

Immunterapi ved lungekreft

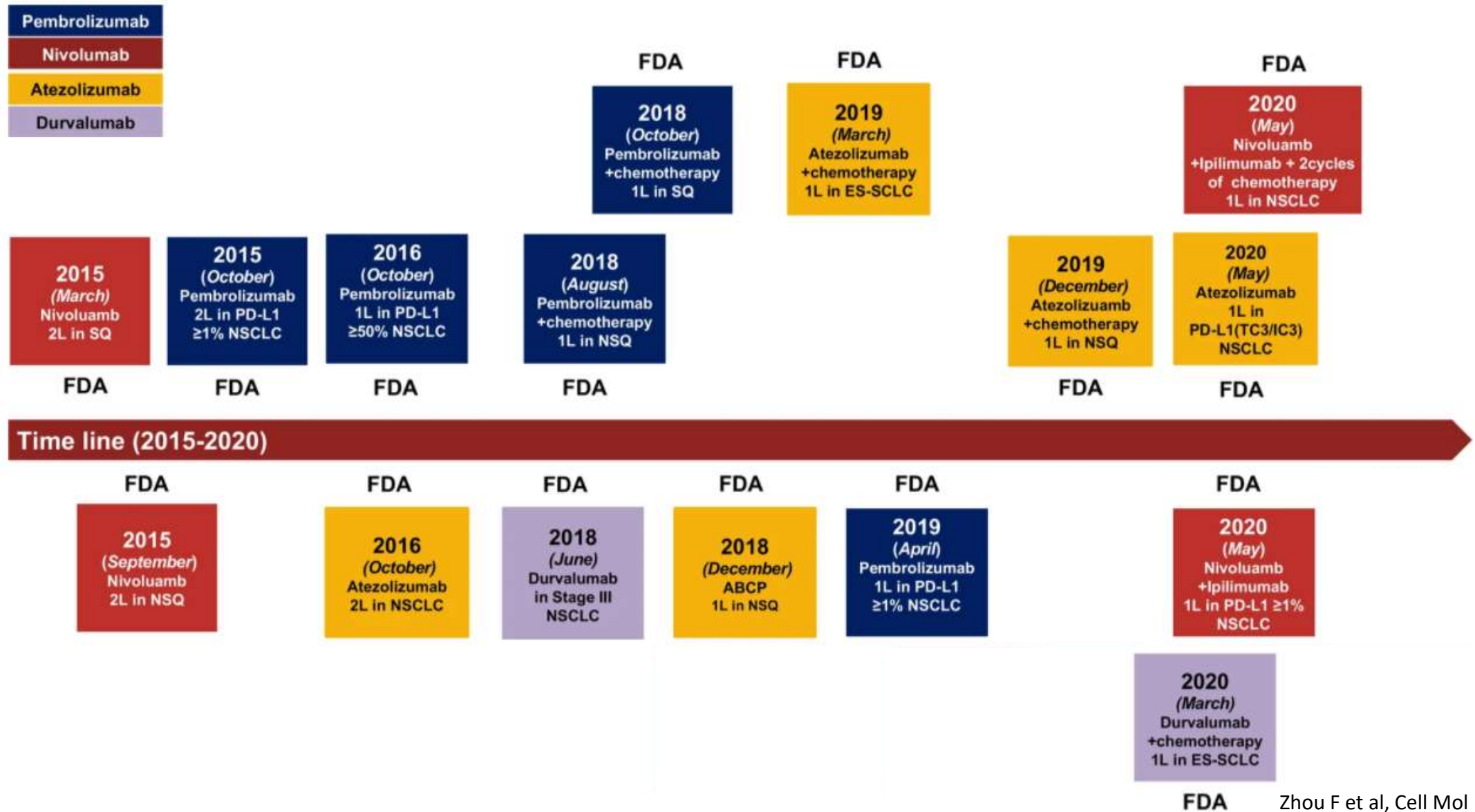
Odd Terje Brustugun

Onkolog dr med

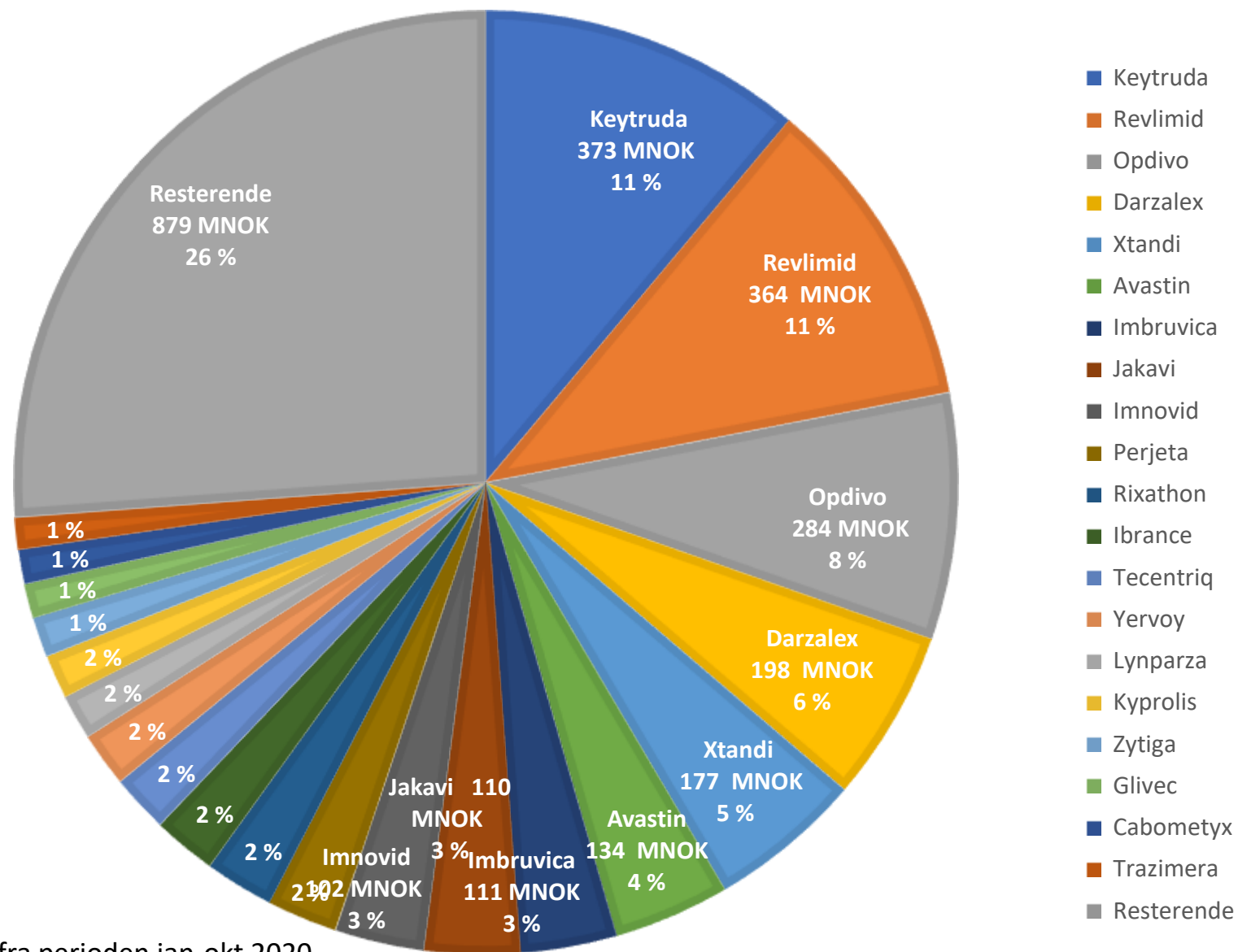
Onkologisk seksjon, Drammen sykehus

Leder, Norsk lungekreftgruppe

Immunterapi-godkjenninger ved lungekreft

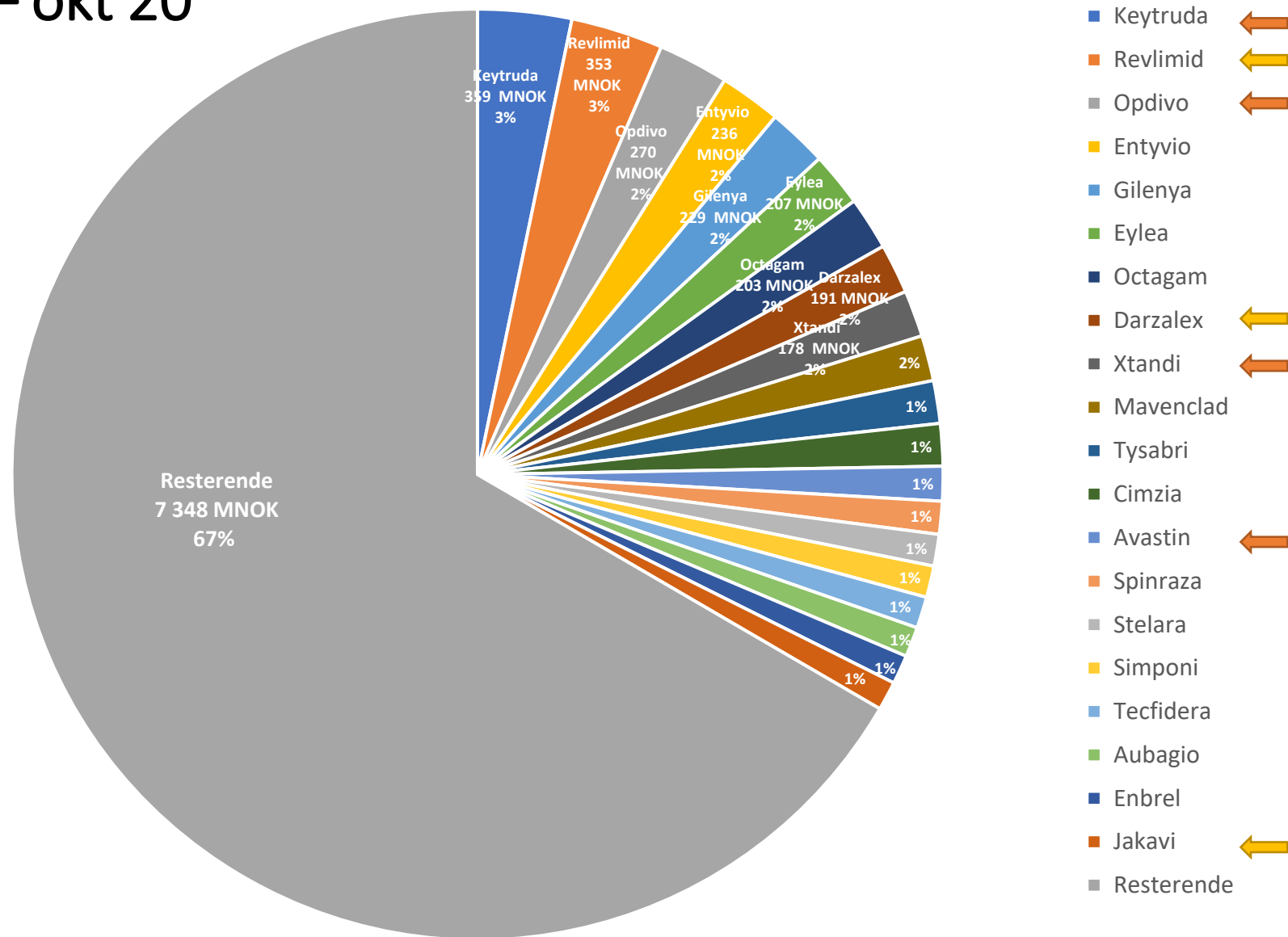


Andel kostnader topp 20 onkologi-legemidler

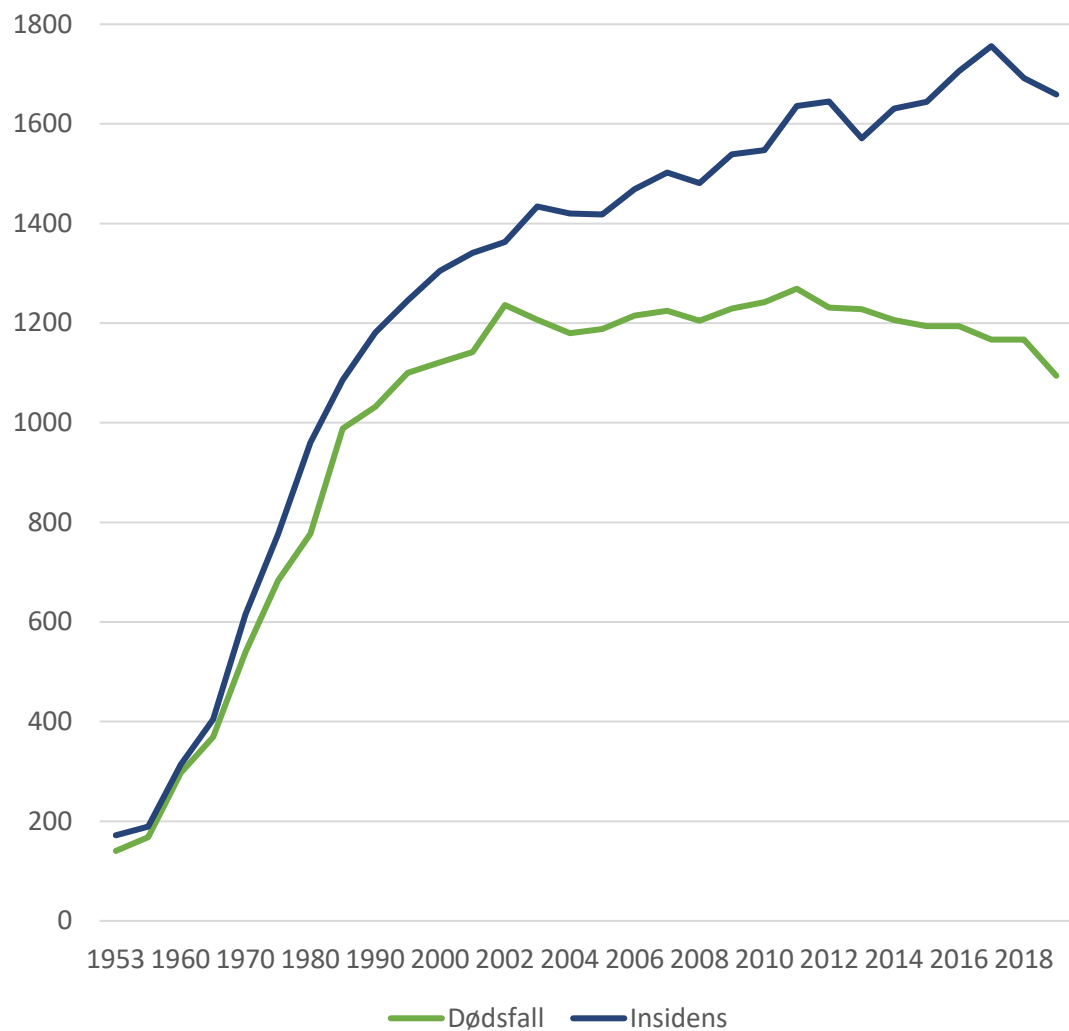


*2020 estimert fra perioden jan-okt 2020

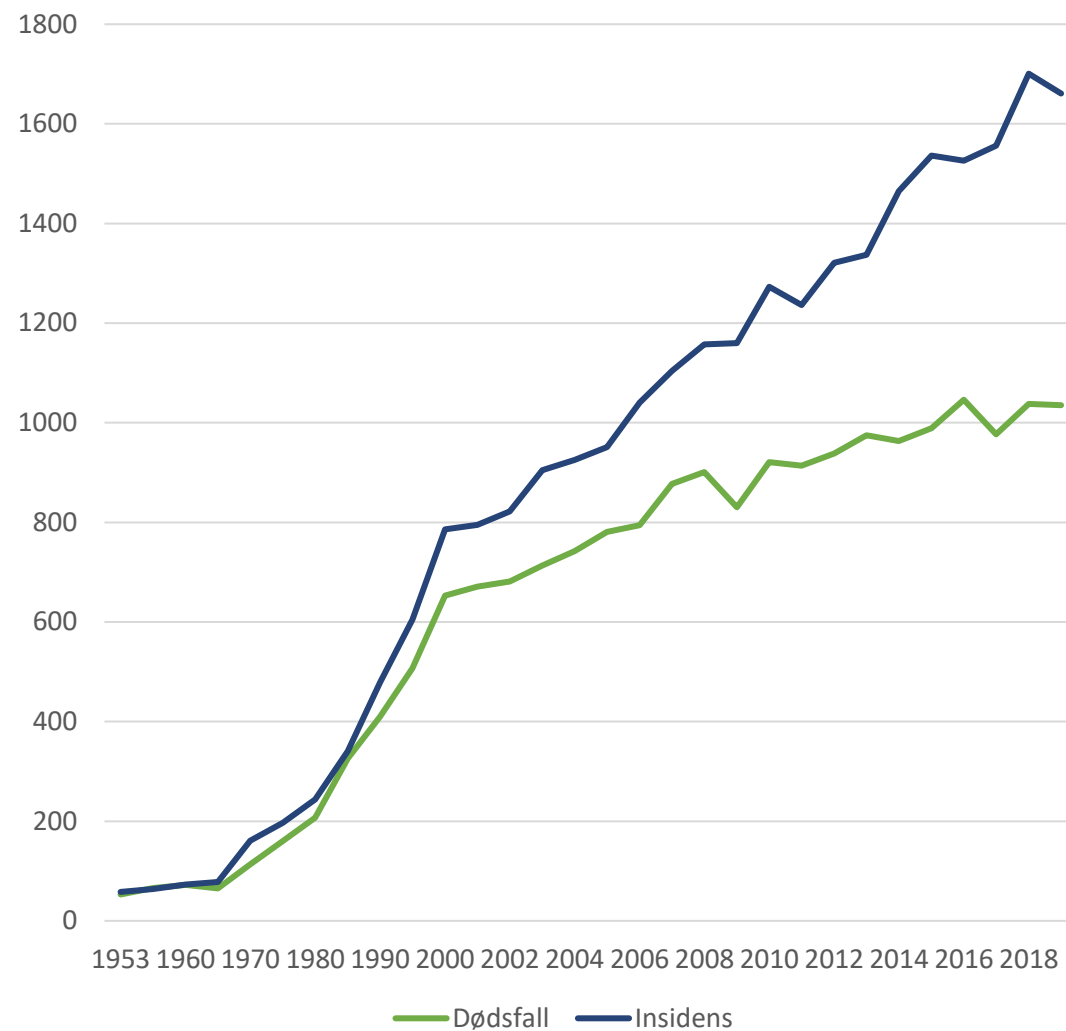
Andel kostnader topp 20 legemidler med HF-finansiering nov 19 – okt 20



Insidens og dødsfall, lungekreft, menn



Insidens og dødsfall, lungekreft, kvinner





Nyheter

Retningslinjer

Studier

Publikasjoner

Aktiviteter og referater

Lenker

Om NLCG

Norsk lungekreftgruppe

Nasjonalt handlingsprogram

Publikasjoner

Studier

Kalender

Kommende møter

Nyheter

- **Koronavaksine og kreft** 15.01.21

Kreftpasienter ble ikke inkluderte i de første koronavaksinestudiene, og det har vært stilt noen spørsmål omkring vaksinerings av slike pasienter. Tidsskriftet har idag publisert en artikkel som diskuterer noen aspekter ved dette.

- **Ny versjon av Handlingsprogrammet** 04.01.21

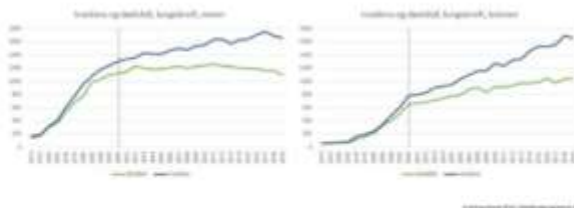
Etter innføring av lorlatinib som andrelinjebehandling ved ALK-positiv sykdom, er **Handlingsprogrammet** blitt revidert. Følgende endringer er gjort:

Lorlatinib (Lorviqua) som andrelinjebehandling for ALK-positiv lungekreft er omtalt, etter at behandlingsmuligheten nå har positivt vedtak i Beslutningsforum – med innføringsdato 15. januar 2021 (avsnitt 6.4.2). Nye resultater ved adjuvant kjemoterapi med inklusjon av cisplatin/pemetreksed som et alternativ til cisplatin/vinorelbin ved ikke-plateepitelkarsinom er også omtalt (avsnitt 