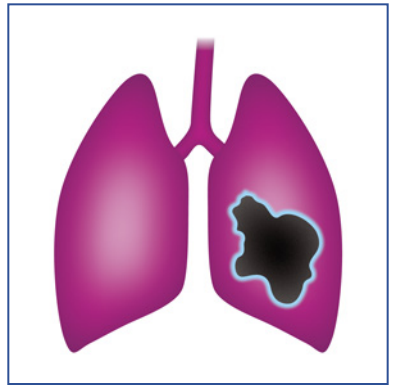
Pneumo Update Europe 2018

15 - 16 June, Budapest

Oncology



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Content

1. Early stage NSCLC
2. Locally advanced NSCLC
3. Advanced NSCLC with oncogene addiction
4. Advanced NSCLC no oncogene addiction including

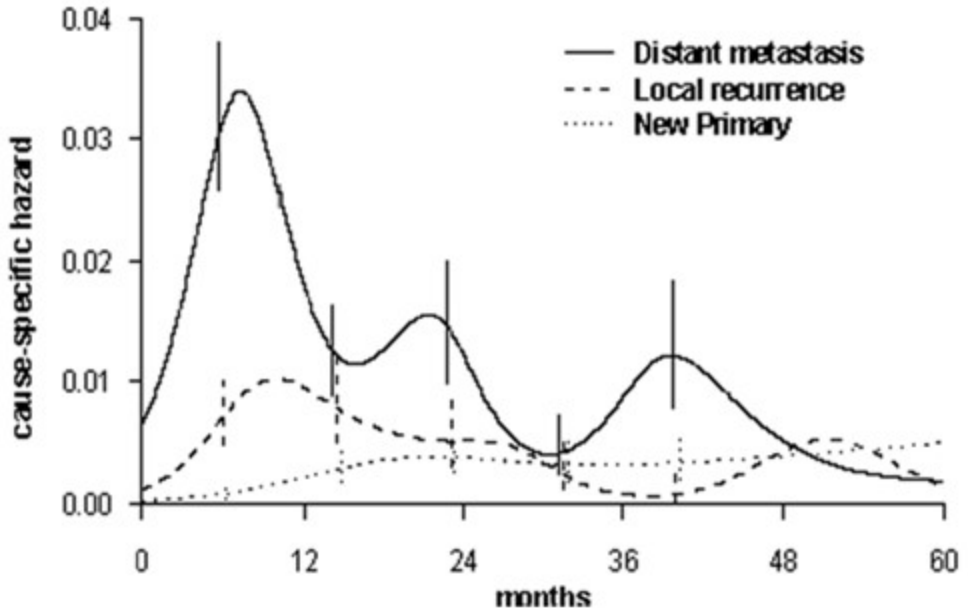
AACR April 14-18, 2018
ASCO June 1-5, 2018
Late Breaking News

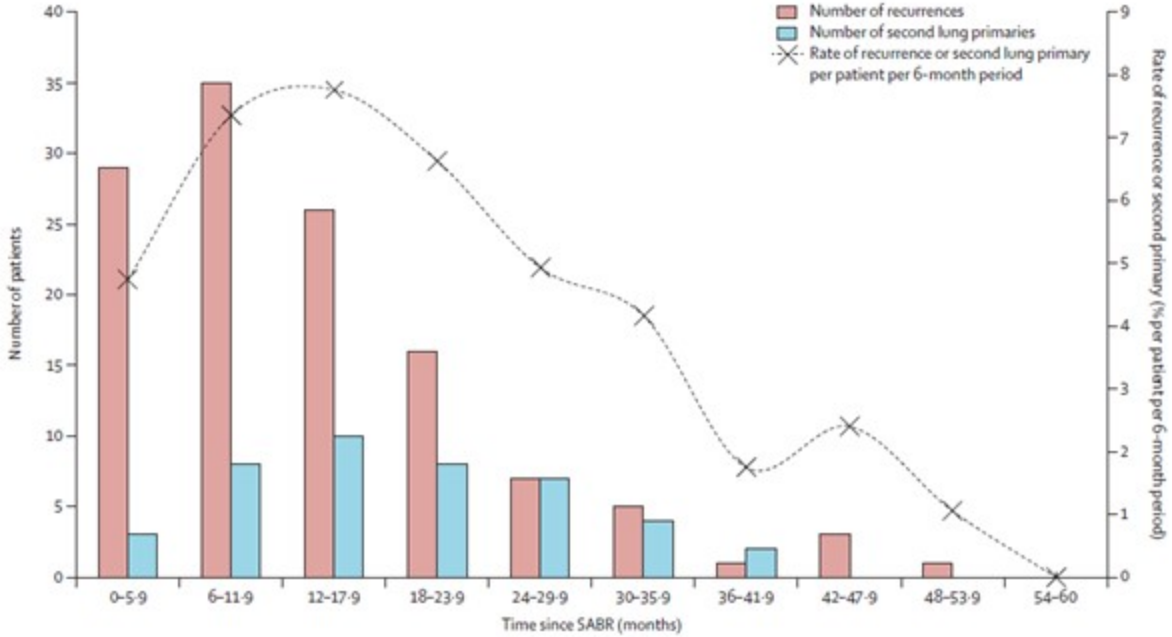
Early stage NSCLC

Follow-up after radical therapy

State of the art

Follow-up after radical therapy for early stage NSCLC





Demicheli et al, J Thorac Oncol 7:723-730, 2012 ; Senthi et al, Lancet Oncol 13:802-809, 2012

State of the art

Follow-up after radical therapy for early stage NSCLC: clinical practice guidelines

- **ACCP 2013**
  - For 2 years : q6 months history/exam + chest CT
  - Thereafter : q1 year history/exem + chest CT
- **ESMO 2017**
  - For 2 years : q6 months history/exam + chest CT
  - Thereafter : q1 year history/exam + low dose non-CE chest CT
- **NCCN 2017**
  - For 2 years : q6-12 mo history/exam + chest CT
  - Thereafter : q1 year history/exam low dose non-CE chest CT

Detterbeck et al, Chest 143 Suppl 5:7S-37S, 2013 ; Postmus et al, Ann Oncol 28 Suppl 4:iv1-21, 2017
https://www.nccn.org/store/login/login.aspx?ReturnURL=https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf

Early stage NSCLC
> ph3 IFCT 0302 follow-up study

IFCT 0302

Clinical stage I-II-IIIA [TNM6]

- **≤8 weeks post-resection**
- **Perioperative therapy allowed**
- **No wedge resection**
- **No other cancer ≤5 years**

N=887

R

N=888

Stratified
- Center
- Stage
- Histology
- Perioperative therapies

Maximal follow-up
- **history/exam/X-ray**
- **Contrast-enhanced CT**
- **Bronchoscopy (non-adeno)**

At months 6, 12, 18, 24 then 36, 48 and 60

Minimal follow-up
- **history/exam/X-ray**
- **CT only on indication**

Primary endpoint
- **OS**

Other endpoints
- DFS
- OS from recurrence or 2nd primary
- HRQoL
- Cost-effectiveness
- Prognostic signature

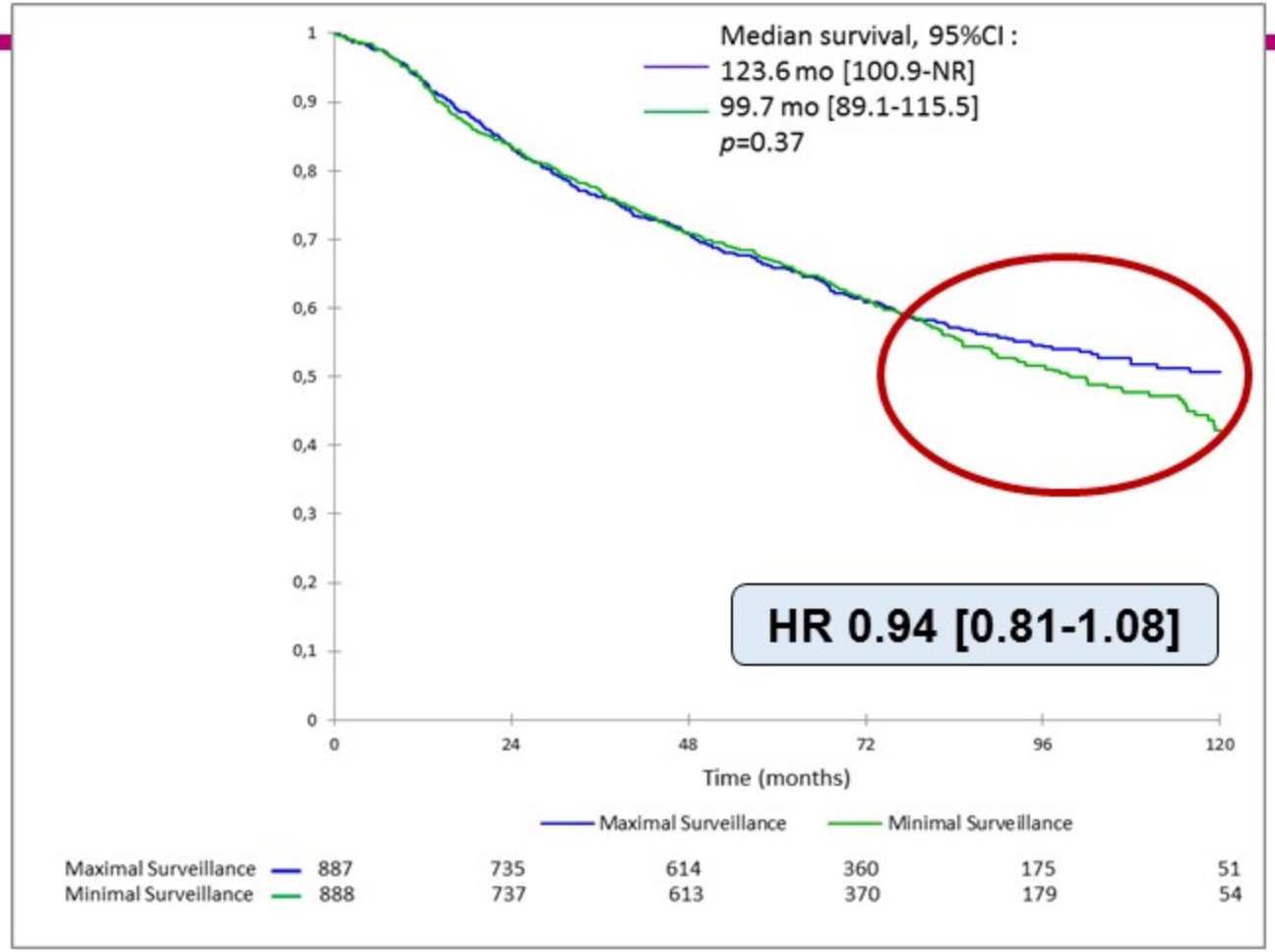
Westeel et al, ESMO 2017 and Westeel et al, WCLC 2017

Early stage NSCLC
> ph3 follow-up study: demographics

	Minimal N=888 (%)	Maximal N=887 (%)
Gender: Men	678 (76)	677 (76)
Median age (range)	63 (37-88)	63 (34-87)
Smoking: never smokers	68 (8)	80 (9)
Histology		
Squamous	302 (34)	304 (34)
Adenocarcinoma	504 (57)	503 (57)
Large cell	50 (6)	44 (5)
Clinical stage		
I-II	725 (82)	724 (82)
III	161 (18)	162 (18)
Surgery		
Lobectomy	758 (86)	775 (88)
Pneumonectomy	111 (12)	95 (11)
Segmentectomy	16 (2)	15 (2)
Preop CT and/or RT	110 (12)	116 (13)
Postop CT and/or RT	342 (39)	350 (39)

Westeel et al, ESMO 2017 and Westeel et al, WCLC 2017

Early stage NSCLC
> ph3 follow-up study: OS



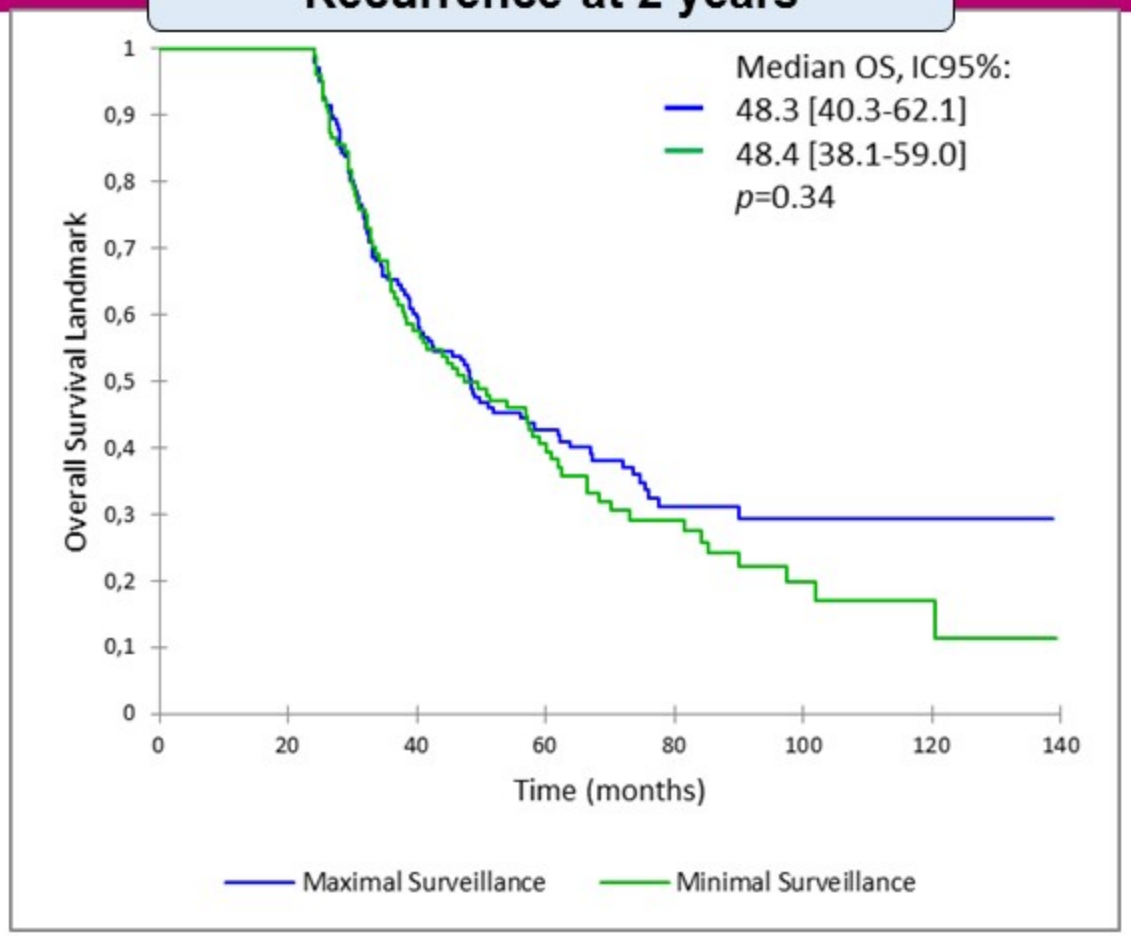
OS (95% CI)	3 years	5 years	8 years
Minimal	77.3% (74.5 – 80%)	66.7% (63.6 – 69.9%)	51.7% (47.8 – 55.5%)
Maximal	76.1% (73.3 – 78.9%)	65.8% (62.6 – 68.9%)	54.6 % (50.9 – 58.3%)

