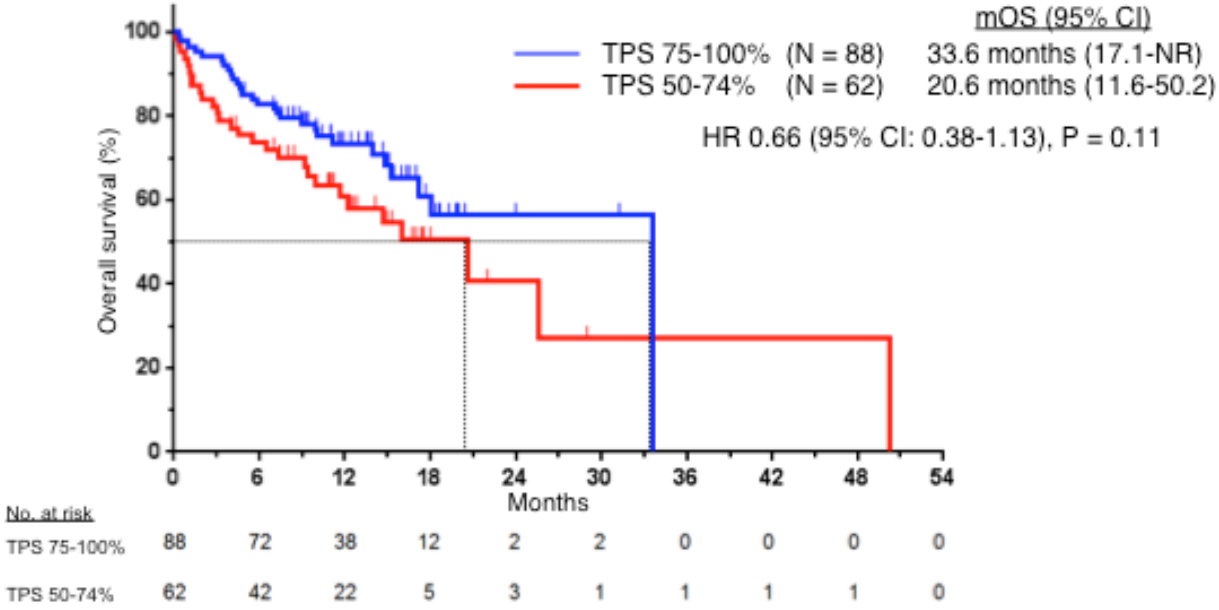
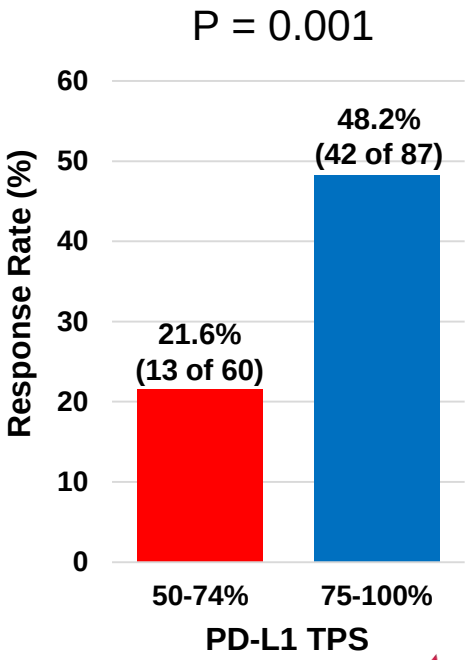
Outcomes in NSCLC Patients Treated with First-Line Pembrolizumab and a PD-L1 TPS of 50-74% vs 75-100% or 50-89% vs 90-100%

Elizabeth Jimenez Aguilar[1], Biagio Ricciuti[1], Justin F. Gainor[2], Mizuki Nishino[1], Sasha Kravets[1], Suzanne Dahlberg[1], Sara Khosrowjerdi[2], Christine A. Lydon[1], Anika Adeni[1], Safiya Subegdjo[1], Hira Rizvi[3], Matthew D. Hellmann[3], Mark M. Awad[1]

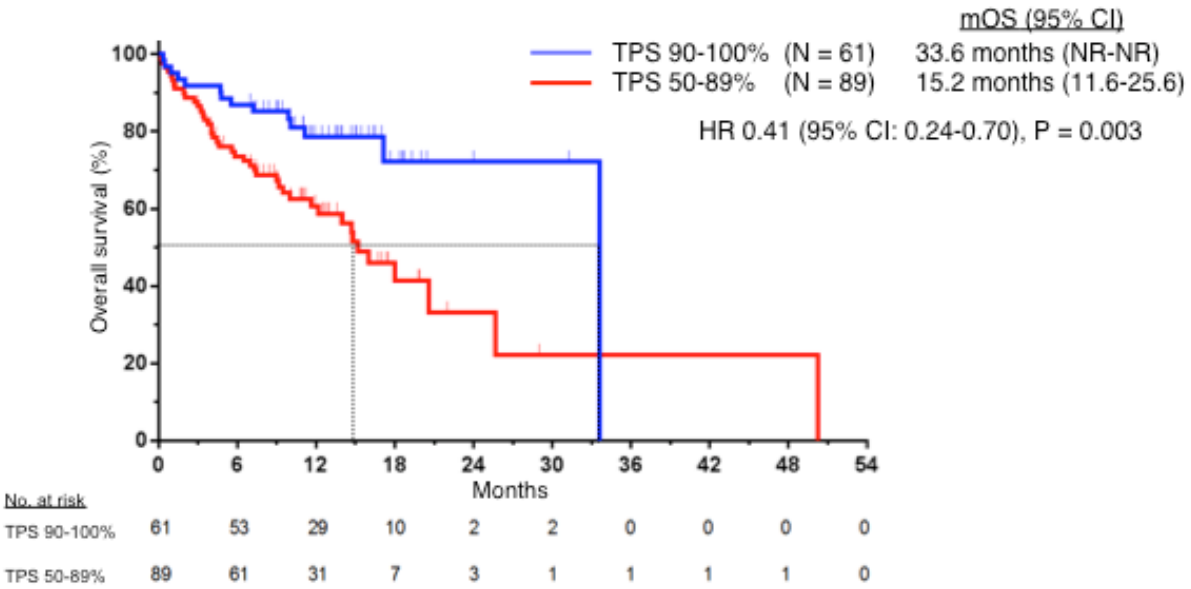
- Retrospective review of 150 patients treated with 1st line pembrolizumab
- In the first-line setting, are there better (higher) PD-L1 TPS cutoffs?