7.3.1). Videre er teksten ved hjermetastaser justert ved at systemisk behandling kan forsøkes i stedet for helhjernebestråling (avsnitt 8.1.2). Endelig er moderne behandlingsprinsipper ved dyp venetrombose/lungeemboli beskrevet, idet DOAK er omtalt som behandling i stedet for lavmolekylært heparin (avsnitt 11.5).

Handlingsprogrammet er nå også publisert på [Helsedirektoratets](#) sider.

- **Insidens og dødsfall** 16.12.20

Antall lungekreftforårsakede dødsfall blant norske menn fortsetter å falle, og har ikke vært så lavt siden 1994, ifølge oppdaterte tall fra Dødsårsaksregisteret. For kvinner er 2019-tallet også såvidt lavere enn i fjor, men det tredje høyeste som er registrert. Gapet mellom insidens og dødsfall fortsetter å øke (tall fra [Kreftregisteret 2020](#), og [Dødsårsaksregisteret 2020](#)).



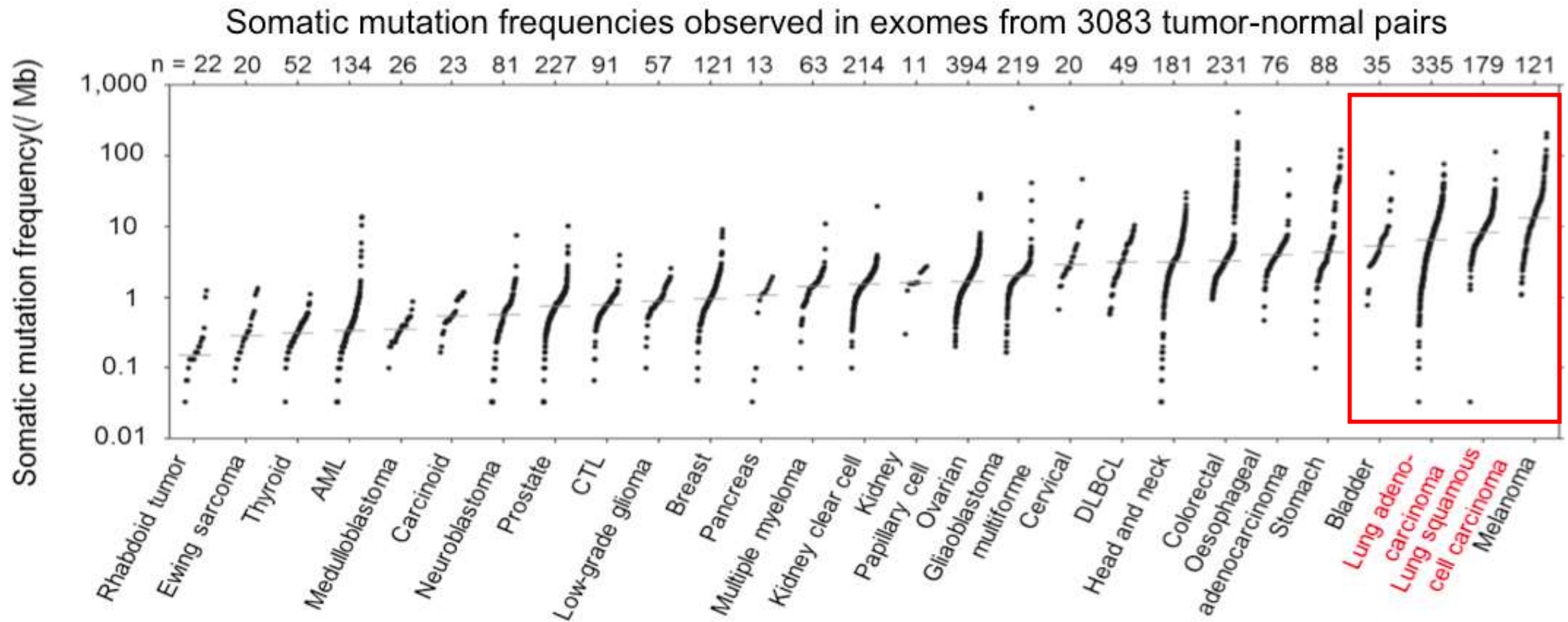
- **Lorlatinib besluttet innført** 14.12.20

I dagens **Beslutningsforum-møte** (14.12.20) ble ALK-hemmeren lorlatinib besluttet innført til behandling av ALK-positiv avansert

Agenda

- Ørlite diagnostikk
- Immunterapi ved NSCLC
- Immunterapi ved SCLC
- Immunterapi ved mesoteliom
- Studier

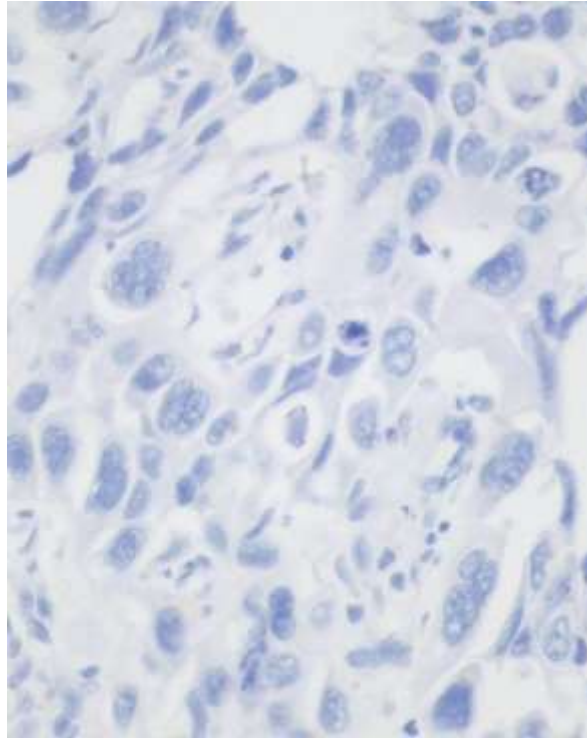
Mutasjoner i kreftceller gjør at de blir “fremmede” og synlige for immunsystemet



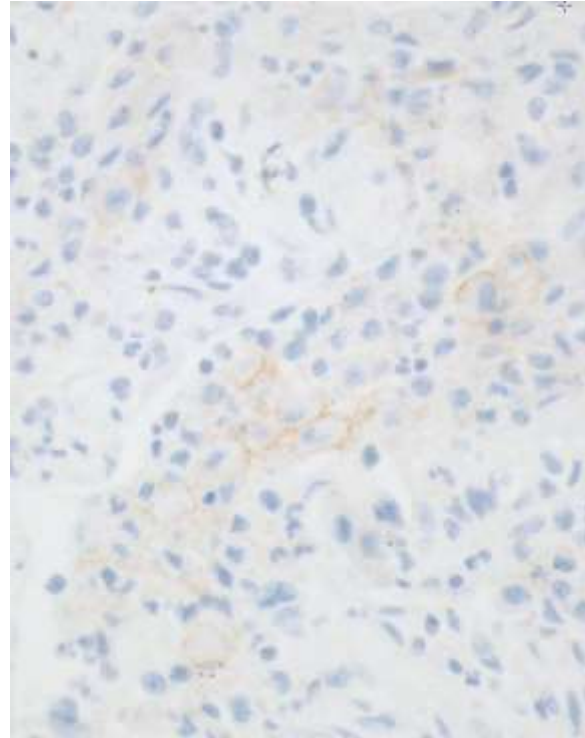
Immunterapi virker best når PD-L1 er uttrykt på kreftcellene

NSCLC

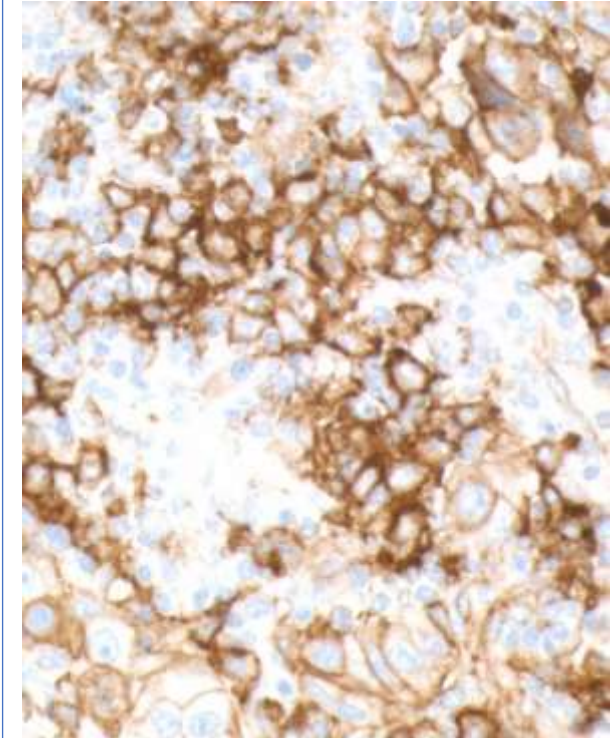
PD-L1 <1%



PD-L1 1-49%



PD-L1 ≥50%



Non-plateepitelkarsinom

Immunok**j**emoterapi i **1.** linje

Pembro + pemetreksed
+ karboplatin

Plateepitelkarsinom

Immunok**j**emoterapi i **1.** linje

Pembro + paklitaksel
+ karboplatin

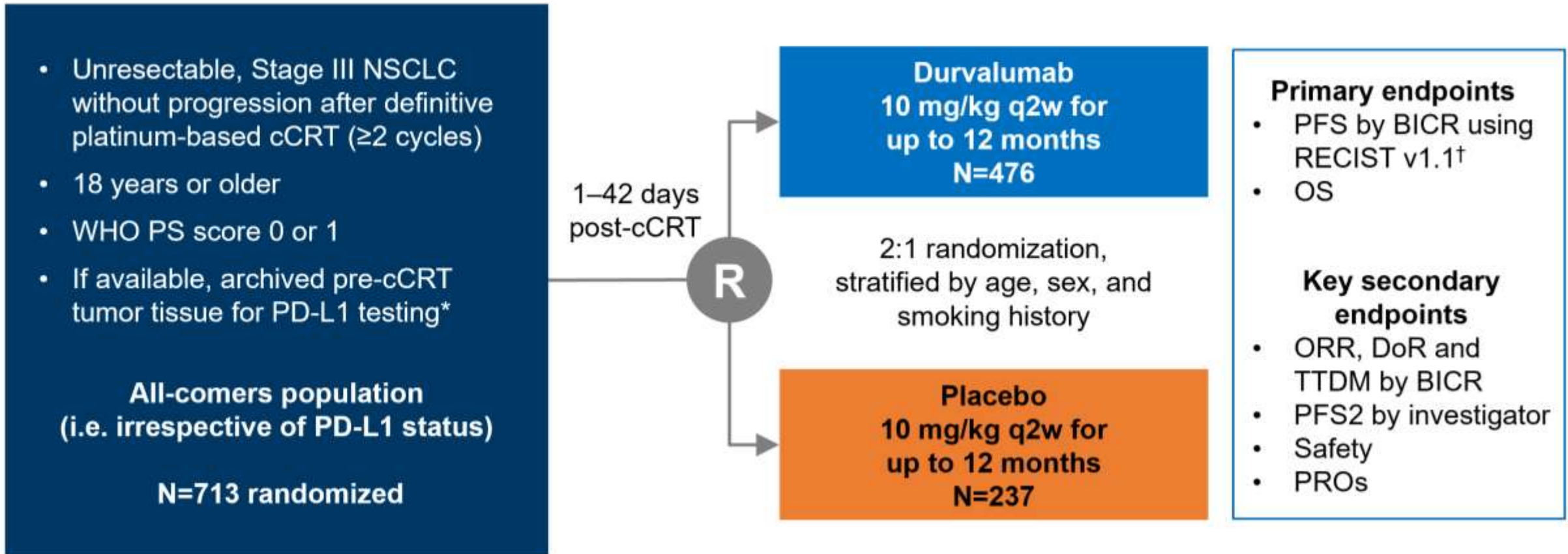
Immunom**o**noterapi i 1. linje
(pembrolizumab)