Median follow-up: 8 years 10 months (minimal: 4 years)

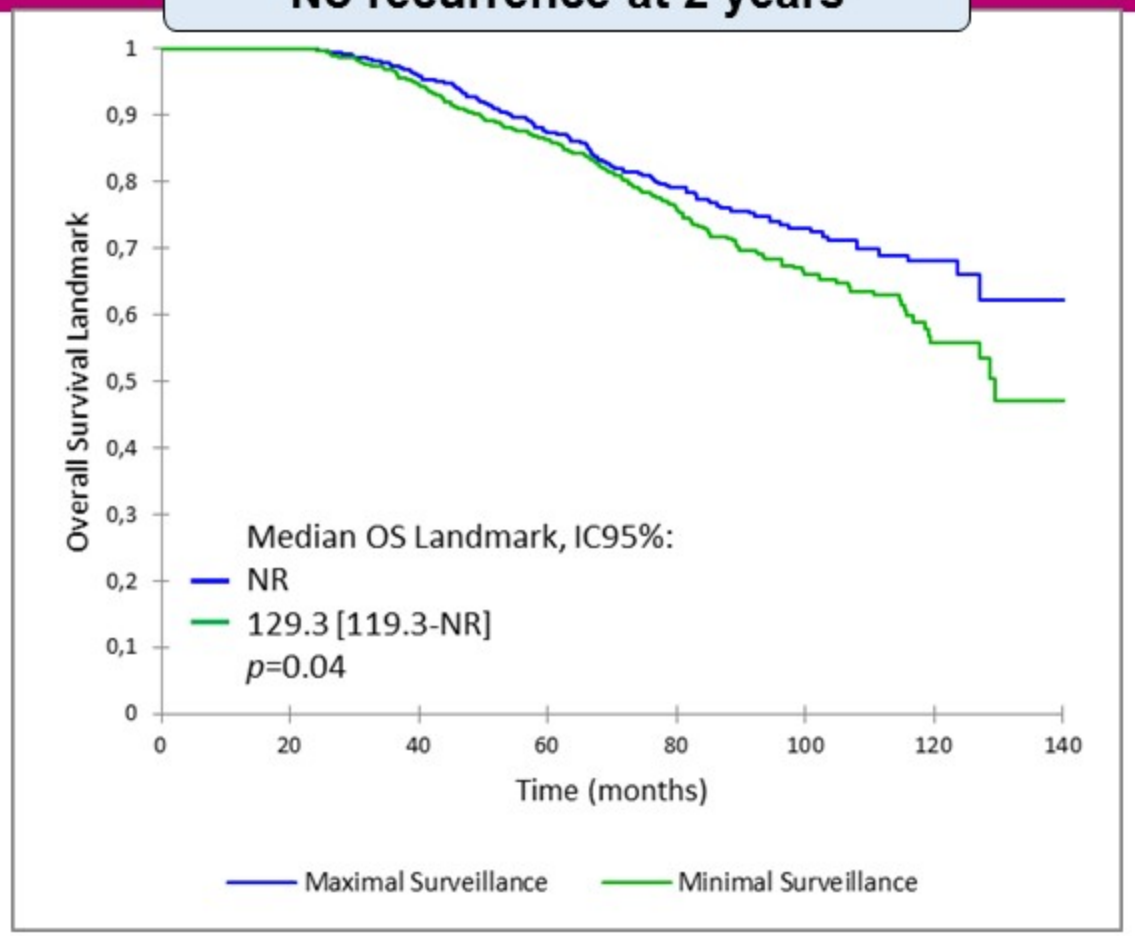
Westeel et al, ESMO 2017 and Westeel et al, WCLC 2017

Early stage NSCLC
> ph3 follow-up study: exploratory OS analysis

Recurrence at 2 years



No recurrence at 2 years



Westeel et al, ESMO 2017 and Westeel et al, WCLC 2017

Early stage NSCLC
> ph3 follow-up study: second primary lung cancers

	Minimal	Maximal	*P*
2nd primary lung cancer Before 2 year Beyond 2 year	26 (2.9%) 10 (38.5%) 16 (61.5%)	40 (4.5%) 17 (42.5%) 23 (57.5%)	NS
Symptomatic	14 (53.8%)	7 (17.5%)	0.001
Surgery alone Before 2year Beyond 2 year	5 (19.2%) 1 (20%) 4 (80%)	18 (45%) 9 (50%) 9 (50%)	0.03
Radiotherapy alone Before 2 year Beyond 2 year	3 (11.5%) 1 (33.3%) 2 (66.7%)	1 (2.5%) 0 1 (100%)	NS

Westeel et al, ESMO 2017 and Westeel et al, WCLC 2017

Take-Home Message

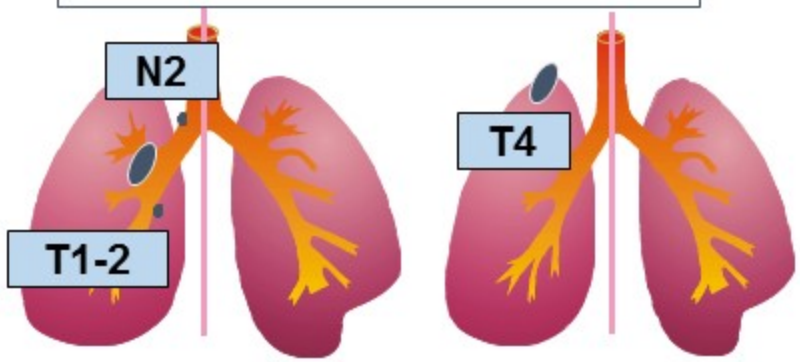
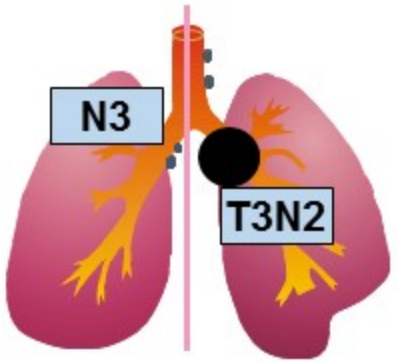
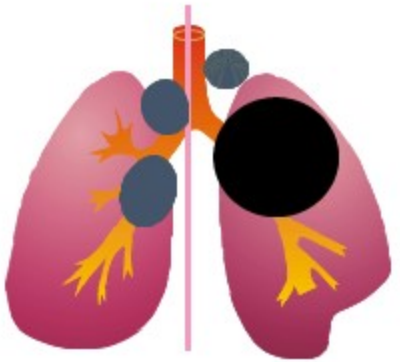
- **Trend for an earlier diagnosis of recurrences and 2nd primary cancers**
- **Potential long-term benefit in maximal arm**
  - **Recurrences: more detected, less symptomatic, more surgery (OS benefit ≈ different biology of late events)**
  - **2nd primary lung cancers: more detected, less symptomatic, more surgery (especially beyond 2 years)**
- **Suggestion for practice**
  - **Keep CT-scan every 6 months during the first 2 years = ?**
  - **Keep a yearly CT-scan, and for long-term**

Locally advanced NSCLC

Consolidation immunotherapy

Stage III NSCLC – State of the art

A heterogeneous group of patients

Potentially resectable (20%)	Unresectable (60%)	Non-radical setting (20%)
Some IIIA: T1-2N2; T3N1; T4N0-1	Bulky IIIA; every IIIB and IIIC	Very bulky disease
		
"Surgical multimodality"	"Non-surgical multimodality"	"Stage IV therapy"
Chemo(radio)therapy + surgery	Concurrent chemoRT Sequential chemoRT	Systemic therapy alone Palliative RT alone

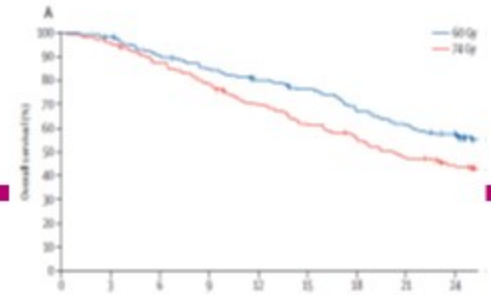
Unresectable stage III NSCLC
> recent RCTs *[10 years effort in one slide]*

2 cycles of cis-etoposide

Radiotherapy 60 / 2 Gy

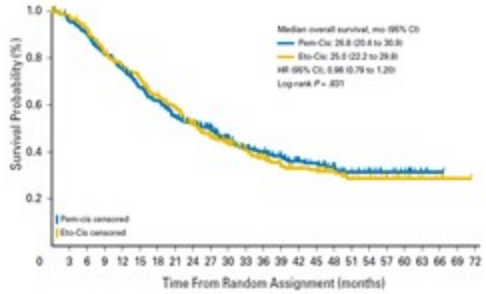
1/ Improve local therapy ?

- RTOG 0617 (ASCO 2013) [1]
  - ➢ 74 Gy vs. 60 Gy



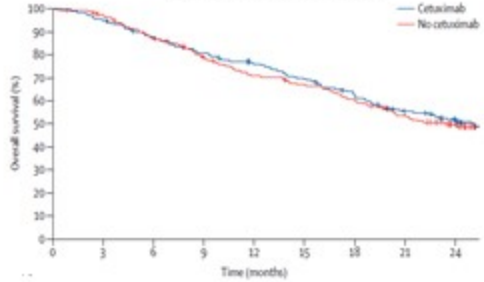
2/ Improve chemotherapy ?

- PROCLAIM (ASCO 2015) [2]
  - ➢ Cis-pemetrexed vs. cis-etoposide



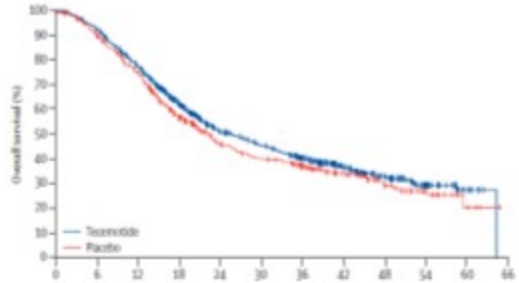
3/ Targeted therapy ?

- RTOG 0617 (WCLC 2013) [3]
  - ➢ Cetuximab add-on



4/ Immuno-therapy ?

- START: MUC1 immunotherapy [4]
  - ➢ MUC1 immunotherapy add-on



1 Bradley et al, ASCO 2013 *and* Lancet Oncol 16:187-199, 2015
2 Senan et al, ASCO 2015 and J Clin Oncol 34:953-962, 2016
3 Bradley et al, WCLC 2013 *and* Lancet Oncol 16:187-199, 2015
4 Butts et al, ASCO 2013 *and* Lancet Oncol 15:59-68, 2014

Unresectable stage III NSCLC
> ph3 PACIFIC study

PACIFIC

Stage III unresectable NSCLC
- **Non-progressing after concurrent chemoradiotherapy**
- **PS 0-1**
- **Archived tissue**
- **Any PD-L1**

R

N=476 → **Durvalumab 10 mg/kg q2w for 1 year**

N=237 → **Placebo q2w for 1 year**

Stratified
- Age
- Gender
- Smoking

Primary endpoint
- **PFS by BICR**
- **OS**

Other endpoints
- ORR (BICR)
- DoR (BICR)
- Safety
- PROs

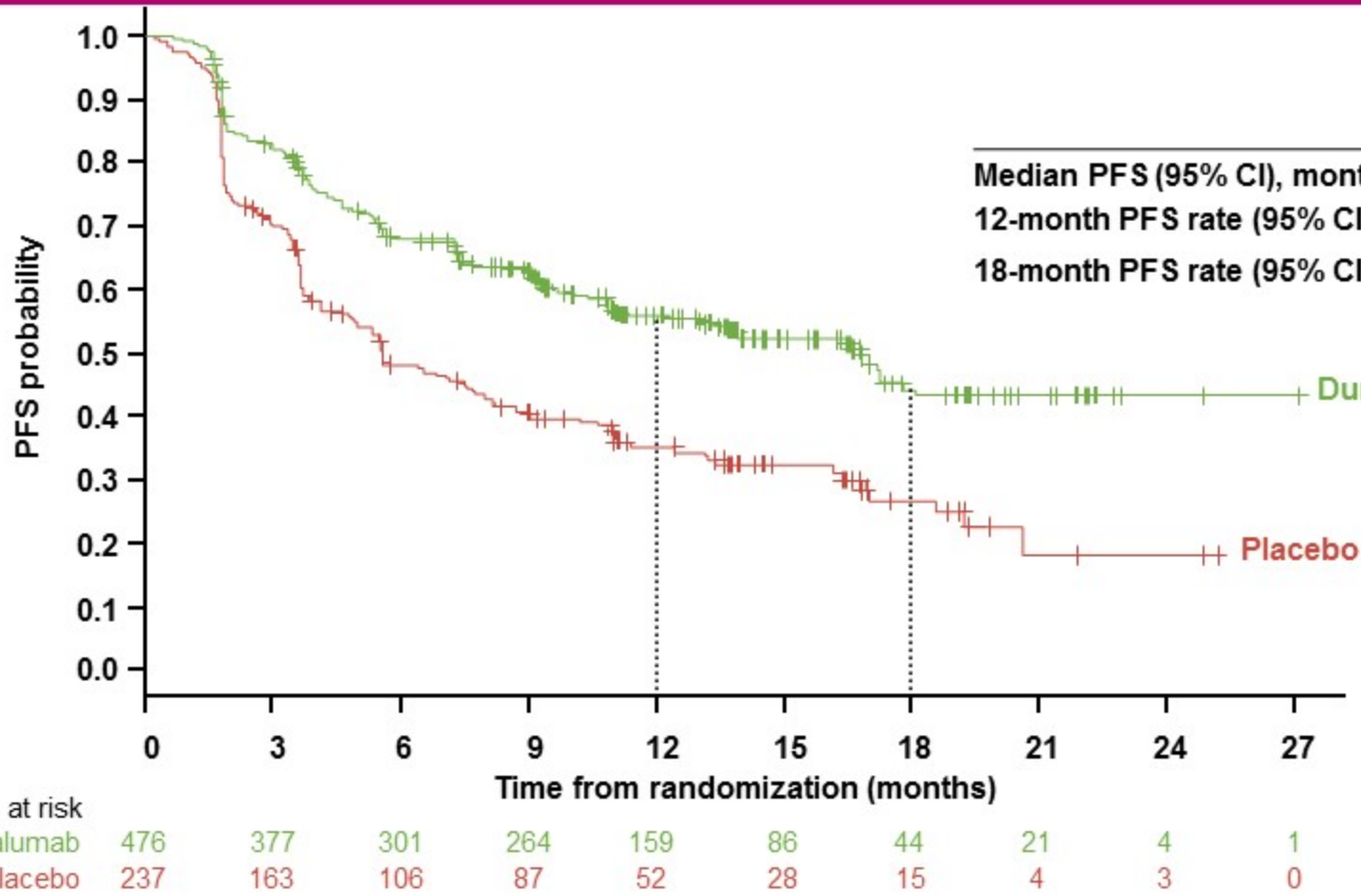
Paz-Ares et al, ESMO 2017 *and* Antonia et al, N Engl J Med Sep 9, 2017

