LUNG CANCER IMMUNOTHERAPY

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9th Annual Puerto Rico Winter Cancer Sympsium 2020

Speaker Bureau: Astrazeneca, BMS, Janssen, BI, Takeda, Caris, Biodexic

Consultancy: None

Royalties: None

Research: None

Employment: None

Stocks: None

Other: None

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Background…..

- What is the standard of care until today, prior to LALCA….
  - Non-squamous PD-L1 > 50%→ Pembro alone or Plat/Pem/Pem (KN-24, KN-189) **CAT 1**
  - Non-squamous PD-L1 1-49%→ Pembro alone or Plat/Pem/Pem (KN-042, KN-189) **CAT 1**
  - Non-squamous PD-L1 <1%→ Plat/Pem/Pem (KN-189) **CAT 1**
  - Non-squamous (regardless PD-L1)→ Plat/Pac/Bev/Atezo (IMpower-150) **CAT 1**

  - Squamous PD-L1 > 50%→ Pembro alone or Plat/Pac or nab-Pac/Pem (KN-24, KN-407) **CAT 1**
  - Squamous PD-L1 1-49%→ Pembro alone or Plat/Pac or nab-Pac/Pem (KN-042, KN-407) **CAT 1**
  - Squamous PD-L1 <1%→ Plat/Pac or nab-Pac/Pem (KN-407) **CAT 1**

Initial Systemic Therapy Options
Adenocarcinoma, Large Cell, NSCLC NOS (PS 0-1)
No contraindications to the addition of pembrolizumab or atezolizumab[c]
- **Pembrolizumab/carboplatin/pemetrexed (category 1)[1,2,d] (preferred)**
- **Pembrolizumab/cisplatin/pemetrexed (category 1)[2,d] (preferred)**
- **Atezolizumab/carboplatin/paclitaxel/bevacizumab[e] (category 1)[3,d,f,g,h]**

Squamous Cell Carcinoma (PS 0-1)
No contraindications to the addition of pembrolizumab[c]
- **Pembrolizumab/carboplatin/paclitaxel[31,d] (category 1) (preferred)**
- **Pembrolizumab/carboplatin/albumin-bound paclitaxel[31,d] (category 1) (preferred)**
- **Pembrolizumab/cisplatin/paclitaxel[d]**
- **Pembrolizumab/cisplatin/albumin-bound paclitaxel[d]**

NCCN. Version 7.2019

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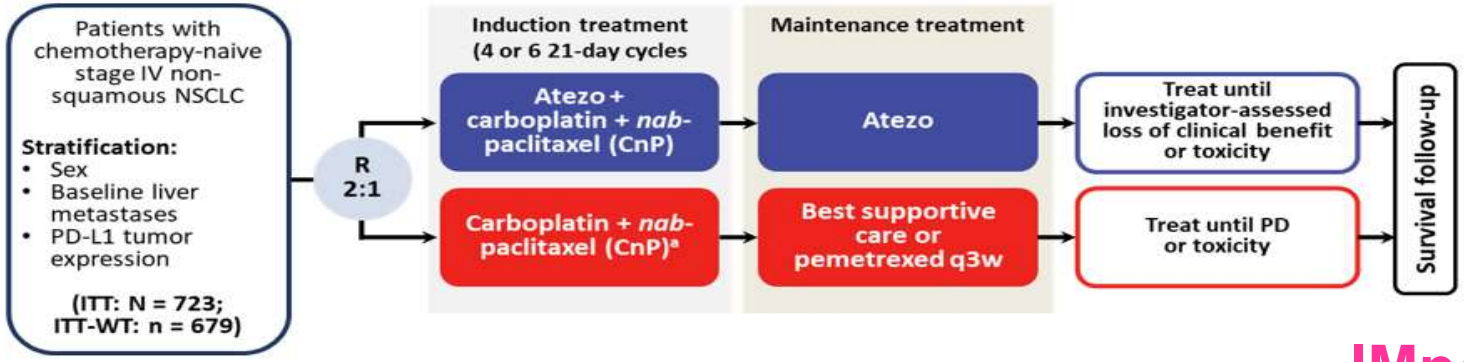
Recent new Standard of Care?

Atezolizumab in combination with carboplatin plus nab-paclitaxel chemotherapy compared with chemotherapy alone as first-line treatment for metastatic non-squamous non-small-cell lung cancer (IMpower130)



IMpower130

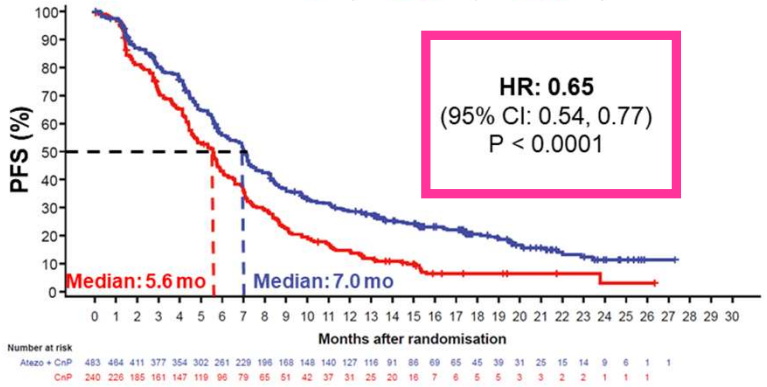
- Co-primary endpoints: investigator-assessed PFS and OS (ITT-WT population)
  - ITT-WT population: randomised patients excluding those with *EGFR* or *ALK* genomic alterations
- Key secondary endpoints: OS and PFS (ITT population and by PD-L1 expression), ORR and safety
  - ITT population could be formally tested for OS/PFS if ITT-WT OS was positive

Atezo 1200 mg IV q3w; carboplatin area under the curve 6 mg/mL/min q3w; *nab*-paclitaxel 100 mg/m^2 IV q3w. PD-L1 status tested with VENTANA SP142 IHC assay. Data cutoff: 15 March 2018. [a] Crossover to receive atezo at PD was permitted only for patients enrolled to protocol versions 1 - 4.

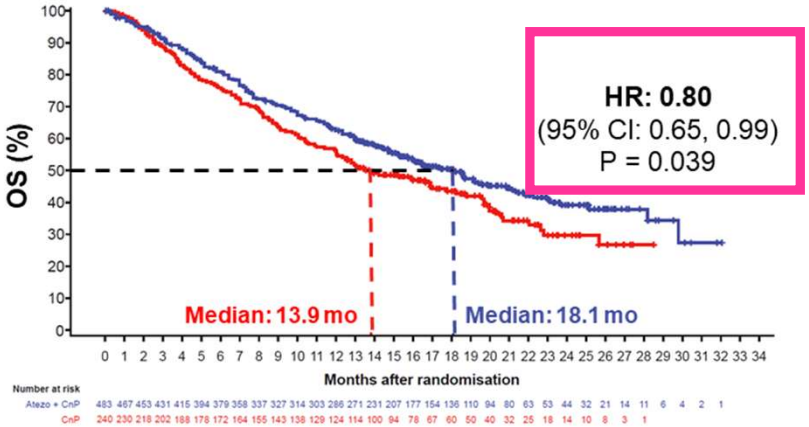
Cappuzzo F, et al. IMpower130. ESMO 2018 [Abstract LBA53].

Investigator-assessed PFS and OS (ITT)

PFS (%)	6 months	12 months
Atezo + CnP	56.4%	28.9%
CnP	42.9%	14.2%

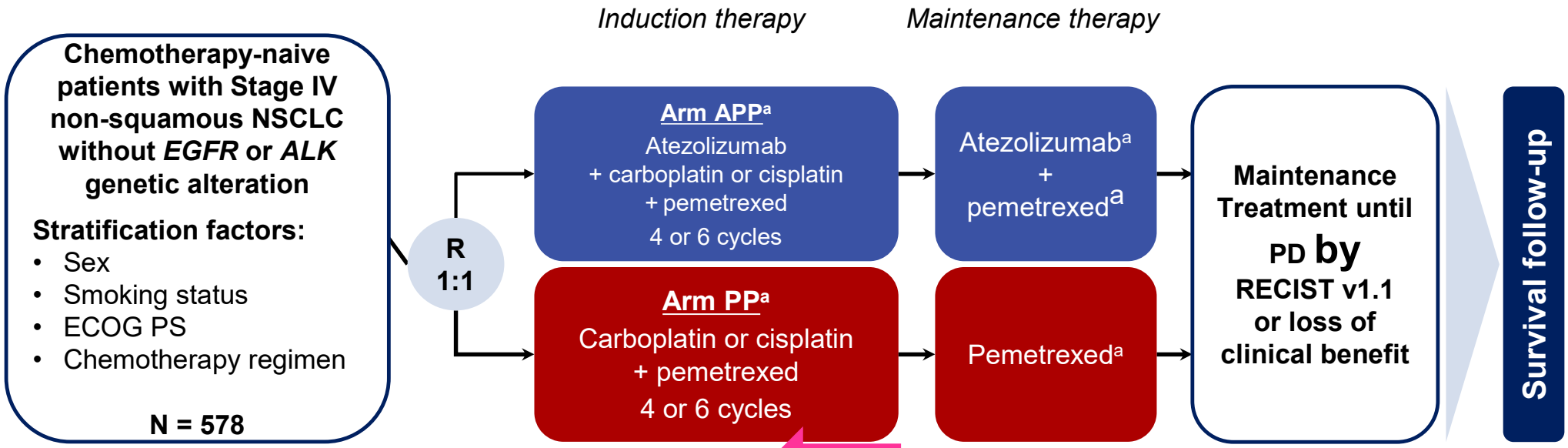


OS (%)	1 year	2 years
Atezo + CnP	62.7%	39.3%
CnP	55.1%	29.9%



Cappuzzo F, et al. IMpower130. ESMO 2018 [Abstract LBA53].

IMpower132: PFS and Safety Results with 1L Atezolizumab + Carboplatin/Cisplatin + Pemetrexed in Stage IV Non-Squamous NSCLC



- 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)

DOR, duration of response; INV, investigator; R, randomization; ORR, objective response rate; OS, overall survival; PD, progressive disease, PFS, progression-free survival; 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

Vassiliki A. Papadimitrakopoulou

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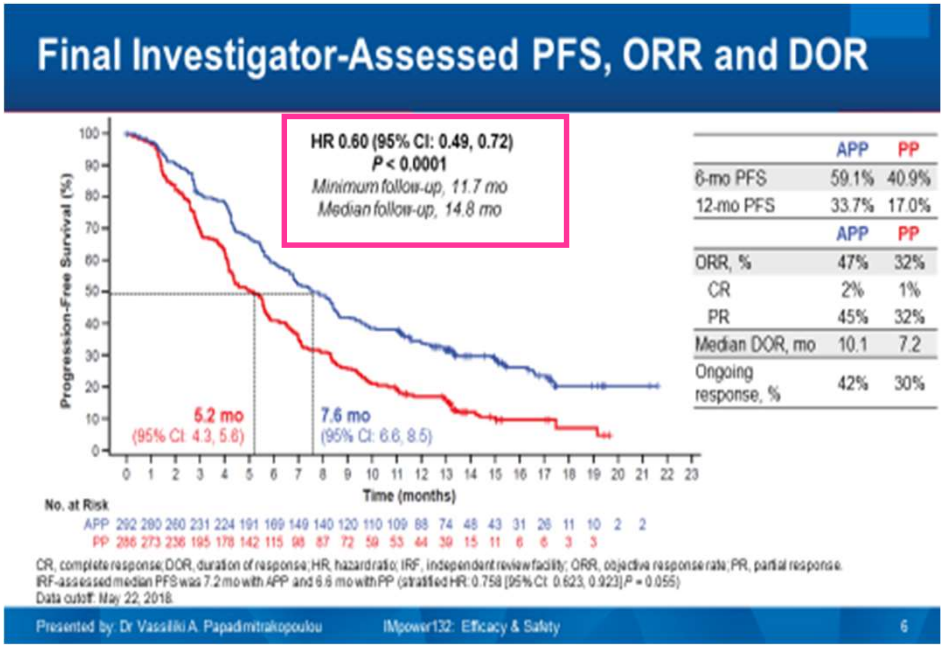
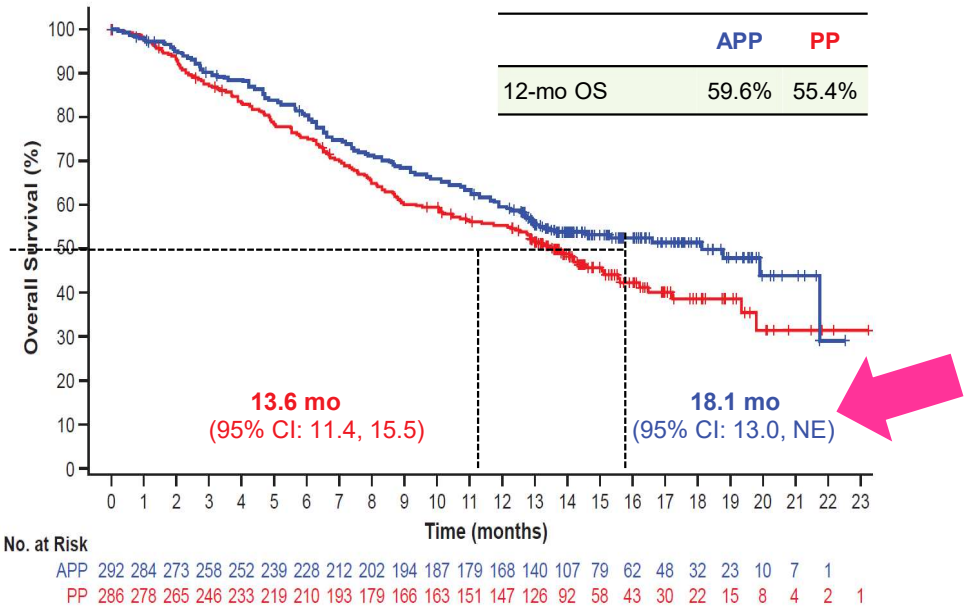


Vassiliki A. Papadimitrakopoulou



HR: 0.81 (95% CI: 0.64, 1.03)
***P* = 0.0797**
Minimum follow-up: 11.7 mo
Median follow-up: 14.8 mo

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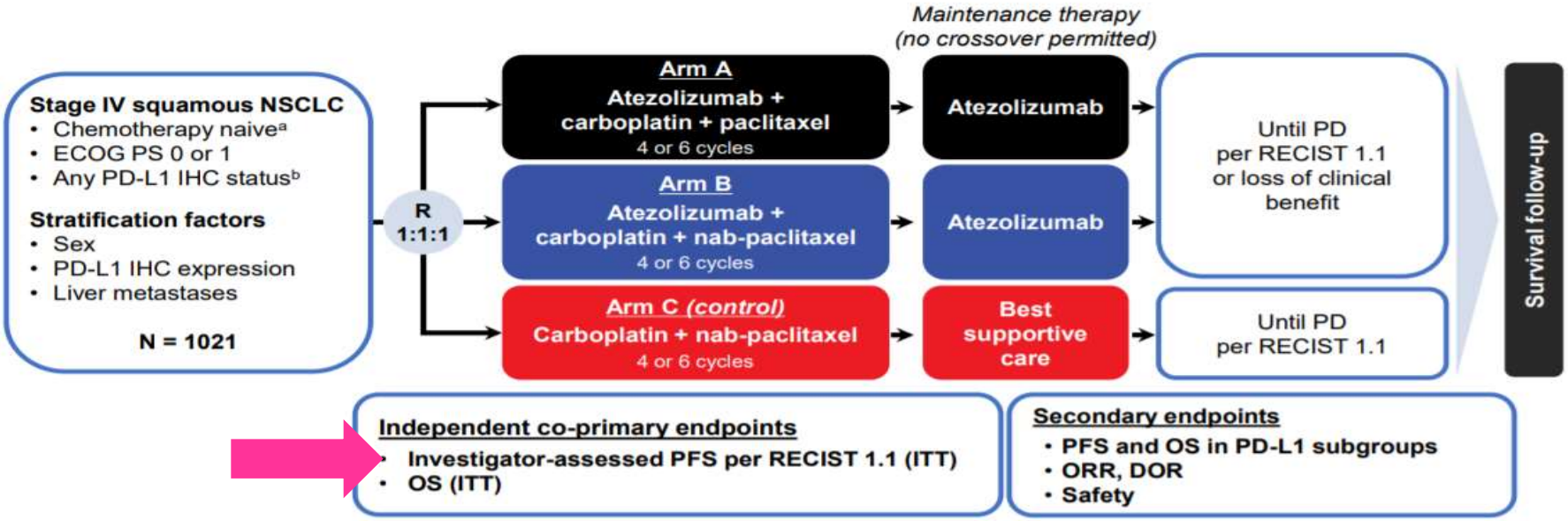
IMpower131: study design



Atezolizumab 1200 mg IV q3w; carboplatin AUC 6 IV q3w; nab-paclitaxel 100 mg/m² IV qw; paclitaxel 200 mg/m² (175 mg/m² in Asian patients) IV q3w.
[a] Patients with a sensitising *EGFR* mutation or *ALK* translocation must have disease progression or intolerance to treatment with ≥ 1 approved targeted therapies. Testing for *EGFR* mutation or *ALK* translocation was not mandatory. [b] PD-L1 expression was evaluated using the VENTANA SP142 IHC assay.