Stadium III NSCLC

Immunoterapi etter kjemoradioterapi

PACIFIC: Study Design

Phase 3, Randomized, Double-blind, Placebo-controlled, Multicenter, International Study¹



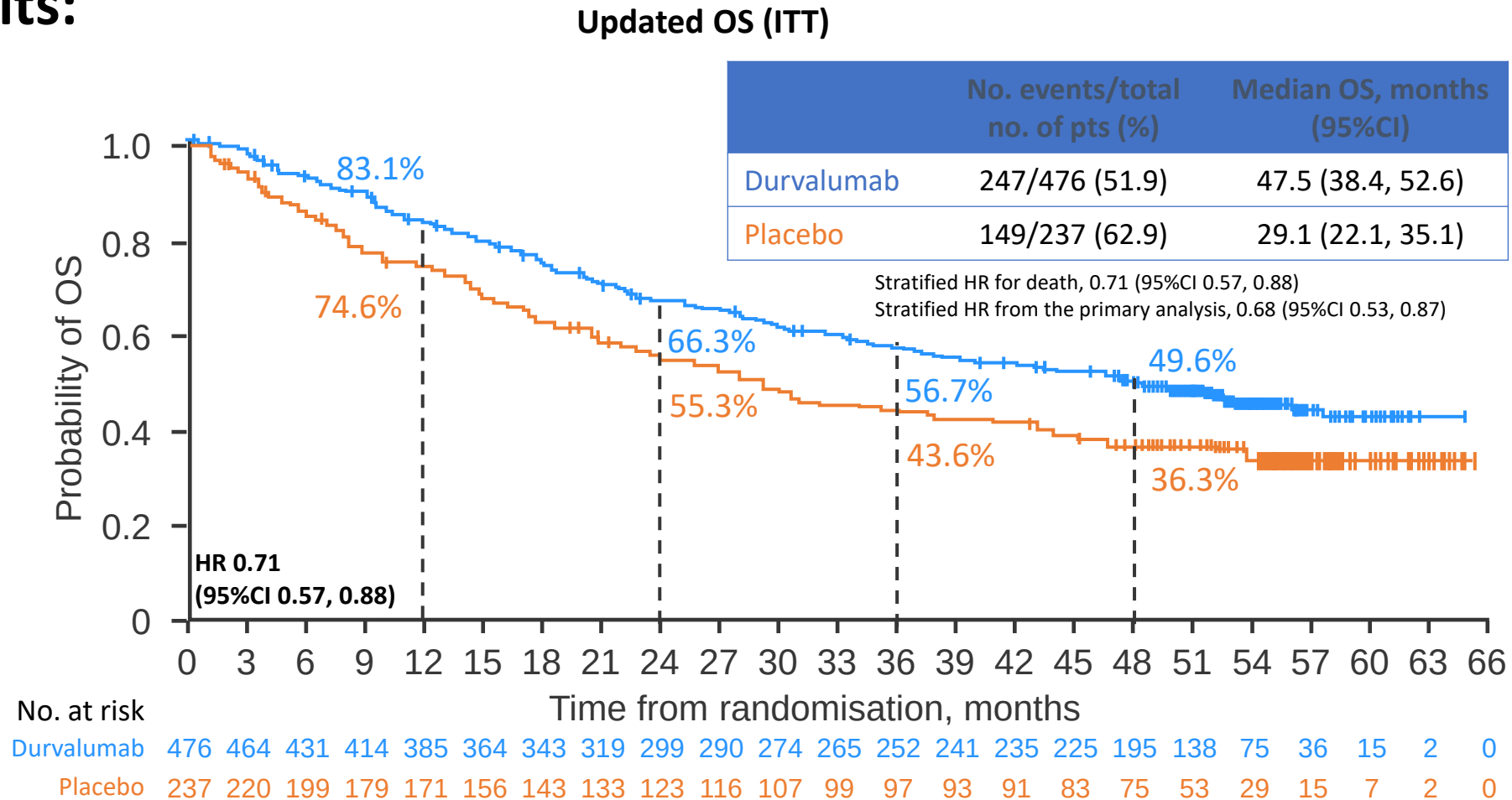
*Using the Ventana SP263 immunohistochemistry assay

[†]Defined as the time from randomization until the date of objective disease progression or death by any cause in the absence of progression. BICR, blinded independent central review; cCRT, concurrent CRT; PFS2, time to second progression; RECIST, Response Evaluation Criteria in Solid Tumors; TTDM, time to death or distant metastasis. ClinicalTrials.gov number: NCT02125461

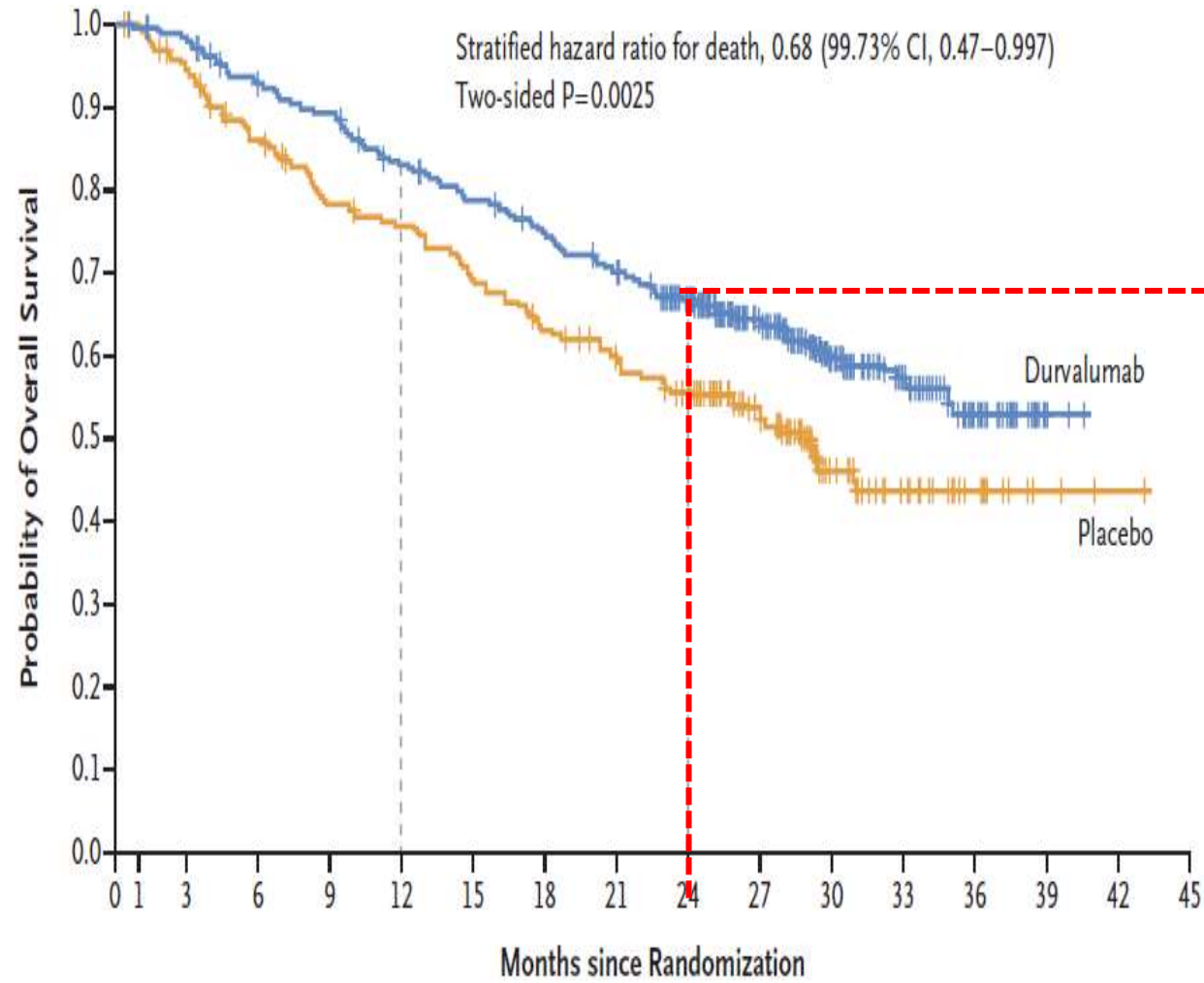


LBA49: Durvalumab after chemoradiotherapy in stage III NSCLC: 4-year survival update from the phase 3 PACIFIC trial – Faivre-Finn C, et al

- Key results:

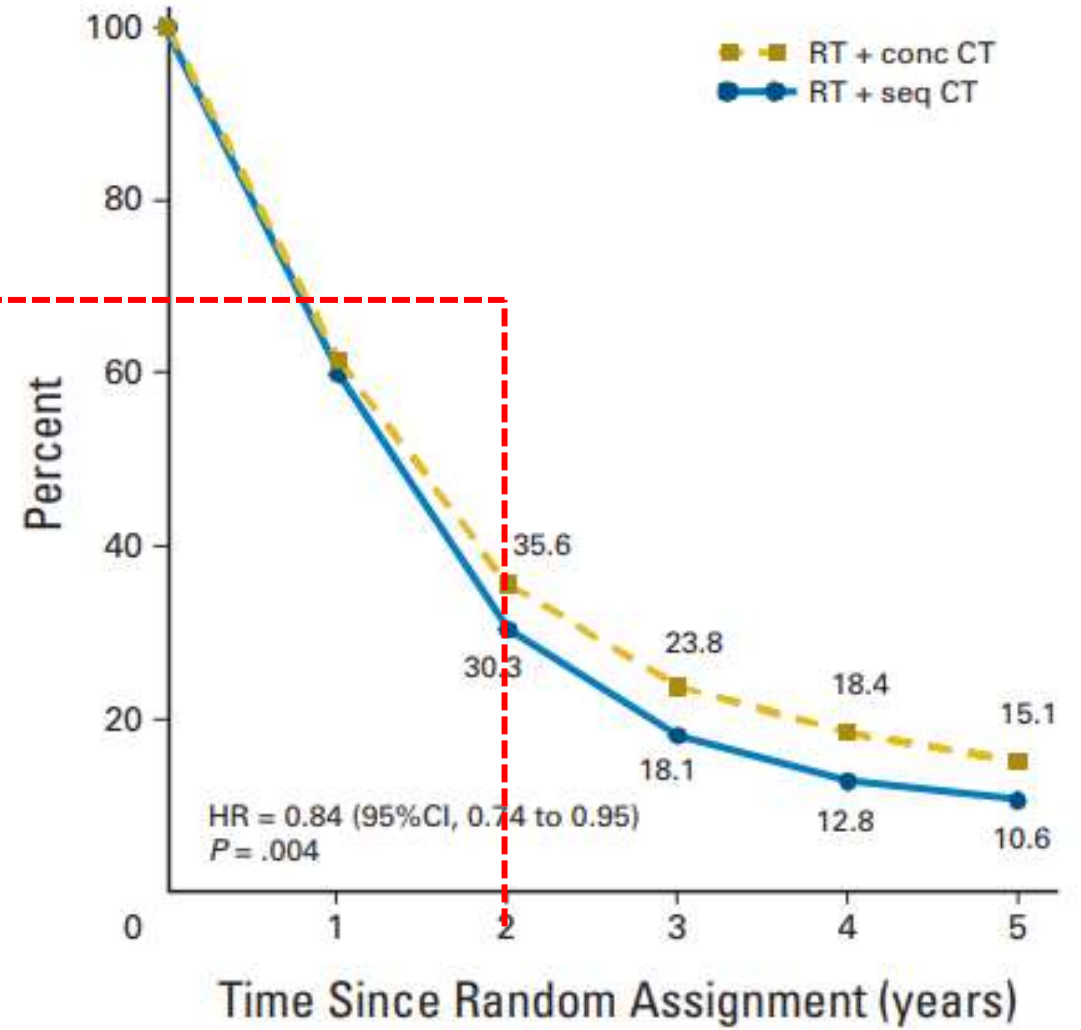


Nytt regime



Antonia et al, NEJM 2018

Gammelt regime



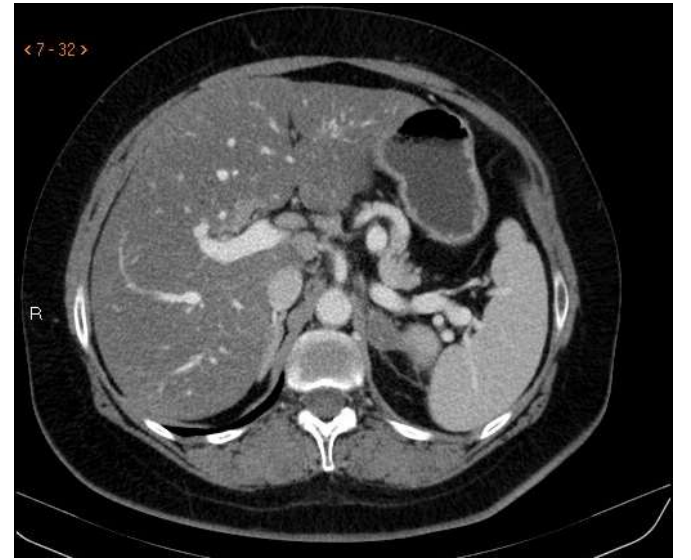
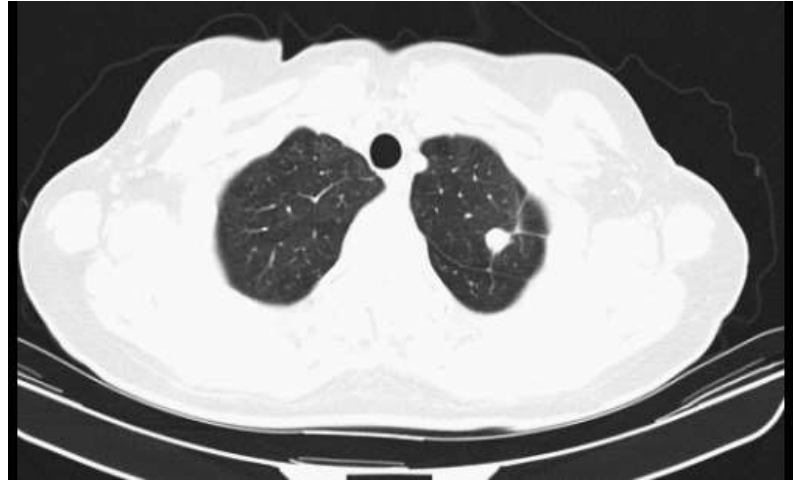
Auperin et al, JCO 2010

Table 3. Adverse Events of Any Cause.