Unresectable stage III NSCLC
> ph3 PACIFIC study: demographics

		Durvalumab (N=476)	Placebo (N=237)
Age	Median (range), years ≥65 years, %	64 (31–84) 45.2	64 (23–90) 45.1
Male, %		70.2	70.0
WHO performance status score, %*	0 / 1	49.2 / 50.4	48.1 / 51.5
Smoking status, %	Current / Former / Never	16.6 / 74.4 / 9.0	16.0 / 75.1 / 8.9
Disease stage, %†	IIIA / IIIB	52.9 / 44.5	52.7 / 45.1
Histology, %	Squamous / Non-squamous	47.1 / 52.9	43.0 / 57.0
PD-L1 status, %	Known: TC <25% / TC ≥25% Unknown‡	39.3 / 24.2 36.6	44.3 / 18.6 37.1
Prior chemotherapy, %	Induction / Definitive cCRT	25.8 / 99.8	28.7 / 99.6
Prior radiotherapy, %*	<54 Gy 54 to ≤66 Gy >66 to ≤74 Gy	0.6 92.9 6.3	0 91.6 8.0
Best response to prior cCRT, %¶	CR / PR / SD / PD	1.9 / 48.7 / 46.6 / 0.4	3.0 / 46.8 / 48.1 / 0

Paz-Ares et al, ESMO 2017 *and* Antonia et al, N Engl J Med Sep 9, 2017

Unresectable stage III NSCLC
> ph3 PACIFIC study: PFS



	Durvalumab (N=476)	Placebo (N=237)
Median PFS (95% CI), months	16.8 (13.0–18.1)	5.6 (4.6–7.8)
12-month PFS rate (95% CI)	55.9% (51.0–60.4)	35.3% (29.0–41.7)
18-month PFS rate (95% CI)	44.2% (37.7–50.5)	27.0% (19.9–34.5)

HR 0.52 [95%CI 0.42–0.65]
***P*<0.0001**

Median FU 14.5 months (range 0.2–29.9)

Paz-Ares et al, ESMO 2017 *and* Antonia et al, N Engl J Med Sep 9, 2017

Unresectable stage III NSCLC
> ph3 PACIFIC study: adverse events

Event	Durvalumab (N=475)		Placebo (N=234)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
Any event, n (%)	460 (96.8)	142 (29.9)	222 (94.9)	61 (26.1)
Cough	168 (35.4)	2 (0.4)	59 (25.2)	1 (0.4)
Pneumonitis/radiation pneumonitis†	161 (33.9)	16 (3.4)	58 (24.8)	6 (2.6)
Fatigue	113 (23.8)	1 (0.2)	48 (20.5)	3 (1.3)
Dyspnea	106 (22.3)	7 (1.5)	56 (23.9)	6 (2.6)
Diarrhea	87 (18.3)	3 (0.6)	44 (18.8)	3 (1.3)
Pyrexia	70 (14.7)	1 (0.2)	21 (9.0)	0
Decreased appetite	68 (14.3)	1 (0.2)	30 (12.8)	2 (0.9)
Nausea	66 (13.9)	0	31 (13.2)	0
Pneumonia	62 (13.1)	21 (4.4)	18 (7.7)	9 (3.8)
Arthralgia	59 (12.4)	0	26 (11.1)	0
Pruritus	58 (12.2)	0	11 (4.7)	0
Rash	58 (12.2)	1 (0.2)	17 (7.3)	0
Upper respiratory tract infection	58 (12.2)	1 (0.2)	23 (9.8)	0
Constipation	56 (11.8)	1 (0.2)	20 (8.5)	0
Hypothyroidism	55 (11.6)	1 (0.2)	4 (1.7)	0
Asthenia	51 (10.7)	3 (0.6)	31 (13.2)	1 (0.4)
Back pain	50 (10.5)	1 (0.2)	27 (11.5)	1 (0.4)

Paz-Ares et al, ESMO 2017 *and* Antonia et al, N Engl J Med Sep 9, 2017

Unresectable stage III NSCLC
> ph3 PACIFIC study: pneumonitis

Pneumonitis (grouped terms), n (%)	Durvalumab (N=475)	Placebo (N=234)
Any grade	161 (33.9)	58 (24.8)
Grade 3/4	16 (3.4)	6 (2.6)
Grade 5	5 (1.1)	4 (1.7)
Leading to discontinuation	30 (6.3)	10 (4.3)

Paz-Ares et al, ESMO 2017 *and* Antonia et al, N Engl J Med Sep 9, 2017

Take-Home Message

- The first positive ph3 trial on systemic therapy for stage III NSCLC over a decade
- The first translation of immunotherapy benefits to non-metastatic setting
  - Significant improvement in PFS (HR 0.52; P<0.0001)
  - Good tolerance and manageable safety profile
- Overall survival data awaited

FDA

---------- INDICATIONS AND USAGE ----------

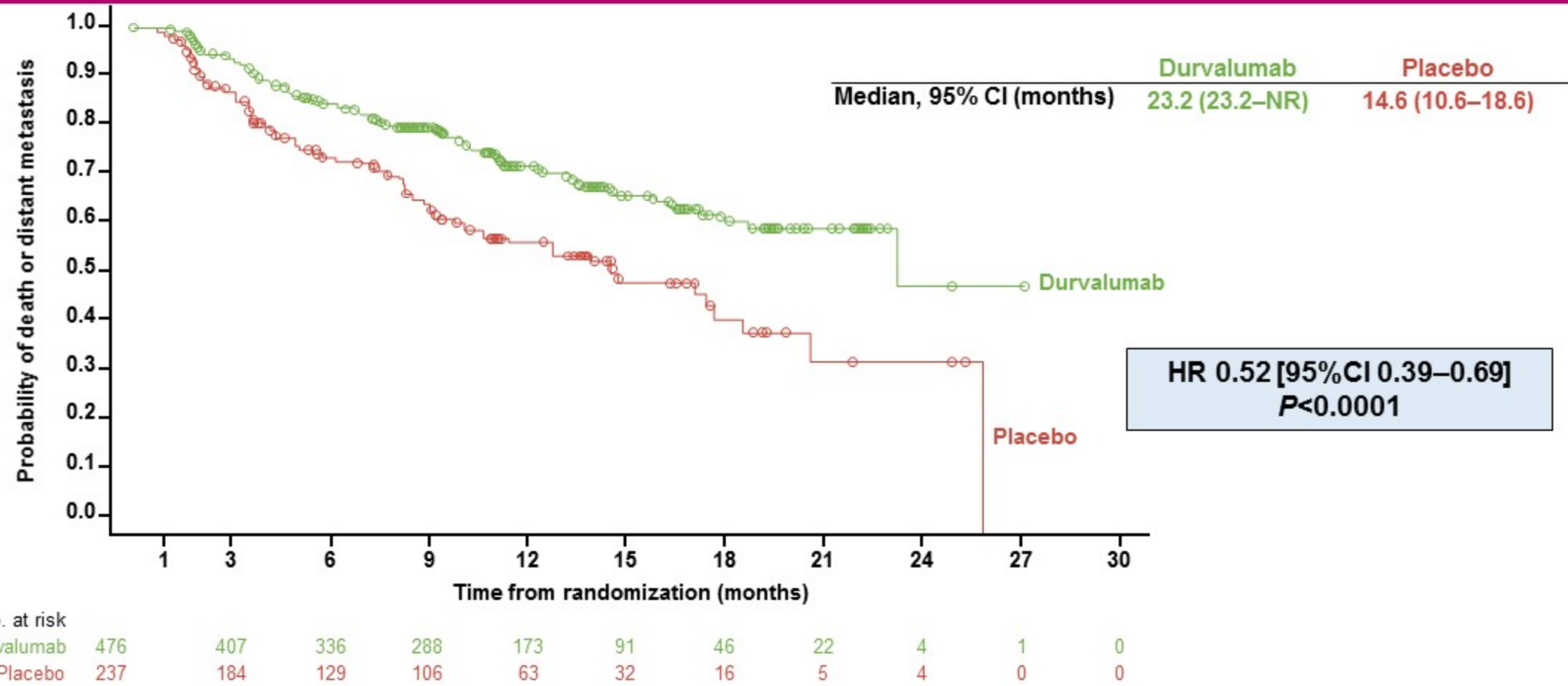
IMFINZI is a programmed death-ligand 1 (PD-L1) blocking antibody indicated for the treatment of patients with:

Unresectable, Stage III non-small cell lung cancer (NSCLC) whose disease has not progressed following concurrent platinum-based chemotherapy and radiation therapy. (1.2)