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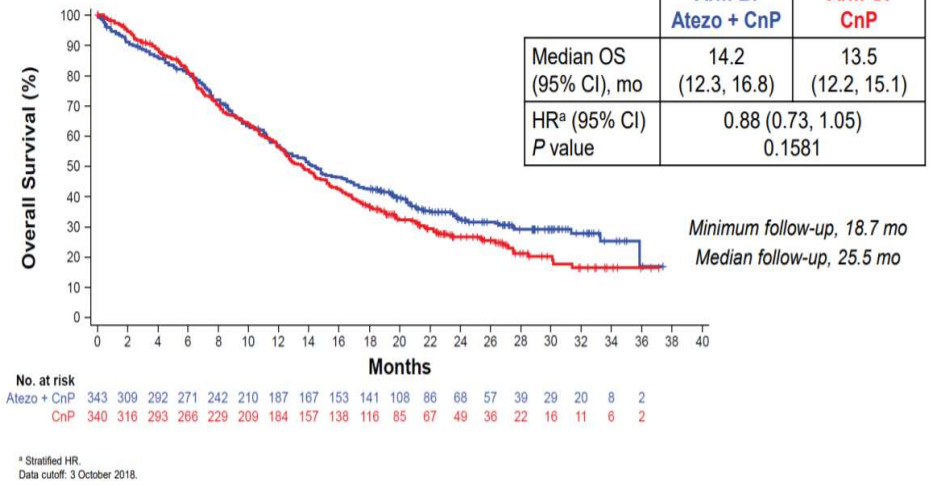
Final OS in the ITT population (Arm B vs Arm C)

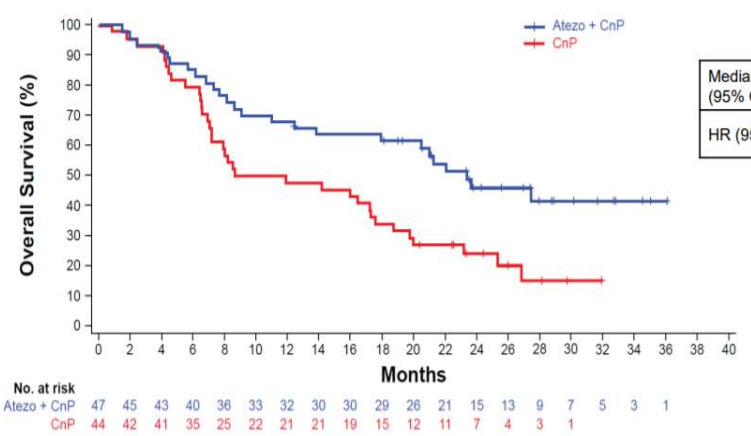


	Arm B: Atezo + CnP	Arm C: CnP
Median OS (95% CI), mo	14.2 (12.3, 16.8)	13.5 (12.2, 15.1)
HR[a] (95% CI) *P* value	0.88 (0.73, 1.05) 0.1581	

Minimum follow-up, 18.7 mo
Median follow-up, 25.5 mo

[a] Stratified HR.
Data cutoff: 3 October 2018.

Final OS in PD-L1 High (TC3 or IC3) (Arm B vs Arm C)



	Arm B: Atezo + CnP (n = 47)	Arm C: CnP (n = 44)
Median OS (95% CI), mo	23.4 (17.8, NE)	10.2 (7.1,17.5)
HR (95% CI)	0.48 (0.29, 0.81)	

Data cutoff: 3 October 2018.

For Squamous NSCLC

IMpower131 was a positive study that met its PFS independent co-primary endpoint

Meaningful survival difference was observed in patients with strongly PD-L1–positive tumours suggesting that they may benefit from combining carboplatin and nab-paclitaxel with atezolizumab

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BARCELONA 2019 ESMO congress

Nivolumab + Low-Dose Ipilimumab Versus Platinum-Doublet Chemotherapy as First-Line Treatment for Advanced Non-Small Cell Lung Cancer: CheckMate 227 Part 1 Final Analysis

Solange Peters,[1] Suresh Ramalingam,[2] Luis Paz-Ares,[3] Reyes Bernabe Caro,[4] Bogdan Zurawski,[5] Sang-We Kim,[6] Aurelia Alexandru,[7] Lorena Lupinacci,[8] Emmanuel de la Mora Jimenez,[9] Hiroshi Sakai,[10] István Albert,[11] Alain Vergnenegre,[12] Martin Reck,[13] Hossein Borghaei,[14] Julie R. Brahmer,[15] Kenneth O'Byrne,[16] William J. Geese,[17] Prabhu Bhagavatheeswaran,[17] Faith E. Nathan,[17] Matthew D. Hellmann[18]

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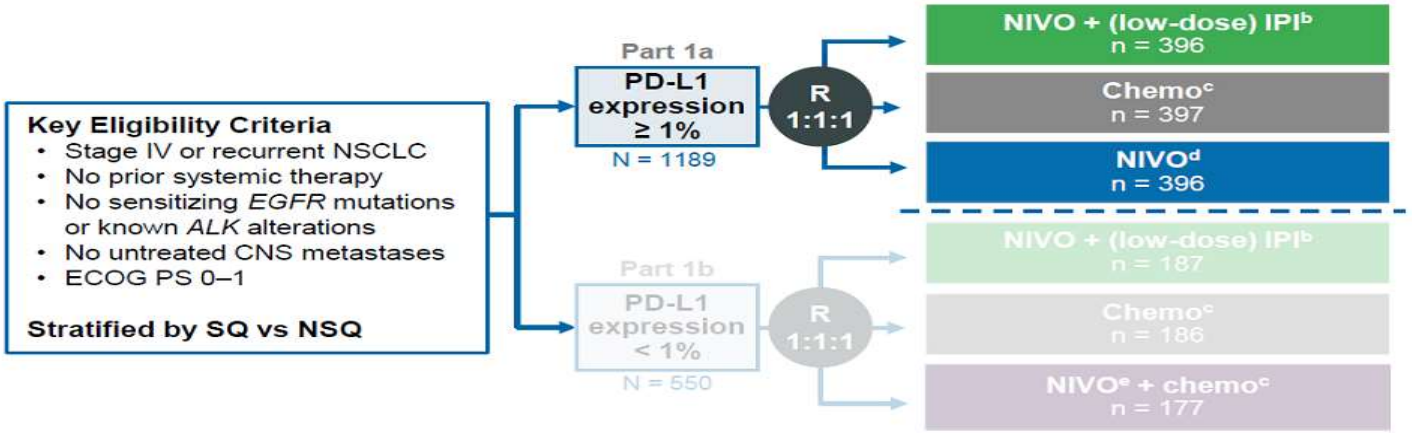
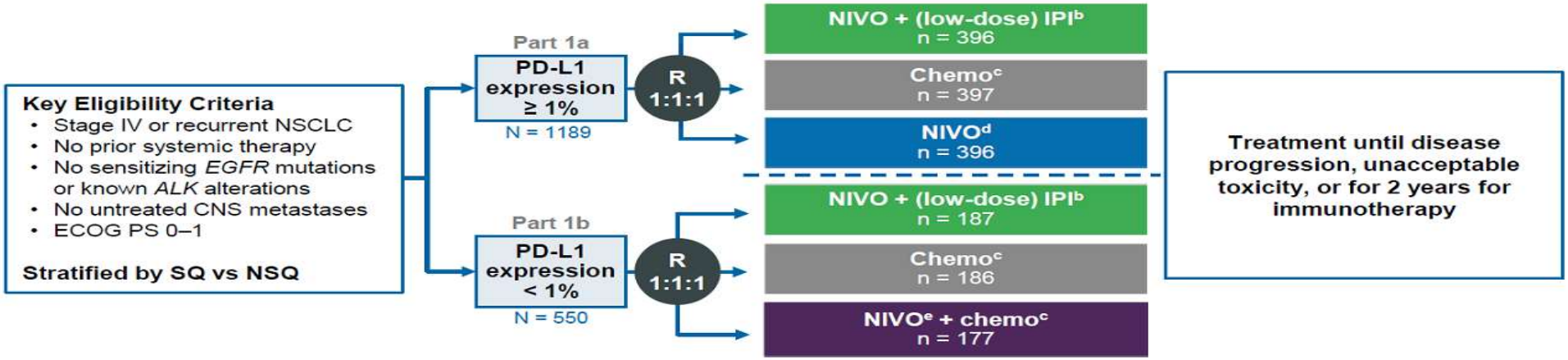
CheckMate 227 Part 1 Study Design[a]



Database lock: July 2, 2019; minimum follow-up for primary endpoint: 29.3 months

[a]NCT02477826; [b]NIVO (3 mg/kg Q2W) + IPI (1 mg/kg Q6W); [c]**NSQ:** pemetrexed + cisplatin or carboplatin, Q3W for ≤ 4 cycles, with optional pemetrexed maintenance following chemo or NIVO + pemetrexed maintenance following NIVO + chemo; **SQ:** gemcitabine + cisplatin, or gemcitabine + carboplatin, Q3W for ≤ 4 cycles; [d]NIVO (240 mg Q2W); [e]NIVO (360 mg Q3W); [f]TMB primary endpoint analysis conducted at January 24, 2018 database lock in subset of patients randomized to NIVO + IPI or chemo; alpha allocated was 0.025; [g]Alpha allocated was 0.025 overall (0.023 for final analysis)

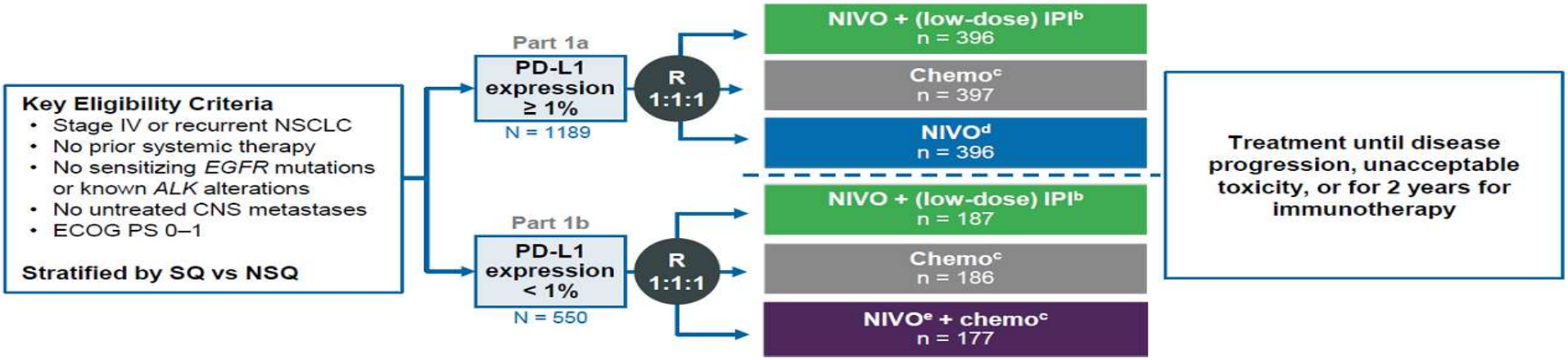
CheckMate 227 Part 1 Study Design[a]



Database lock: July 2, 2019; minimum follow-up for primary endpoint: 29.3 months

[a]NCT02477826; [b]NIVO (3 mg/kg Q2W) + IPI (1 mg/kg Q6W); [c]**NSQ:** pemetrexed + cisplatin or carboplatin, Q3W for ≤ 4 cycles, with optional pemetrexed maintenance following chemo or NIVO + pemetrexed maintenance following NIVO + chemo; **SQ:** gemcitabine + cisplatin, or gemcitabine + carboplatin, Q3W for ≤ 4 cycles; [d]NIVO (240 mg Q2W); [e]NIVO (360 mg Q3W); [f]TMB primary endpoint analysis conducted at January 24, 2018 database lock in subset of patients randomized to NIVO + IPI or chemo; alpha allocated was 0.025; [g]Alpha allocated was 0.025 overall (0.023 for final analysis)

CheckMate 227 Part 1 Study Design[a]



Independent co-primary endpoints: NIVO + IPI vs chemo
- PFS in high TMB (≥10 mut/Mb) population[f]
- OS in PD-L1 ≥ 1% population[g]

Secondary endpoints (PD-L1 hierarchy):
- PFS: **NIVO + chemo vs chemo** in PD-L1 < 1%
- OS: **NIVO + chemo vs chemo** in PD-L1 < 1%
- OS: **NIVO vs chemo** in PD-L1 ≥ 50%

Database lock: July 2, 2019; **minimum follow-up for primary endpoint: 29.3 months**

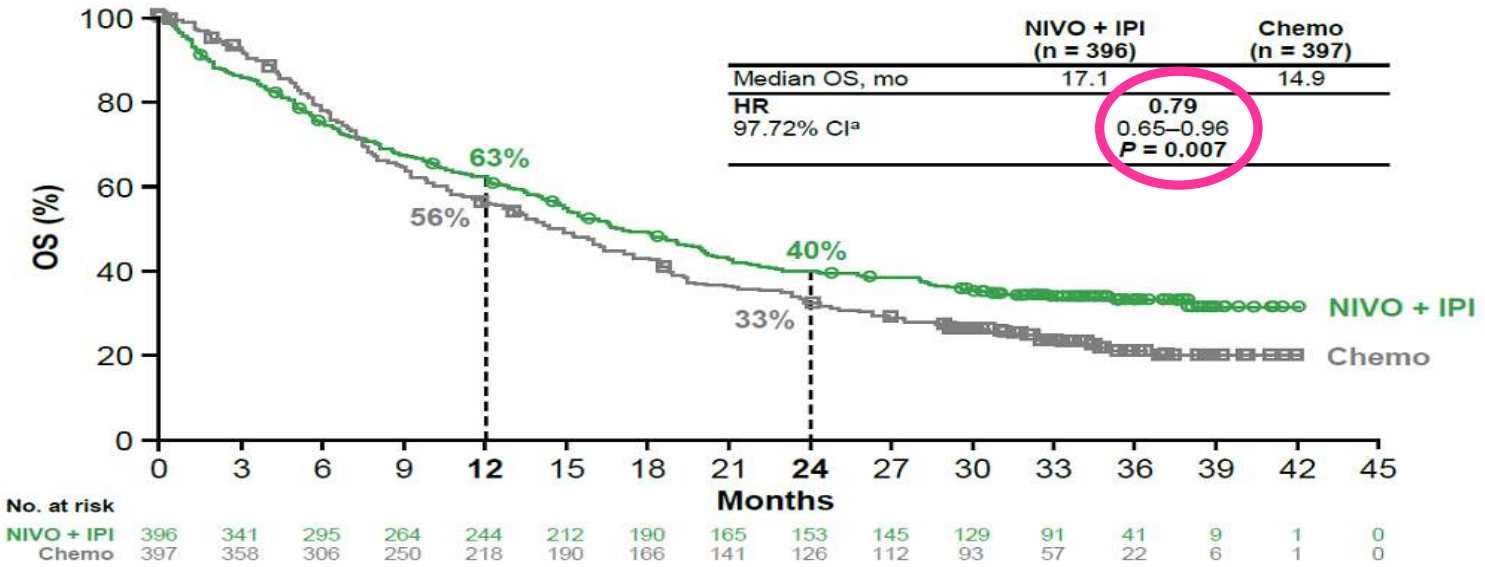
[a]NCT02477826; [b]NIVO (3 mg/kg Q2W) + IPI (1 mg/kg Q6W); [c]**NSQ:** pemetrexed + cisplatin or carboplatin, Q3W for ≤ 4 cycles, with optional pemetrexed maintenance following chemo or NIVO + pemetrexed maintenance following NIVO + chemo; **SQ:** gemcitabine + cisplatin, or gemcitabine + carboplatin, Q3W for ≤ 4 cycles; [d]NIVO (240 mg Q2W); [e]NIVO (360 mg Q3W); [f]TMB primary endpoint analysis conducted at January 24, 2018 database lock in subset of patients randomized to NIVO + IPI or chemo; alpha allocated was 0.025; [g]Alpha allocated was 0.025 overall (0.023 for final analysis)

CheckMate 227 Part 1: NIVO + IPI in 1L NSCLC

Primary Endpoint: OS With NIVO + IPI vs Chemo in Patients With Tumor PD-L1 Expression ≥ 1%

Part 1a
NIVO + IPI
Chemo
NIVO

Study!!