Event	Durvalumab (N = 475)		Placebo (N = 234)	
	Any Grade*	Grade 3 or 4	Any Grade*	Grade 3 or 4
	<i>number of patients with event (percent)</i>			
Any event	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 or 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
Headache	52 (10.9)	1 (0.2)	21 (9.0)	2 (0.9)
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)
Musculoskeletal pain	39 (8.2)	3 (0.6)	24 (10.3)	1 (0.4)
Anemia	36 (7.6)	14 (2.9)	25 (10.7)	8 (3.4)

Stadium IV NSCLC

-Monoterapi eller kombinasjon med cytostatika

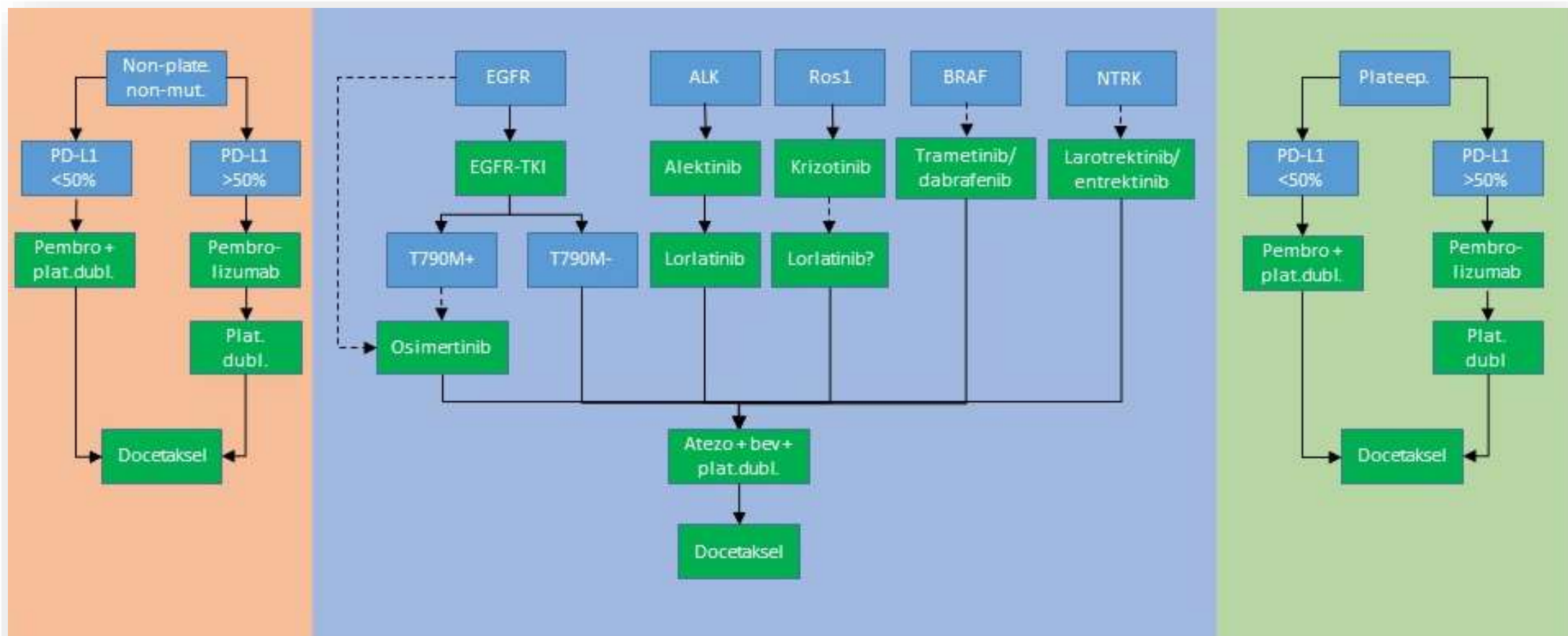


Juli 2015

Nov 2015

Okt 2020

Behandlingsalgoritme, NSCLC

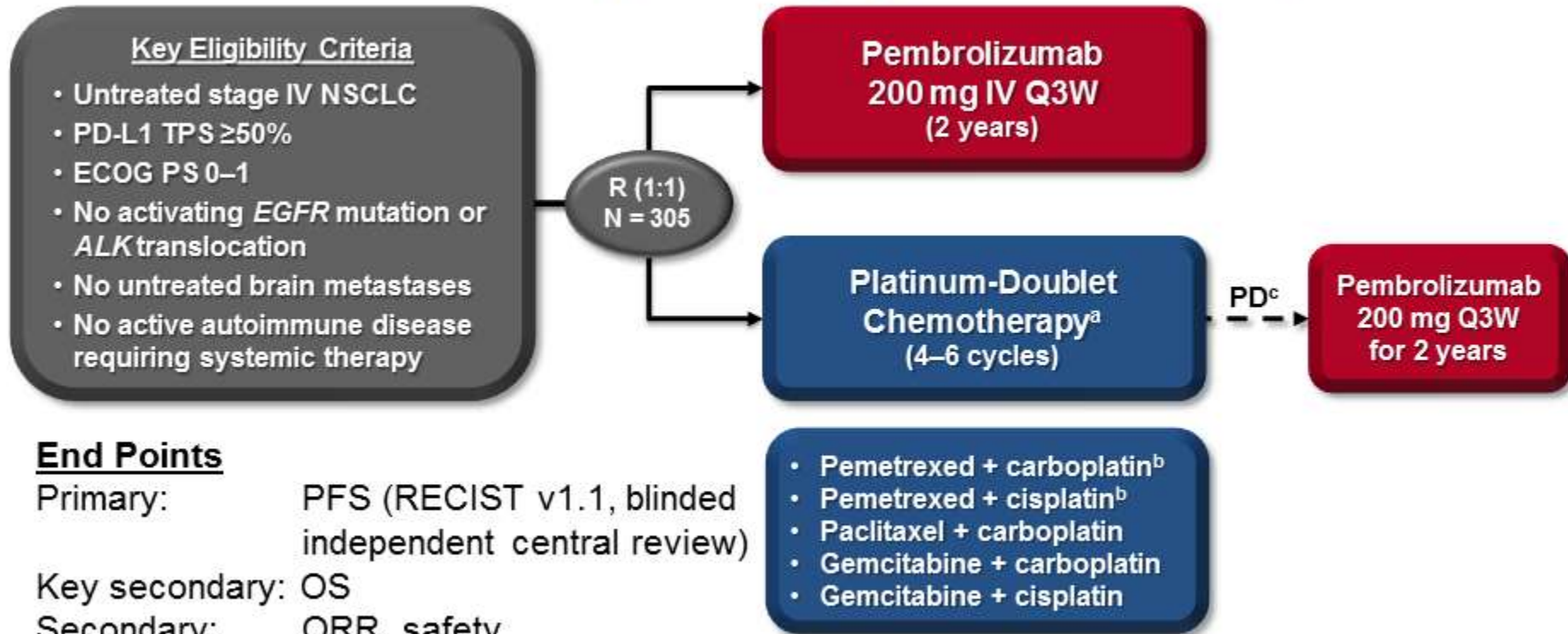


Vurdør alltid inklusjon i kliniske studier!

Immunoterapi som 1. linje

Alle NSCLC $\geq$ 50%, uten mutasjoner

KEYNOTE-024 Study Design (NCT02142738)



End Points

Primary: PFS (RECIST v1.1, blinded independent central review)

Key secondary: OS

Secondary: ORR, safety

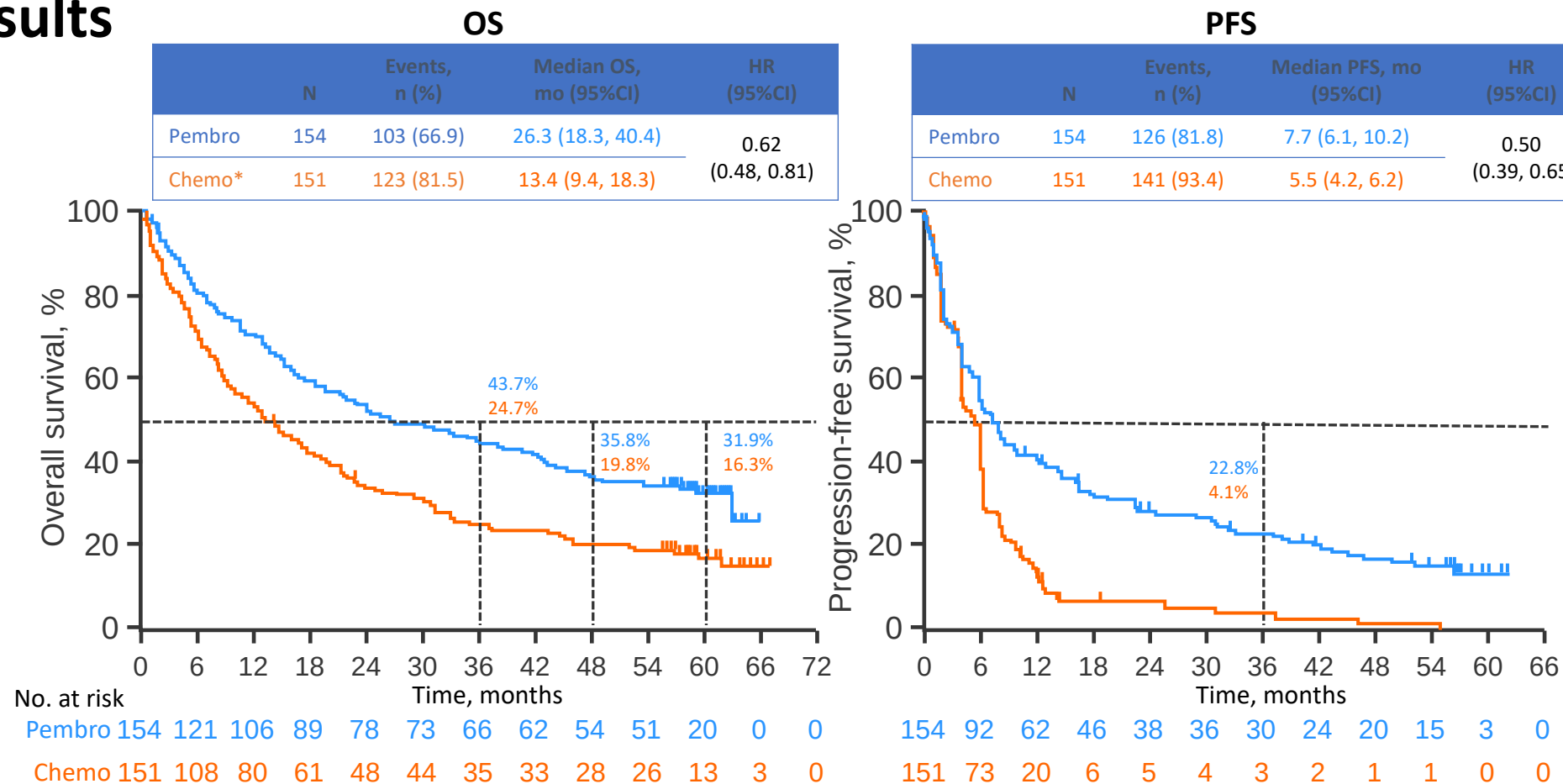
Exploratory: DOR

^aOptional pemetrexed maintenance therapy for nonsquamous disease. ^bPermitted for nonsquamous disease only.

^cPrior to the DMC recommendation and amendment 6, which permitted those in the chemotherapy arm to be offered pembrolizumab (based on interim analysis 2 data), patients were eligible for crossover when PD was confirmed by blinded, independent central radiology review.

LBA51: KEYNOTE-024 5-year OS update: first-line (1L) pembrolizumab (pembro) vs platinum-based chemotherapy (chemo) in patients (pts) with metastatic NSCLC and PD-L1 tumor proportion score (TPS) ≥50%

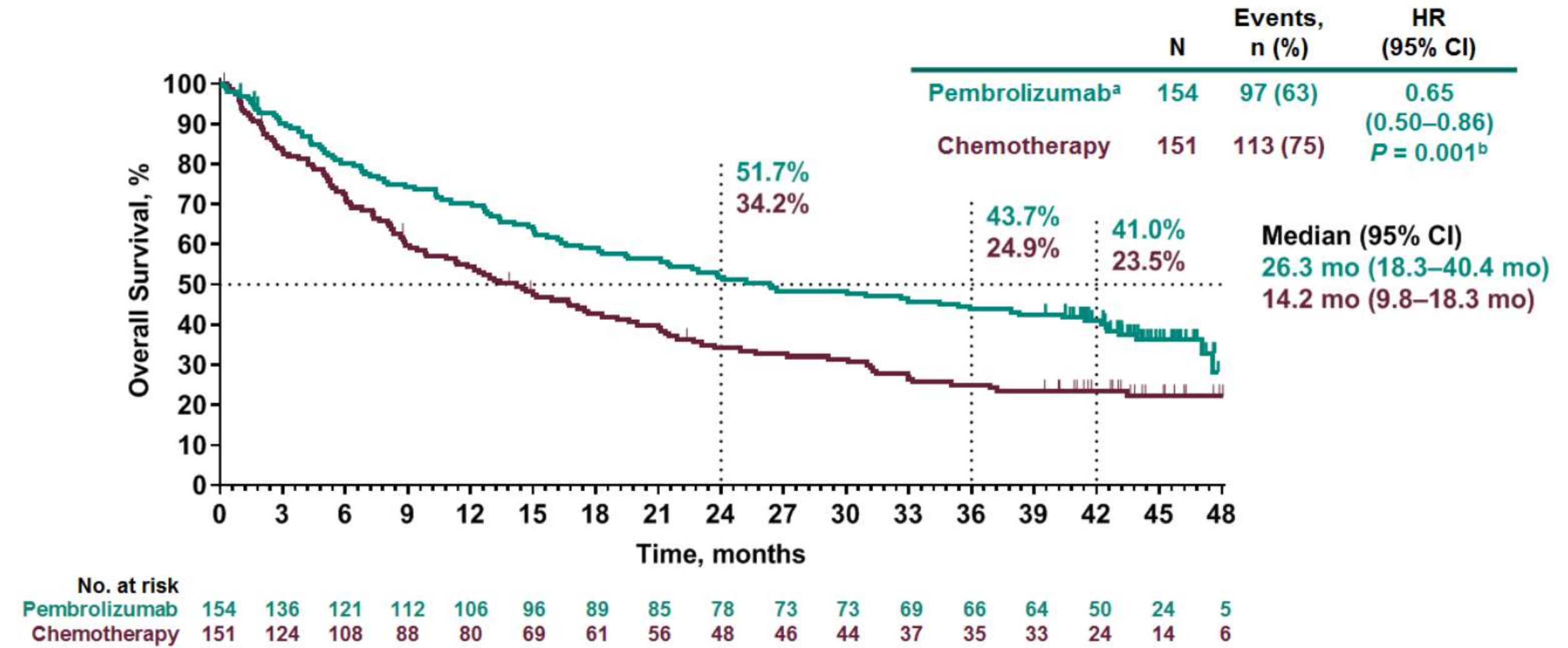
• Key results



*83 patients crossed over to pembro during the study, and 16 patients received subsequent anti-PD-(L)1 therapy outside of crossover, patients may have received >1 subsequent anti-PD-(L)1 therapy

Median DoR (range), months:
29.1 (2.2–60.8+) vs. 6.3 (3.1–52.4)

Overall Survival: Updated Analysis



^aEffective crossover rate from chemotherapy to anti-PD-L1 therapy, 64.9% (98 patients in total crossed over to anti-PD-[L]1 therapy: 83 patients crossed over to pembrolizumab during the study, and 21 patients received subsequent anti-PD-L1 therapy outside of crossover; patients may have received >1 subsequent anti-PD-L1 therapy). ^bNominal *P* value.
Data cutoff: February 15, 2019.