EMA

Still pending

Unresectable stage III NSCLC
> ph3 PACIFIC study

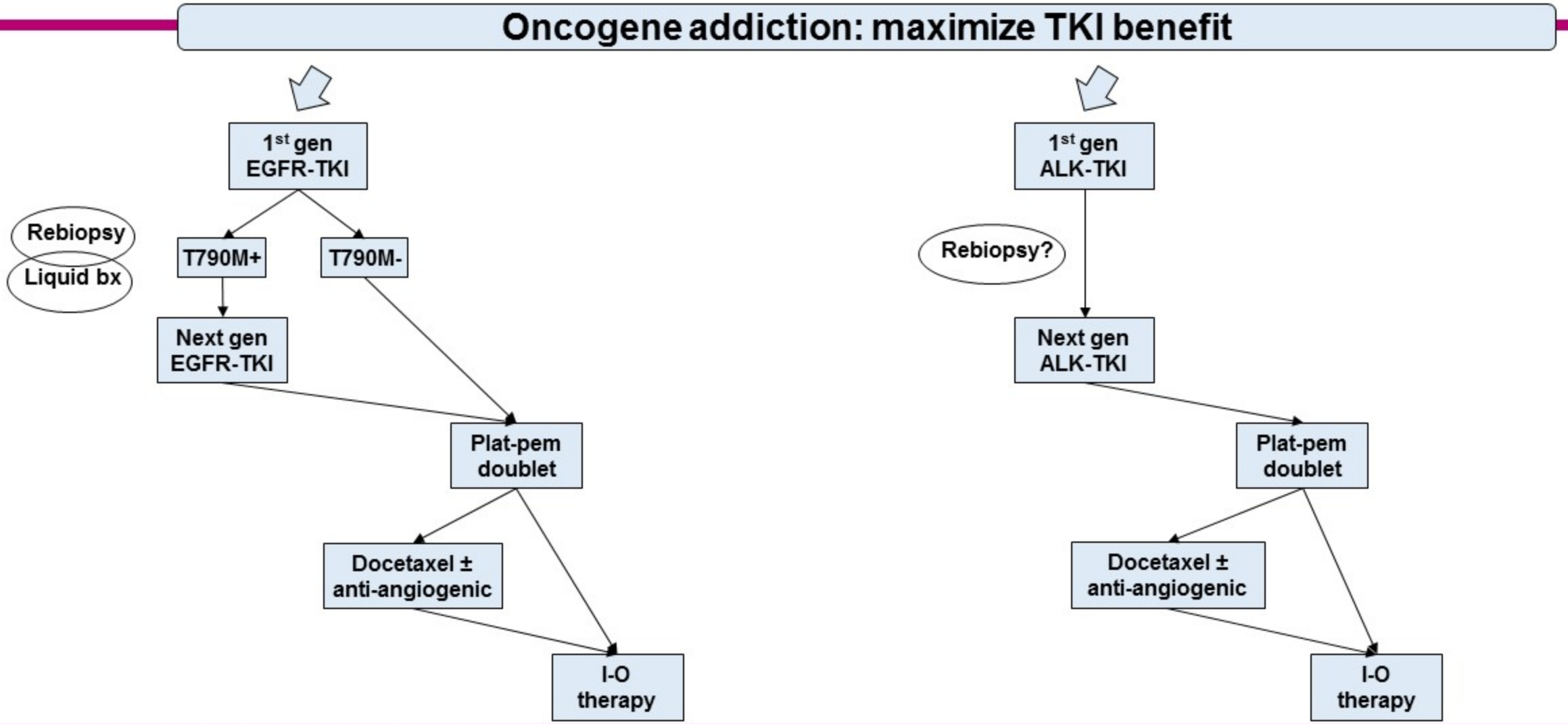


Paz-Ares et al, ESMO 2017 *and* Antonia et al, N Engl J Med Sep 9, 2017

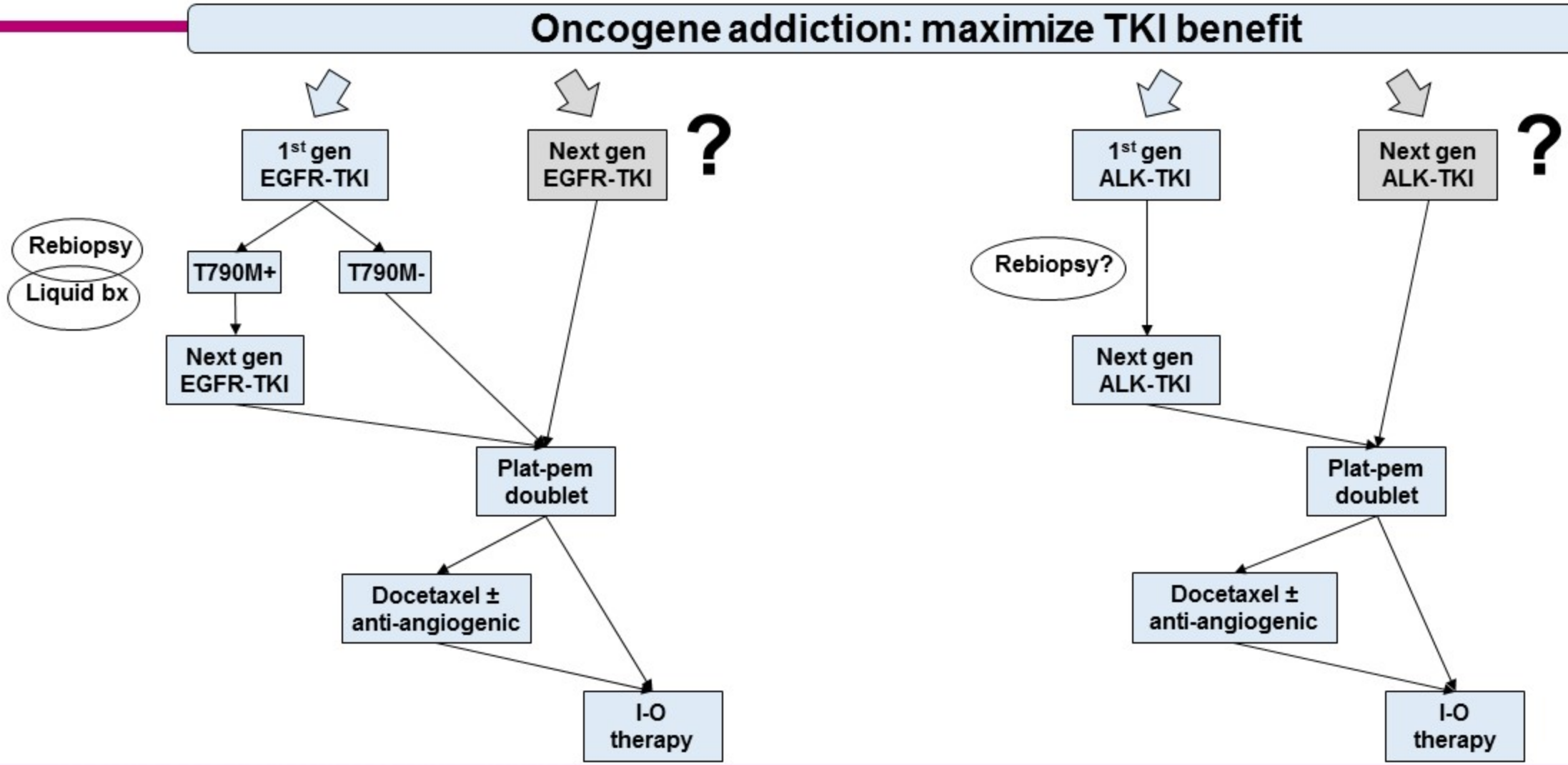
Advanced NSCLC with oncogene addiction

Moving new TKIs to front-line therapy

State of the art



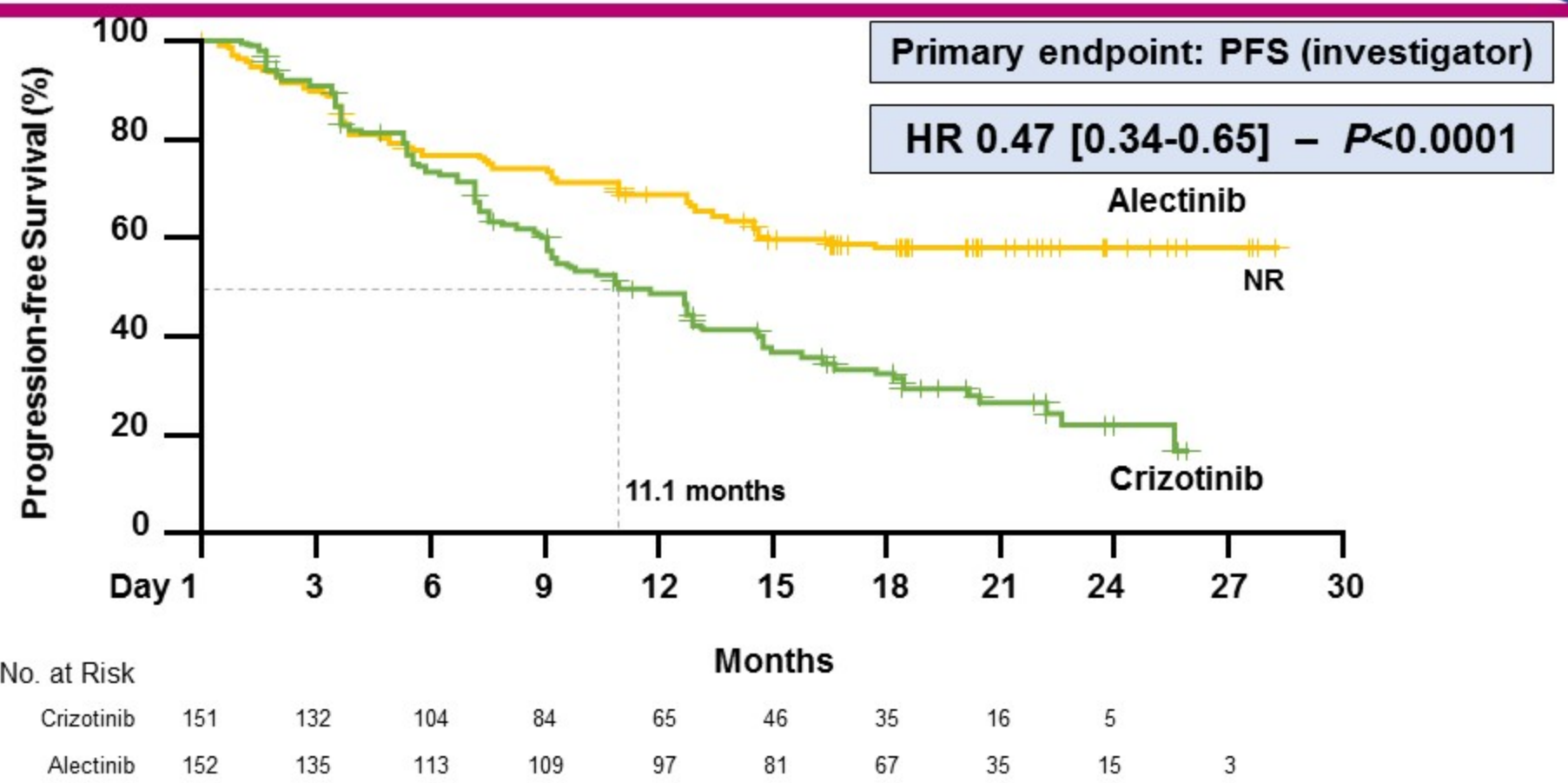
State of the art



Advanced ALK+ NSCLC

Ph3 ALEX study [Alectinib vs. Crizotinib]

------ASCO 2017------
Late Breaking News

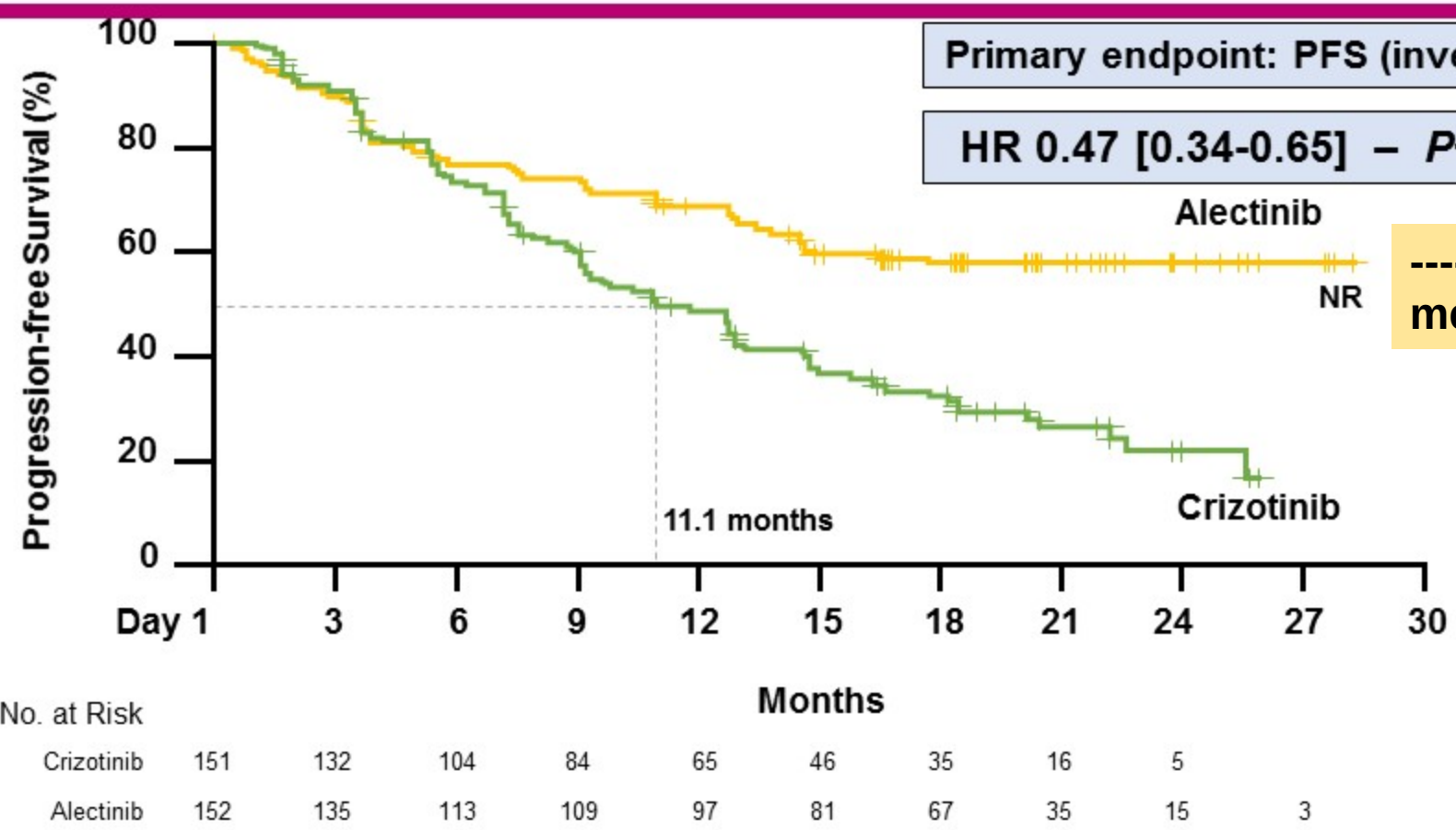


Shaw et al, abstract LBA9008, ASCO 2017 and Peters et al, N Engl J Med 377:829-838, 2017

Advanced ALK+ NSCLC

Ph3 ALEX study [Alectinib vs. Crizotinib]

------ASCO 2017------
Late Breaking News



----> ASCO 2018: median PFS 34 mo

Shaw et al, abstract LBA9008, ASCO 2017 and Peters et al, N Engl J Med 377:829-838, 2017

Advanced EGFR mutation+ NSCLC
> ph3 FLAURA study: Osimertinib *vs.* SoC-TKI

FLAURA

Advanced NSCLC

- **EGFRmut+**
  - **Exon 19 del or exon 21 L858R**
  - **Local or central testing**
- **No prior systemic therapy**
- **Stable CNS allowed**
- **PS 0-1**

° **gefitinib or erlotinib**

Stratified
- Mutation type
- Race (Asian/non-Asian)

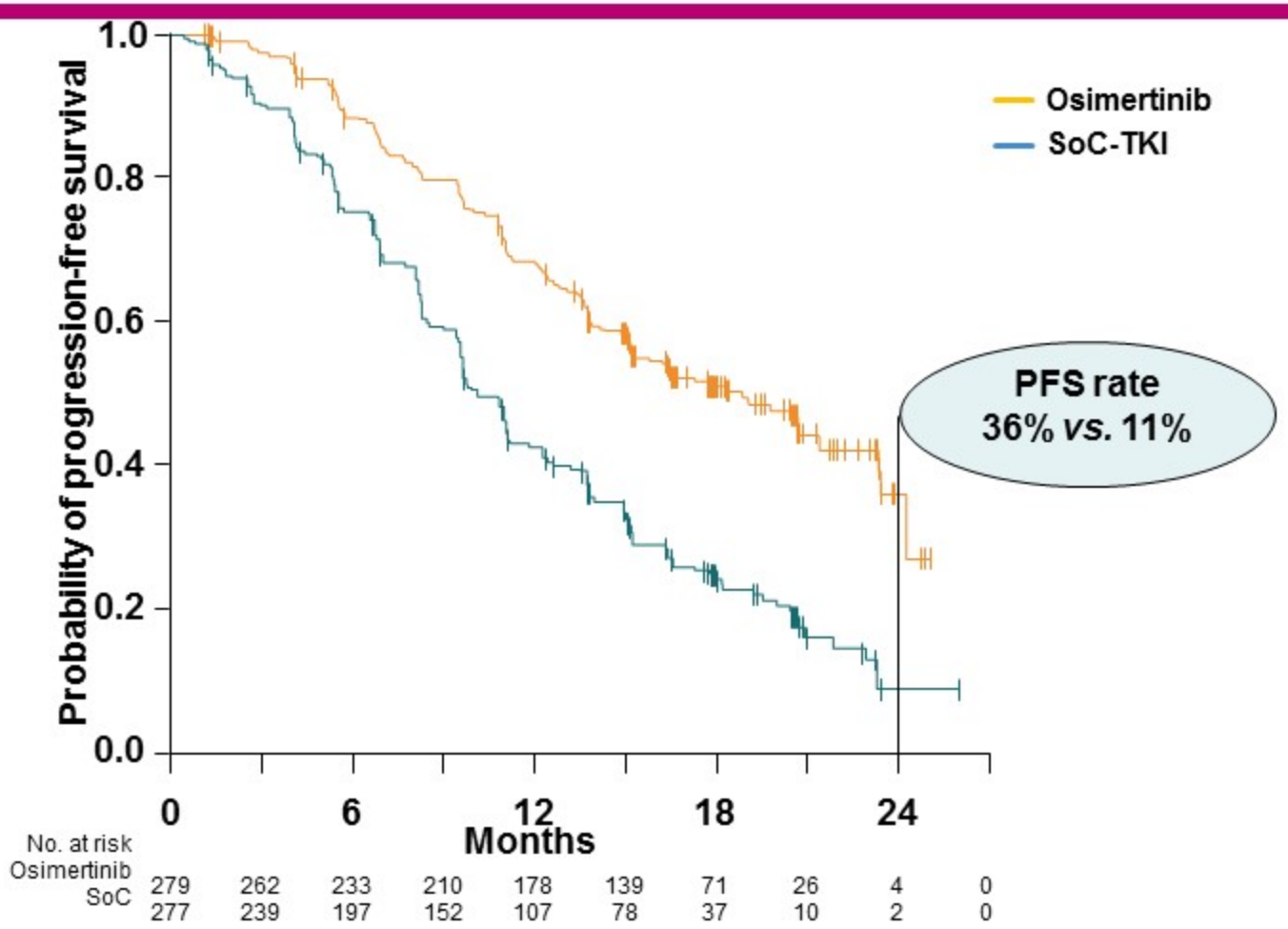
* **cross-over allowed if BICR confirmed PD and T790M**

Primary endpoint
- **PFS (investigator)**

Other endpoints
- ORR & DoR
- DCR
- OS
- PRO
- Safety

Ramalingam et al, ESMO 2017 *and* Soria et al, N Engl J Med 378:113-125, 2018

Advanced EGFR mutation+ NSCLC
> ph3 FLAURA study: PFS



	Osimertinib (N=279)	SoC-TKI (N=277)
Median PFS (95% CI)	18.9 [15.2-21.4]	10.2 [9.6-11.1]