	NIVO + IPI (n = 396)	Chemo (n = 397)
Median OS, mo	17.1	14.9
HR 97.72% CI[a]	0.79 0.65–0.96 *P* = 0.007	

Minimum follow-up for primary endpoint: 29.3 months.
NIVO + IPI dosage was NIVO (3 mg/kg Q2W) + IPI (1 mg/kg Q6W). Subsequent systemic therapy was received by 35% of patients in the NIVO + IPI arm and 54% of patients in the chemo arm; subsequent immunotherapy was received by 6% and 43%, respectively.
[a]95% CI, 0.67–0.94.

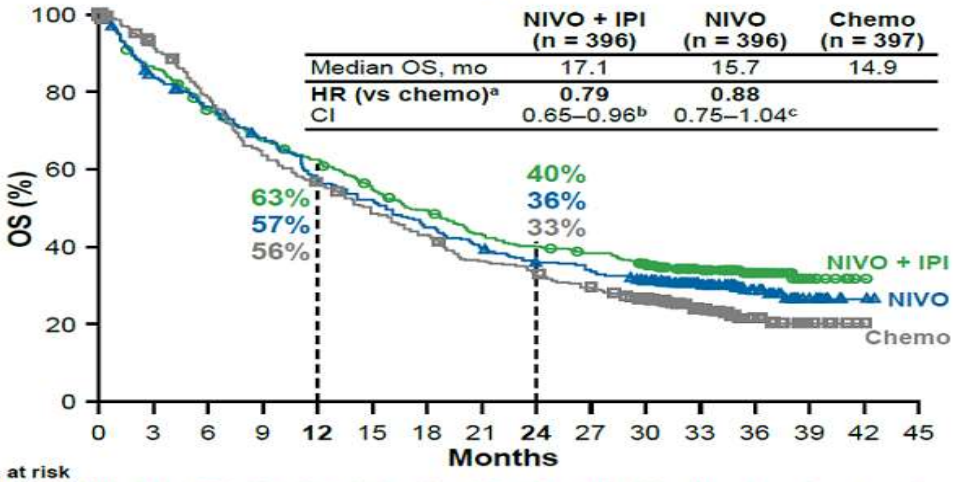
CheckMate 227 Part 1: NIVO + IPI in 1L NSCLC

OS and PFS With NIVO + IPI vs NIVO vs Chemo in Patients With Tumor PD-L1 Expression ≥ 1%

Part 1a
NIVO + IPI
Chemo
NIVO

OS

	NIVO + IPI (n = 396)	NIVO (n = 396)	Chemo (n = 397)
Median OS, mo	17.1	15.7	14.9
HR (vs chemo)[a]	0.79	0.88	
CI	0.65–0.96[b]	0.75–1.04[c]	

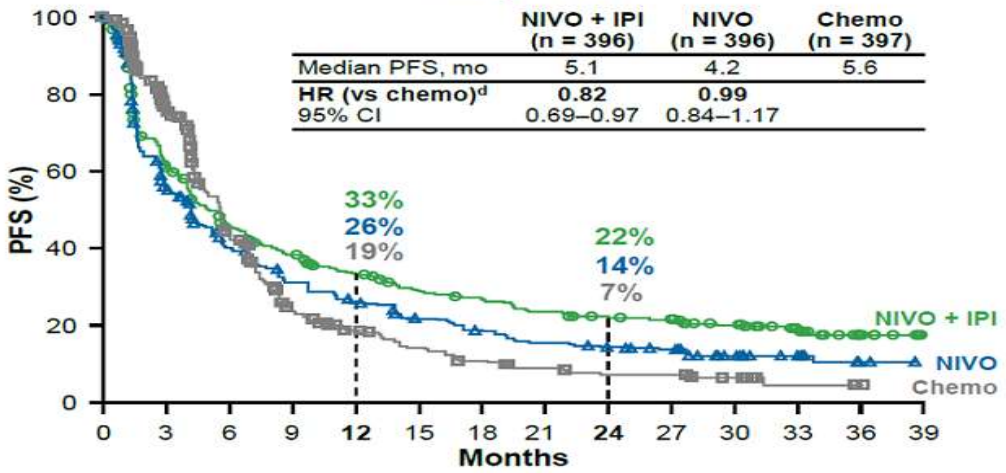


No. at risk

NIVO + IPI	396	341	295	264	244	212	190	165	153	145	129	91	41	9	1	0
NIVO	396	330	299	265	220	201	176	153	139	129	115	70	36	10	2	0
Chemo	397	358	306	250	218	190	166	141	126	112	93	57	22	6	1	0

PFS by BICR

	NIVO + IPI (n = 396)	NIVO (n = 396)	Chemo (n = 397)
Median PFS, mo	5.1	4.2	5.6
HR (vs chemo)[d]	0.82	0.99	
95% CI	0.69–0.97	0.84–1.17	



	396	221	158	130	108	91	83	73	65	62	47	31	7	0	
	396	199	136	104	85	68	56	47	42	37	24	15	3	0	
	397	253	130	63	44	32	23	17	12	12	8	2	1	0	

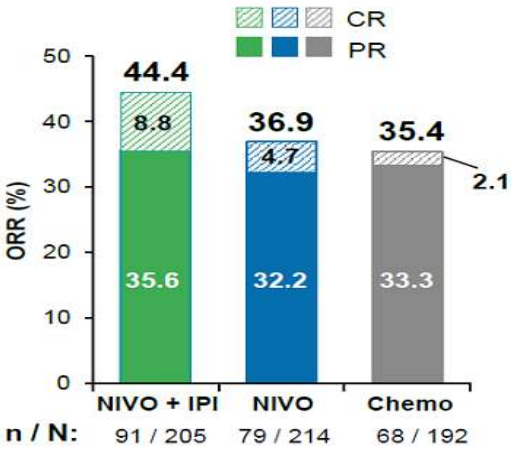
Dosages were NIVO (3 mg/kg Q2W) + IPI (1 mg/kg Q6W), and NIVO (240 mg Q2W). Subsequent systemic therapy was received by 35% of patients in the NIVO + IPI arm, 44% of patients in the NIVO arm, and 54% of patients in the chemo arm; subsequent immunotherapy was received by 6%, 8%, and 43%, respectively.
[a]HR (95% CI) for NIVO + IPI vs NIVO, 0.90 (0.76–1.07); [b]97.72% CI; [c]95% CI; [d]HR (95% CI) for NIVO + IPI vs NIVO, 0.83 (0.71–0.97).

CheckMate 227 Part 1: NIVO + IPI in 1L NSCLC

Efficacy With NIVO + IPI and NIVO vs Chemo in Patients With Tumor PD-L1 Expression ≥ 50%

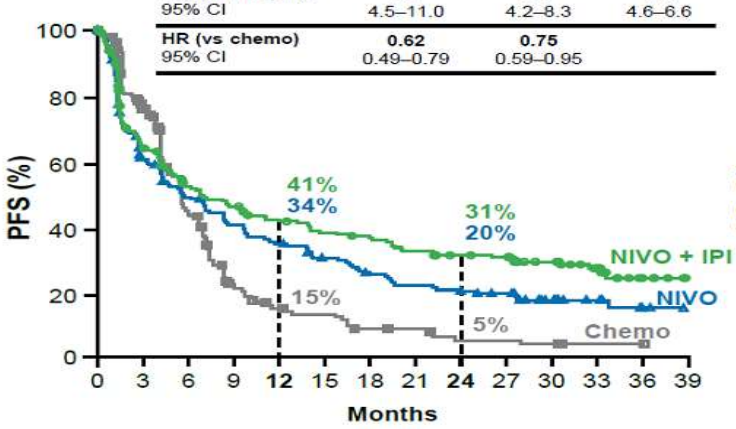
Part 1a
NIVO + IPI
Chemo
NIVO

ORR by BICR



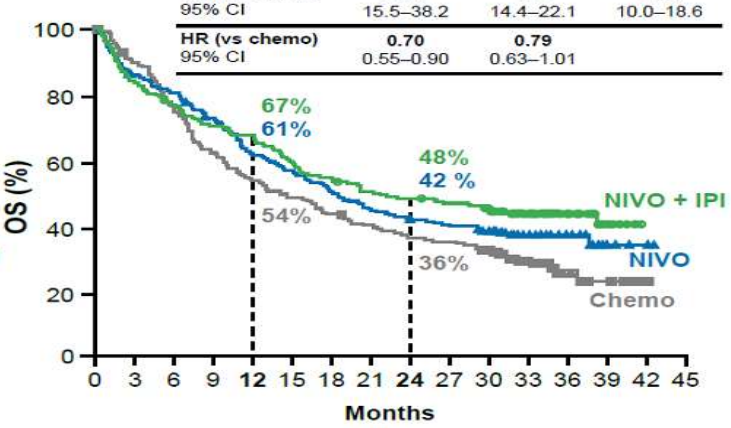
PFS by BICR

	NIVO + IPI (n = 205)	NIVO (n = 214)	Chemo (n = 192)
Median PFS, mo 95% CI	6.7 4.5–11.0	5.6 4.2–8.3	5.6 4.6–6.6
HR (vs chemo) 95% CI	**0.62** 0.49–0.79	**0.75** 0.59–0.95	



OS

	NIVO + IPI (n = 205)	NIVO (n = 214)	Chemo (n = 192)
Median OS, mo 95% CI	21.2 15.5–38.2	18.1 14.4–22.1	14.0 10.0–18.6
HR (vs chemo) 95% CI	**0.70** 0.55–0.90	**0.79** 0.63–1.01	



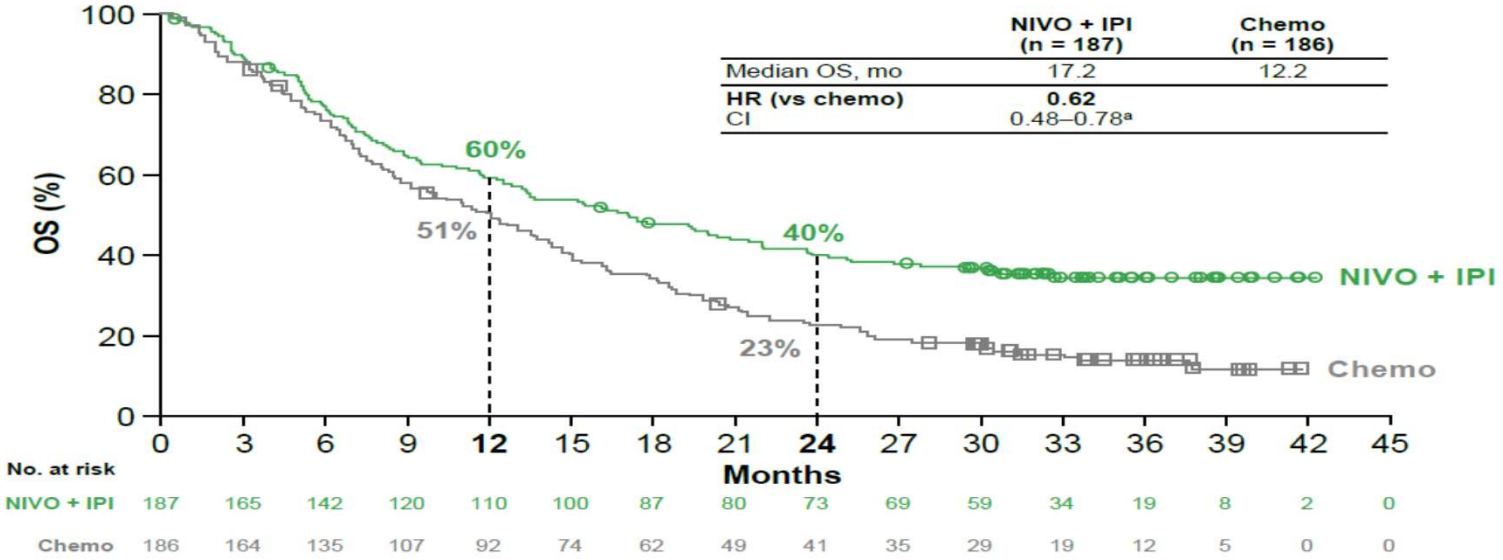
- Median DOR with NIVO + IPI, NIVO and chemo was 31.8, 17.5 and 5.8 months, respectively

Dosages were NIVO (3 mg/kg Q2W) plus IPI (1 mg/kg Q6W), and NIVO (360 mg Q3W) plus chemo.