OS: TPS 50-74% vs. TPS 75-100%

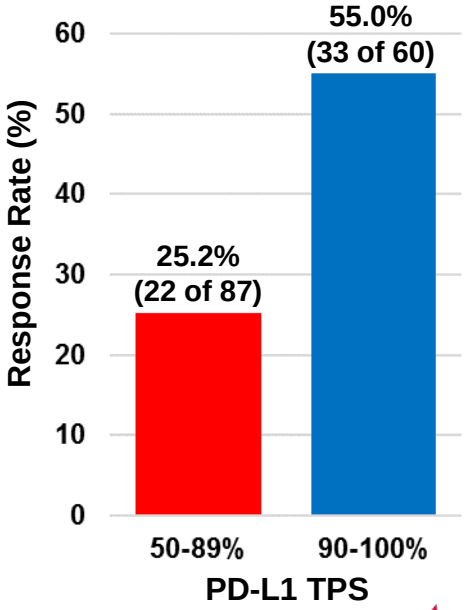




OS: TPS 50-89% vs. TPS 90-100%

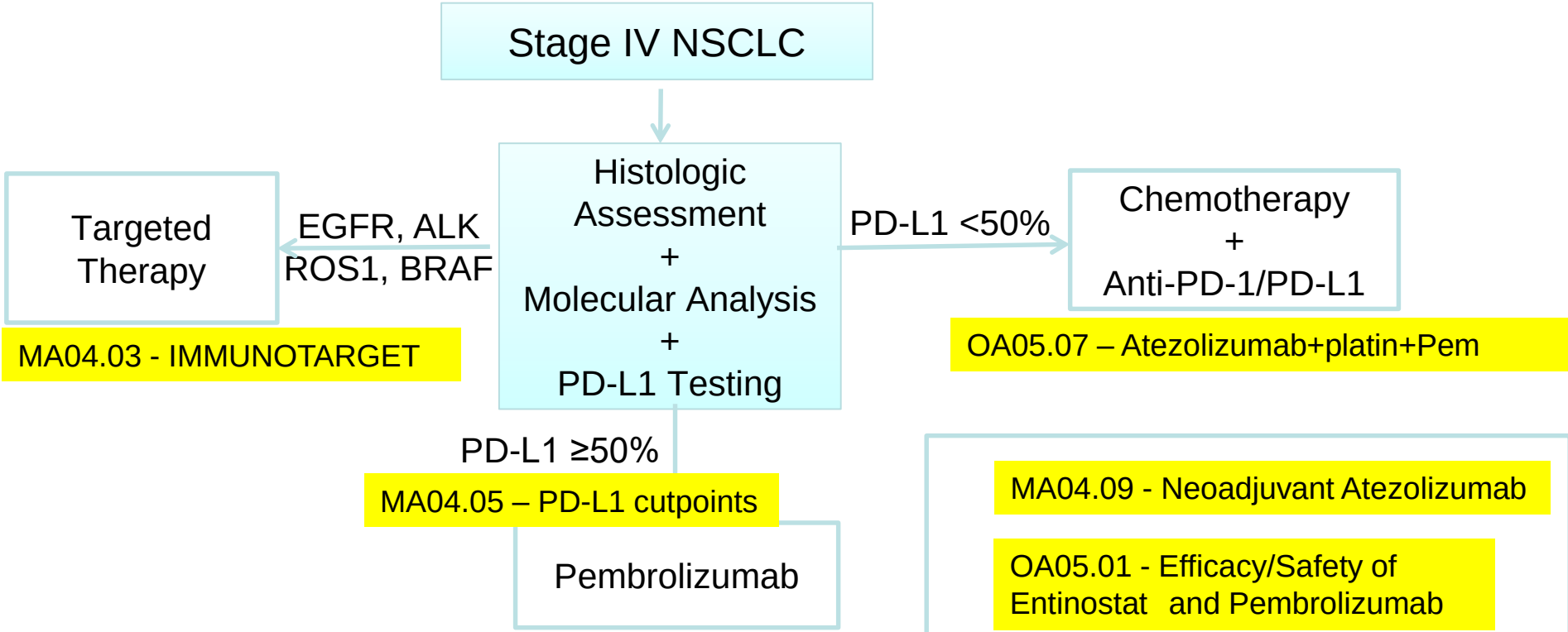


P = 0.0005



Key points from looking at higher PD-L1 cutpoints

- Cutoffs of PD-L1 higher than 50% can predict greater RR, PFS, and OS in the first line setting with pembrolizumab treatment.
- The ideal PD-L1 TPS cutoff for using pembrolizumab monotherapy over pembrolizumab + platinum doublet chemotherapy remains unclear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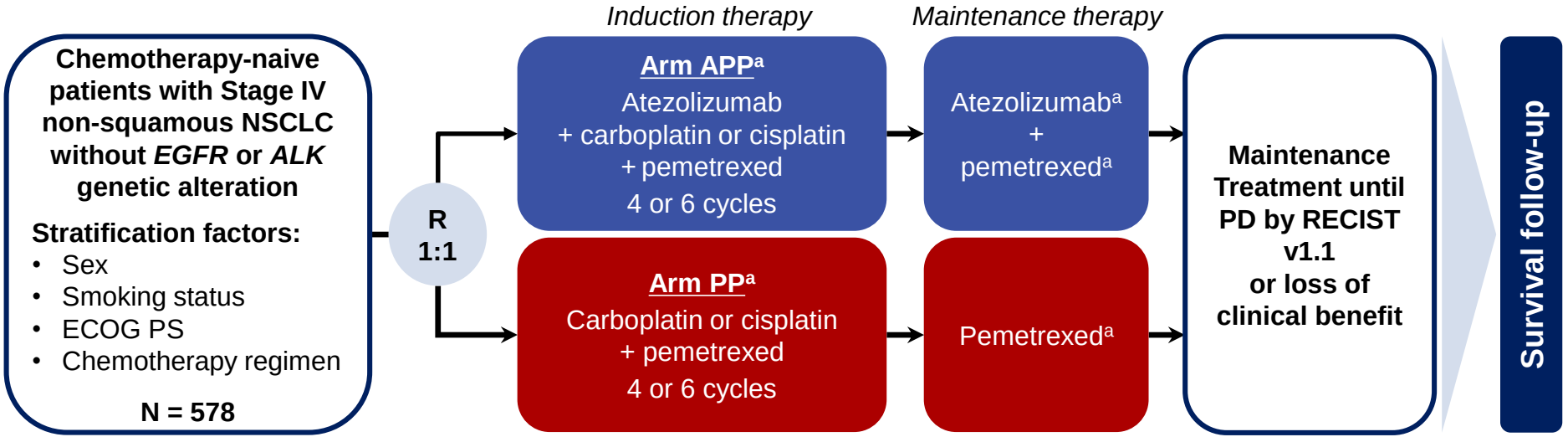
IMpower132 Study Design



- Co-primary endpoints: INV-assessed PFS and OS
- Secondary endpoints: INV-assessed ORR and DOR, PRO and safety measures
- Exploratory analyses: clinical and biomarker subgroup analyses
  - Biomarker-evaluable tissue not mandatory for enrolment (was available from 60% of patients)

PRO, patient-reported outcomes. [a] Atezolizumab: 1200 mg IV q3w; Carboplatin: AUC 6 mg/mL/min IV q3w; Cisplatin: 75 mg/m^2 IV q3w; Pemetrexed: 500 mg/m^2 IV q3w.
NCT02657434. Data cutoff: May 22, 2018

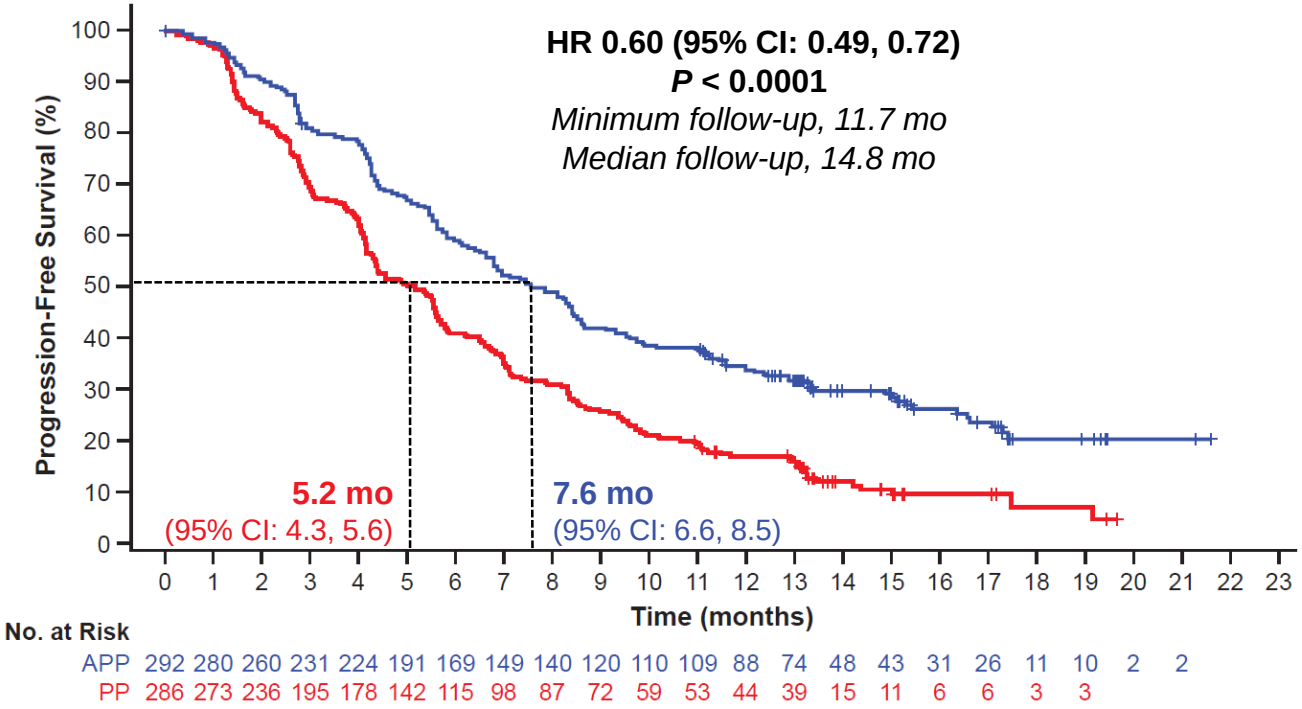
Baseline Characteristics

Characteristic	APP (n = 292)	PP (n = 286)
Median age (range), years	64.0 (31-85)	63.0 (33-83)
< 65 years, n (%)	153 (52.4%)	167 (58.4%)
Sex, male, n (%)	192 (65.8%)	192 (67.1%)
Race, n (%)[a]		
White	193 (66.1%)	203 (71.0%)
Asian	71 (24.3%)	65 (22.7%)
ECOG PS 0, n (%)[b]	126 (43.2%)	114 (40.1%)
Carboplatin, n (%)	177 (60.6%)	175 (61.1%)
Intended 4 cycles, n (%)	197 (67.5%)	190 (66.4%)