HR 0.46 [0.37-0.57] - *P* < 0.0001

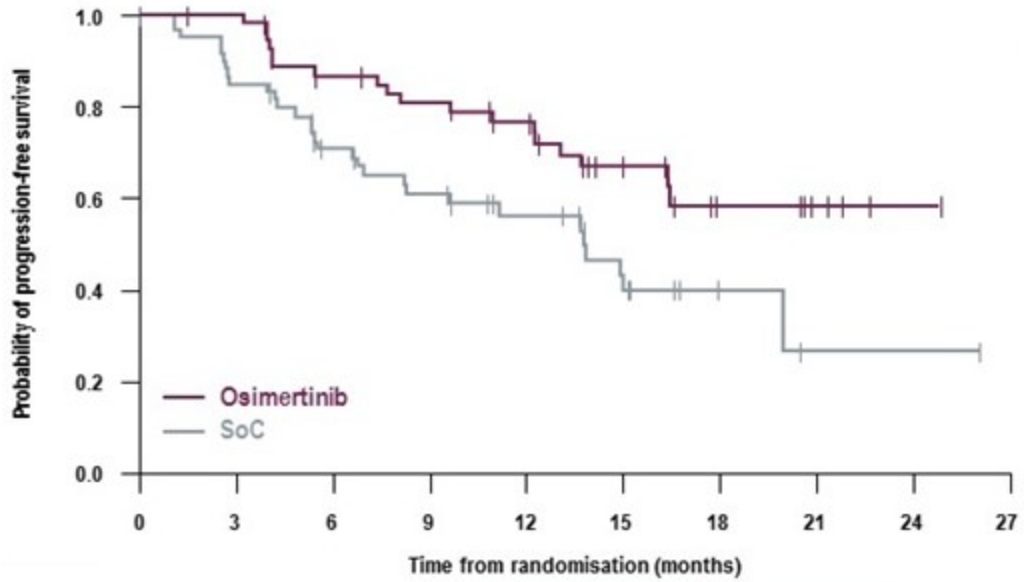
Ramalingam et al, ESMO 2017 *and* Soria et al, N Engl J Med 378:113-125, 2018

Advanced EGFR mutation+ NSCLC
> ph3 FLAURA study: adverse events

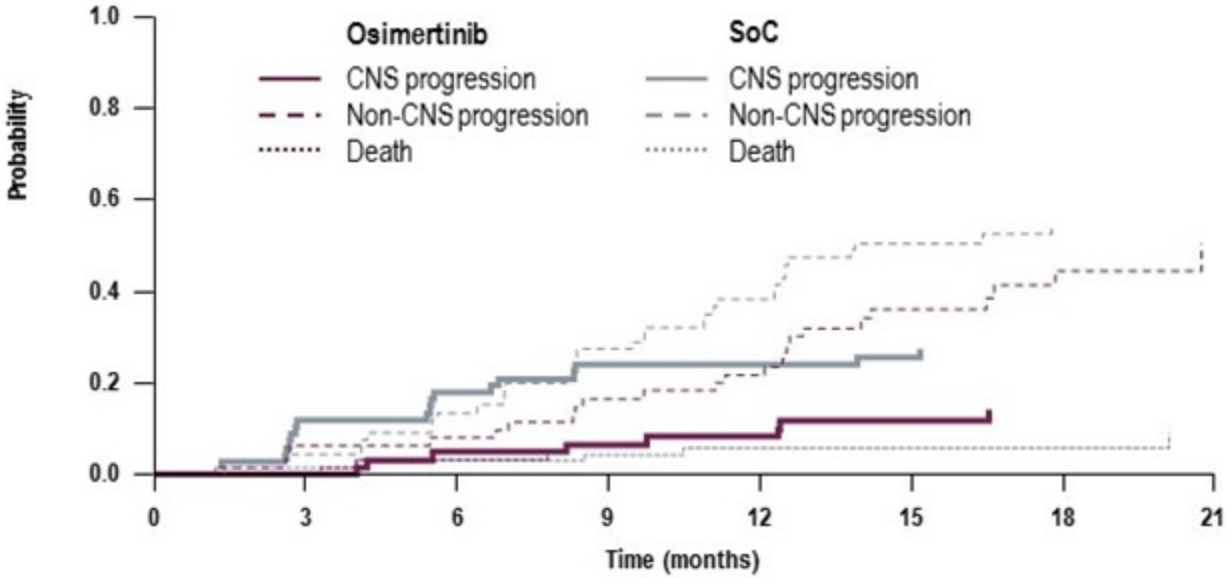
AE any, n (%)	Osimertinib (n=279)	SoC-TKI (n=277)
Any AE	273 (98)	271 (98)
Any AE Grade ≥3	94 (34)	124 (45)
Any AE leading to death	6 (2)	10 (4)
Any serious AE	60 (22)	70 (25)
Any AE leading to discontinuation	37 (13)	49 (18)
AE, possibly causally related, n (%)		
Any AE	253 (91)	255 (92)
Any AE Grade ≥3	49 (18)	78 (28)
Any AE leading to death	0	1 (<1)
Any serious AE	22 (8)	23 (8)

Ramalingam et al, ESMO 2017 *and* Soria et al, N Engl J Med 378:113-125, 2018

Advanced EGFR mutation+ NSCLC
> ph3 FLAURA: CNS lesions activity and CNS lesions prevention



	Osimertinib (n=61)	SoC (n=67)
Median CNS PFS, months (95% CI)	NR (16.5, NC)	13.9 (8.3, NC)
HR* (95% CI); p-value	0.48 (0.26, 0.86); p=0.014	



Conditional probability of CNS progression*, % (95% CI)	Osimertinib (n=61)	SoC (n=67)
At 6 months	5 (1, 13)	18 (10, 28)
At 12 months	8 (3, 16)	24 (15, 35)

Vansteenkiste et al, ESMO-ASIA 2017

Take-Home Message

- **Strong next-generation TKIs may become the preferred 1st line therapy**
  - **Strongly superior PFS compared to previous drugs: Alectinib HR 0.47; Osimertinib HR 0.46 (*P*<0.0001)**
  - **Better tolerated: lower rates of grade ≥3 AEs and discontinuation rates**
  - **Better control of existing CNS metastases and lower probability of development of CNS lesions**

EMA

The CHMP adopted an extension to the existing indication as follows[1]:

"Tagrisso **as monotherapy** is indicated for:

- **the first-line treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating epidermal growth factor receptor (EGFR) mutations.**
- the treatment of adult patients with locally advanced or metastatic EGFR T790M mutation-positive NSCLC."

EMA

4.1 Therapeutic indications

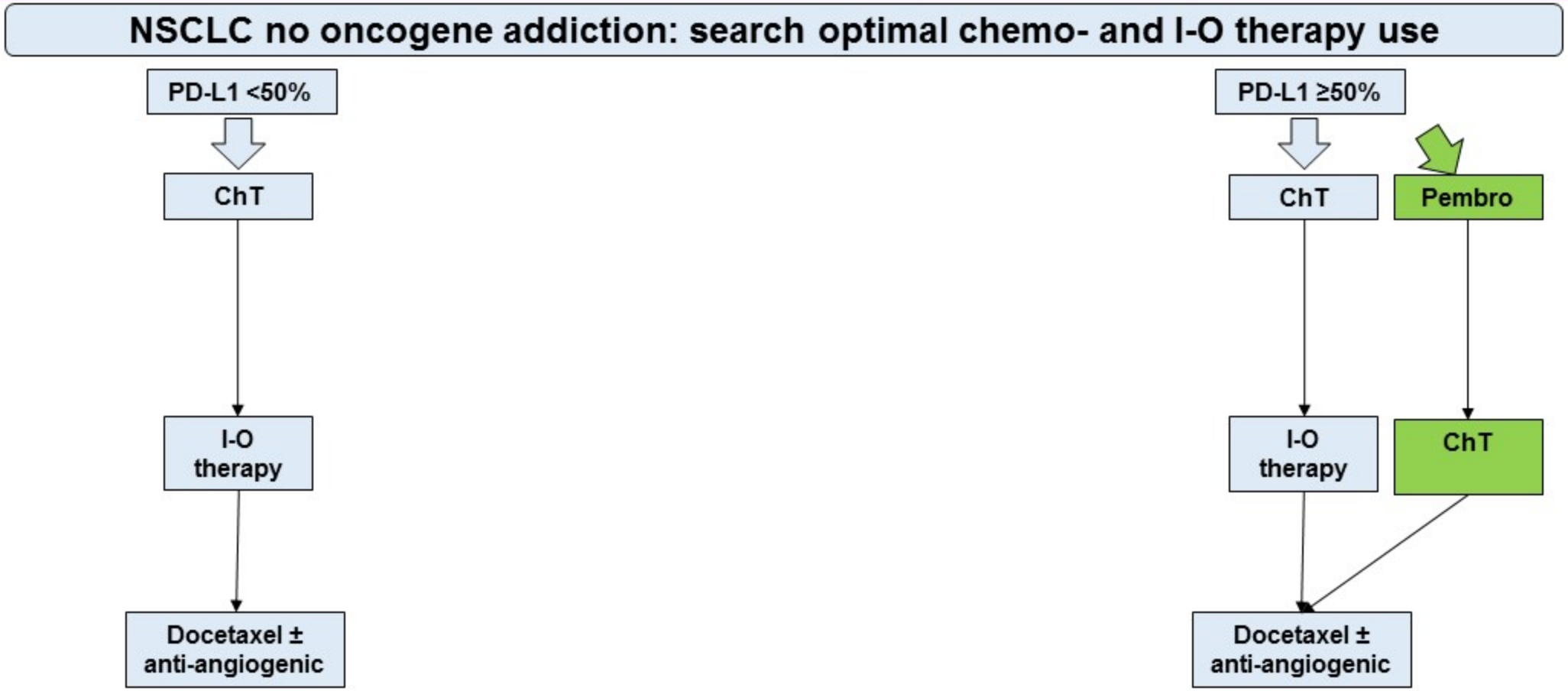
Alecensa as monotherapy is indicated for the first-line treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC).

Alecensa as monotherapy is indicated for the treatment of adult patients with ALK-positive advanced NSCLC previously treated with crizotinib.

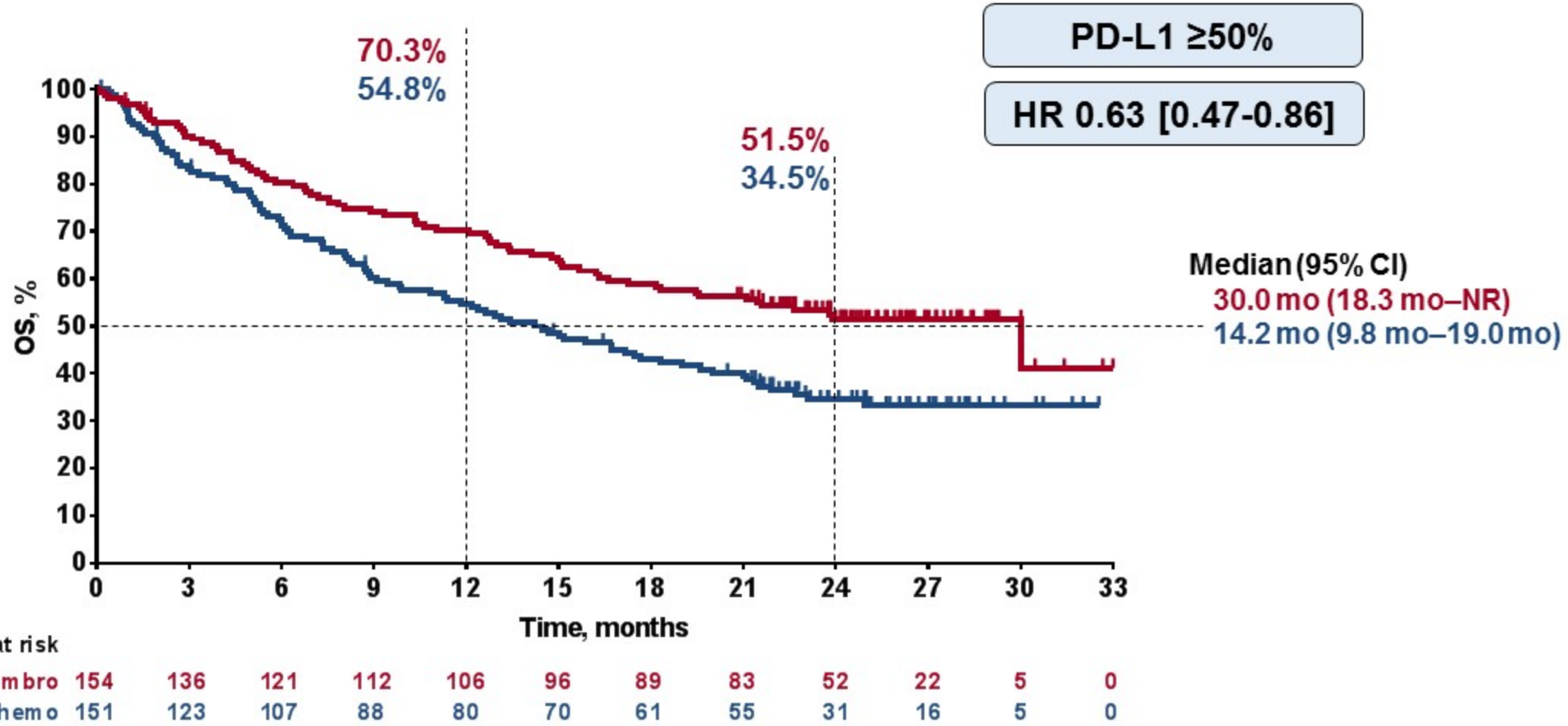
Advanced NSCLC no oncogene addiction

Exploiting immunotherapy in 1st line setting

State of the art



State of the art
2016-2017: Keynote-024 study



Brahmer et al, WCLC 2017

AACR April 14-18, 2018
ASCO June 1-5, 2018
Late-breaking news

NSCLC no oncogene addiction
> which IO biomarker ?