CheckMate 227 Part 1: NIVO + IPI in 1L NSCLC

OS With NIVO + IPI vs Chemo in Patients With Tumor PD-L1 Expression < 1%

Part 1b
NIVO + IPI
Chemo
NIVO + chemo



	NIVO + IPI (n = 187)	Chemo (n = 186)
Median OS, mo	17.2	12.2
HR (vs chemo)	**0.62**	
CI	0.48–0.78[a]	

No. at risk																
NIVO + IPI	187	165	142	120	110	100	87	80	73	69	59	34	19	8	2	0
Chemo	186	164	135	107	92	74	62	49	41	35	29	19	12	5	0	0

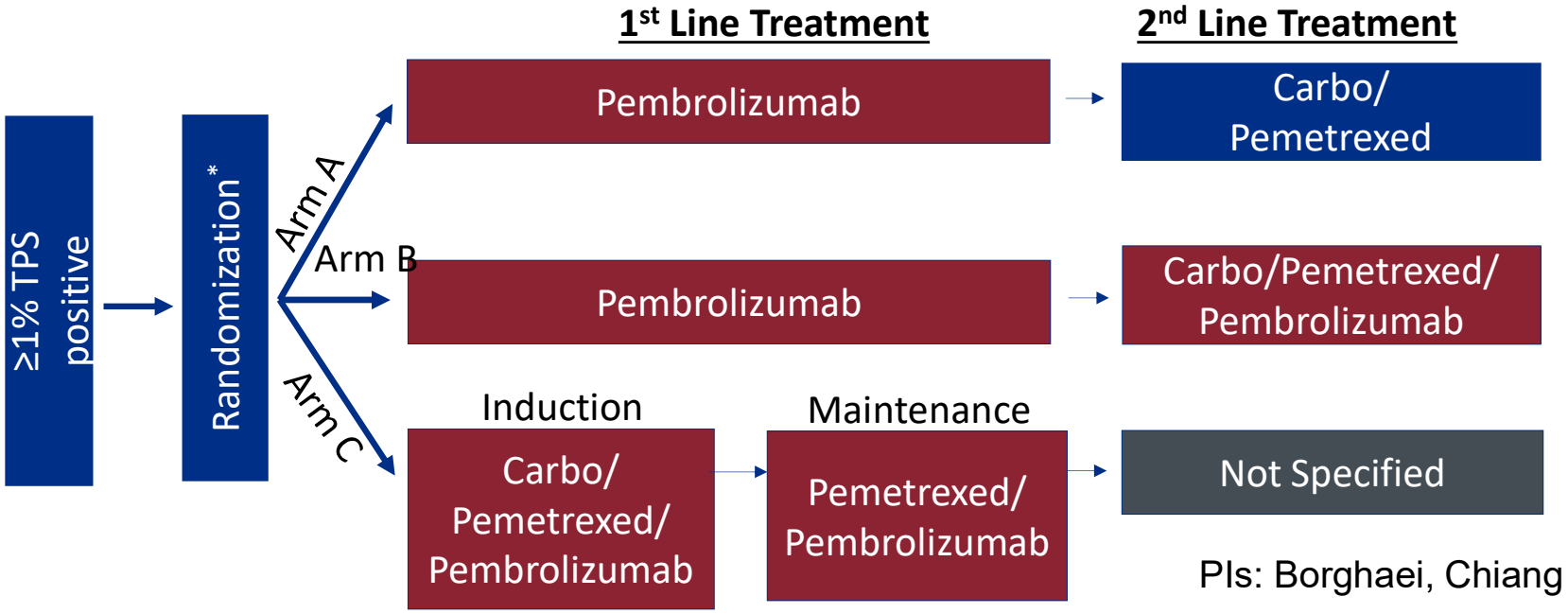
Dosages were NIVO (3 mg/kg Q2W) + IPI (1 mg/kg Q6W), and NIVO (360 mg Q3W) plus chemo. Subsequent systemic therapy was received by 44% of patients in the NIVO + IPI arm, 41% of patients in the NIVO + chemo arm, and 53% of patients in the chemo arm; subsequent immunotherapy was received by 4%, 4%, and 36%, respectively.
[a]95% CI.

Summary: NIVO + IPI in First-Line NSCLC

- CheckMate 227 met its primary endpoint of OS in patients with PD-L1 ≥ 1%
  - First phase 3 study to show PD-1 and CTLA-4 inhibition is effective in NSCLC
- Clinically meaningful OS improvement vs chemo was observed regardless of PD-L1 expression, with deep and durable responses
- Addition of IPI to NIVO improved outcomes
  - vs NIVO monotherapy in PD-L1 ≥ 1%
  - vs NIVO + chemo in PD-L1 < 1%
- No new safety signals were observed for NIVO + low-dose IPI
- This dual immunotherapy represents a potential new first-line treatment option for patients with advanced NSCLC

What's Ongoing?

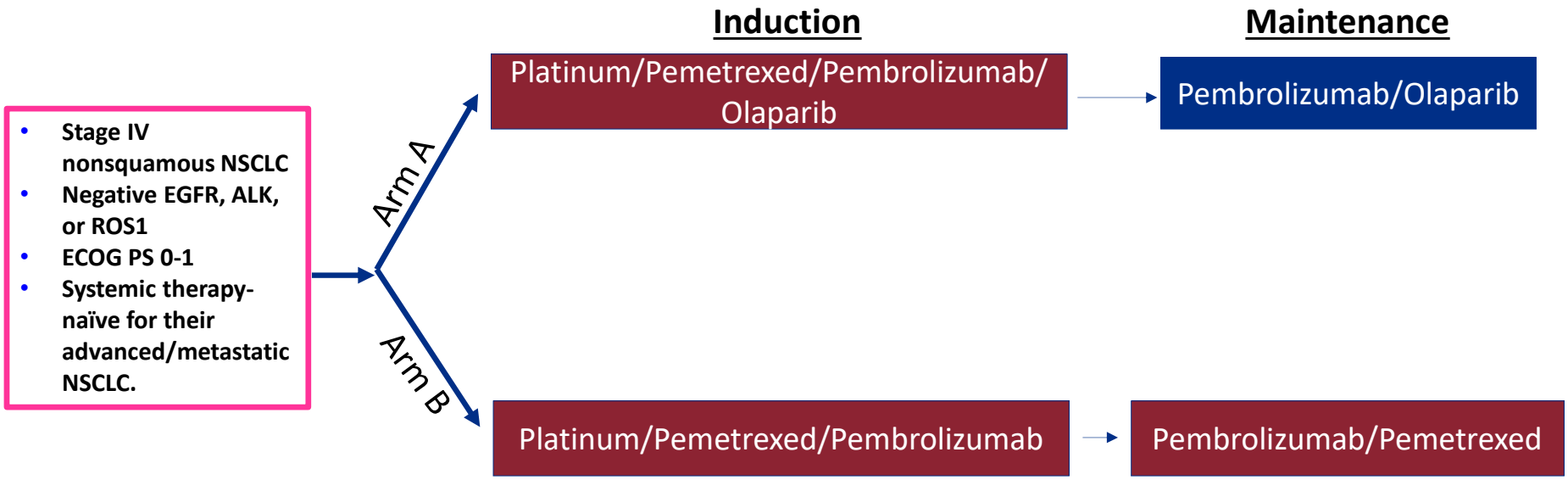
ECOG 5163/SWOG1709



PIs: Borghaei, Chiang

As consequence of KN-42 results

KEYLYNK-006



To improve over KN-189 results

Conclusions

- Expect changes in the next version of the NCCN
- NIVO + IPI works in pts with NSCLC regardless of PD-L1 expression over chemotherapy.
- Anti-PD-1 monotherapy still is not approved for patients with PD-L1 <1% (no expression).
- Some trials will challenge or define better what should be the best frontline therapy for patients with PD-L1 ≥ 1%.
- Other trials will try to improve outcomes over strong platforms such as KN-24, KN-189 and KN-407 bringing other agents with different mechanism of actions (e.g., PARP, VEGF inhibitors, etc)
- IMpower-150 remains as the only data using IO in patients whose tumors harbor EGFR and ALK alterations.

And yet still not change standard of Care in the adj-setting?

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Background…. ADJUVANT SETTING

Role of ADJ-CTX for pathological stage I NSCLC is controversial.

Approximately 10-15% of newly dx NSCLC will be classified as Stage IIIA-N2 disease.

Concurrent chemoradiotherapy (CCRT) w/wo surgery has been the most recent management trend for LA-NSCLC.

Pts w invasive component size > 2cm, lymphatic permeation, vascular invasion or VPI are at high risk for recurrence in p-stage I NSCLC. (Tsutani Y et al, ASCO 2019)

AC may improve survival in pts with high-risk p-stage I NSCLC. (Tsutani Y et al, ASCO 2019)

Adjuvant chemotherapy for pathological stage I non-small cell lung cancer with high-risk factors for recurrence: A multicenter study.

Yasuhiro Tsutani[1], Kentaro Imai[2], Hiroyuki Ito[3], Takahiro Mimae[1], Yoshihiro Miyata[1], Norihiko Ikeda[2], Haruhiko Nakayama[3], Morihito Okada[1]

[1]Department of Surgical Oncology, Hiroshima University, Hiroshima, Japan
[2]Department of Thoracic Surgery, Tokyo Medical University, Tokyo, Japan
[3]Department of Thoracic Surgery, Kanagawa Cancer Center, Yokohama, Japan

PRESENTED AT: 2019 ASCO ANNUAL MEETING #ASCO19

PRESENTED BY: Tsutani Y.

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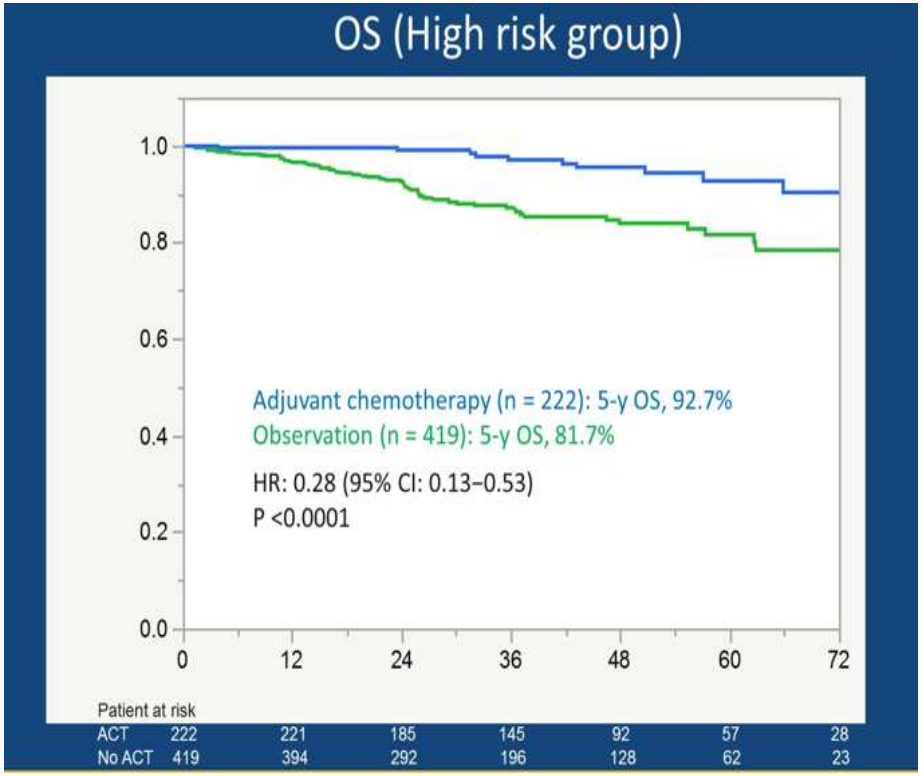
Multivariable Cox analysis (High-risk group)

	RFS			OS			CSS		
Variables	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value
Age (>70 y)	1.70	1.15–2.55	0.008	2.72	1.53–5.11	0.0005	1.16	0.56–2.48	0.7
Gender (Female)	0.82	0.53–1.24	0.34	0.63	0.33–1.14	0.13	0.99	0.43–2.14	0.97
Invasive component size (>2 cm)	1.33	0.89–2.05	0.17	1.41	0.80–2.60	0.24	1.72	0.79–4.17	0.18
Histology (Adenocarcinoma)	0.93	0.61–1.42	0.74	0.63	0.37–1.08	0.09	0.56	0.26–1.19	0.13
Lymphatic permeation	1.54	1.06–2.25	0.025	1.20	0.70–2.00	0.50	1.66	0.82–3.36	0.16
Vascular invasion	2.27	1.51–3.49	< 0.001	2.11	1.23–3.71	0.006	3.46	1.52–8.95	0.003
Visceral pleural invasion	1.89	1.28–2.79	0.001	1.54	0.90–2.60	0.11	2.75	1.31–5.96	0.008
Adjuvant chemotherapy	**0.57**	**0.36–0.87**	**0.008**	**0.31**	**0.15–0.59**	**0.0002**	**0.27**	**0.10-0.63**	**0.002**



AC is an independent prognostic factor in high-risk p stage I NSCLC.

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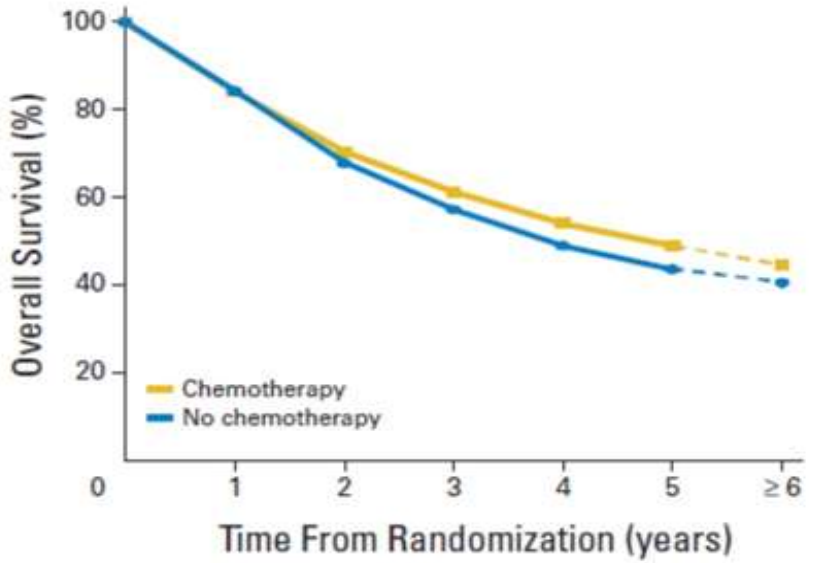
What Have ADJUVANT Chemotherapy (AC) Provide Us Thus Far?

OS benefit from adjuvant cisplatin based chemotherapy in resectable NSCLC: Meta-analysis from LACE Collaborative Group



Deaths / person years by period	Years 0-3	Years 4-5	Years ≥ 6
Control	966 / 5,155	239 / 1,668	49 / 720
Chemotherapy	857 / 5,181	203 / 1,817	76 / 790

Methods

- LACE Collaborative Group
- Data from 5 largest trials (4,584 patients; 2,281 in chemotherapy arm) of adjuvant cisplatin-based chemotherapy
- Completely resected NSCLC (Stages IA-III)

Results

- Median follow-up: 5.2 years
- Overall HR of death was 0.89 (95% CI, 0.82 to 0.96; *P* = .005)
- 5-year OS benefit: 5.4% from adjuvant chemotherapy

AC

- Updated individual patient data of ADJ-Chemo trials from 1965+
- 34 trials - 8,447 patients
- OS HR 0.86 [0.81-0.92], p= <.0001
- **4% absolute OS benefit at 5 years**

Pignon JCO 26:3552, 2008; Lancet 375:1267, 2010

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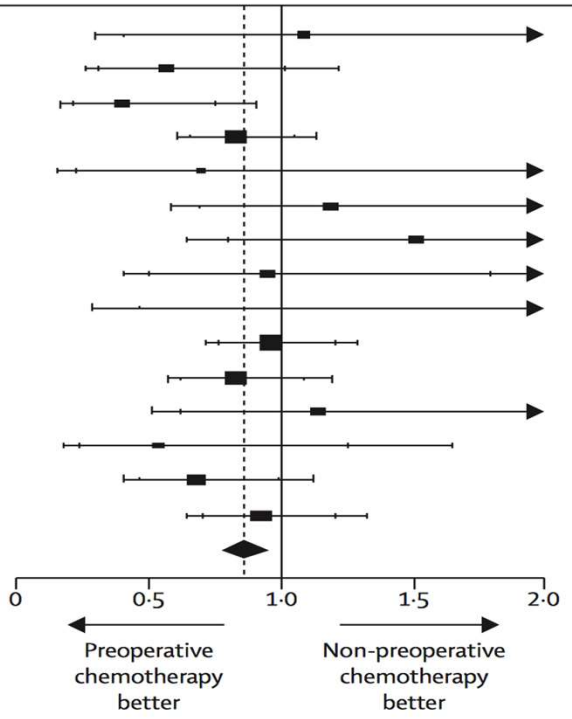
Neo-Adjuvant Chemotherapy (NAC) Meta-analysis

	Preoperative chemotherapy*	Control*	O–E	Variance	HR (95% CI); p value
France 1990	8/13	8/13	0·32	3·97	
MD Anderson 1994	19/28	27/32	−6·40	11·19	
Spain 1994	19/29	27/30	−8·88	9·65	
MIP-91	137/179	146/176	−12·99	70·22	
SWOG S9015	3/5	12/16	−1·04	2·94	
JCOG 9209	28/31	25/31	2·25	12·97	
Netherlands 2000	23/39	15/40	3·86	9·36	
Finland 2003	19/30	19/32	−0·50	9·48	
MRC BLT	4/5	3/5	1·26	1·60	
MRC LU22	151/258	158/261	−2·92	77·01	
SWOG S9900	93/180	103/174	−9·31	48·84	
China 2002	26/32	18/23	1·42	10·78	
China 2005	8/19	14/21	−3·31	5·44	
ChEST	45/129	61/141	−10·27	26·39	
NATCH	99/201	109/212	−4·11	51·95	
Total	**682/1178**	**745/1207**	**−50·62**	**351·78**	**0·87 (0·78–0·96); p=0·007**