Characteristic	APP (n = 292)	PP (n = 286)
Smoking status, n (%)		
Current or former	255 (87.3%)	256 (89.5%)
Never	37 (12.7%)	30 (10.5%)
Liver metastases, n (%)	37 (12.7%)	36 (12.6%)
PD-L1 expression, n (%)[c]	n = 176	n = 168
Negative	88 (50.0%)	75 (44.6%)
Positive	88 (50.0%)	93 (55.4%)
PD-L1–low	63 (35.8%)	73 (43.5%)
PD-L1–high	25 (14.2%)	20 (11.9%)

APP, atezolizumab + carboplatin/cisplatin + pemetrexed; PP, carboplatin/cisplatin + pemetrexed.
[a] American Indian or Alaska Native race (n = 2), Black or African American (n = 6) and Unknown race (n = 38) not included in table. [b] 2 patients had missing baseline ECOG PS. [c] PD-L1 status available in 60% of patients. PD-L1–high (TC3/IC3): patients with PD-L1 expression in ≥50% of tumor cells or ≥10% of tumor-infiltrating immune cells; PD-L1–low (TC12/IC12): patients with PD-L1 expression in ≥1% and <50% of tumor cells or ≥1% and <10% of tumor-infiltrating immune cells; and PD-L1–negative (TC0/IC0): patients with PD-L1 expression in <1% of tumor cells and <1% of tumor-infiltrating immune cells.

Final Investigator-Assessed PFS, ORR and DOR

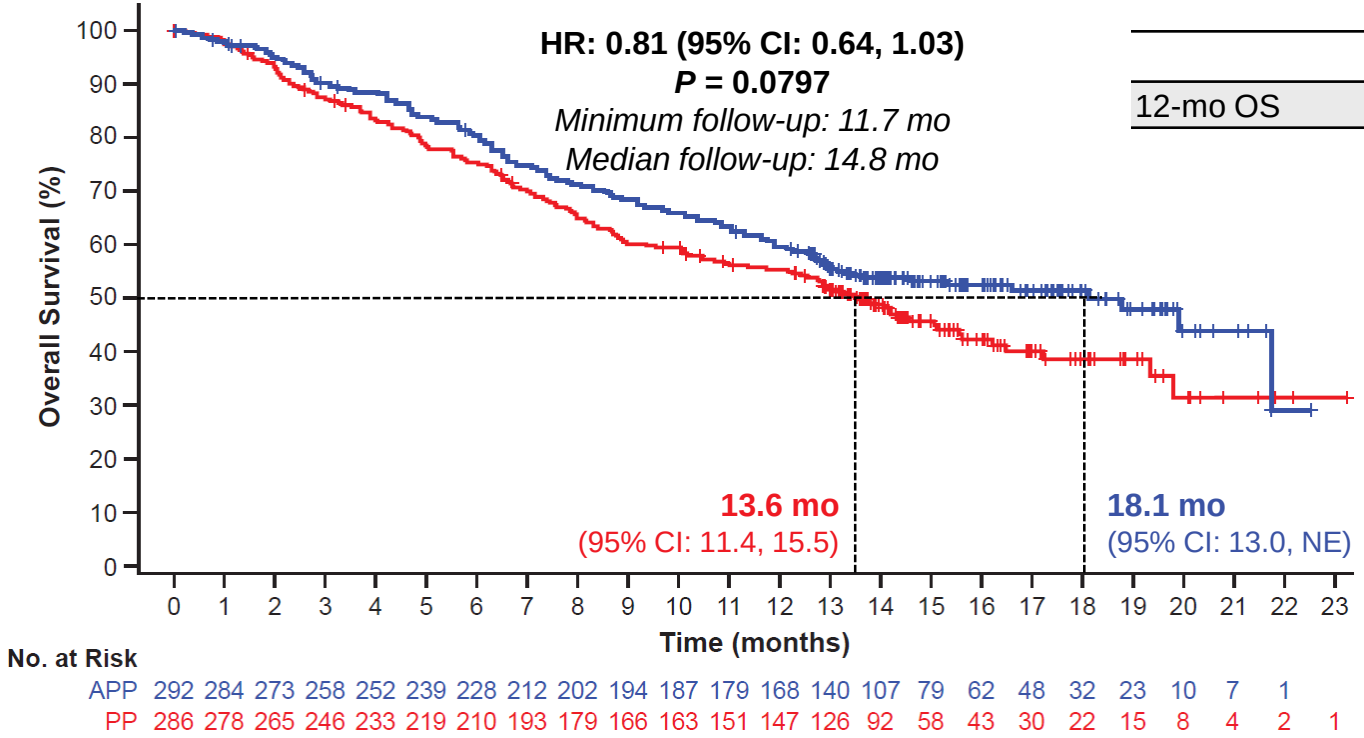


	APP	PP
6-mo PFS	59.1%	40.9%
12-mo PFS	33.7%	17.0%

	APP	PP
ORR, %	47%	32%
CR	2%	1%
PR	45%	32%
Median DOR, mo	10.1	7.2
Ongoing response, %	42%	30%

APP, atezolizumab + carboplatin/cisplatin + pemetrexed; CR, complete response; DOR, duration of response; HR, hazard ratio; IRF, independent review facility; ORR, objective response rate; PP, carboplatin/cisplatin + pemetrexed; PR, partial response.
IRF-assessed median PFS was 7.2 mo with APP and 6.6 mo with PP (stratified HR: 0.758 [95% CI: 0.623, 0.923] *P* = 0.055)
Data cutoff: May 22, 2018.

Interim OS Analysis

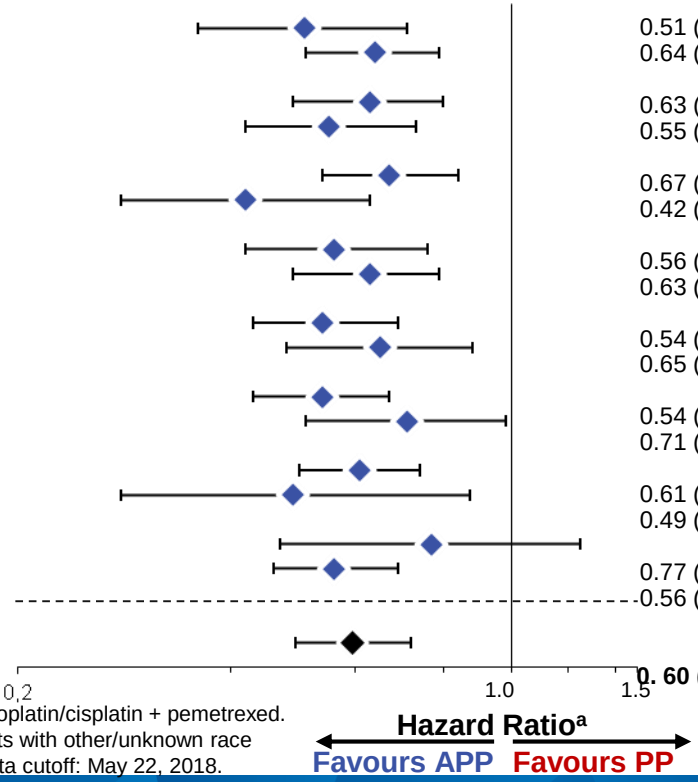


	APP	PP
12-mo OS	59.6%	55.4%

APP, atezolizumab + carboplatin/cisplatin + pemetrexed; PP, carboplatin/cisplatin + pemetrexed.
Data cutoff: May 22, 2018. Frequency of OS events: 44% and 49% in arms APP and PP respectively.