Oppsummering, NSCLC, PD-L1 >50%

- Enten

Pembrolizumab 200 mg iv hver 3. uke i inntil 2 år

Ved progresjon – vurdere platinum-dublett
Ved non-progresjon – følges med regelmessige kontroller

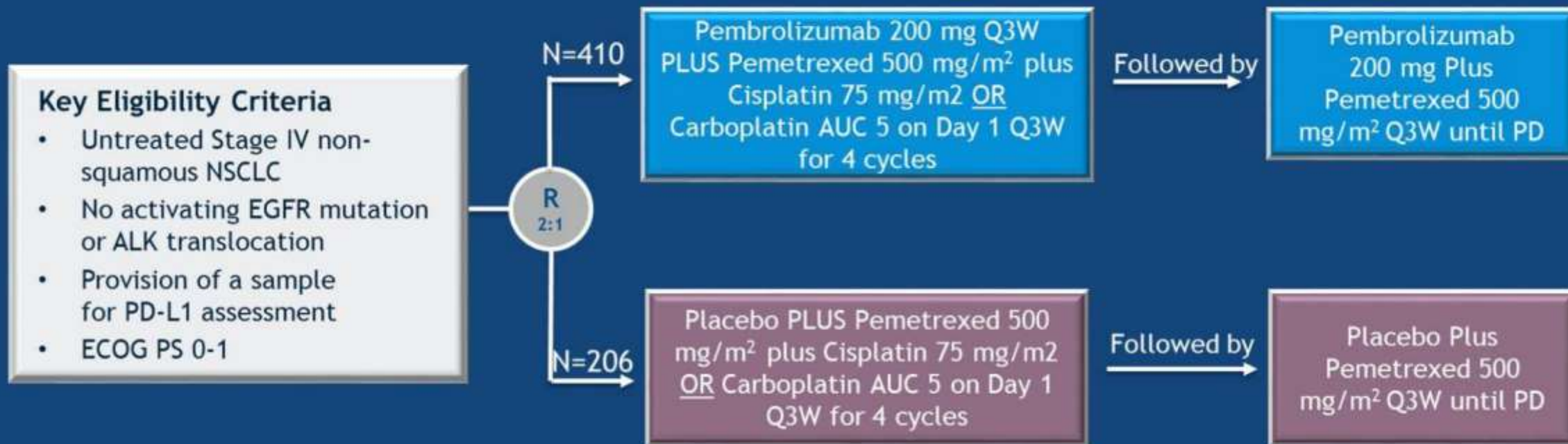
- Eller

Pembrolizumab 400 mg iv hver 6. uke i inntil 2 år

Kombinasjonsbehandling i 1.-linje

Non-plateepitelkarsinom, PD-L1 <50%

KEYNOTE 189: Randomized, Double-Blind, Phase III Study of Platinum+Pemetrexed Chemotherapy With or Without Pembrolizumab in First Line Metastatic Non-squamous Non-small Cell Lung Cancer Subjects

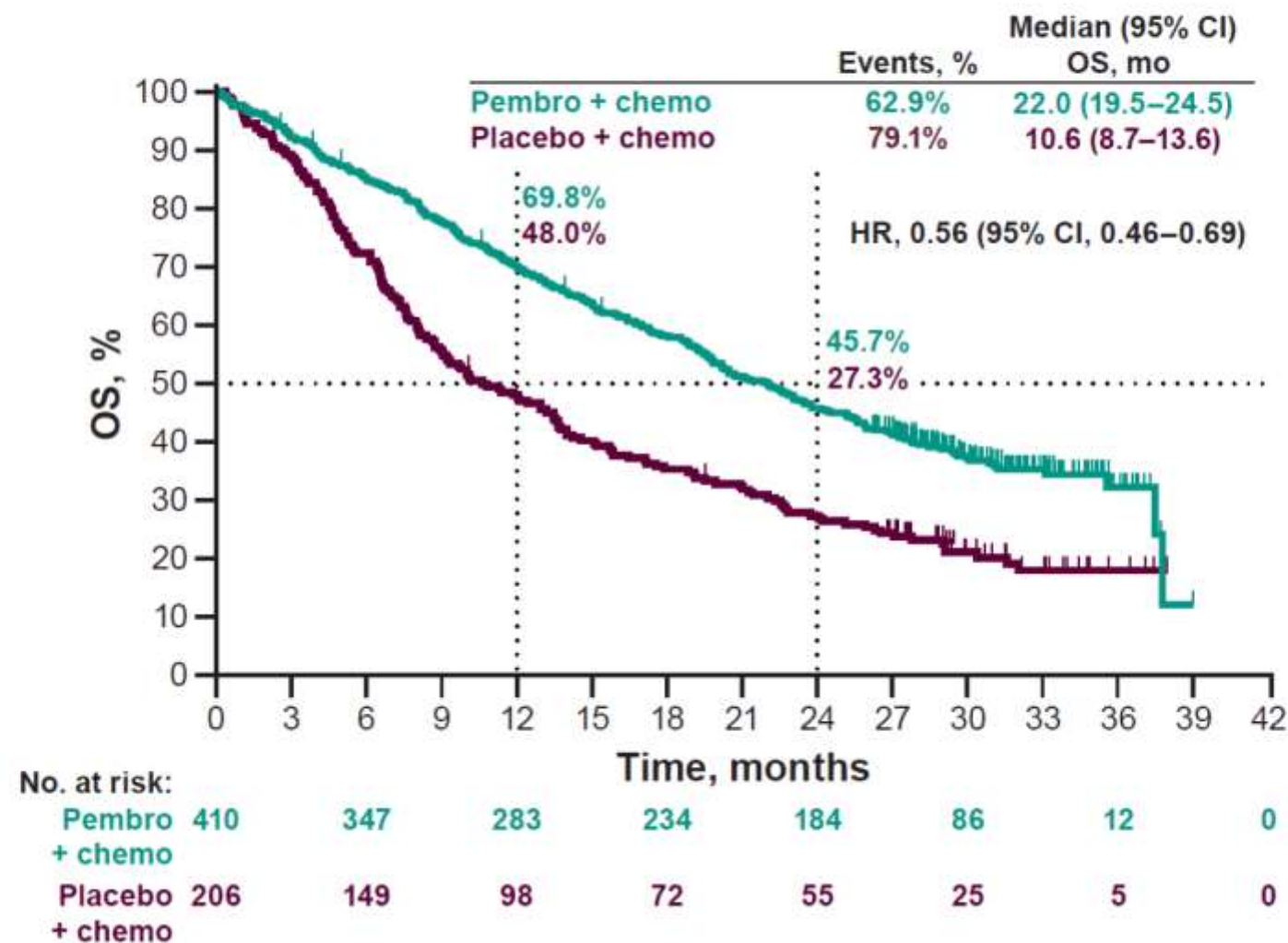


Stratification Factors:

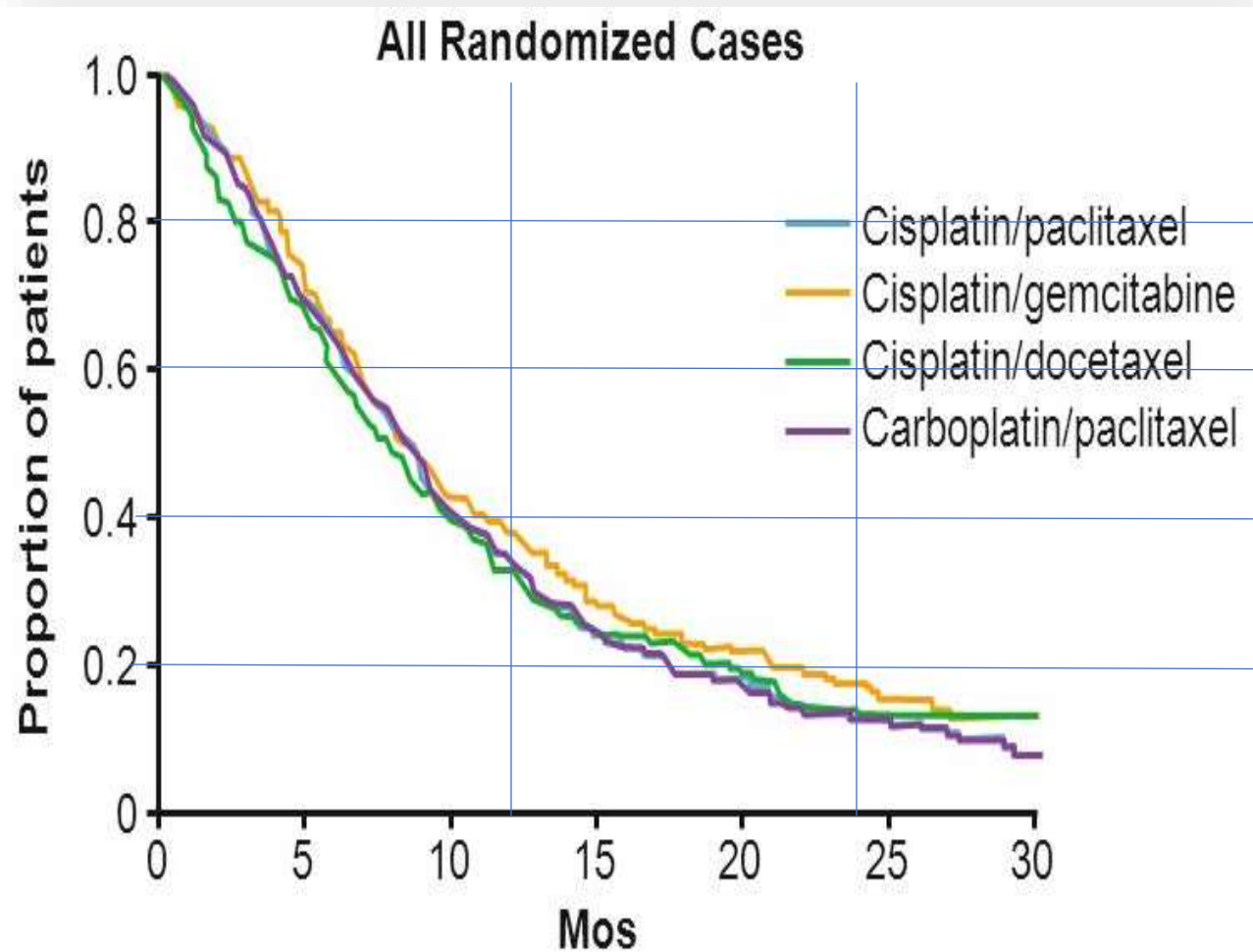
- PDL1 expression (TPS <1% vs ≥1%)
- Platinum (cisplatin vs carboplatin)
- Smoking history (never vs former/current)

Frequency of PDL1 TPS	<1%	1-49%	≥50%	NE
Pembro/Chemo	31	31.2	32.2	5.6
Chemo	30.6	28.2	34	7.3

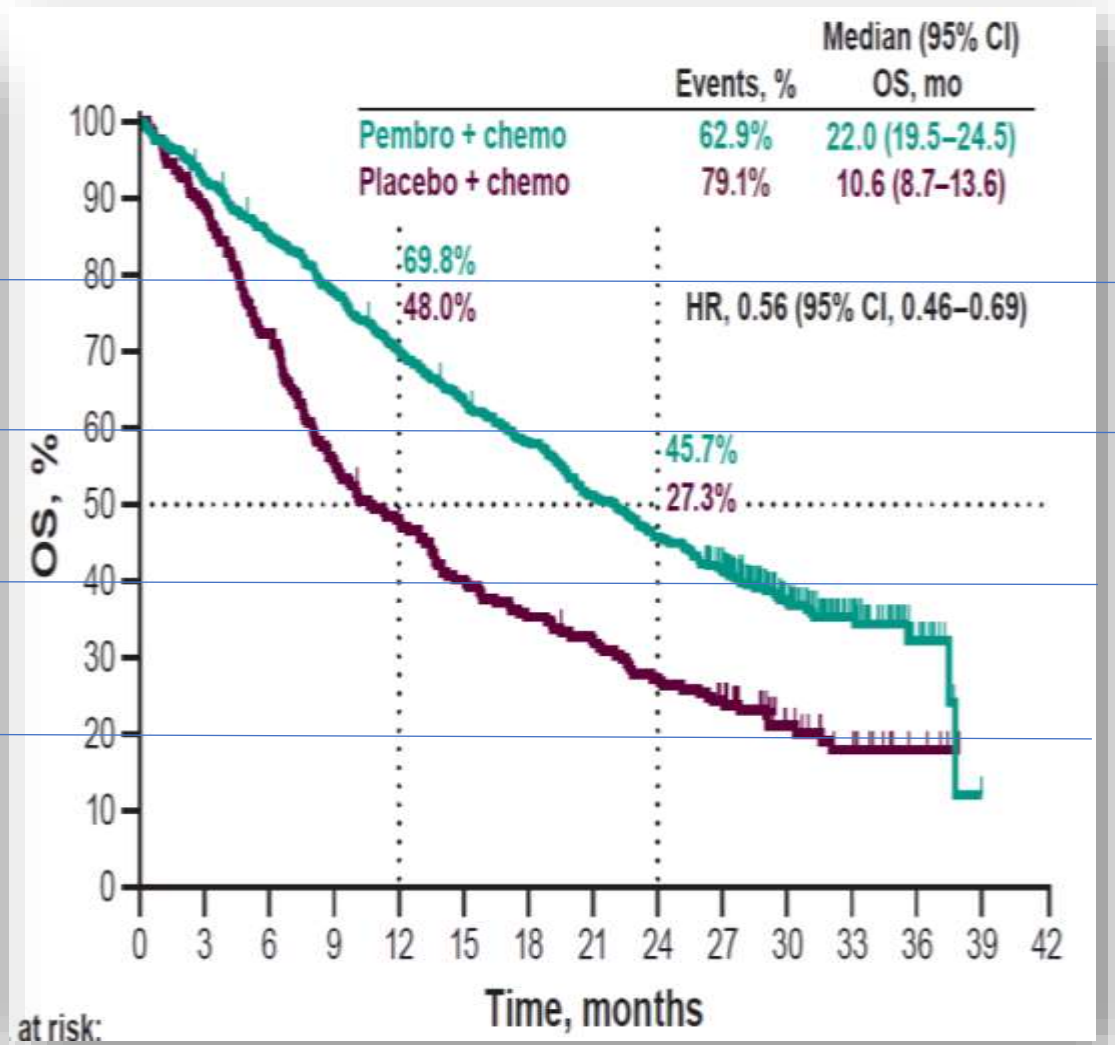
Kaplan-Meier Estimate of OS in the ITT Population