Overall HR

0·87 (0·78–0·96). p=0·007 (fixed effect)

0·86 (0·75–0·98), p=0·03 (random effects)

Heterogeneity: χ^2=18·75, df=14, p=0·18, I^2=25%

Pre vs Post-Op Chemo Meta-analysis 2008

- 31 peri-op chemo trials (21 post-op)/ (10 pre-op)
- Used indirect comparison meta-analysis
- OS HR of post- vs pre-operative chemo: 0.99 [0.81-1.21, *P* = 0.9]
- DFS HR of post- vs pre-operative chemo: 0.96 [0.74-1.26, *P* = 0.77]

NAC or AC Seem equivalent; Adjuvant remains the Standard

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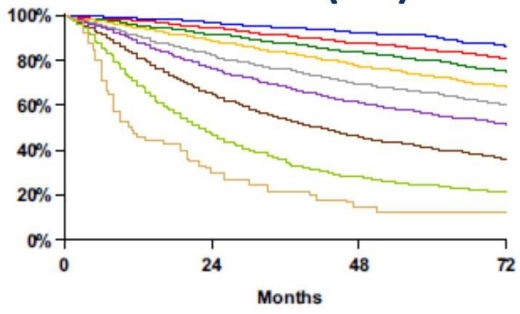
Overall survival (OS) of surgically resectable NSCLC (8th ed. TNM)



Proposed	Events / N	MST	24 Month	60 Month
IA1	139 / 1389	NR	97%	90%
IA2	823 / 5633	NR	94%	85%
IA3	875 / 4401	NR	92%	80%
IB	1618 / 6095	NR	89%	73%
IIA	556 / 1638	NR	82%	65%
IIB	2175 / 5226	NR	76%	56%
IIIA	3219 / 5756	41.9	65%	41%
IIIB	1215 / 1729	22.0	47%	24%
IIIC	55 / 69	11.0	30%	12%

- Resectable NSCLC: Stage I-IIIA and selected IIIB
- Significant drop in OS for stages IB-IIIB
- Need for better perioperative therapies

Even these early stage NSCLC need to be addressed; at 5 years, 10-20% pts have deceased.

Where Are We with AC?

Overall Survival as Primary Endpoint in Perioperative NSCLC trials

Study	Treatment	Time from enrollment to publication of data
IALT	Adjuvant therapy	9 years
JBR.10	Adjuvant therapy	11 years
ANITA	Adjuvant therapy	12 years
CALBG 9633	Adjuvant therapy	12 years
NATCH	Neoadjuvant vs adjuvant therapy	10 years
GLCCG	Neoadjuvant chemotherapy vs chemoradiation	13 years

Slow progress in clinical trials for stage I-IIIA NSCLC where OS is the primary endpoint

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How Can We Improve?

Any Role for Immune-Oncology (IO) Adjuvant Therapy?

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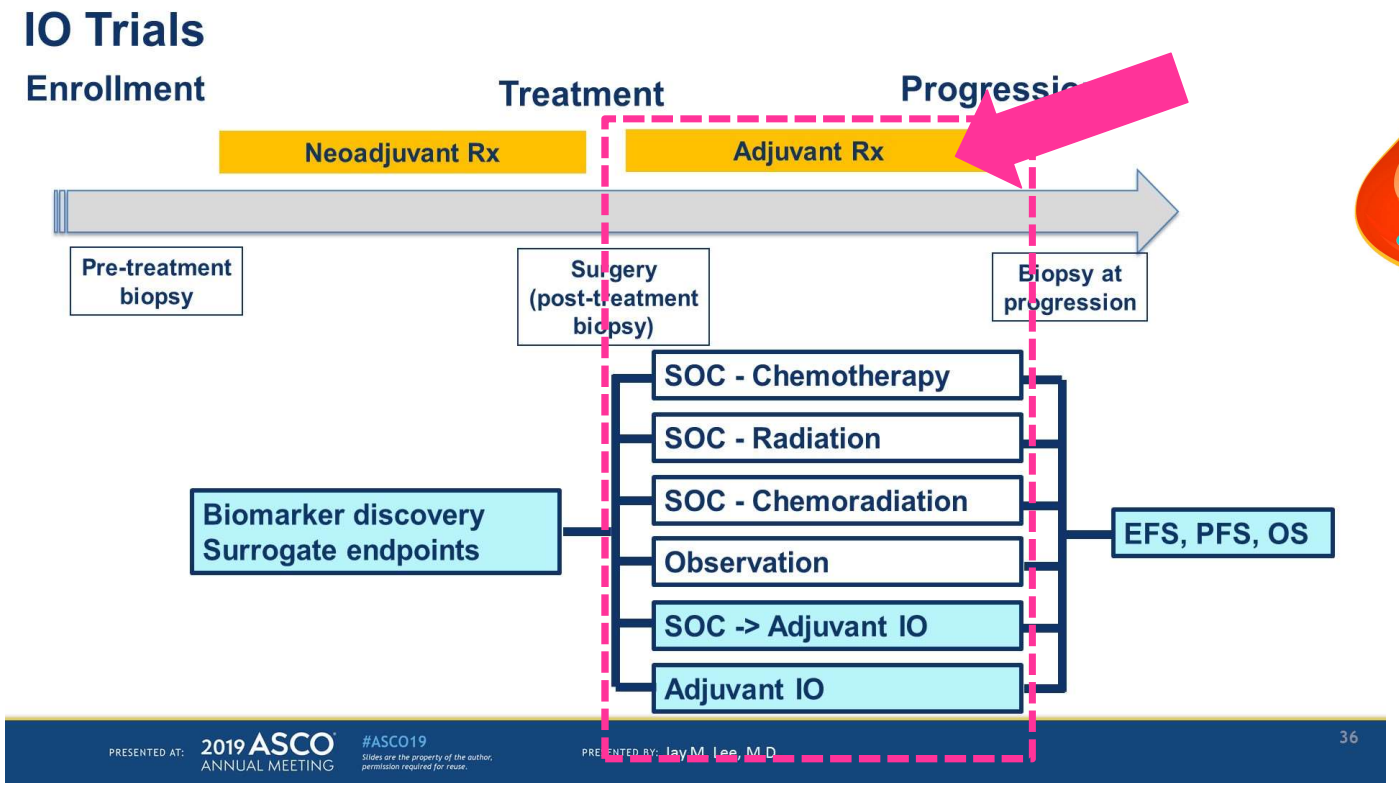

Ongoing Adjuvant Trials With Checkpoint Inhibitors (CPI)

Drug/Trial	N	Stages Entered	Description	Primary Endpoint
ALCHEMIST/ANVIL -> NIVOLUMAB	900	IB (4cm) – IIIA after AC and/or RT	Phase 3 Allows PD-L1 +/-	OS/DFS
IMpower010 ->ATEZOLIZUMAB	1280	IB (4cm) – IIIA after AC	Phase 3 Allows PD-L1 +/-	DFS
MEDI4736 -> DURVALUMAB	1360	IB (4cm) – IIIA after AC	Phase 3 Allows PD-L1 +/-	DFS
KEYNOTE-091 -> Pembrolizumab	1080	IB (4cm) – IIIA after AC	Phase 3 Allows PD-L1 +/-	DFS

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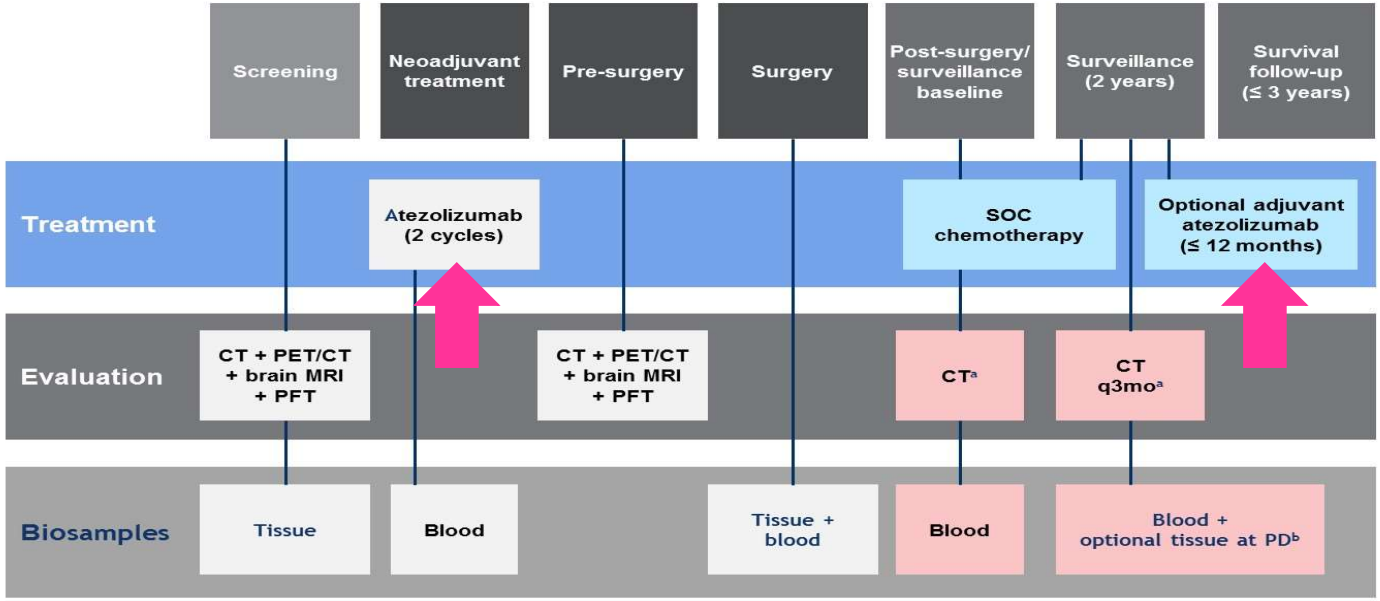
LCMC3 Study Design



Primary endpoint:

- MPR at surgical resection, defined as ≤ 10% viable tumor cells

Secondary endpoints:

- Disease-free survival
- Response rate by RECIST 1.1
- OS
- Biomarkers
- Adverse events

MPR, major pathologic response, locally assessed; PFT, pulmonary function test; q3mo, every 3 months.
[a] Extended chest CT, including liver and adrenals. [b] At progression and/or recurrence. NCT02927301.

Lee JM, ASCO 2019; Courtesy of David Kwiatkowski

Successful Story of Adjuvant IO Therapy in Other Solid Tumors

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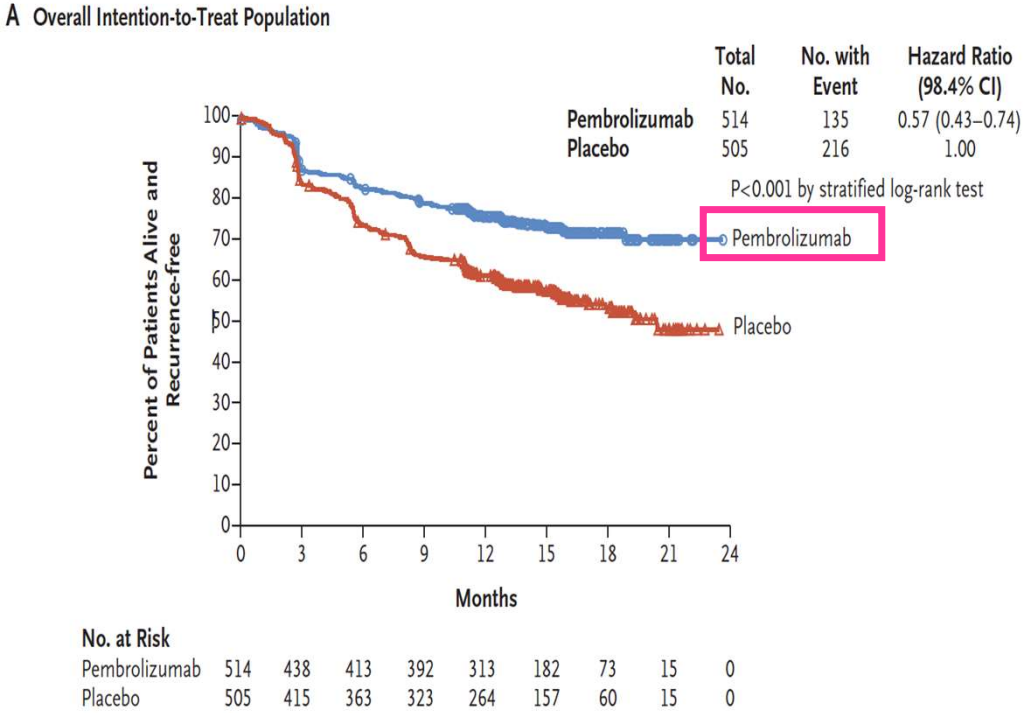
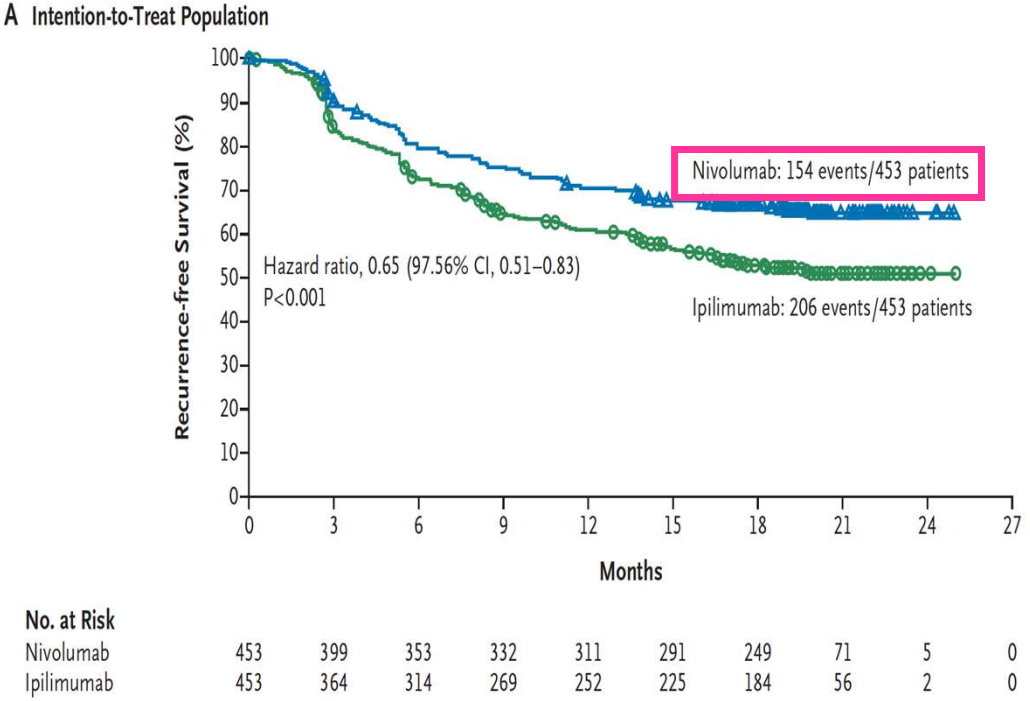
Adjuvant PD-1 Inhibitors Improves RFS…..in Melanoma