PFS in Key Patient Subgroups

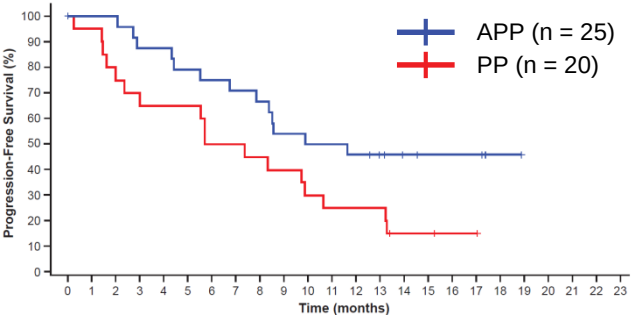
Subgroup	n (%)	HR (95% CI)[a]	Median PFS, mo	
			APP	PP
Female	194 (34)	0.51 (0.36–0.71)	8.3	5.3
Male	384 (66)	0.64 (0.51–0.79)	7.5	4.9
< 65 y	320 (55)	0.63 (0.49–0.80)	6.9	4.4
≥ 65 y	258 (45)	0.55 (0.42–0.73)	8.4	5.6
White[b]	396 (69)	0.67 (0.54–0.84)	6.9	4.9
Asian	136 (24)	0.42 (0.28–0.63)	10.2	5.3
ECOG PS 0[b]	240 (42)	0.56 (0.42–0.76)	8.6	5.8
ECOG PS 1	336 (58)	0.63 (0.49–0.79)	6.8	4.4
Received carboplatin	352 (61)	0.54 (0.43–0.69)	8.1	5.5
Received cisplatin	226 (39)	0.65 (0.48–0.88)	7.1	4.4
Intended 4 cycles	387 (67)	0.54 (0.43–0.67)	7.8	4.5
Intended 6 cycles	191 (33)	0.71 (0.51–0.98)	7.6	5.6
Current or former smoker	511 (88)	0.61 (0.50–0.74)	7.5	5.1
Never smoker	67 (12)	0.49 (0.28–0.87)	8.6	5.5
Liver metastases	73 (13)	0.77 (0.47–1.25)	4.4	4.0
No liver metastases	505 (87)	0.56 (0.46–0.69)	8.4	5.5
ITT population	**578 (100)**	**0. 60 (0.49–0.72)**	**7.6**	**5.2**



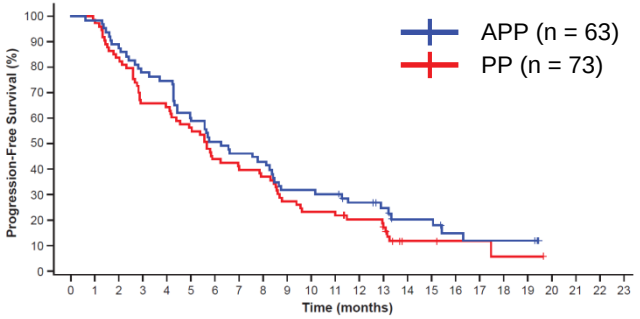
APP, atezolizumab + carboplatin/cisplatin + pemetrexed; PP, carboplatin/cisplatin + pemetrexed.
[a] Stratified HR for ITT; unstratified for all other subgroups. [b] Patients with other/unknown race (n = 46) and unknown baseline ECOG PS (n = 2) not included. Data cutoff: May 22, 2018.

Exploratory Analysis: PFS by PD-L1 Status in Biomarker-Evaluable Patients[a]

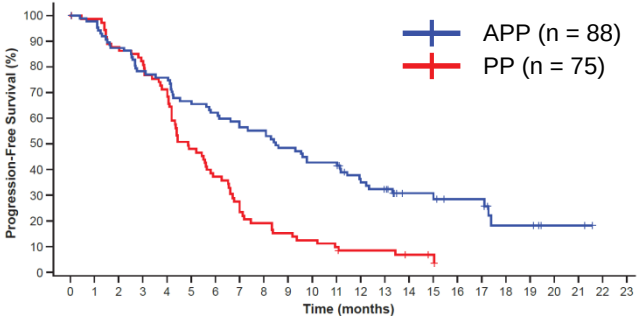
PD-L1 High
TC3 or IC3



PD-L1 Low
TC1/2 or IC1/2



PD-L1 Negative
TC0 and IC0



	APP	PP		APP	PP		APP	PP
ORR, %	72%	55%		38%	38%		44%	27%
CR | PR, %	0 | 72%	5% | 50%		2% | 37%	0 | 38%		2% | 42%	0 | 27%
Median DOR, mo	NE	7.2		7.2	7.2		10.1	4.2
12-month PFS	46%	25%		27%	20%		35%	8%
Median PFS, mo	10.8	6.5		6.2	5.7		8.5	4.9
HR[b] (95% CI)	0.46 (0.22, 0.96)			0.80 (0.56, 1.16)			0.45 (0.31, 0.64)	

APP, atezolizumab + carboplatin/cisplatin + pemetrexed; PP, carboplatin/cisplatin + pemetrexed.
[a] Overall HR 0.57 (0.45, 0.73) in biomarker-evaluable patients (60% of ITT). [b] Unstratified HR. Data cutoff: May 22, 2018.

Safety Summary

	APP (n = 291)	PP (n = 274)
All-cause AEs, n (%)	286 (98%)	266 (97%)
Grade 3-4	181 (62%)	147 (54%)
Grade 5	21 (7%)	14 (5%)
TRAEs, n (%)	267 (92%)	239 (87%)
Grade 3-4	156 (54%)	107 (39%)
Grade 5	11 (4%)	7 (3%)
SAEs, n (%)	134 (46%)	84 (31%)
Tx-related SAEs	96 (33%)	43 (16%)
AEs leading to withdrawal, n (%)		
Of any treatment	69 (24%)	48 (18%)
Of atezolizumab	44 (15%)	0
AESI, n (%)	141 (49%)	104 (38%)

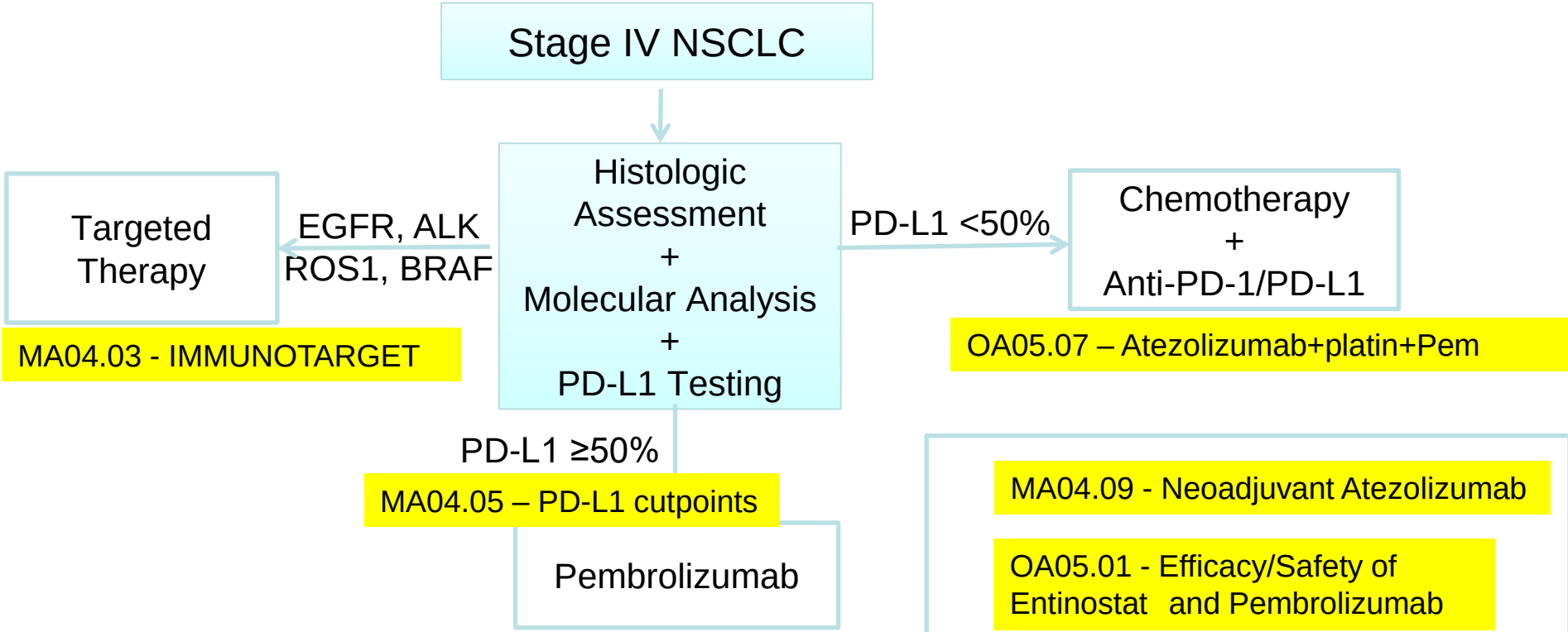
	APP (n = 291)		PP (n = 274)	
AEs of Special Interest, n (%)	All Grade	Grade 3-4	All Grade	Grade 3-4
Rash	71 (24%)	9 (3%)	58 (21%)	5 (2%)
Hypothyroidism	23 (8%)	1 (<1%)	6 (2%)	0
Pneumonitis	16 (6%)	6 (2%)[a]	6 (2%)	3 (1%)[a]
Hepatitis (Diagnosis)	13 (5%)	7 (2%)[a]	2 (1%)	0
Infusion-Related Reactions	8 (3%)	1 (<1%)	2 (1%)	1 (<1%)
Hyperthyroidism	6 (2%)	1 (<1%)	3 (1%)	0
Severe Cutaneous Adverse Reaction	4 (1%)	2 (1%)	2 (1%)	0
Pancreatitis	4 (1%)	1 (<1%)	2 (1%)	2 (1%)
Colitis	5 (2%)	2 (1%)	0	0