Ny førstelinjes behandling, lungekreft



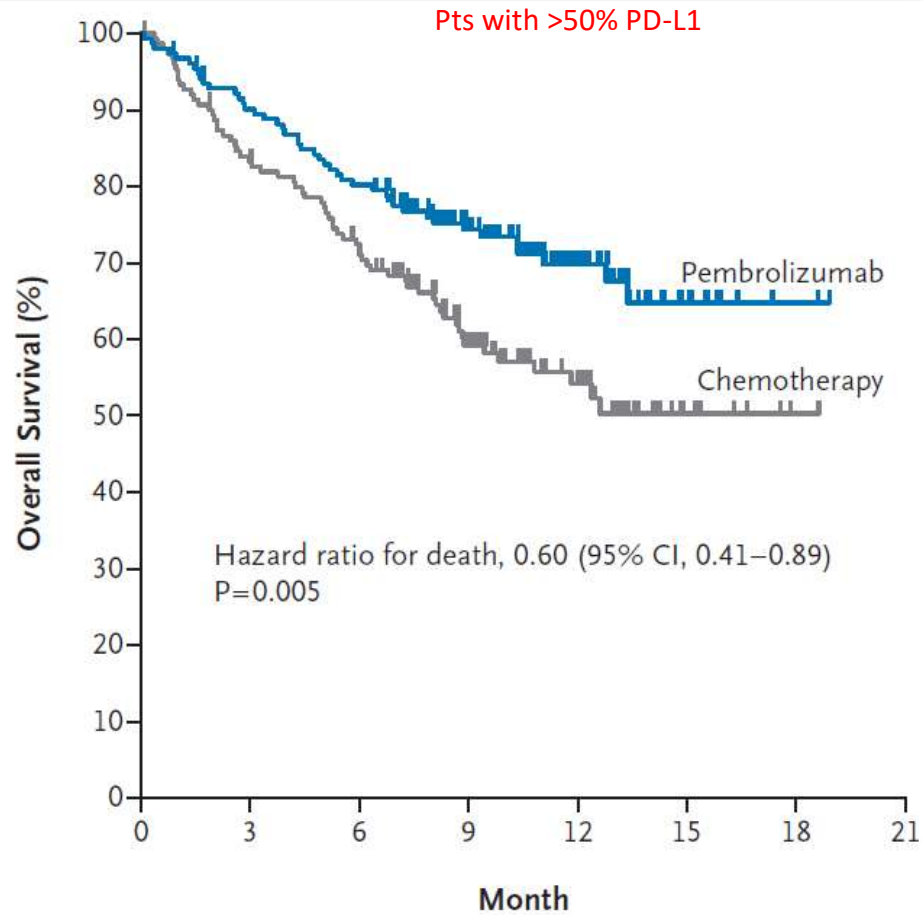
Schiller et al, NEJM 2002



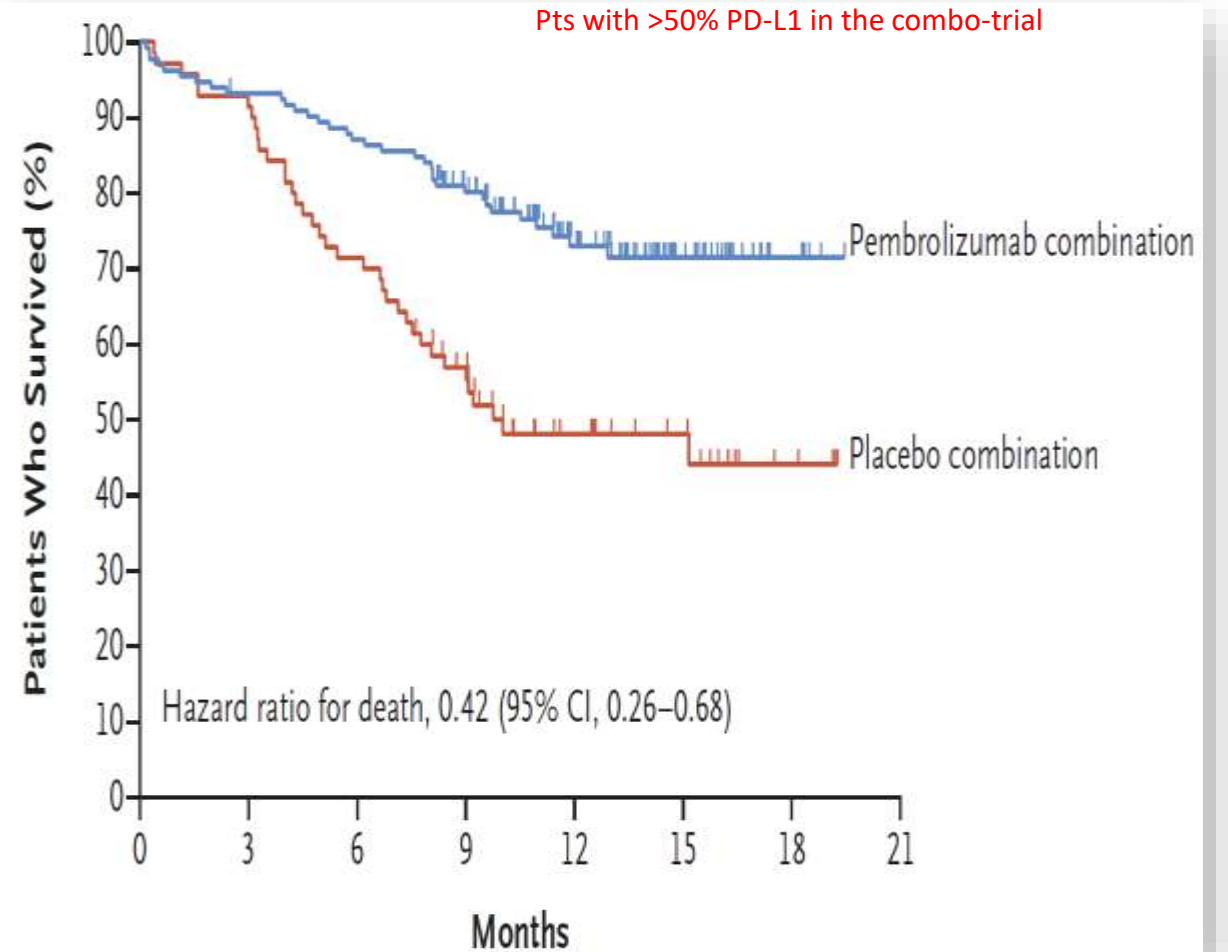
Gandhi et al, NEJM 2018
Rodriguez-Abreu, ASCO 2020

«All-comers» in both studies

Combo or mono in PD-L1 >50%?



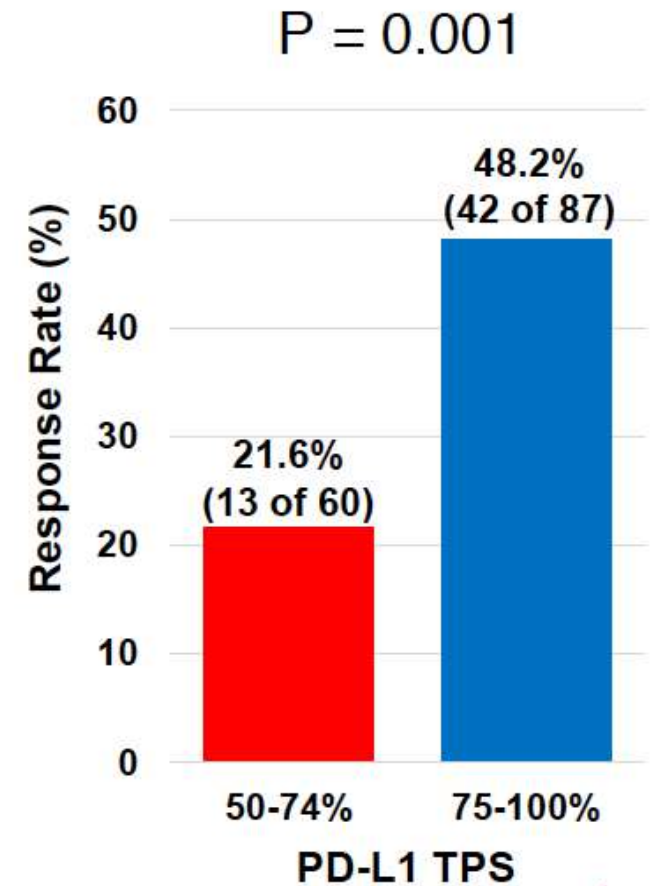
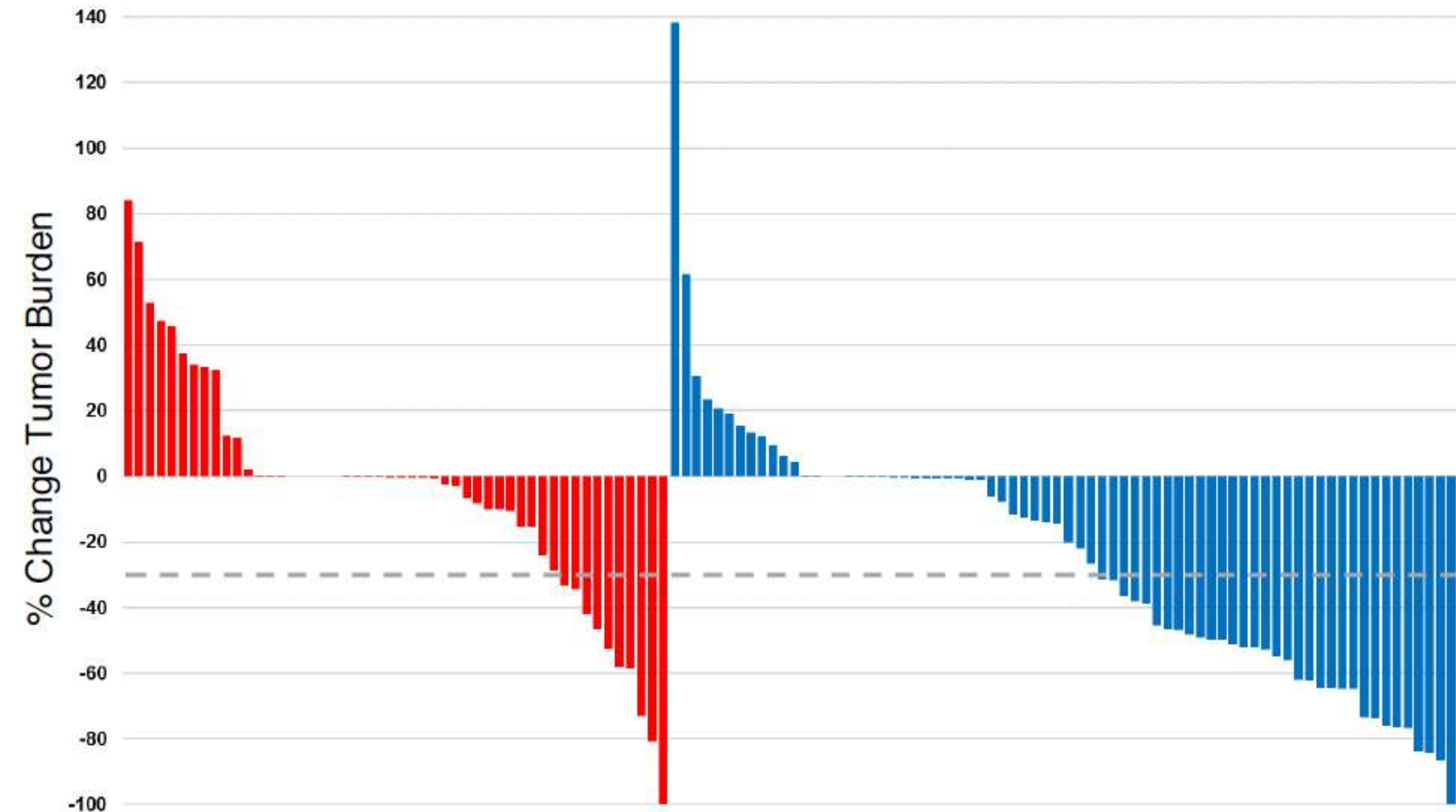
Reck et al, NEJM Nov 2016



Gandhi et al, NEJM 2018

Pembro monoterapi ved PD-L1 50-74 vs 75-100%

ORR: **TPS 50-74%** vs. **TPS 75-100%**



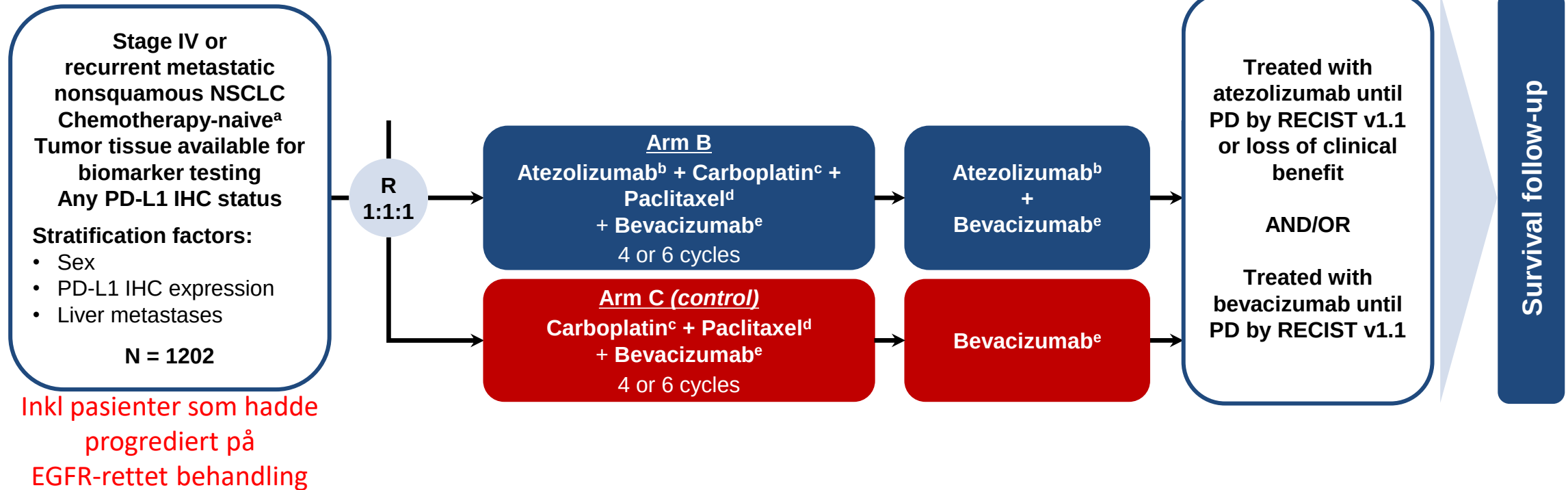
IO in EGFR-mut?