Eggermont NEJM 2018, Weber NEJM 2017

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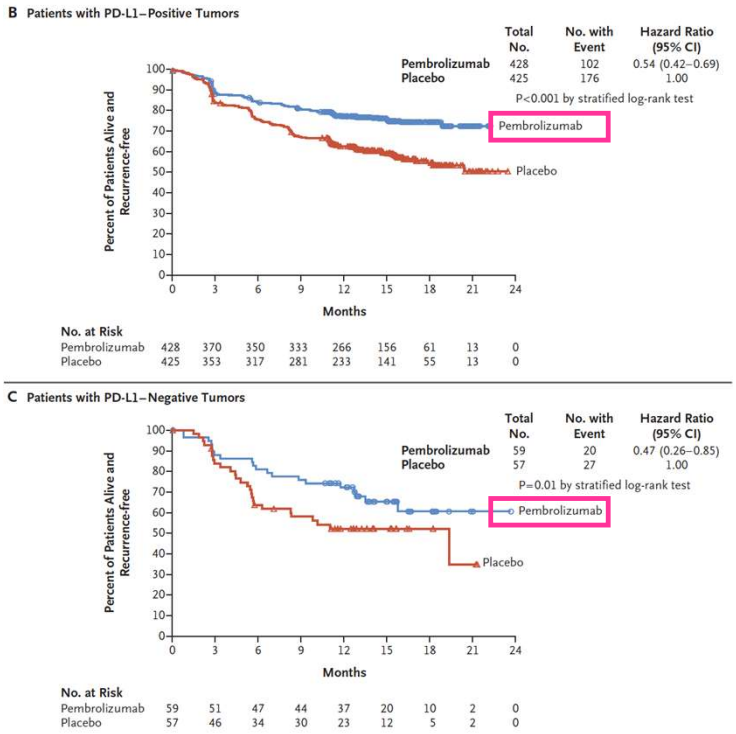
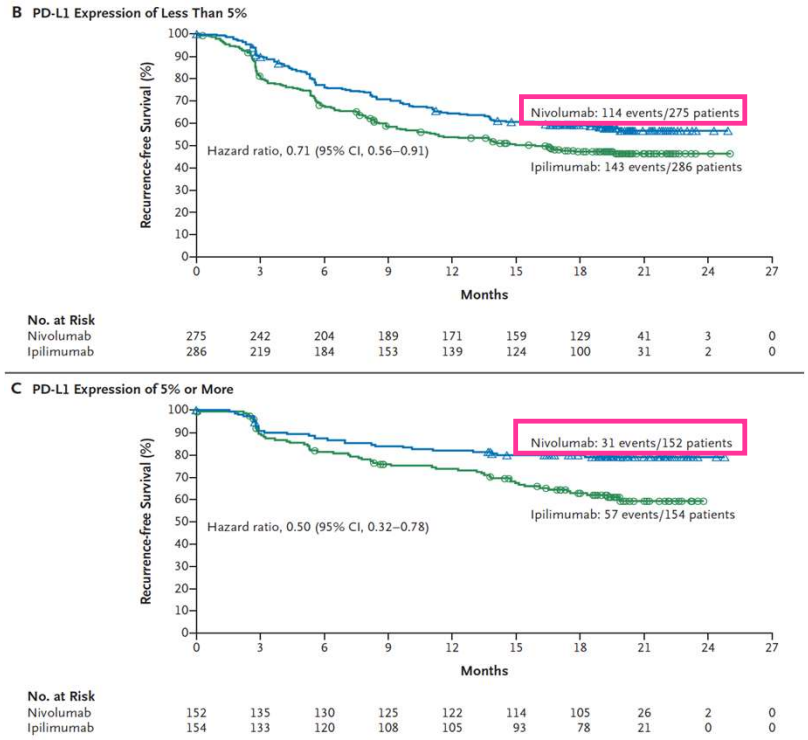
Adjuvant IO Improves RFS…..in Melanoma, regardless of PD-L1 Expression!!





Eggermont NEJM 2018, Weber NEJM 2017

Final Thoughts…..

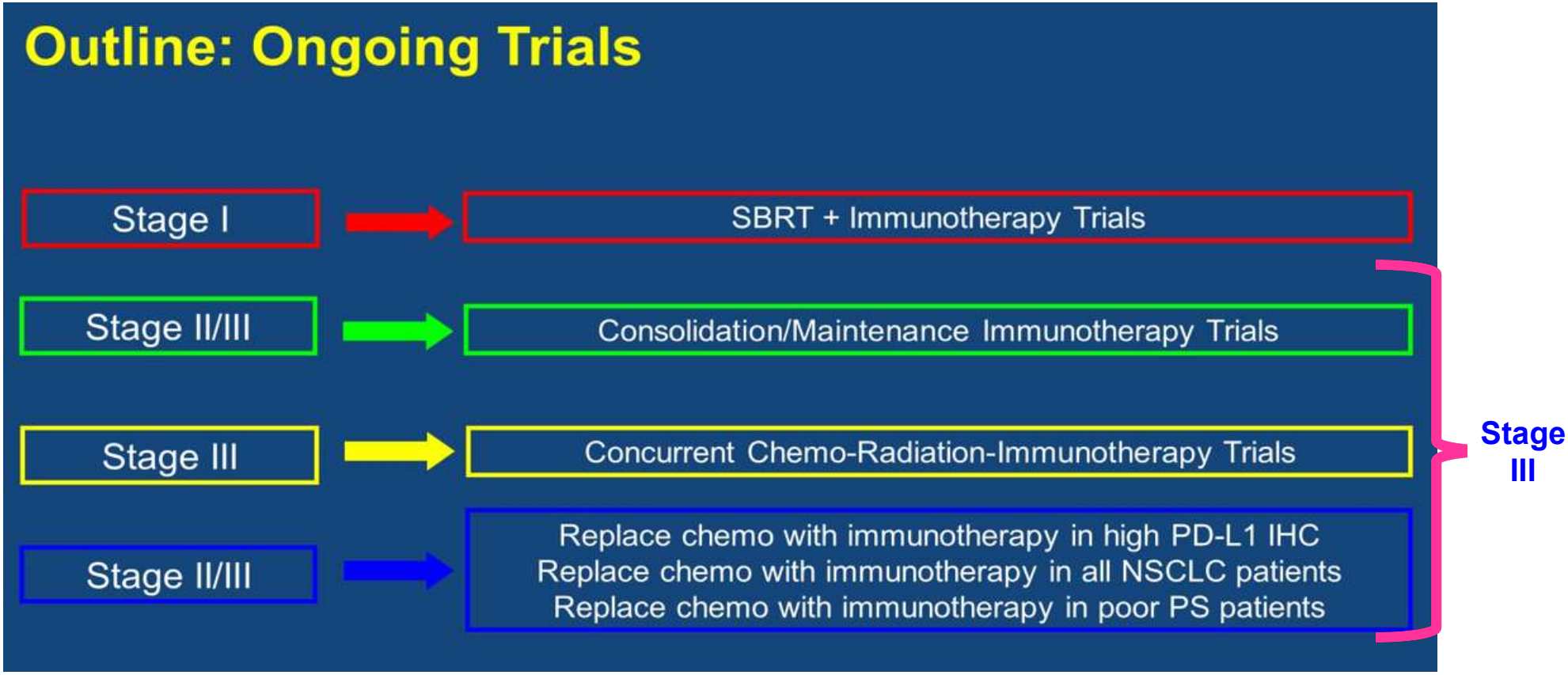
In other solid tumors (e.g., melanoma), ADJ-IO has improved outcomes (RFS)

ADJ-IO in NSCLC looks promising; clinical trials ongoing.

In the NeoADJ setting, IO has shown to be feasible, low toxicity and major pathological response (MPR) has been reported. Will MPR translate into survival advantage?

What is the best way to incorporate IO in the management of early stage NSCLC? NeoADJ?, ADJ?, sequential?, chemo-IO combination?

What biomarkers will help us to sort out this? PD-L1?, TMB?, ctDNA?, inflammatory signatures?


Outline: Ongoing Trials
Stage I
SBRT + Immunotherapy Trials
Stage II/III
Consolidation/Maintenance Immunotherapy Trials
Stage III
Concurrent Chemo-Radiation-Immunotherapy Trials
Stage II/III
Replace chemo with immunotherapy in high PD-L1 IHC
Replace chemo with immunotherapy in all NSCLC patients
Replace chemo with immunotherapy in poor PS patients
Stage III

Consolidation/Maintenance Immunotherapy Trials

Trial	NCT	Phase of Trial	N	NSCLC Stage	Type of Radiation	Systemic Therapy	Biomarker Eligibility Requirement
PACIFIC 6	03693300	II	150	III	Completed chemo-radiation	Durvalumab 1500 mg IV Q4 weeks for 24 months	None
University of Turin	03379441	II	126	III	Completed chemo-radiation	Pembrolizumab Q3 weeks x 35 doses vs Observation	None
Big Ten Cancer Research Consortium LUN16-081	03285321	II	108	IIIA/B	Completed chemo-radiation	A: Nivolumab 480 mg Q4 weeks x 6 doses B: Nivolumab 3 mg/kg Q2 weeks +/- Ipilimumab 1 mg/kg Q6 weeks x 4 doses	None

NCI Clinicaltrials.gov May 2019

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Concurrent Immunotherapy + Chemo-radiation Trials

Trial	NCT	Phase of Trial	N	NSCLC Stage	Type of Radiation	Systemic Therapy	Biomarker Eligibility Requirement
CLOVER NSCLC (Arms 1-3)	03509012	I	300 solid tumors	III	Conventional	Durvalumab with platinum doublet concurrent chemoradiation	None
PACIFIC 2	03519971	III	300	III	Conventional	Concurrent Durvalumab vs placebo with concurrent chemo-radiation followed by Durvalumab x 1 year	
KEYNOTE-799	03631784	II	216	III	Conventional	Chemo-radiation with Pembrolizumab followed by Pembrolizumab x 14	None
H. Lee Moffitt Cancer Center	03663166	I/II	50	III	Conventional	Chemo-radiation with Ipilimumab x 1 followed by Nivolumab x 12	None
NICOLAS (ETOP)	02434081	II	94	IIIA/B	Conventional	Nivolumab with concurrent chemo-radiation then nivolumab x 1 year	None
Alliance Foundation	03102242	II	63	IIIA/B	Conventional	Induction Atezolizumab then concurrent chemo-radiation, consolidation chemo, adjuvant Atezolizumab	None
Rutgers	02621398	I	30	II - IIIA/B	Conventional or IMRT	Pembrolizumab added in 3+3 cohorts from consolidation to concurrent chemo-radiation	None
DETERRED	02525757	II	52	II-III	Conventional	Part 1: chemo-radiation then chemo-Atezolizumab x 2 then Atezolizumab x 1 year Part 2: Atezolizumab with concurrent chemo-radiation followed by chemo-Atezolizumab x 2 then Atezolizumab x 1 year	None
EMD Serono	03840902	II	350	III	IMRT	M7824 with concurrent chemo-radiation followed by M7824 versus PACIFIC	None

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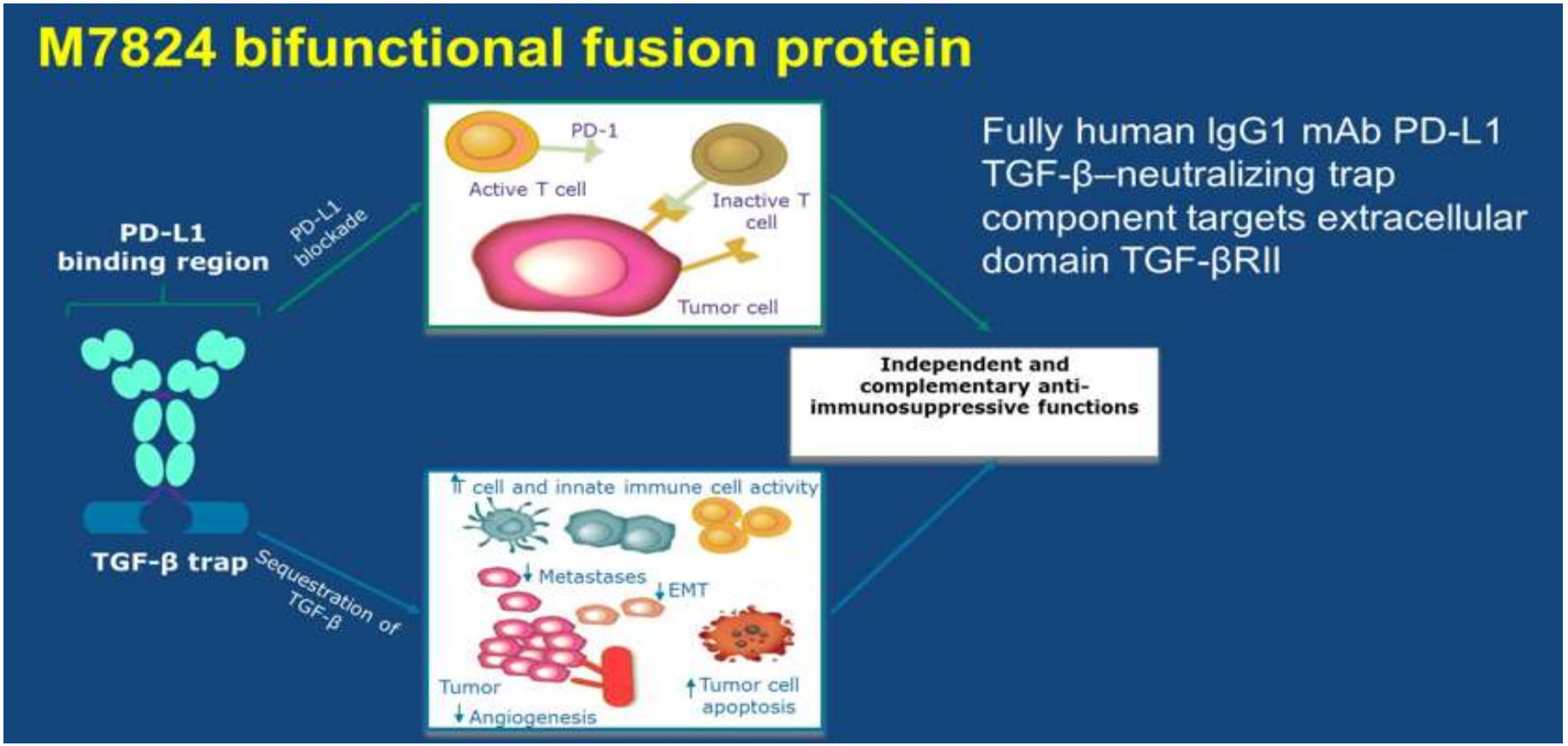
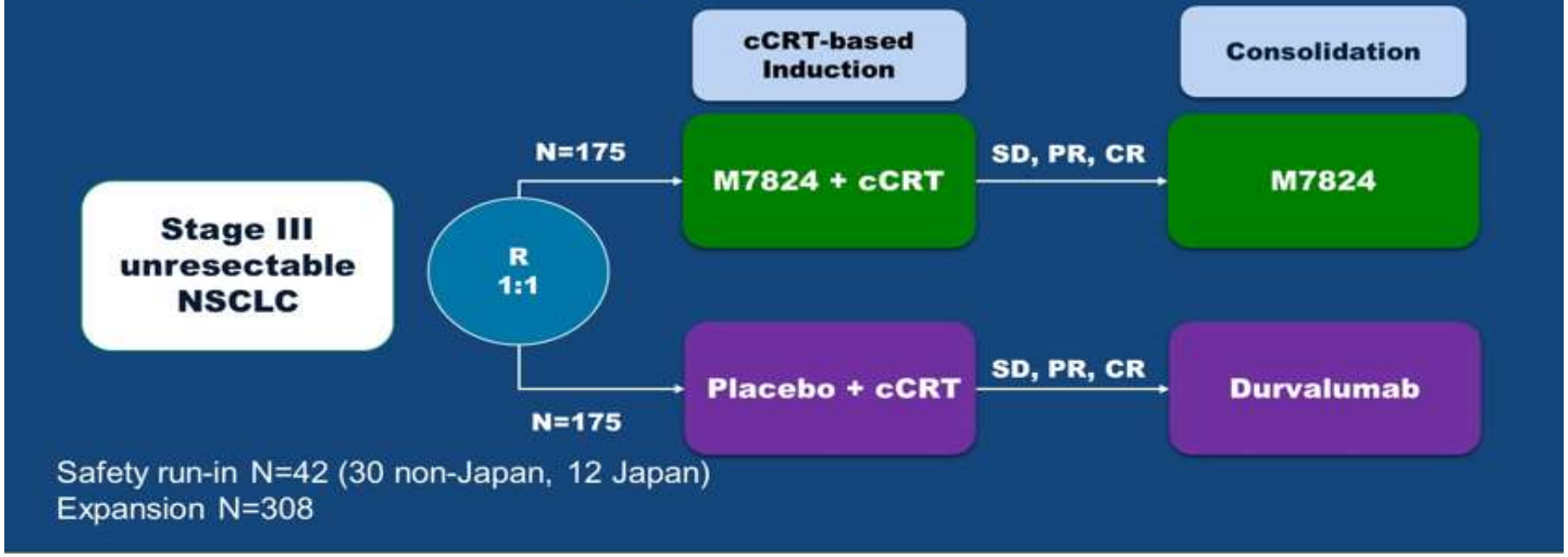
Concurrent Immunotherapy + Chemo-radiation Trials