- PRO data also support the positive benefit-risk profile demonstrated by these clinical data

APP, atezolizumab + carboplatin/cisplatin + pemetrexed; AE, adverse event; AESI, adverse event of special interest; PP, carboplatin/cisplatin + pemetrexed; SAE, serious adverse event; TRAE, treatment-related adverse event.[a] Grade 5 event observed. Data cutoff: May 22, 2018.

Conclusions

- IMpower132 met its co-primary endpoint of investigator-assessed PFS in the ITT population
- The addition of atezolizumab to carboplatin/cisplatin + pemetrexed improved median PFS in the ITT population (7.6 mo vs 5.2 mo, HR 0.60) and across key clinical subgroups
- Atezolizumab + pemetrexed + carboplatin or cisplatin has a manageable safety profile consistent with known safety risks of the individual therapies; no new safety signals were identified
- OS data showed a numerical improvement of 4.5 months at this interim analysis; final analysis is anticipated in 1H 2019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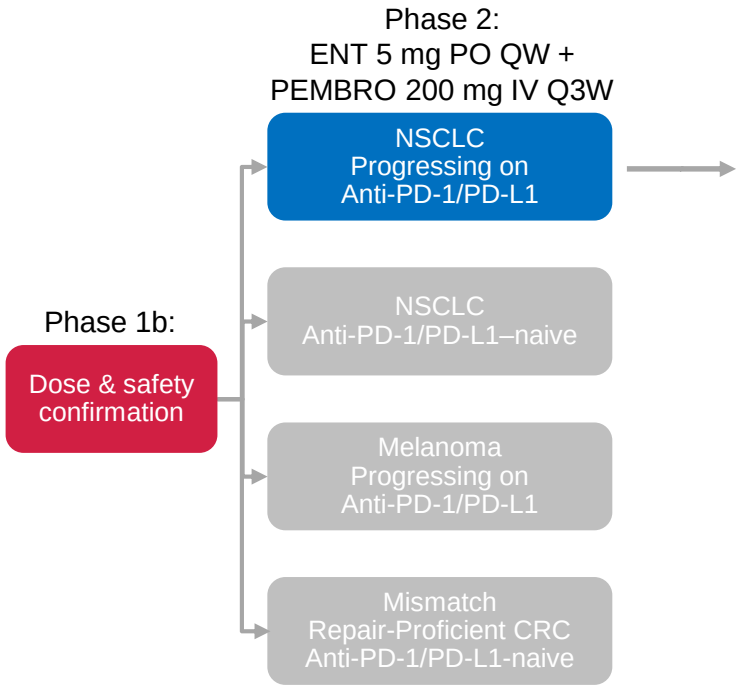
ENCORE-601: Open-label study evaluating ENT + PEMBRO in patients with recurrent or metastatic NSCLC and prior progression on anti-PD-1/PD-L1 therapy



Inclusion Criteria:

- Recurrent or metastatic NSCLC, measurable by RECIST 1.1
- Prior progression on anti-PD(L1) treatment
- Prior chemotherapy in the advanced/metastatic setting
- Prior ALK or EGFR treatment if indicated
- ECOG Performance Status < 2
- Willingness to baseline and on-Tx biopsy and blood samples

Phase 2 Primary Endpoint

- ORR (irRECIST)

Phase 2 Secondary Endpoints

- PFS, OS, safety & tolerability

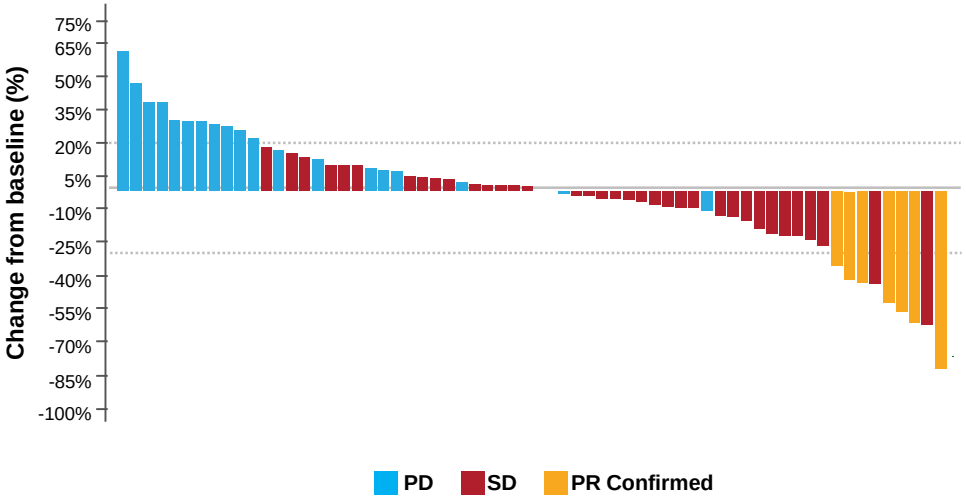
76 patients enrolled (72 efficacy evaluable*), last patient enrolled December 2017

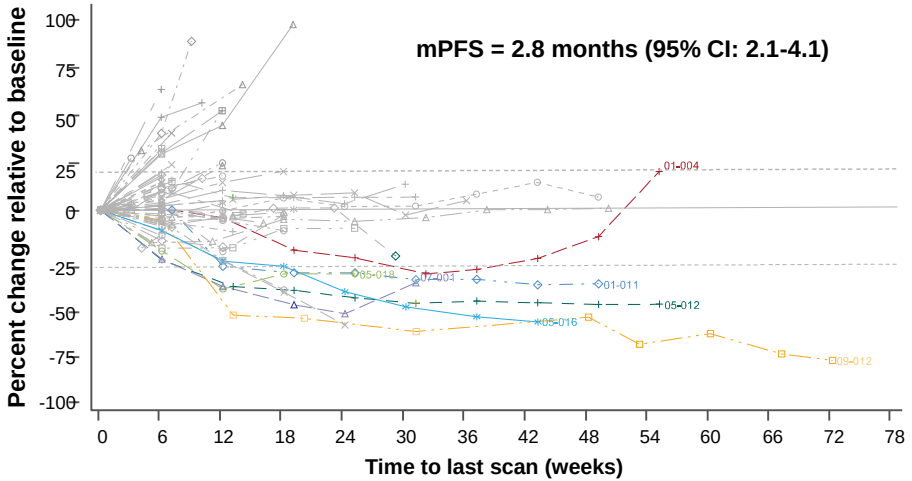
- Sample size was based on single proportion binomial test, assuming a true ORR of 15% & lower threshold of 5%, with 90% power and a 1-sided significance level of 5%.

*4 patients were non-evaluable due to withdrawal of consent or discontinuations for administrative reasons prior to the first tumor assessment.

ALK, anaplastic lymphoma kinase; CRC, colorectal cancer; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; ENT, entinostat; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PEMBRO, pembrolizumab; PFS, progression-free survival; PO, orally; RECIST, Response Evaluation Criteria in Solid Tumors; QW, once a week; Q3W, every 3 weeks.