- For the time being, PD-L1 expression
  - Not perfect, but prospectively validated for ORR, PFS and OS
  - Important for 1st line choices
  - ASCO #9030: validation for long-term OS (4-year survival in PD-L1 ≥50%: 48% !)
  - Most of the technical issues are settled
  - Well implemented in clinical practice
    - Standard IHC, part of baseline diagnostic assessment
    - Fast result
    - Acceptable cost

High	Low	None
PD-L1 ≥50%	PD-L1 1-49%	PD-L1 <1%
TC/IC 3	TC/IC 1 or 2	TC/IC = 0

- Tumor mutation burden (TMB): under development, not prospectively validated

NSCLC 1L immunotherapy

IO versus chemo				
Keynote-024	**Pembro vs. doublet**	**All NSCLC**	**PD-L1 ≥50%**	Reck et al. ESMO 2016 / NEJM
Checkmate-026	**Nivo vs. doublet**	**All NSCLC**	**PD-L1 ≥5%**	Socinski et al ESMO 2016 / NEJM 2017
Keynote-042	**Pembro vs. doublet**	**All NSCLC**	**PD-L1 ≥1%**	Lopes et al. ASCO 2018 #LBA4
sub 1-49% and ≥50%				
IO + chemo				
IMpower150	**Atezo + CarPacBeva**	**Nsq-NSCLC**	**All PD-L1**	Socinski et al. ASCO 2018 #9002 / NEJM
sub TC/IC 0 and 1-2 and 3				
Keynote-189	**Pembro + PlatPem**	**Nsq-NSCLC**	**All PD-L1**	Gandhi et al. AACR 2018 : NEJM
sub <1% and 1-49% and ≥50%				
IMpower131	**Atezo + CarNabPacli**	**Sq-NSCLC**	**All PD-L1**	Jotte et al. ASCO 2018 #9000
sub TC/IC 0 and 1-2 and 3				
Keynote-407	**Pembro + Car(Nab)Pacli**	**Sq-NSCLC**	**All PD-L1**	Paz-Ares et al. ASCO 2018 #105
sub <1% and 1-49% and ≥50%				
Checkmate-227	**Nivo + doublet**	**All NSCLC**	**PD-L1 <1%**	Borghaei et al. ASCO 2018 #9001

NSCLC 1L immunotherapy

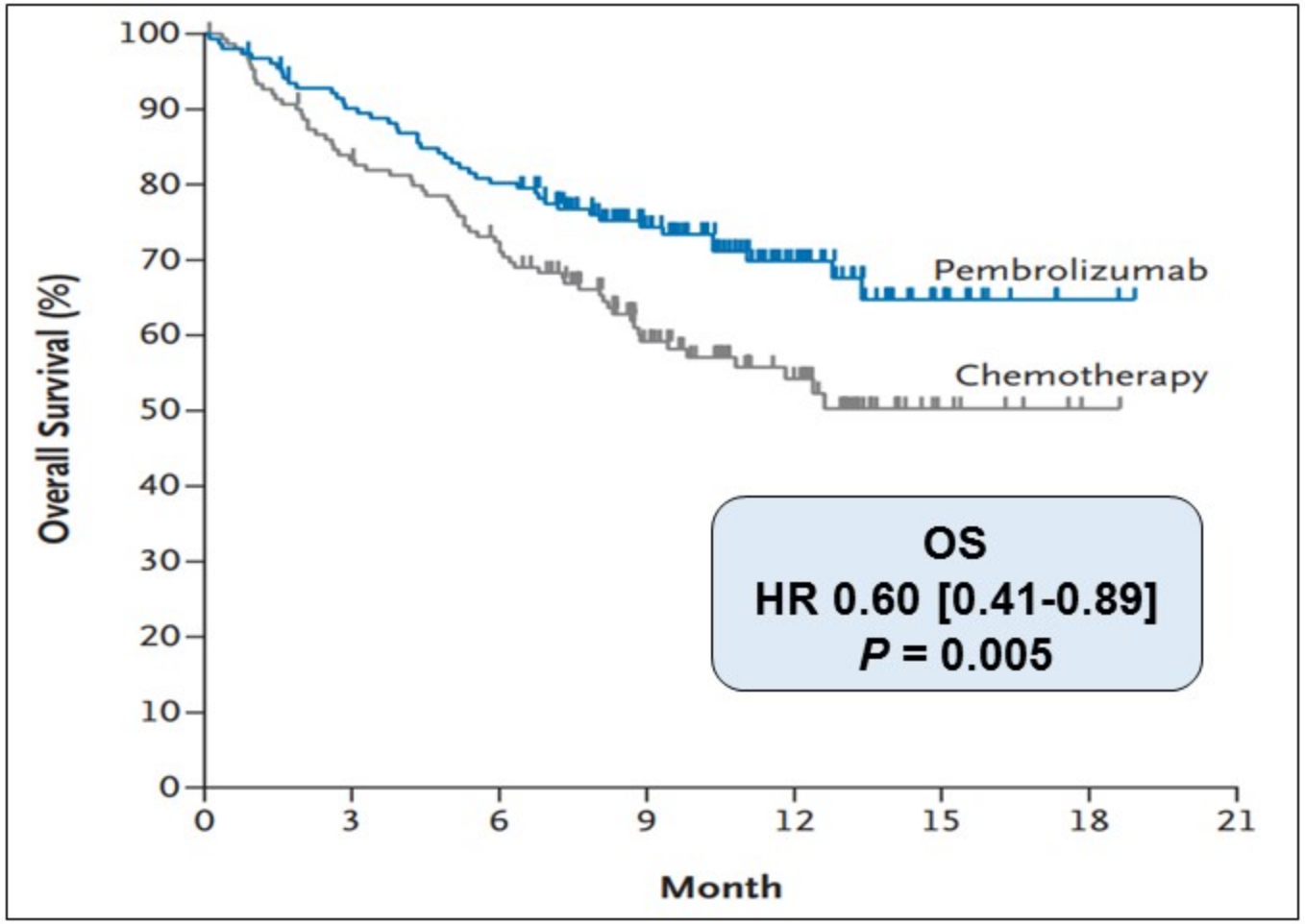
Keynote-024 study

- Advanced NSCLC
- PD-L1 ≥50%
- PS 0-1

R

Pembrolizumab (N=154)

Platinum doublet (N=151)

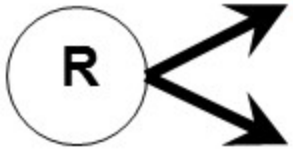


Reck et al, ESMO 2016 *and* N Engl J Med 375:1823-1833, 2016

NSCLC 1L immunotherapy

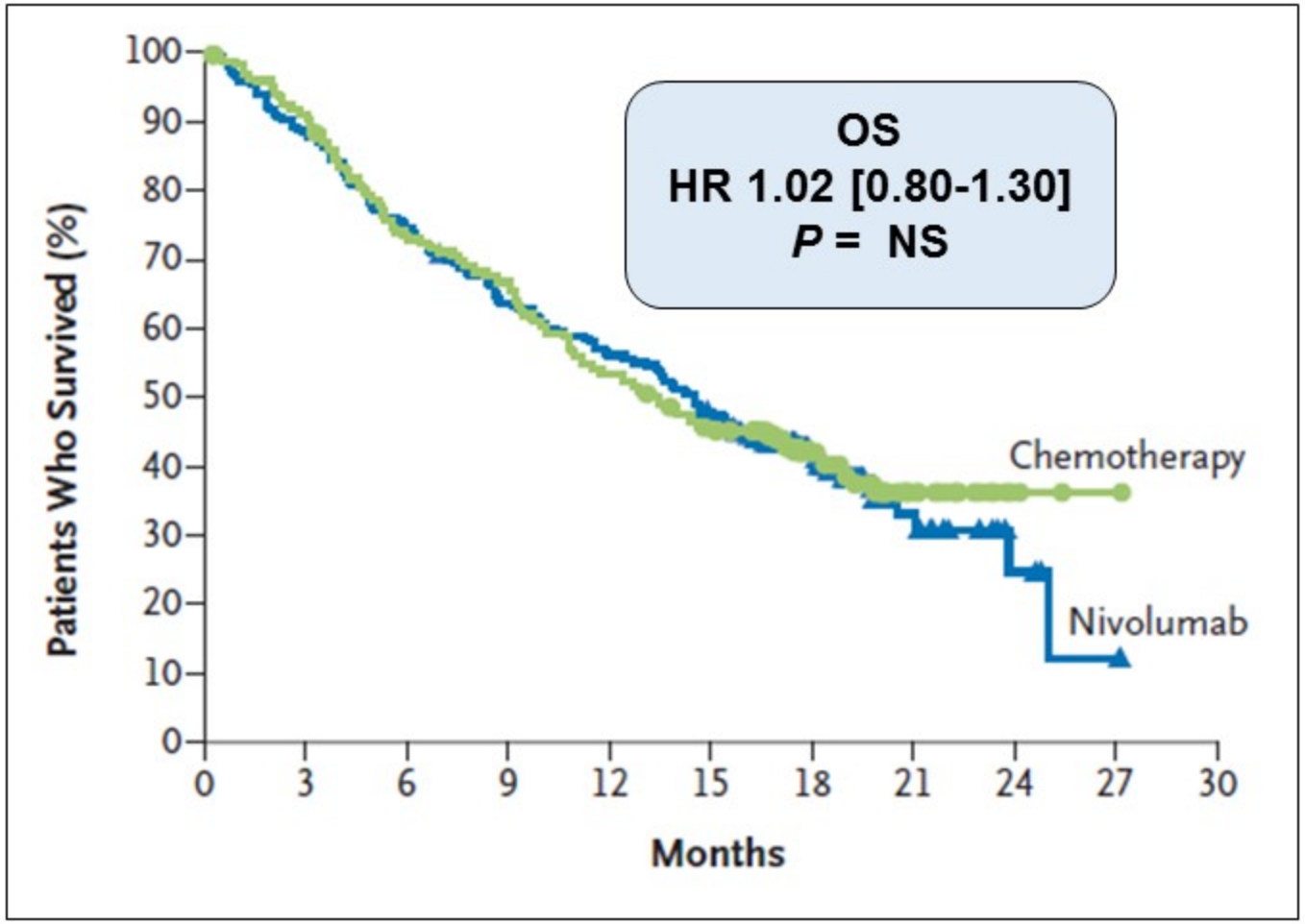
Checkmate-026 study

- Advanced NSCLC
- PD-L1 ≥5%
- PS 0-1



Nivolumab (N=225)

Platinum doublet (N=225)