Trial	NCT	Phase of Trial	N	NSCLC Stage	Type of Radiation	Systemic Therapy	Biomarker Eligibility Requirement
CLOVER NSCLC (Arms 1-3)	03509012	I	300 solid tumors	III	Conventional	Durvalumab with platinum doublet concurrent chemoradiation	None
PACIFIC 2	03519971	III	300	III	Conventional	Concurrent Durvalumab vs placebo with concurrent chemo-radiation followed by Durvalumab x 1 year	None
KEYNOTE-799	03631784	II	216	III	Conventional	Chemo-radiation with Pembrolizumab followed by Pembrolizumab x 14	None
H. Lee Moffitt Cancer Center	03663166	I/II	50	III	Conventional	Chemo-radiation with Ipilimumab x 1 followed by Nivolumab x 12	None
NICOLAS (ETOP)	02434081	II	94	IIIA/B	Conventional	Nivolumab with concurrent chemo-radiation then nivolumab x 1 year	None
Alliance Foundation	03102242	II	63	IIIA/B	Conventional	Induction Atezolizumab then concurrent chemo-radiation, consolidation chemo, adjuvant Atezolizumab	None
Rutgers	02621398	I	30	II - IIIA/B	Conventional or IMRT	Pembrolizumab added in 3+3 cohorts from consolidation to concurrent chemo-radiation	None
DETERRED	02525757	II	52	II-III	Conventional	Part 1: chemo-radiation then chemo-Atezolizumab x 2 then Atezolizumab x 1 year Part 2: Atezolizumab with concurrent chemo-radiation followed by chemo-Atezolizumab x 2 then Atezolizumab x 1 year	None
EMD Serono	03840902	II	350	III	IMRT	M7824 with concurrent chemo-radiation followed by M7824 versus PACIFIC	


M7824 bifunctional fusion protein
PD-L1 binding region
PD-L1 blockade
PD-1
Active T cell
Inactive T cell
Tumor cell
Fully human IgG1 mAb PD-L1 TGF-β–neutralizing trap component targets extracellular domain TGF-βRII
Independent and complementary anti-immunosuppressive functions
TGF-β trap
Sequestration of TGF-β
T cell and innate immune cell activity
Metastases
EMT
Tumor
Angiogenesis
Tumor cell apoptosis

Phase II M7824 in Combination with cCRT Followed by M7824 in Consolidation vs cCRT Followed by Durvalumab in Consolidation in Stage III NSCLC (NCT 03840902)



Safety run-in N=42 (30 non-Japan, 12 Japan)
Expansion N=308

Rationale replacing chemo with immunotherapy

- Concurrent chemo-radiation was superior to sequential therapy or radiation alone
- But, no consolidation chemo nor consolidation/maintenance targeted therapy trials in an unselected population have shown a survival benefit.
- Standard of care remains concurrent chemo-radiation followed by 1 year immunotherapy.
- Concurrent chemo regimens do not achieve systemic therapy dosing and their main benefit may be to provide radiosensitization.
- Ongoing studies demonstrate that immunotherapy can be a radiosensitizer.

Bezjak et al. JCO 33 (18):2100-2105, 2015 ; Antonia et al. NEJM 377 (20): 1919-1929, Nov 16, 2017; Antonia S et al. NEJM 379 (24): 2342-2350, Dec 2018, Deng et al. J Clin Invest, 124: 687-695, 2014; Herter-Sprie et al. JCI Insight, e87415. 2016, Gong et al. JTO: 1085-1097, 2017; Mole et al. Br J Radiol 26: 234-241, 1953; Furuse et al JCO 17:2692-2699, 1999; Hanna et al. JCO 26: 5755-5760, 2008; Ahn et al. JCO 33 (24): 2660-2666, 2015; Kelly et al. 33 (34): 4007-4014, 2015

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Replacing Chemotherapy with Immunotherapy Trials

Trial	NCT	Phase of Trial	N	NSCLC Stage	Type of Radiation	Systemic Therapy	Biomarker Eligibility Requirement
NRG LUN004	03801902	I	24	IIA-IIIC	Accelerated hypofractionated and conventional fractionated	Durvalumab	PD-L1 IHC ≥ 50%
SPRINT	03523702	II	63	II-III	Conventional	PD-L1 IHC ≥ 50% receives Pembrolizumab while <50% receives concurrent chemotherapy	PD-L1 IHC status
MDACC	pending	I	20	II-III	Conventional	Nivolumab-Ipilimumab	None
Poor PS Trials							
Cleveland Medical Center	03818776	I	27	IIA-IIIC unsuitable for concurrent chemo-radiation	Proton beam (60 or 69 cGy)	Durvalumab	None
PARIS	03245177	I	25	III unsuitable for concurrent chemo-radiation	Conventional	Pembrolizumab	None

NCI Clinicaltrials.gov May 2019

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Stage III NSCLC is heterogeneous – Personalized Therapy is Essential

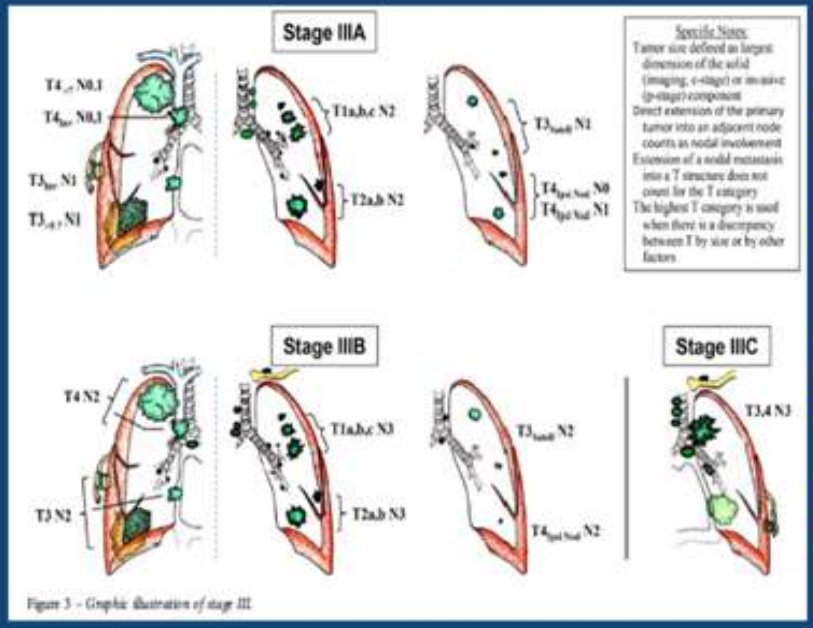


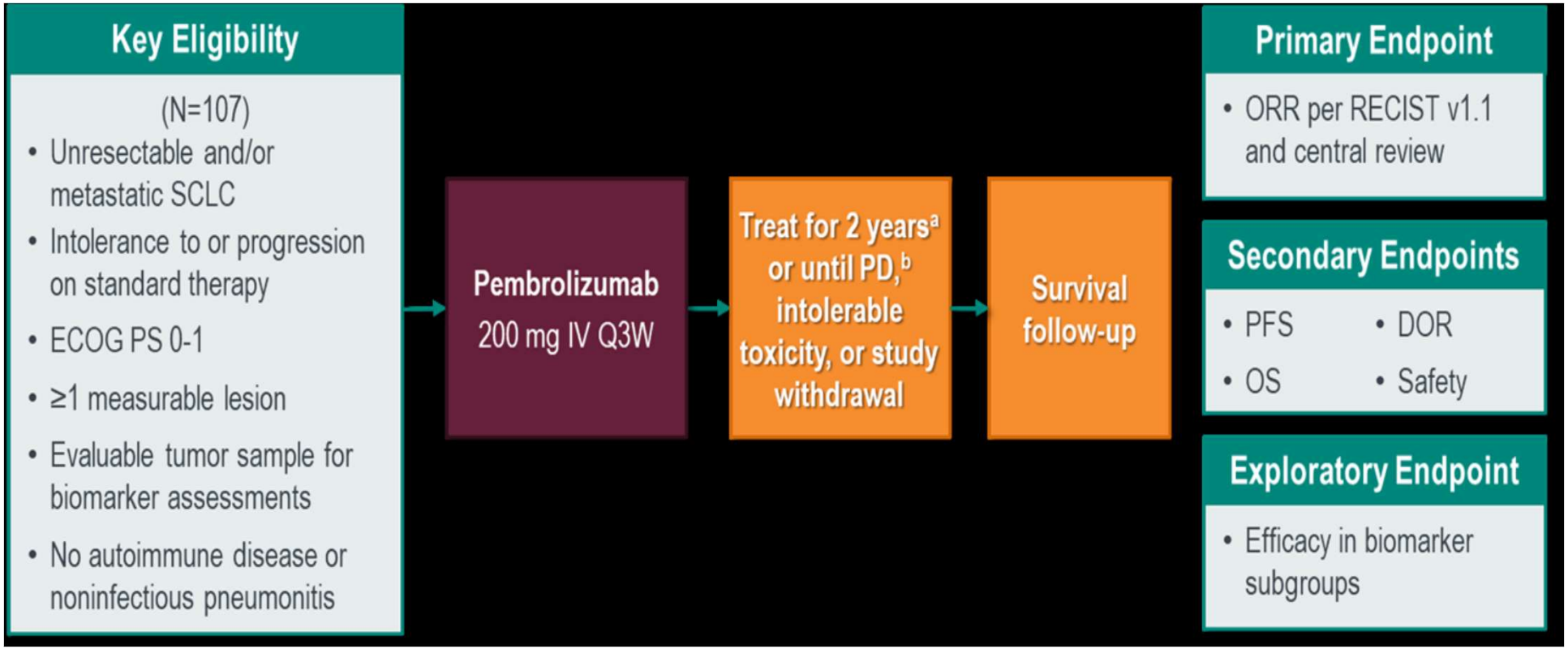
Figure 3 - Graphic illustration of stage III

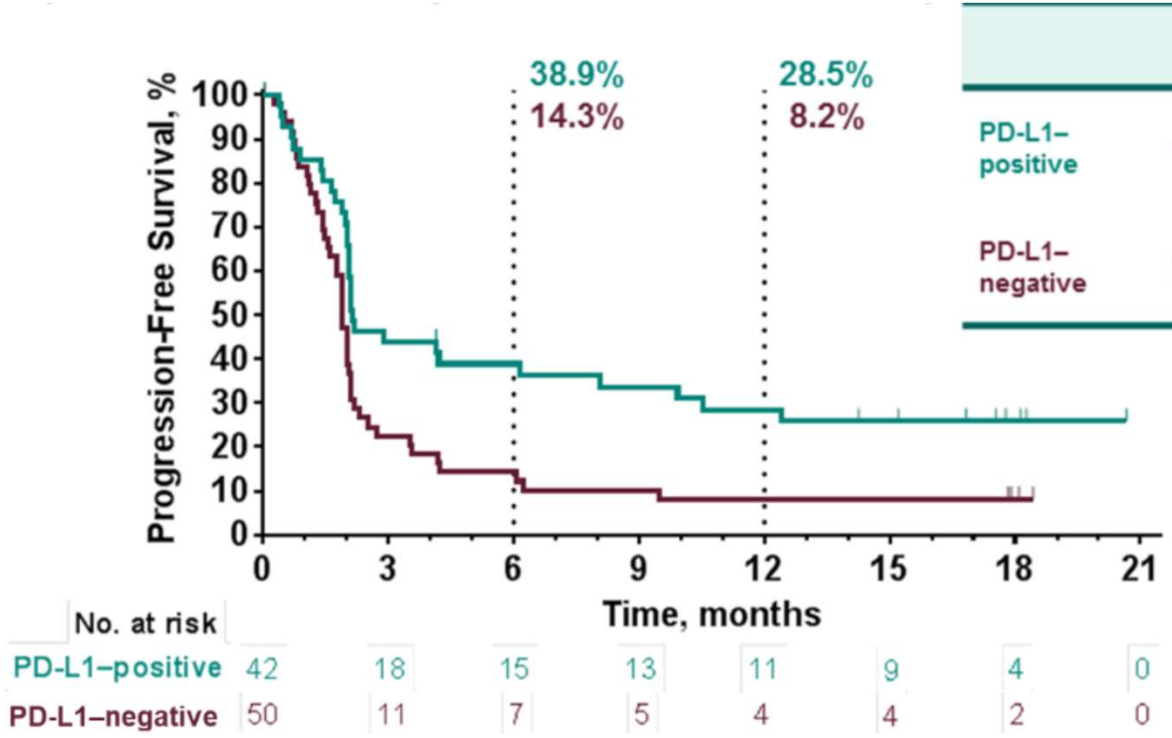
Detterbeck et al. 8th Edition Lung Cancer Stage Classification, Chest 151 (1): 193-203, 2017

Hypothetical Future Strategies

Unresectable Large T or N3 or Bulky or multi-station N2 LN	Neoadjuvant chemo-immunotherapy Concurrent immuno-radiation then 1 year immunotherapy
Small T, PD-L1 IHC high, small multi-station N2 LN	Concurrent immuno-radiation then 1 year immunotherapy
Small T, PD-L1 IHC low, small multi-station N2 LN	Concurrent chemo-radiation then 1 year immunotherapy
Large T Single-station N2 LN	Neoadjuvant chemo-immunotherapy, Surgery +/- XRT, then 1 year immunotherapy
Small T Single-station N2 LN	Neoadjuvant immunotherapy, Surgery +/- XRT, then 1 year immunotherapy

KEYNOTE-158: Phase 2 Study of Pembrolizumab in Advanced Solid Tumors (SCLC Cohort)
Study Design and Outcomes Assessed
Chung et al.1 presented results from the SCLC cohort (n=107) of KEYNOTE-158, a phase 2 multicohort study in
advanced solid tumors, regardless of biomarker status (data cutoff date, January 15, 2018). Patients with
unresectable and/or metastatic SCLC with intolerance to or progression on standard therapy were treated with
pembrolizumab monotherapy for 2 years or until PD, intolerable toxicity, or study withdrawal.