Durable responses were observed in patients who experienced progression on prior anti-PD(L)1 therapy



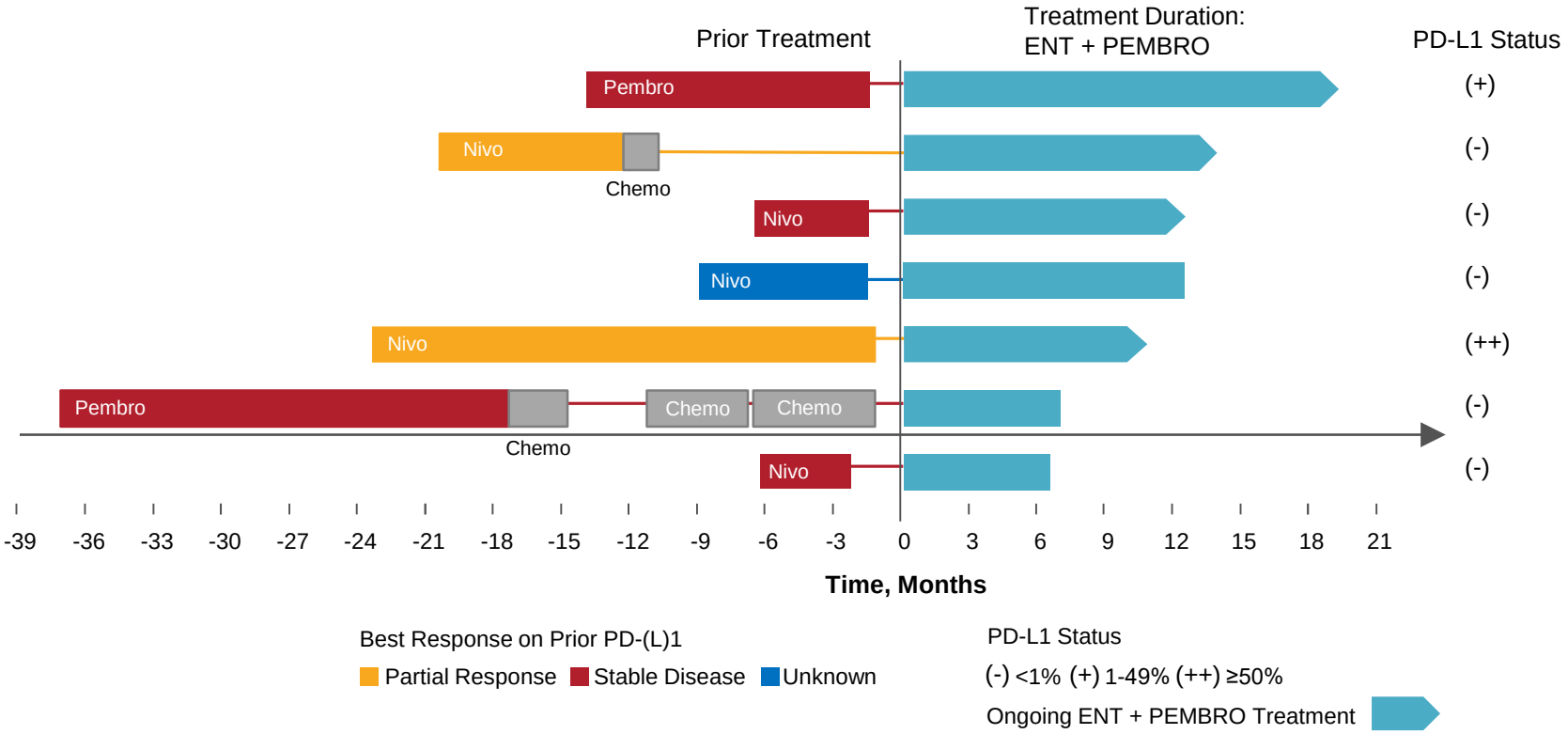


- Objective response rate with ENT + PEMBRO was 10% (7 of 72, 95% CI: 4-19%)
  - Prespecified ORR target not reached; median duration of response was 5.3 months
  - An additional 50% of patients achieved disease stabilization
- Experience similar in PD1-pretreated melanoma (ORR = 18%)[1]

CI, confidence interval; ENT, entinostat; PEMBRO, pembrolizumab; PD, progressive disease; PR, partial response; SD, stable disease.

1. Gandhi L, et al. Presented at ASCO 2018. Abstract 9036.

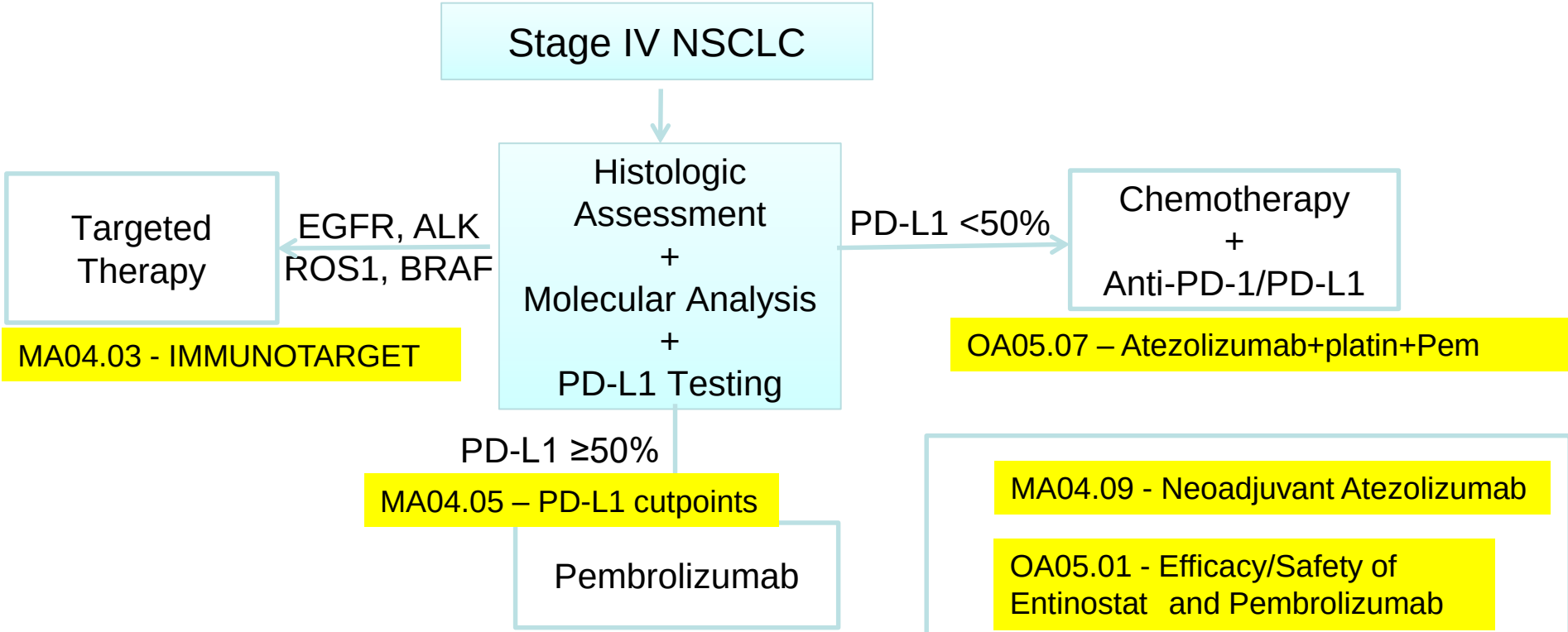
Responses observed regardless of prior treatment history or PD-L1 status



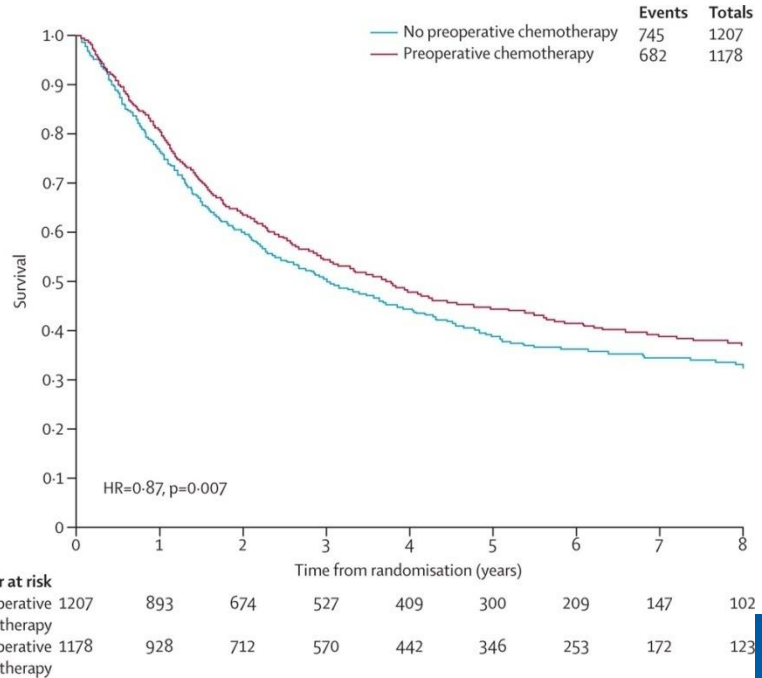
Chemo, chemotherapy; ENT, entinostat; Nivo, nivolumab; PEMBRO, pembrolizumab.