Etter progresjon på EGFR- (eller ALK-) rettet behandling

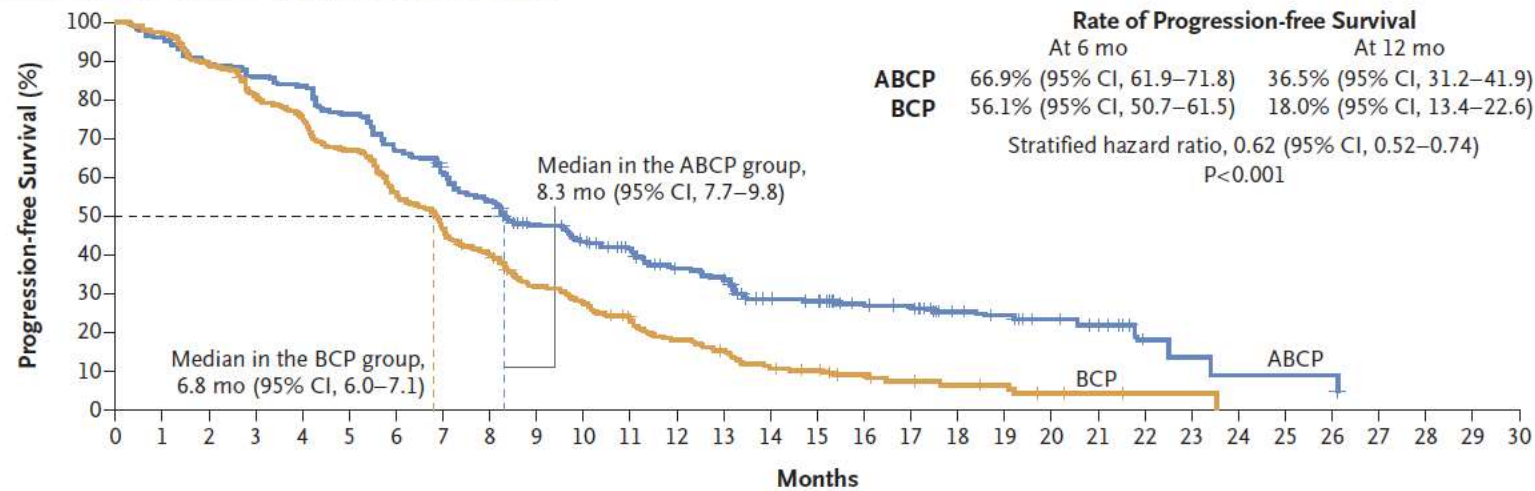
Randomized Trial of Atezolizumab in combination with carboplatin and paclitaxel with bevacizumab

IMpower150 Study Design

*Maintenance therapy
(no crossover permitted)*



A Kaplan–Meier Estimates of Progression-free Survival



No. at Risk

ABCP	356	332	311	298	290	265	232	210	186	151	124	111	87	77	58	55	42	39	27	24	16	12	4	3	2	2	2
BCP	336	321	292	261	243	215	179	147	125	91	69	55	39	32	21	18	12	9	7	6	3	2	1	1			

B Hazard Ratios for Disease Progression or Death in Biomarker Subgroups

Population	No. of Patients (%)	Median Progression-free Survival (mo)		Hazard Ratio (95% CI)	
		ABCP	BCP		
ITT population	800 (100)	8.3	6.8		0.61 (0.52–0.72)
Patients with <i>EGFR</i> or <i>ALK</i> genetic alternations	108 (14)	9.7	6.1		0.59 (0.37–0.94)
WT population	692 (87)	8.3	6.8		0.62 (0.52–0.74)
PD-L1 subgroups (in the WT population)					
TC3 or IC3	135 (20)	12.6	6.8		0.39 (0.25–0.60)
TC1/2/3 or IC1/2/3	354 (51)	11.0	6.8		0.50 (0.39–0.64)
TC1/2 or IC1/2	224 (32)	8.3	6.6		0.56 (0.41–0.77)
TC0/1/2 and IC0/1/2	557 (80)	8.0	6.8		0.68 (0.56–0.82)
TC0 and IC0	338 (49)	7.1	6.9		0.77 (0.61–0.99)
Teff subgroups (in the WT population)					
High gene-signature expression	284 (43)	11.3	6.8		0.51 (0.38–0.68)
Low gene-signature expression	374 (57)	7.3	7.0		0.76 (0.60–0.96)

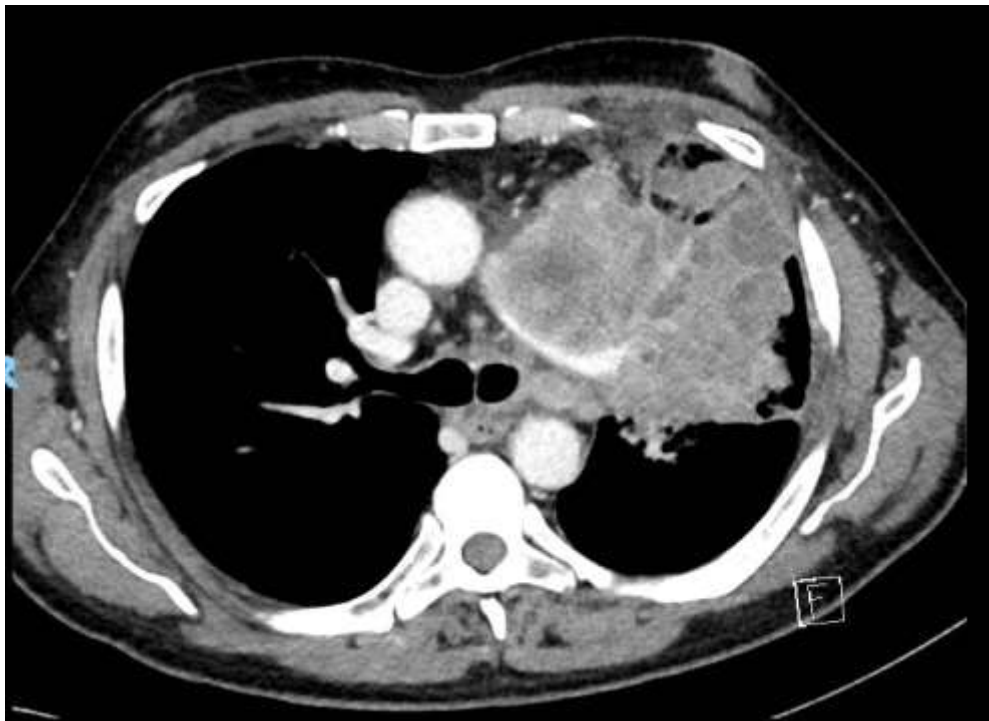
0.25 1.00 1.25

ABCP Better BCP Better

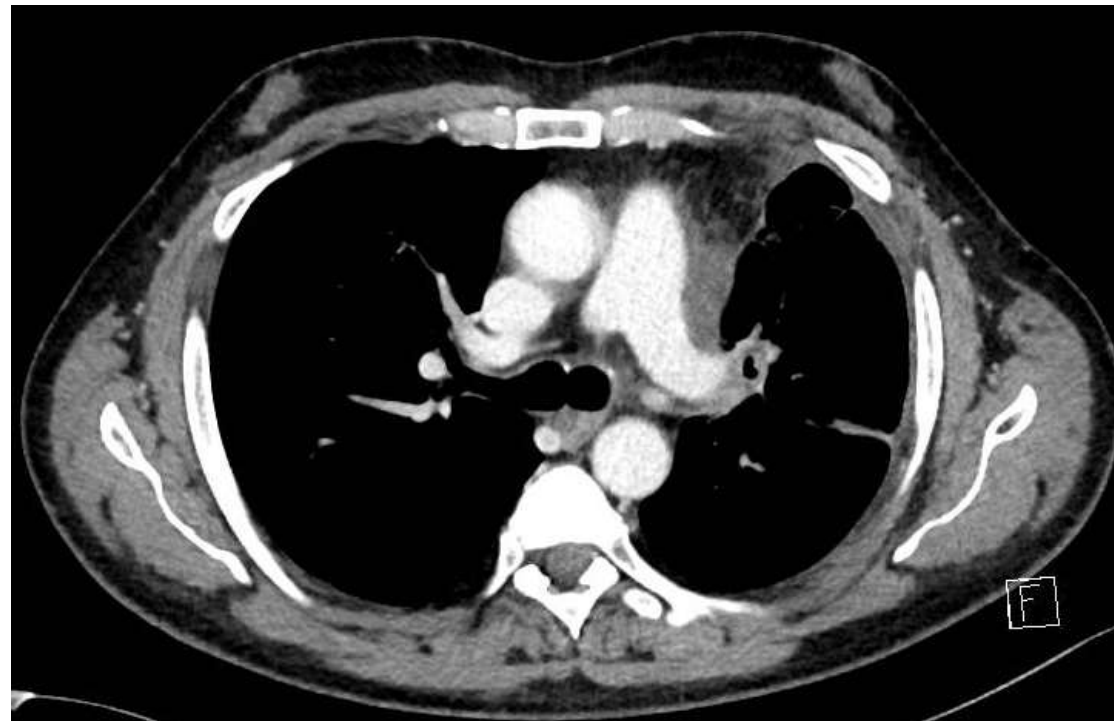
Kombo i plateepitelkarsinom

PD-L1 <50%

Plateepitelkarsinom



Før start



Etter 4 kurer pembrolizumab+paklitaksel+karboplatin

KEYNOTE-407: Study Design

- Randomized, double-blind phase III trial

Stratified by PD-L1 TPS (< 1% vs ≥ 1%), taxane (paclitaxel vs nab-paclitaxel), region (east Asia vs other)

Patients with untreated stage IV squamous NSCLC, ECOG PS 0/1, available tumor biopsy for PD-L1 assessment, no brain mets, and no pneumonitis requiring systemic steroids
(N = 559)

**Pembrolizumab + Carboplatin +
Paclitaxel or nab-Paclitaxel**
3-wk cycles x 4
(n = 278)

**Pembrolizumab
up to 31 cycles**

**Placebo + Carboplatin +
Paclitaxel or nab-Paclitaxel**
3-wk cycles x 4
(n = 281)

**Placebo
up to 31 cycles**

PD

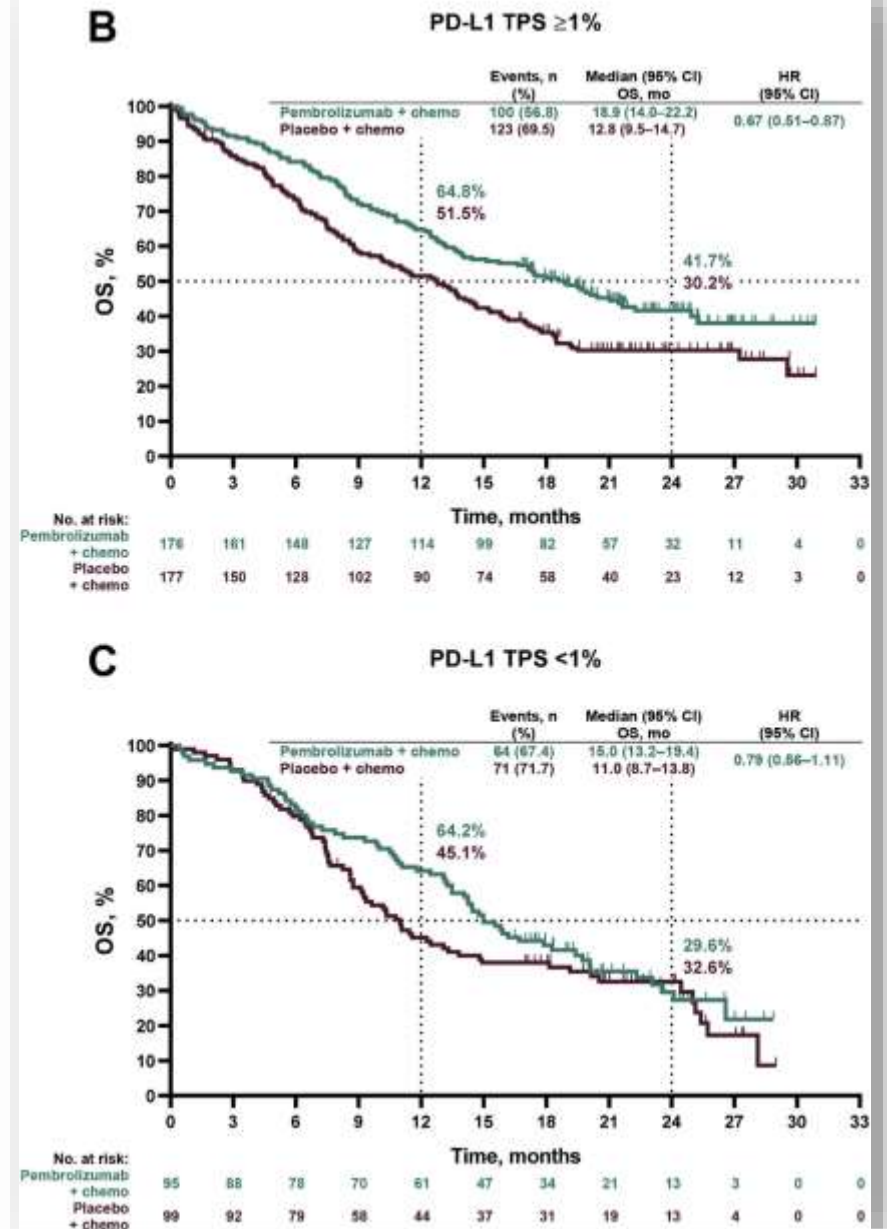
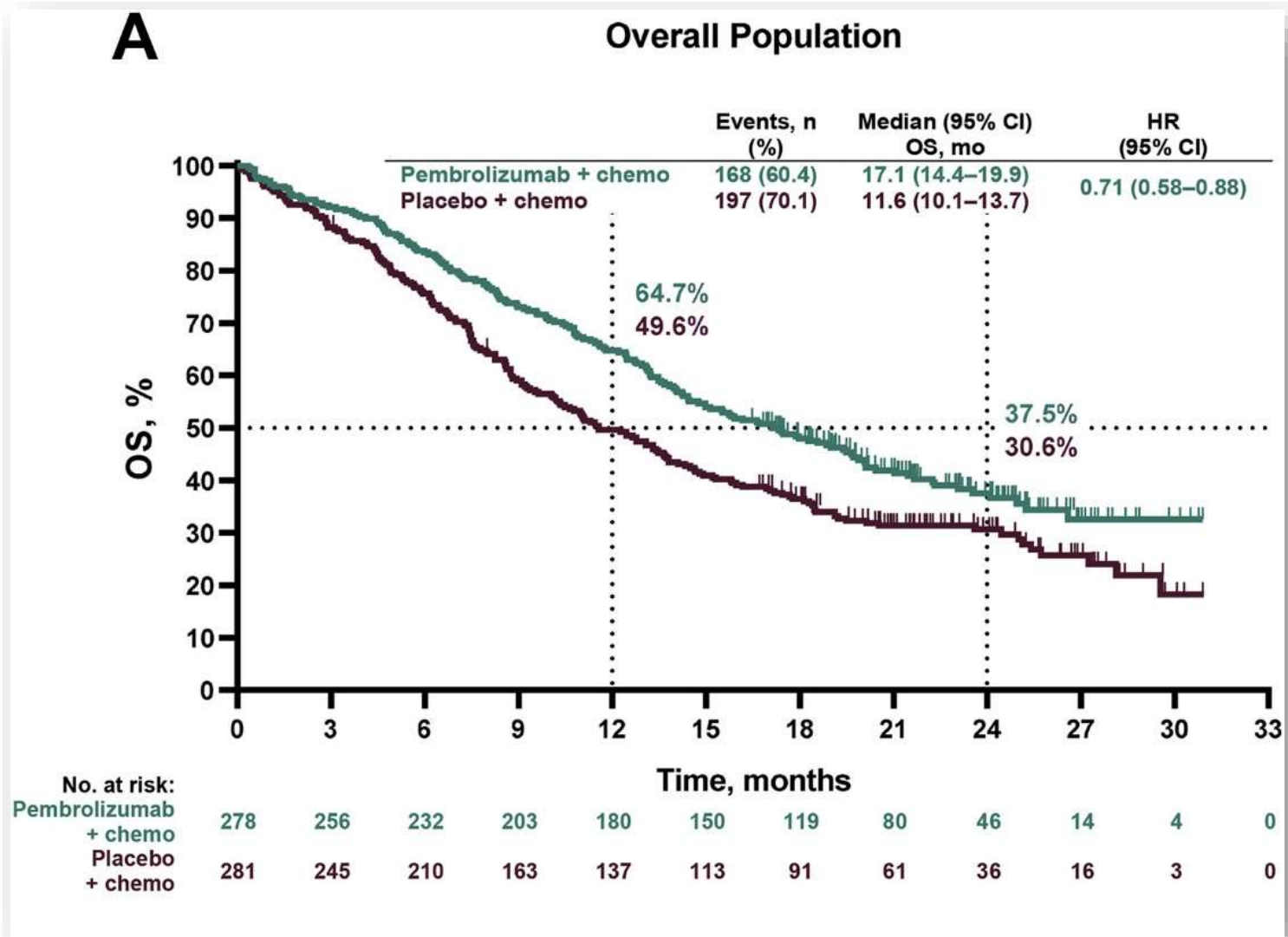
**Pembrolizumab
up to 35 cycles**

*Crossover
allowed**

Carboplatin AUC 6 Q3W, nab-paclitaxel 100 mg/m² QW, paclitaxel 200 mg/m² Q3W, pembrolizumab 200 mg Q3W.