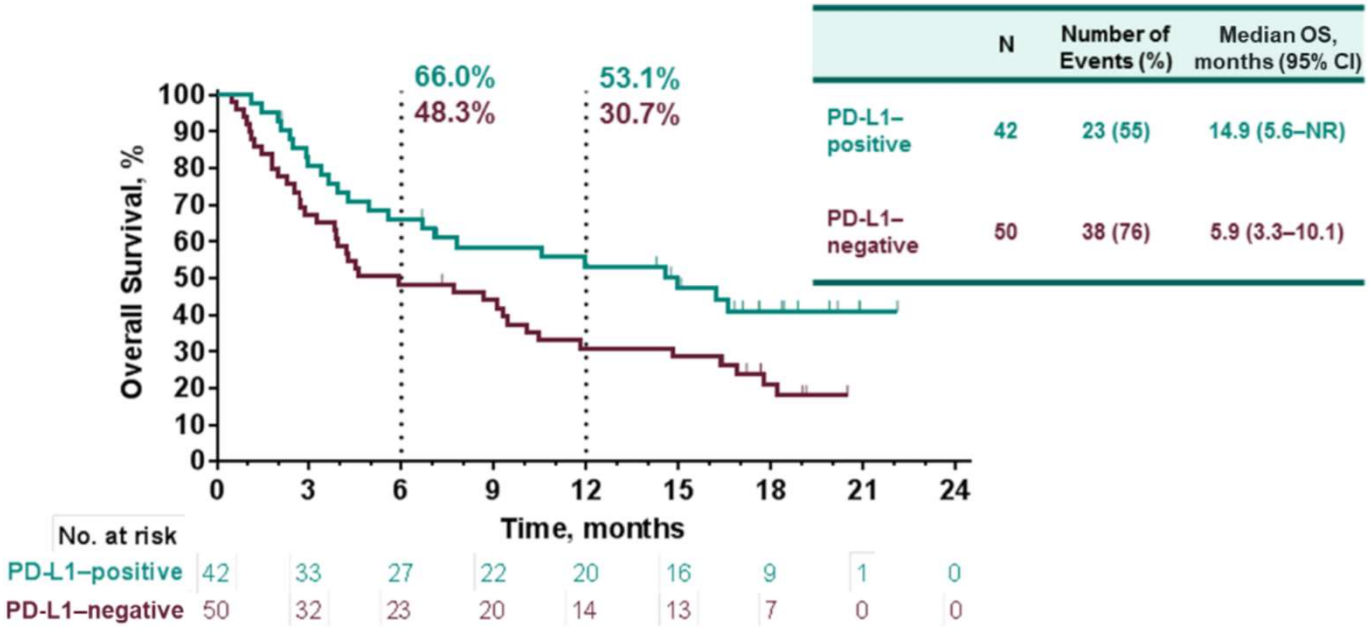




	N	Number of Events (%)	Median PFS, months (95% CI)
PD-L1–positive	42	30 (71)	2.1 (2.0–8.1)
PD-L1–negative	50	45 (90)	1.9 (1.6–2.0)

KEYNOTE-158 Study

PFS by PD-L1 Status



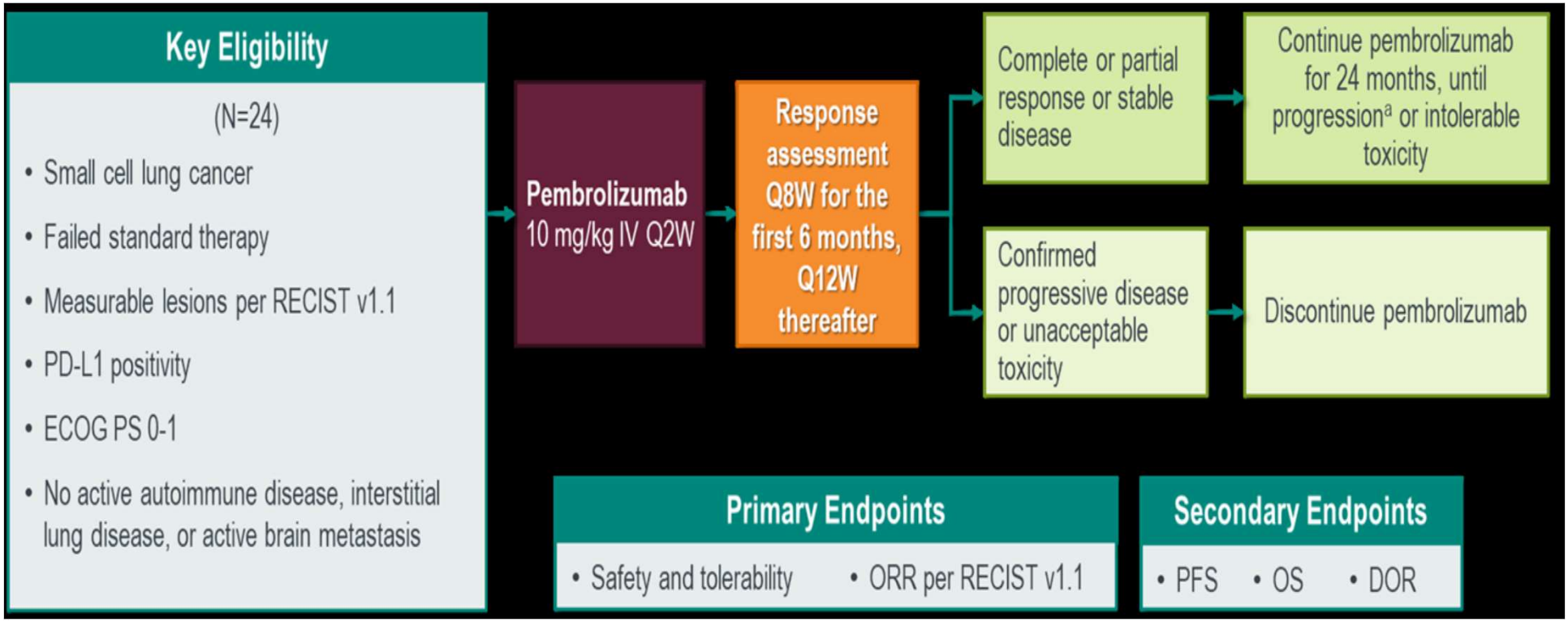
	N	Number of Events (%)	Median OS, months (95% CI)
PD-L1–positive	42	23 (55)	14.9 (5.6–NR)
PD-L1–negative	50	38 (76)	5.9 (3.3–10.1)

- **KEYNOTE-158 Study OS by PD-L1 Status**[1]

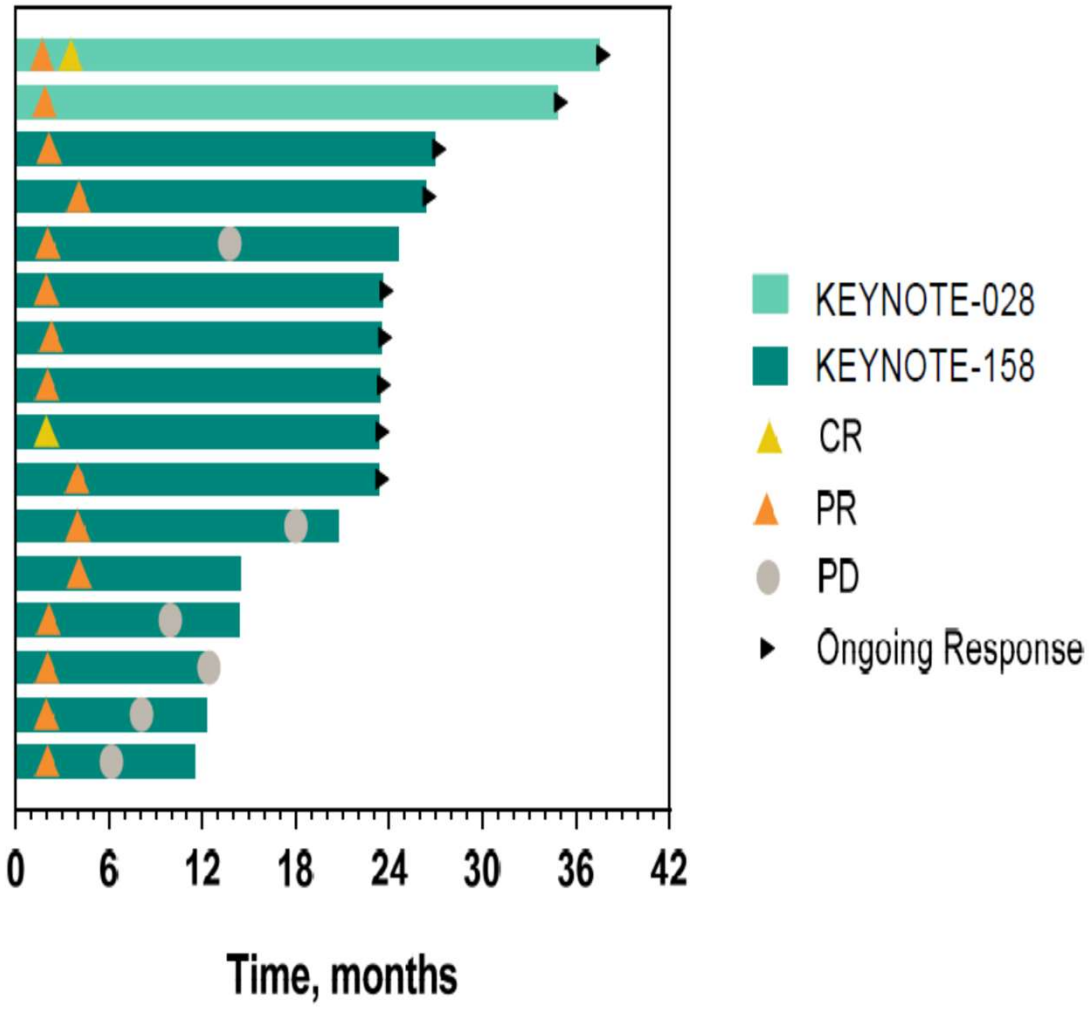
KEYNOTE-028: **Pembrolizumab in Advanced Solid Tumors (PD-L1–Positive SCLC Cohort)**

Study Design and Outcomes Assessed

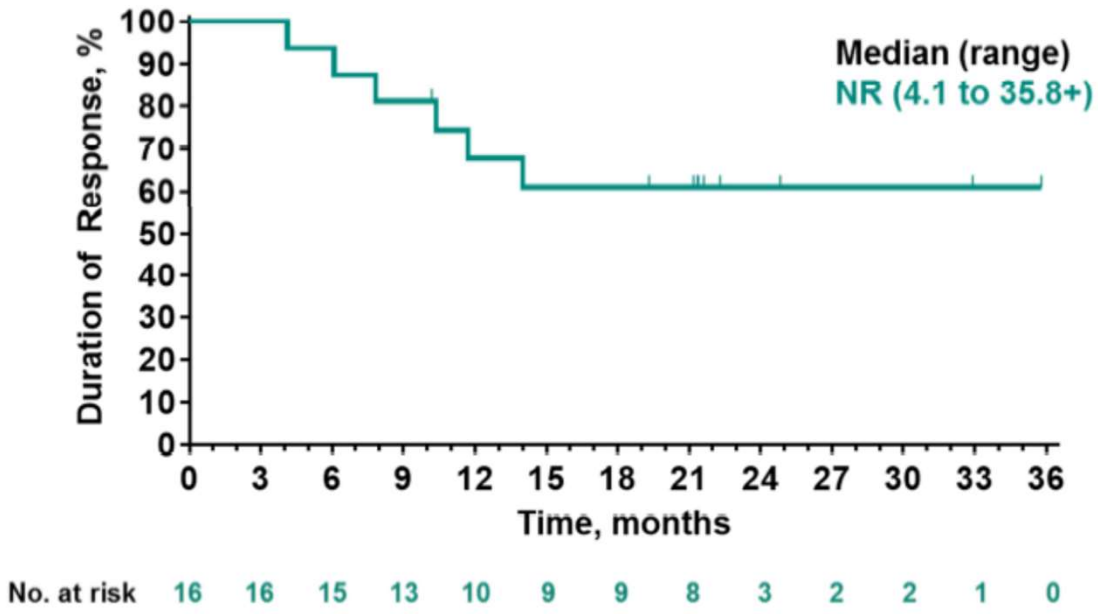
Ott et al.2 reported the efficacy and safety results from a cohort of participants with PD-L1–positive ES-SCLC in
KEYNOTE-028, an open-label phase 1b multicohort study of pembrolizumab for PD-L1–positive advanced solid tumors. The data cutoff date was June 20, 2016. Participants in the SCLC cohort who failed standard therapy and
were PD-L1–positive were treated with pembrolizumab 10 mg/kg IV Q2W



Time to Response and Time to Progression (RECIST v1.1 by Independent Review)3,4

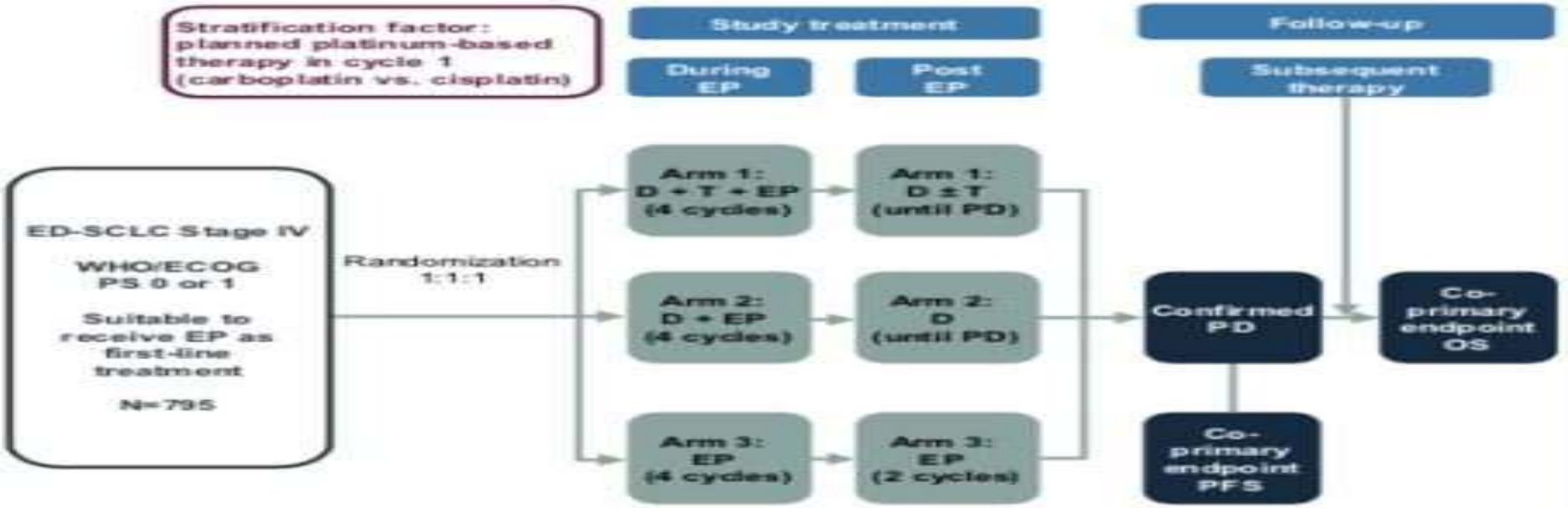


Duration of Response by RECIST v1.1 by Independent Review[4]



- Data cutoff dates: KEYNOTE-028, July 31, 2018; KEYNOTE-158, July 13, 2018.
- Analysis included patients who achieved a confirmed complete or partial response with pembrolizumab therapy following ≥2 lines of previous
- therapy. Patients with an ongoing response are defined as those who were alive without disease progression, had not initiated a new cancer
- treatment, were not lost to follow-up, and whose last disease assessment was within 5 months of the data cutoff date.
- Figure reprinted from Chung HC, et al. Pembrolizumab After Two or More Lines of Previous Therapy in Patients With Recurrent or Metastatic
- Small-Cell Lung Cancer: Results From the KEYNOTE-028 and KEYNOTE-158 Studies. [published online ahead of print December 20, 2019]. *J*
- *Thorac Oncol*. doi: 10.1016/j.jtho.2019.12.109., with permission from Elsevier.

CASPIAN trial
Imfinzi in SCLC



CASPIAN data presentation in H2 2019
Recent Orphan Drug Designation (US)

Conclusion:

- PACIFIC trial established a new standard of care for patients with Stage III NSCLC.
- First time ever, consolidation therapy after definitive CRT improves OS.
- New approaches are undergoing introducing IO in combination w RT, or prior to RT, or after CRT with other agents; so many research options.
- Await for efficacy data of IO w CCRT, consolidation/maintenance and replacing CTx.
- More questions: sequencing?, duration of IO therapy?, hypofractionated or conventional RT?, role of tri-modality therapy w IO?, role of adjuvant versus neoadjuvant IO therapy?, predictive biomarkers?, etc..

9th Annual Puerto Rico Winter Cancer Sympsium 2020

THE END