Entinostat + Pembrolizumab Key Messages

- ENT + PEMBRO demonstrated anti-tumor activity (ORR 10%) in patients with NSCLC who have progressed on prior PD-(L)1 blockade
- Prespecified ORR target not reached
- Most patients tolerated the therapy well
- Responses to ENT+ PEMBRO were independent of baseline PD-L1 expression

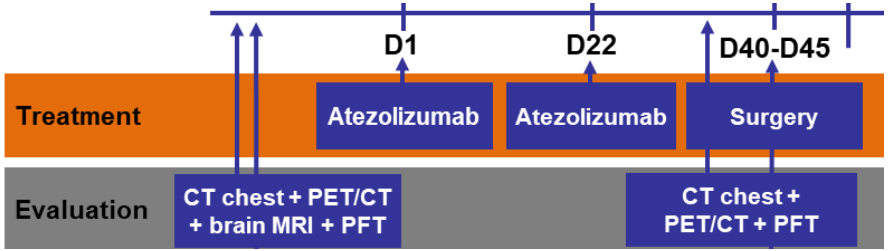

Stage IV NSCLC
Histologic Assessment + Molecular Analysis + PD-L1 Testing
EGFR, ALK ROS1, BRAF
Targeted Therapy
MA04.03 - IMMUNOTARGET
PD-L1 <50%
Chemotherapy + Anti-PD-1/PD-L1
OA05.07 – Atezolizumab+platin+Pem
PD-L1 ≥50%
MA04.05 – PD-L1 cutpoints
Pembrolizumab
MA04.09 - Neoadjuvant Atezolizumab
OA05.01 - Efficacy/Safety of Entinostat and Pembrolizumab

Preoperative chemotherapy for non-small-cell lung cancer: a systematic review and meta-analysis of individual participant data *The Lancet* ,Volume 383, Issue 9928, Pages 1561-1571 (May 2014) DOI: 10.1016/S0140-6736(13)62159-5



Neoadjuvant Atezolizumab in Resectable Non-Small Cell Cancer (NSCLC): Updated Results From a Multicentre Study (LCMC3)

Valerie W. Rusch,[1] Jamie E. Chaft,[1] Bruce E. Johnson,[2] Ignacio Wistuba,[3] Mark G. Kris,[1] Jay M. Lee,[4] Paul Bunn,[5] David J. Kwiatkowski,[2] Karen L. Reckamp,[6] David Finley,[7] Eric B. Haura,[8] Saiama N. Waqar,[9] Robert Doebele,[5] Edward B. Garon,[4] Justin D. Blasberg,[10] Alan Nicholas,[11] Katja Schulze,[11] See Phan,[11] Ann Johnson,[11] David P. Carbone[12]



Neoadjuvant Therapy for Resectable NSCLC

PROS

Attack Micrometastases earlier

Compliance, Feasibility of systemic therapy

Evaluate Efficacy, prognosis ?

Biomarkers, MOA (mechanism of action)

CONS

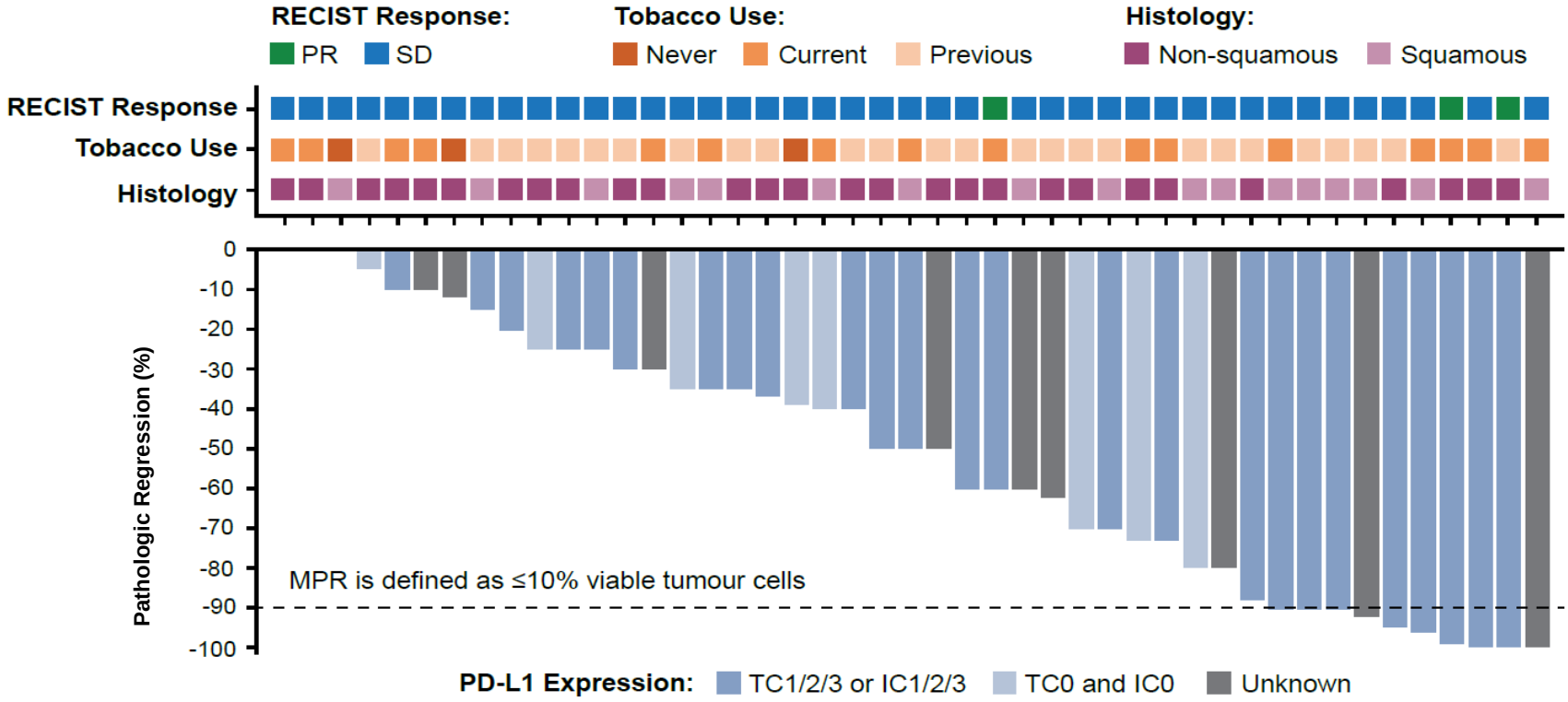
Delays and may preclude surgery

No effective alternatives if therapy ineffective

No validated predictive endpoints

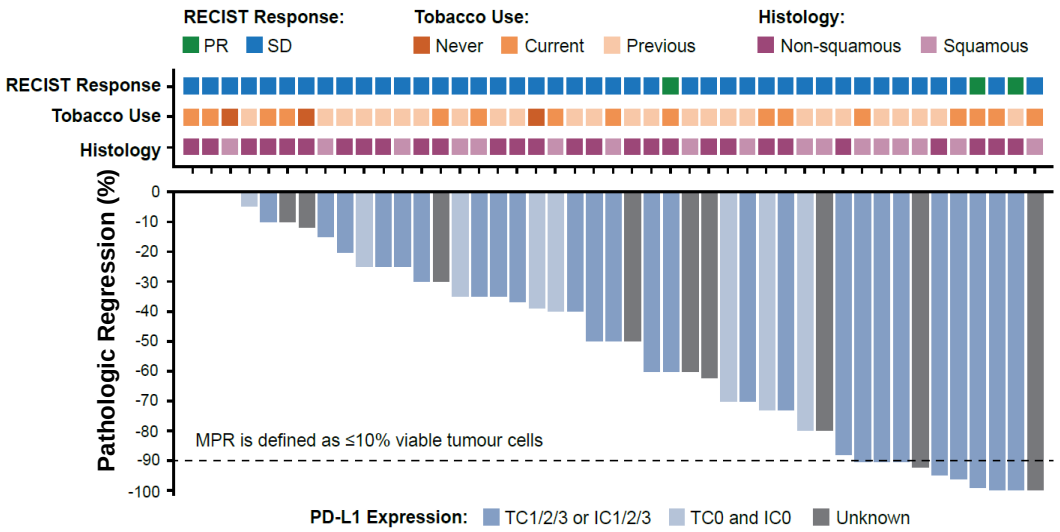
No survival advantage over adjuvant therapy