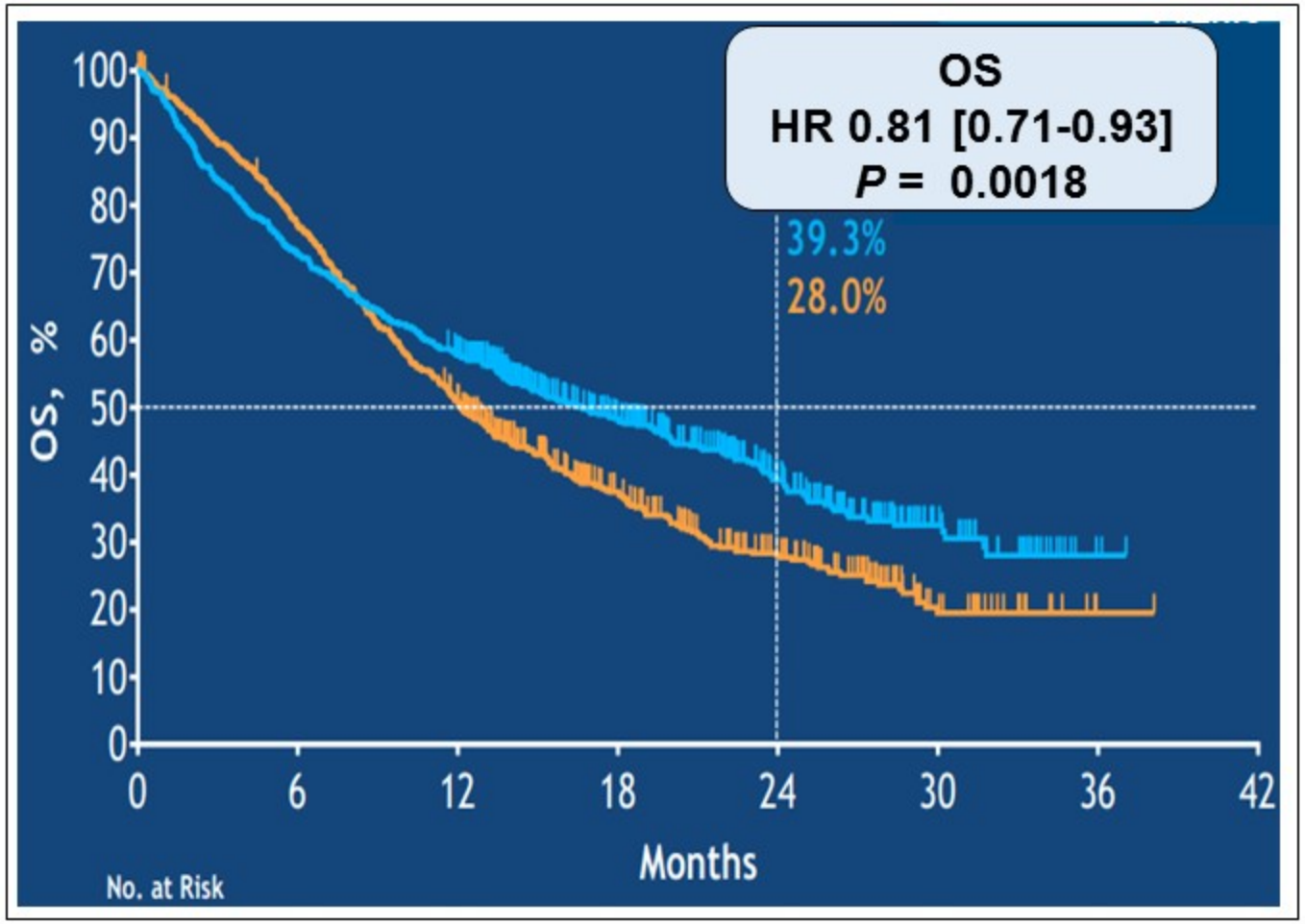


Socinski et al, ESMO 2016 *and* Carbone N Engl J Med 376:2415-2426, 2017

NSCLC 1L immunotherapy

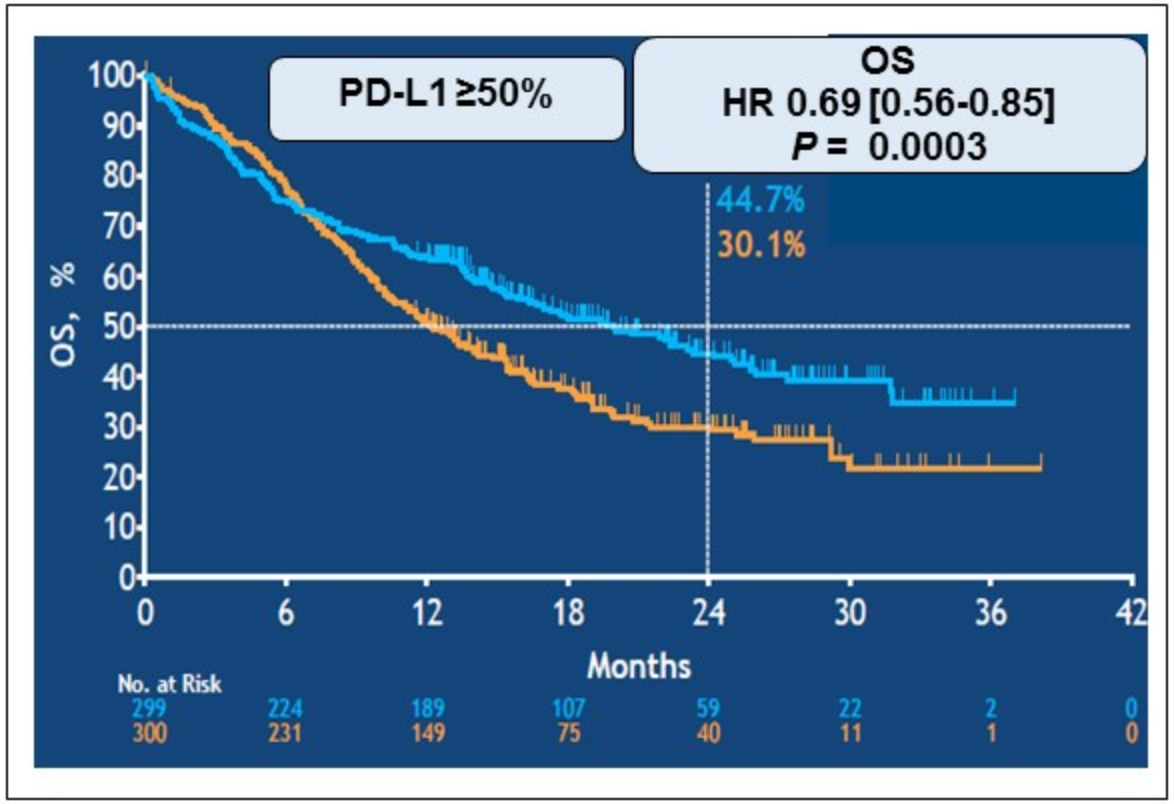
Keynote-042 study

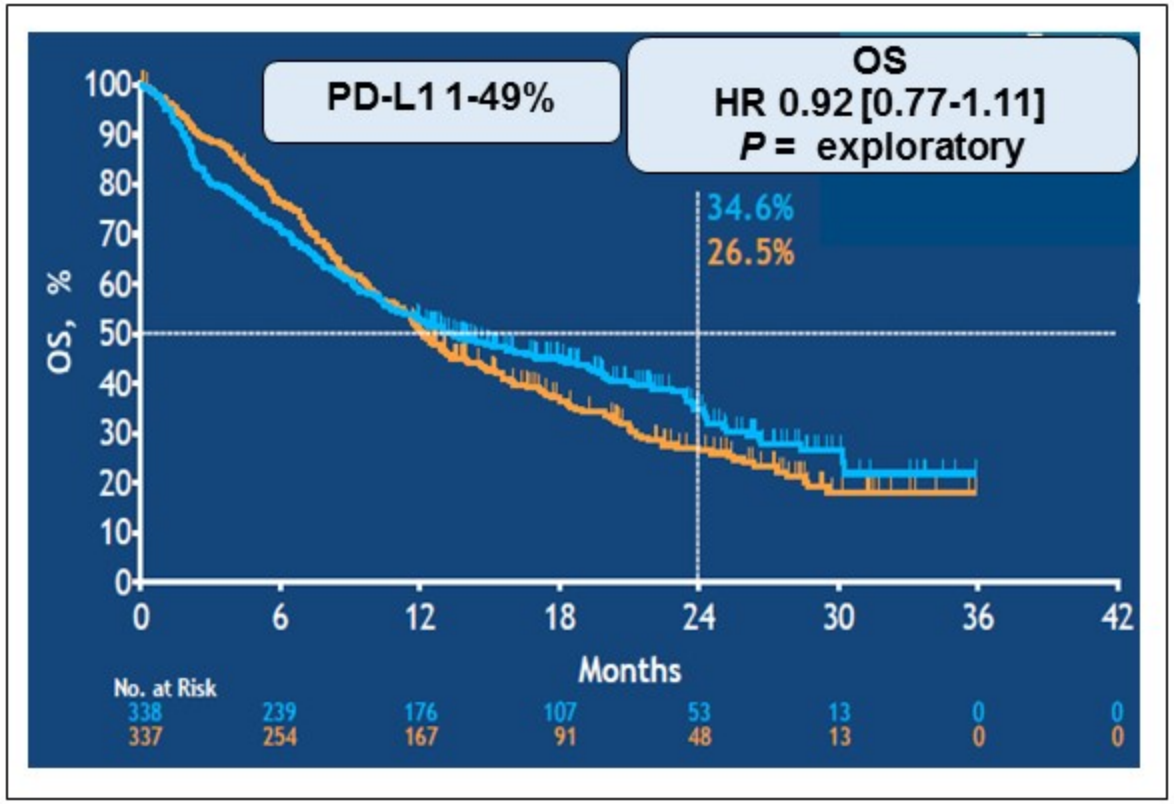
- Advanced NSCLC
- PD-L1 ≥1%
- PS 0-1



Lopes et al, ASCO 2018 #LBA4

NSCLC 1L immunotherapy





Keynote-042 PD-L1 ≥1% → R → Pembrolizumab (N=637)

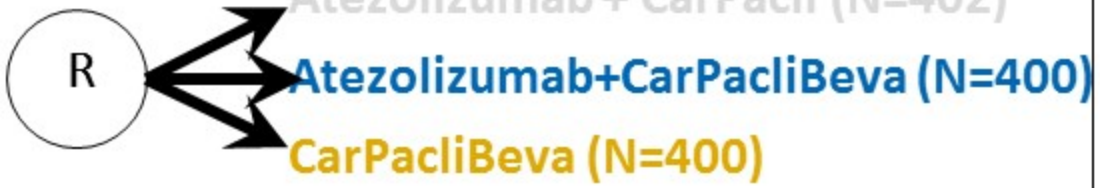
R → Platinum doublet (N=637)

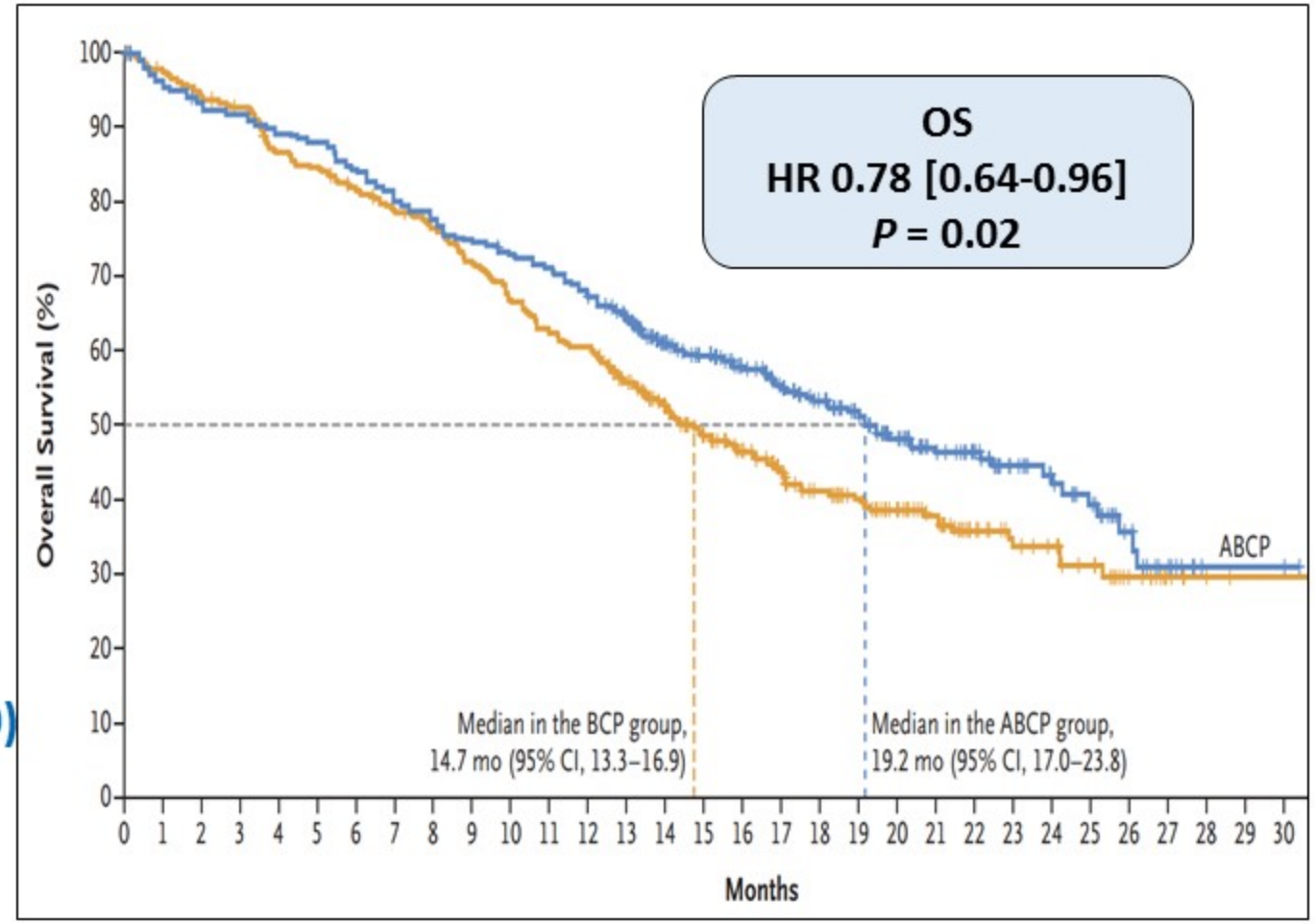
Lopes et al, ASCO 2018 #LBA4

NSCLC 1L immunotherapy

IMpower150 study

- **Advanced Nsq-NSCLC**
- **Any PD-L1**
- **PS 0-1**



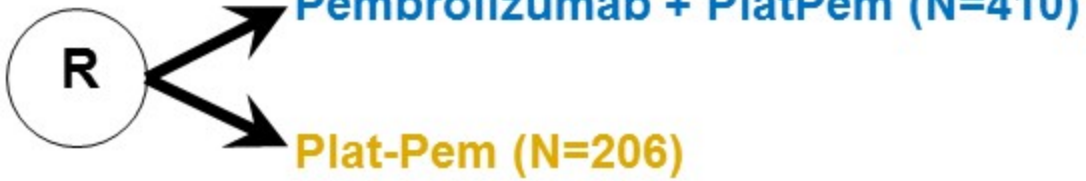


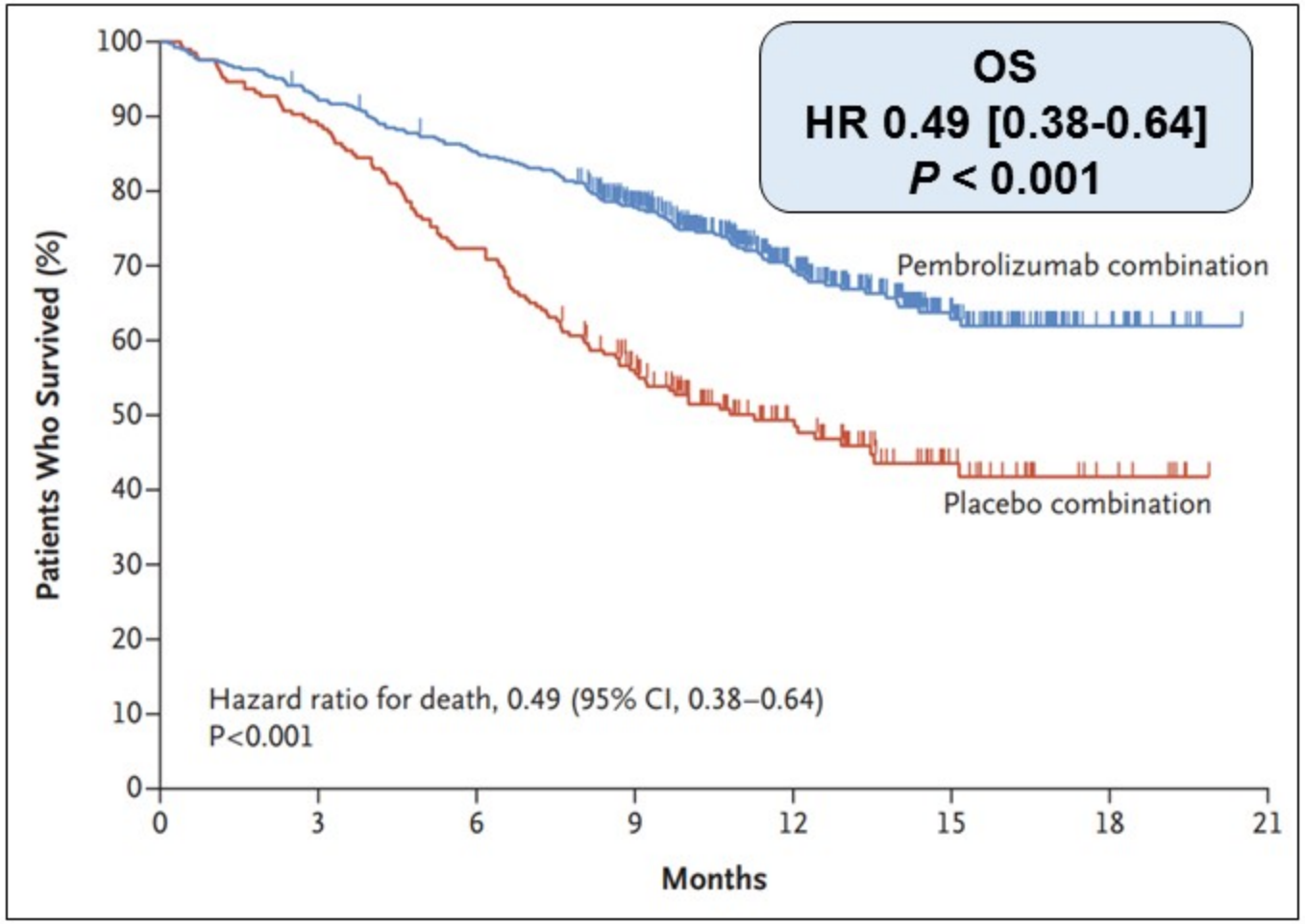
Reck et al, ESMO-IO 2017 and Socinski et al, N Engl J Med June 4, 2018

NSCLC 1L immunotherapy

Keynote-189 study

- **Advanced Nsq-NSCLC**
- **Any PD-L1**
- **PS 0-1**



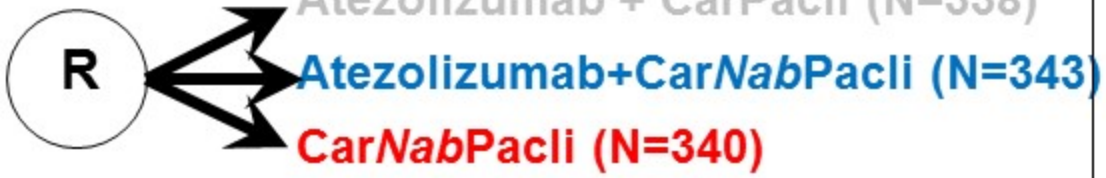


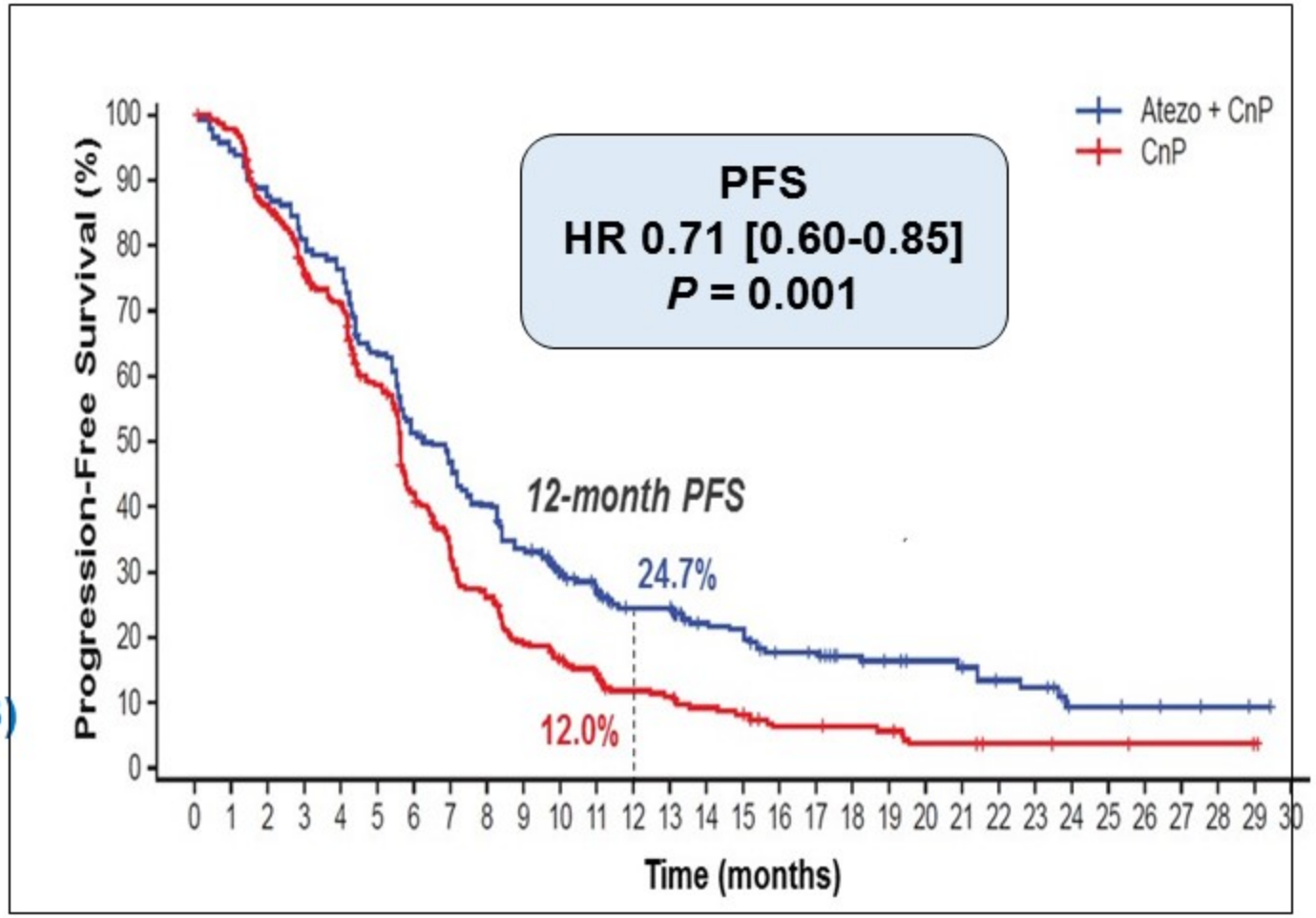
Gandhi et al, AACR 2018 and N Engl J Med 378:2078-2092, 2018