Major Pathological Response (≤10% Viable Tumour Cells)



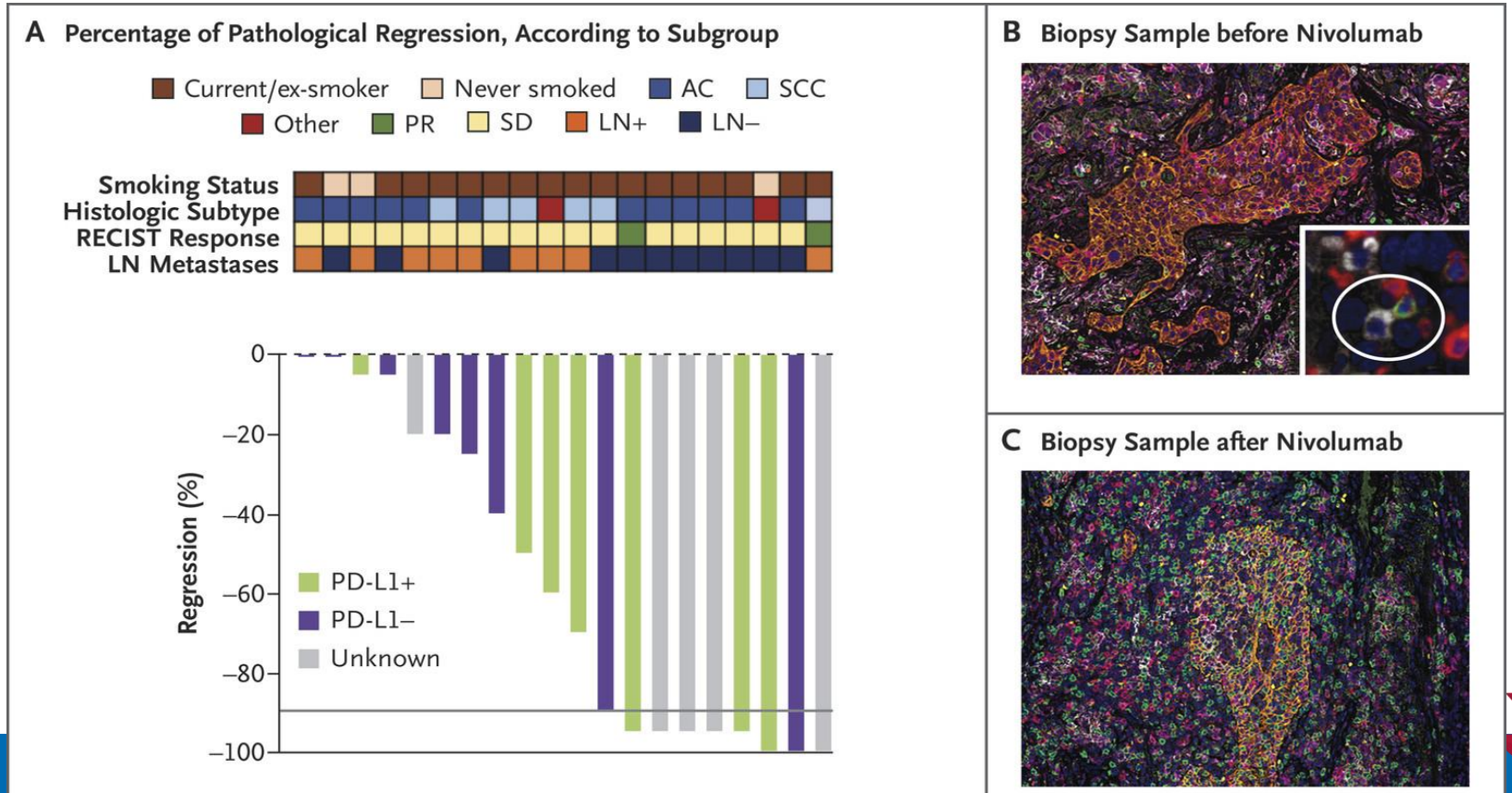
Major Pathological Response (MPR; ≤10% Viable Tumor Cells)

- The efficacy-evaluable population comprised 45 patients who were treated with atezolizumab and underwent surgical resection
  - Per protocol, patients with *EGFR* or *ALK* genetic alterations were excluded from the efficacy-evaluable population
- 3 patients had pCR and 10 patients had a MPR
- No patients in the TC0 and IC0 subgroup had pCR or MPR
- Radiological response did not appear to associate with pathological response



IC, tumour-infiltrating immune cells; pCR, pathologic complete response; TC, tumour cells. TC1/2/3 or IC1/2/3 = PD-L1+ ≥1% on TC or IC; TC0 and IC0 = PD-L1+ <1% on TC and IC.
Pathologic regression defined as viable tumour cells (%) – 100 (%).
Data cutoff: February 2018.

Pathological Assessment of Response to Neoadjuvant Blockade of Programmed Death 1 (PD-1).



Rusch et al

Atezolizumab pre-op was feasible, 22% MPR

7% of patients couldn't have surgery

17% patients had surgery delayed

We need to wait for study completion

Is survival with pre-op ICI superior to adjuvant therapy ?

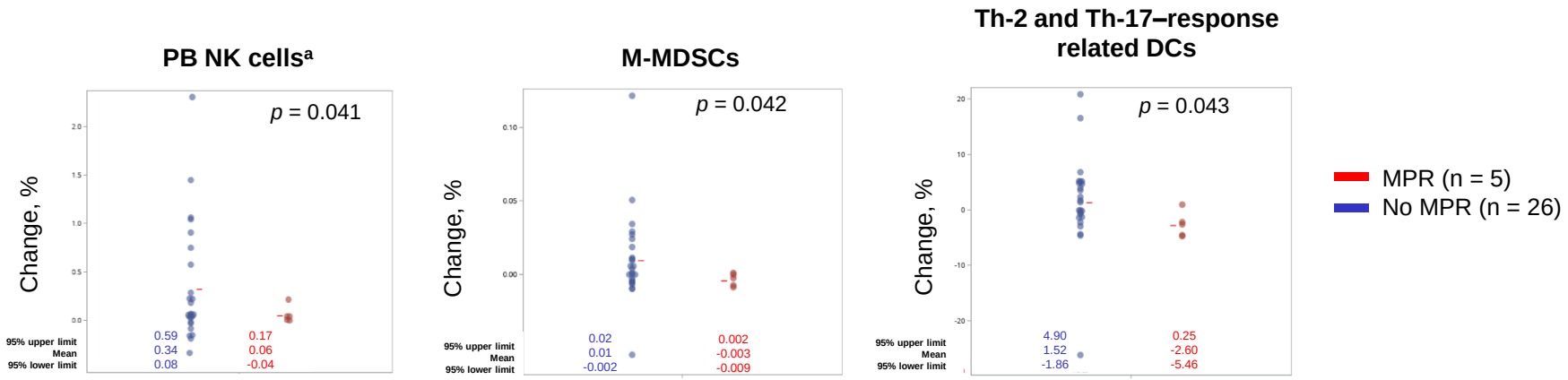
If not, do we get data that positively affects subsequent therapy ?

If no to both questions above, what will argue for pre-op ICI ?

Neoadjuvant Atezolizumab Key Messages

- Neoadjuvant atezolizumab in early stage NSCLC shows promising clinical activity and was well tolerated
- 10 of 45 patients (22% [95% CI: 11, 37]) treated with 2 doses of atezolizumab and underwent surgery had a MPR
- Change in lesion size from baseline and percent viable tumor cells appear to not be associated

Immune Cell Subset Changes After Neoadjuvant Atezolizumab in Patients With MPR Versus No MPR



- Patients who did not achieve a MPR show an increase in late activated NK cells, a monocytic myeloid cell subpopulation, and a Th-2 and Th-17 response related DC subpopulation

DC, dendtritic cells; M-MDSC, monocytic myeloid-derived suppresor cells; PB, peripheral blood; Th, T helper cells. Red hyphens in graphs represent mean.
[a] Late-activated CD16+ CD56+ NK cells.

Ευχαριστώ για την προσοχή σας