NSCLC 1L immunotherapy

IMpower-131 study

- **Advanced Sq-NSCLC**
- **Any PD-L1**
- **PS 0-1**



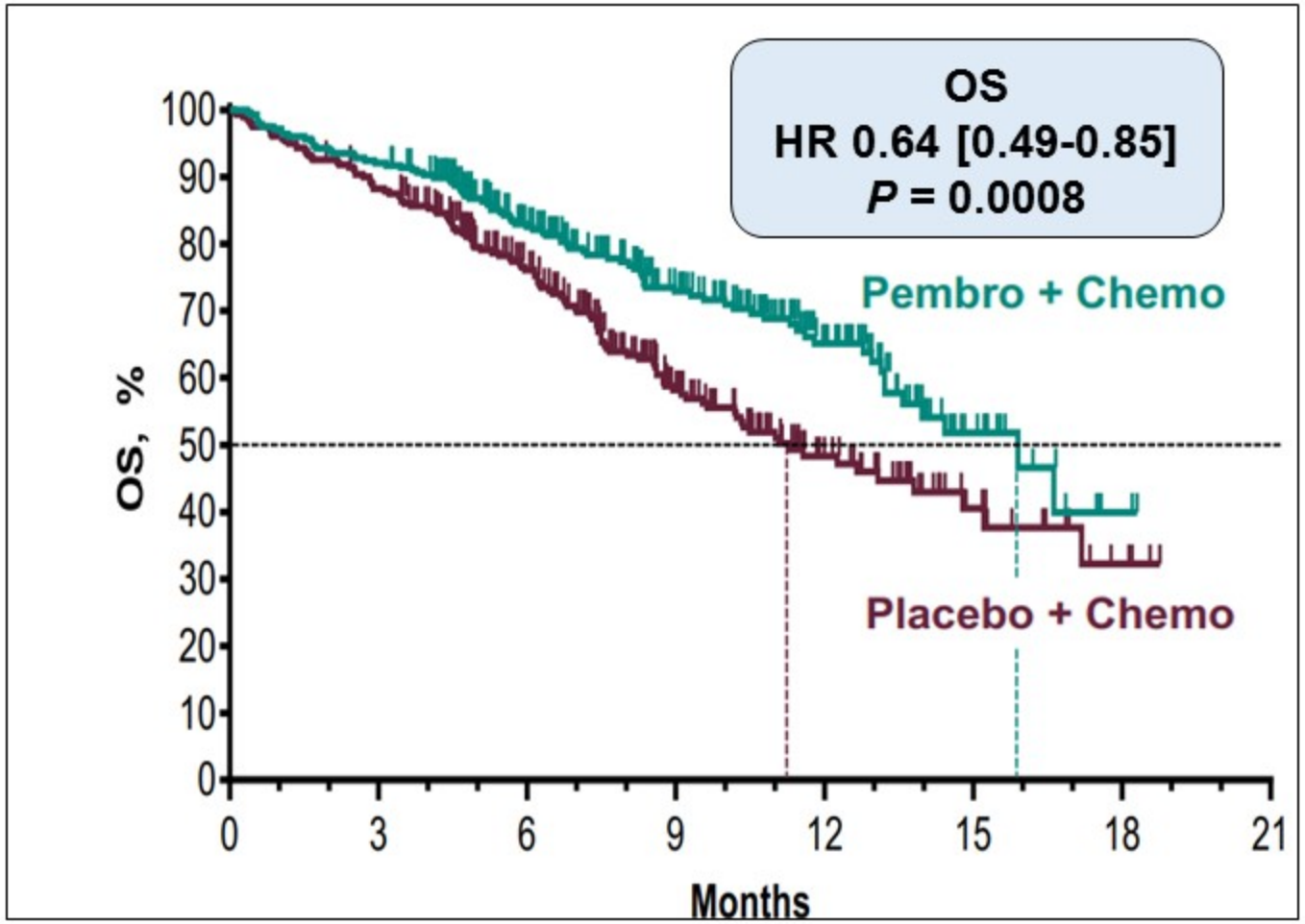


Jotte et al, ASCO 2018 #9000

NSCLC 1L immunotherapy

Keynote-407 study

- Advanced Sq-NSCLC
- Any PD-L1
- PS 0-1

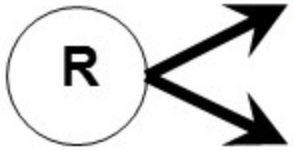


Paz-Ares et al, ASCO 2018 #105

NSCLC 1L immunotherapy

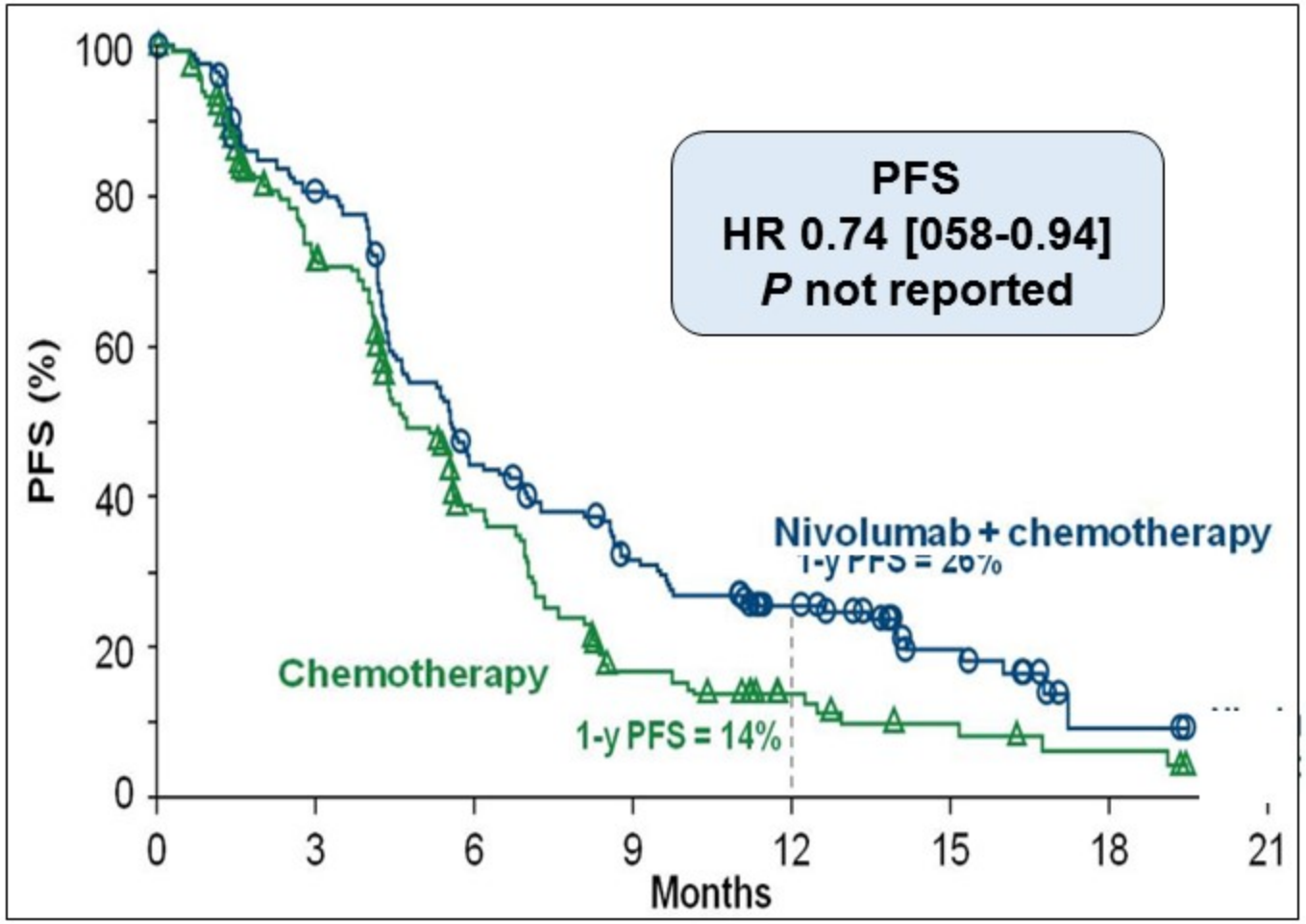
Checkmate-227 study

- Advanced NSCLC
- PD-L1 <1%
- PS 0-1



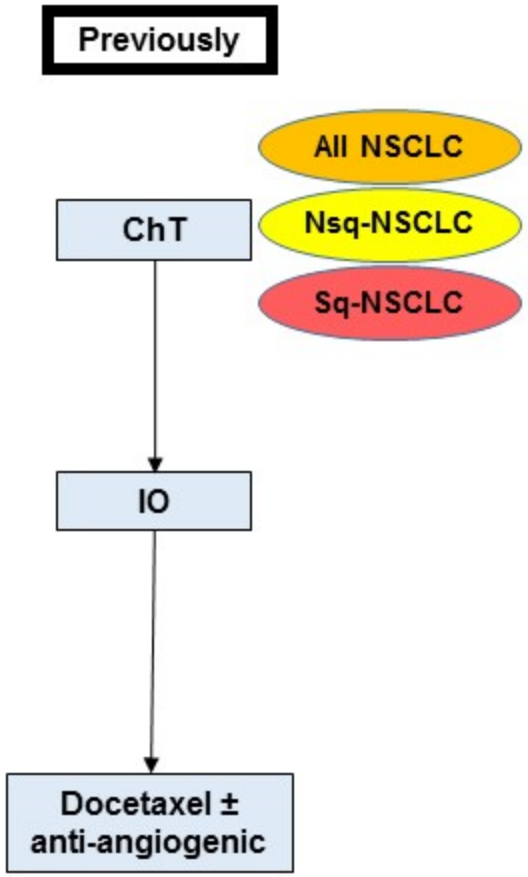
Nivolumab + doublet (N=186)

Platinum doublet (N=177)



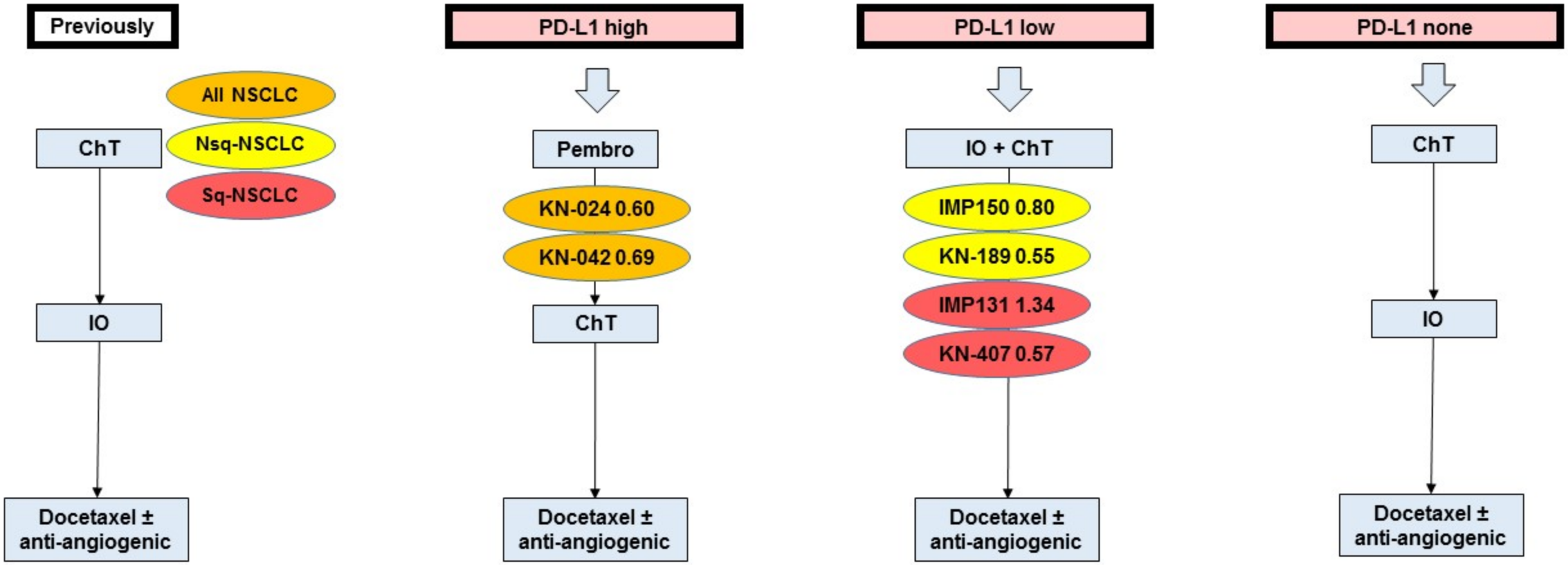
Borghaei et al, ASCO 2018 #9001

NSCLC no oncogene addiction
> histology-based based lanscape



NSCLC no oncogene addiction
> suggestions for a PD-L1 based lanscape

Search optimal chemo- and IO therapy use



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