*Upon confirmation of PD and safety criteria by BICR, optional crossover could occur during combination or monotherapy.

- Primary endpoint: PFS by RECIST v1.1 (BICR), OS
- Secondary endpoints: ORR and DoR by RECIST v1.1 (BICR), safety



Oppsummering, NSCLC PD-L1 <50%

- Non-plateepitelkarsinom uten EGFR/ALK/ROS1, < 50% PD-L1:

Karboplatin x4

Pemetreksed hver 3. uke i inntil 2 år

Pembrolizumab hver 3. uke i inntil 2 år

- Plateepitelkarsinom PD-L1 <50%:

Karboplatin x4

Paklitaksel x4

Pembrolizumab hver 3. uke i inntil 2 år

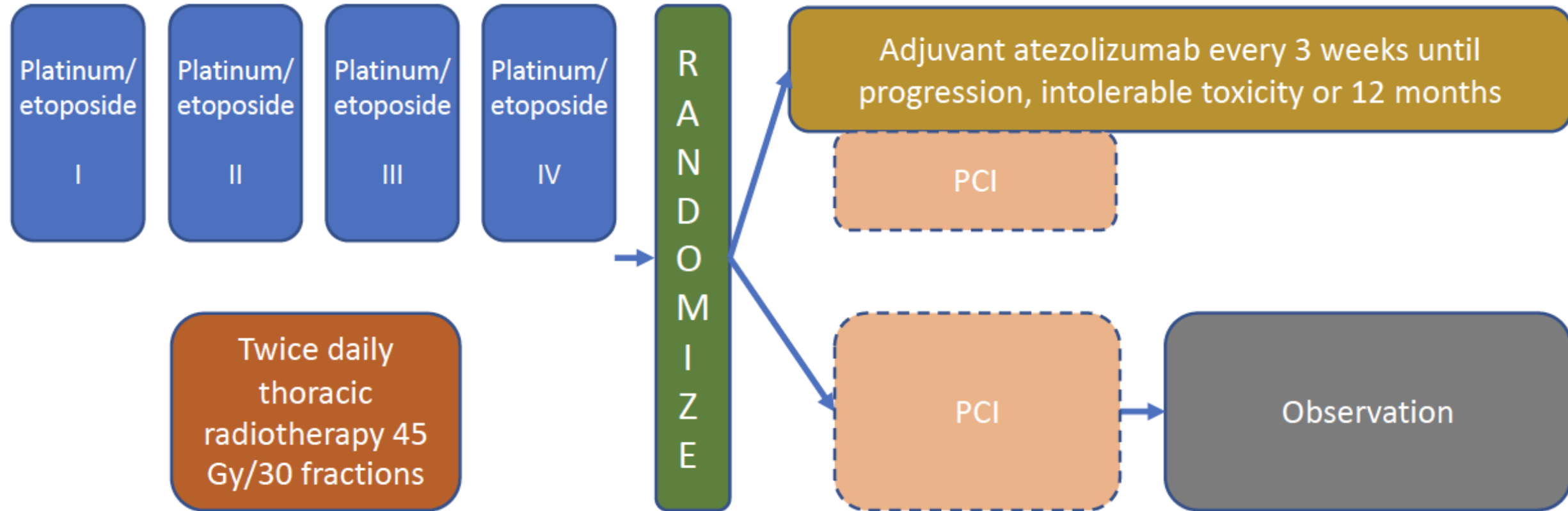
Ved progresjon – vurdere docetaksel
Ved non-progresjon – følges med regelmessige kontroller

Immunterapi ved SCLC-LD

Kun i studie

Nordic Achilles-study for SCLC-LD

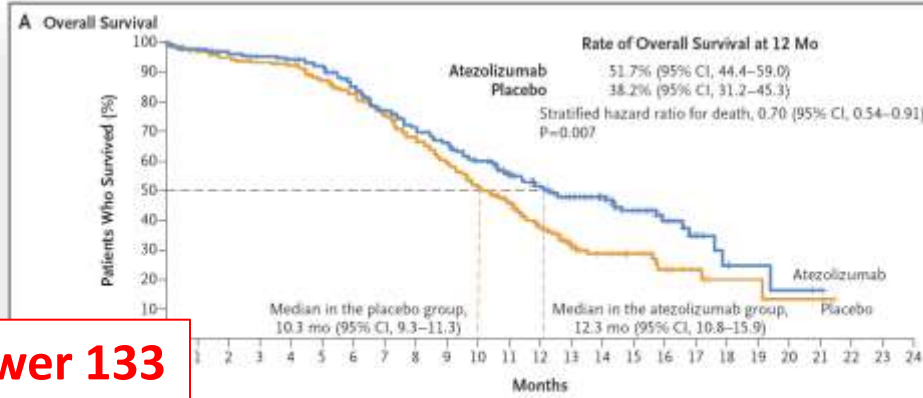
Lead by Norwegian lung cancer study group



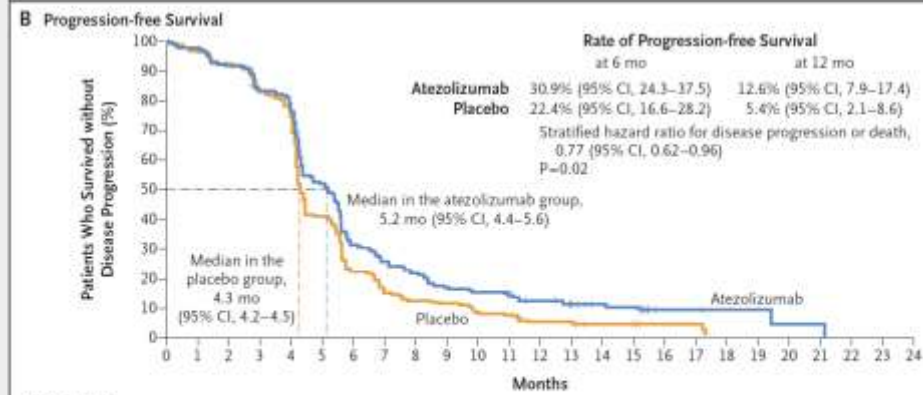
Immunterapi ved SCLC-ED

Foreløpig ikke innført i Norge

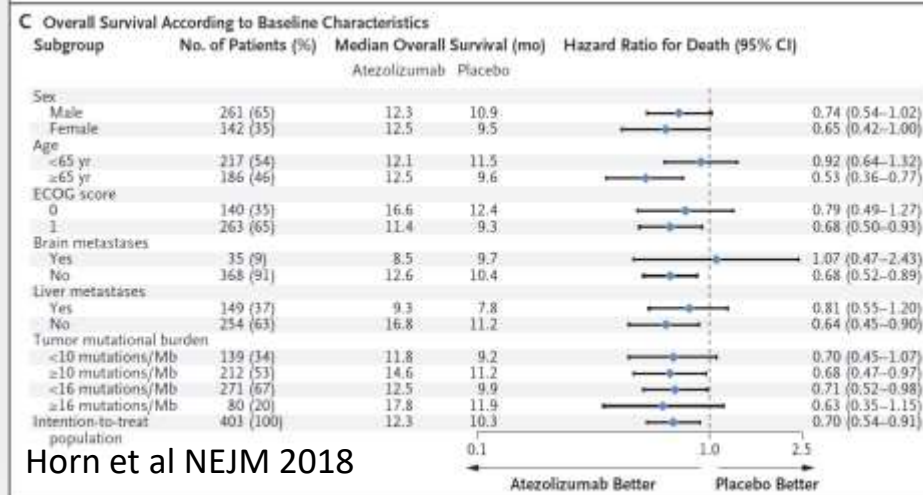
IMpower 133



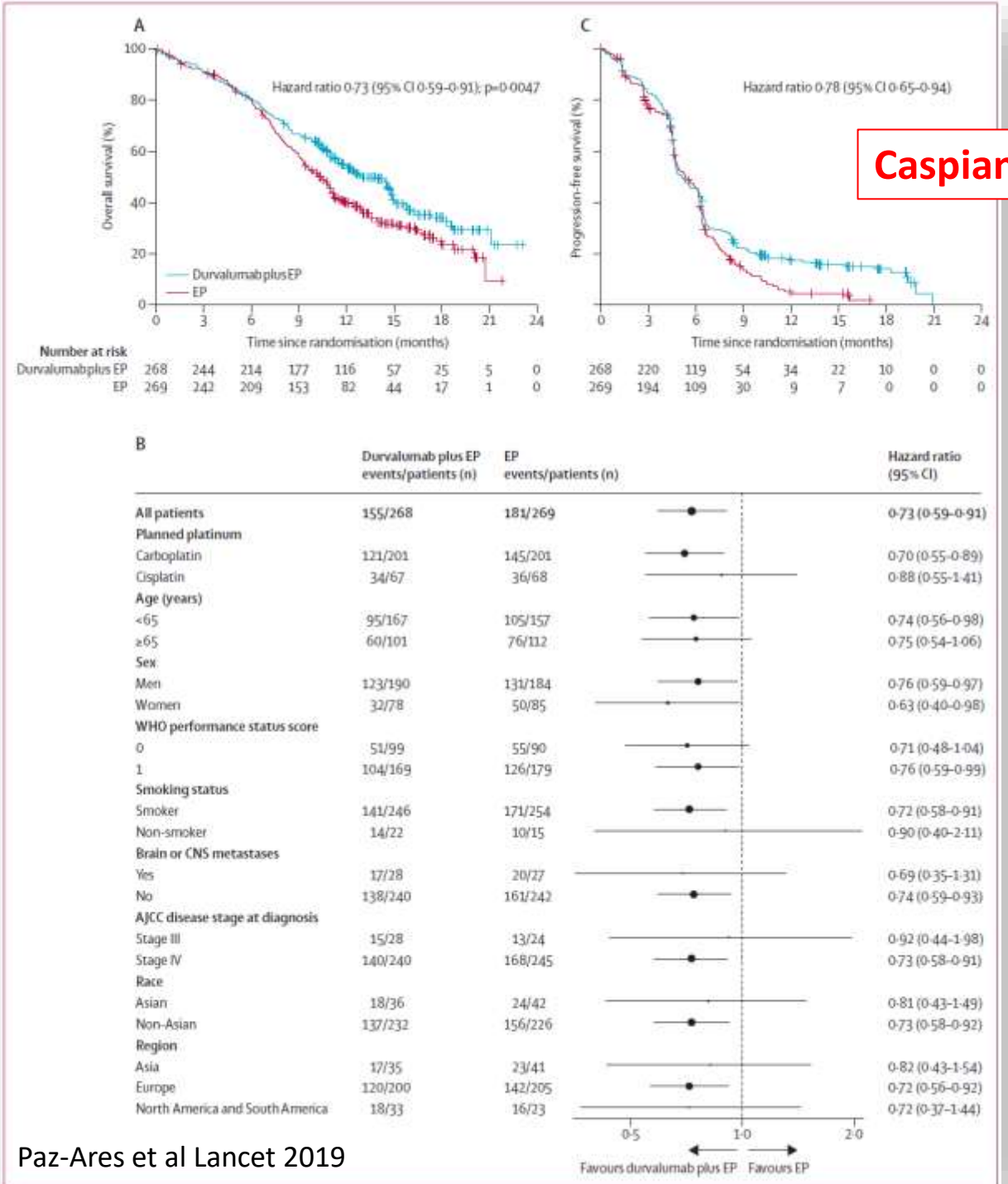
No. at Risk	201	191	187	182	180	174	159	142	130	121	108	92	74	58	46	33	21	11	5	3	2	1
Atezolizumab	201	191	187	182	180	174	159	142	130	121	108	92	74	58	46	33	21	11	5	3	2	1
Placebo	202	194	189	186	183	171	160	146	131	114	96	81	59	36	27	21	13	8	3	3	2	2



No. at Risk	201	190	178	158	147	98	58	48	41	32	29	26	21	15	12	11	3	3	2	2	1	1
Atezolizumab	201	190	178	158	147	98	58	48	41	32	29	26	21	15	12	11	3	3	2	2	1	1
Placebo	202	193	184	167	147	80	44	30	25	23	16	15	9	9	6	5	3	3				



Horn et al NEJM 2018



Caspian

Paz-Ares et al Lancet 2019

Mesoteliom



2020 Presidential
Symposium

AUGUST 8, 2020 | WORLDWIDE

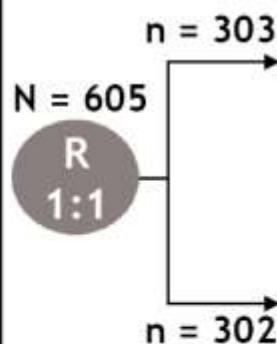
CheckMate 743 study design^a

Key Eligibility Criteria

- Unresectable pleural mesothelioma
- No prior systemic therapy
- ECOG performance status 0-1

Stratified by:

histology (epithelioid vs non-epithelioid)
and gender



**NIVO 3 mg/kg Q2W +
IPI 1 mg/kg Q6W
(for up to 2 years)**

**Cisplatin or carboplatin +
pemetrexed Q3W^b (6 cycles)**

Until disease
progression,
unacceptable toxicity
or for 2 years for
immunotherapy arm

Primary Endpoint

- OS

Secondary Endpoints

- ORR, DCR, and PFS by BICR
- PD-L1^c expression as a predictive biomarker

Database lock: April 3, 2020; minimum follow-up for OS: 22.1 months; median follow-up: 29.7 months.

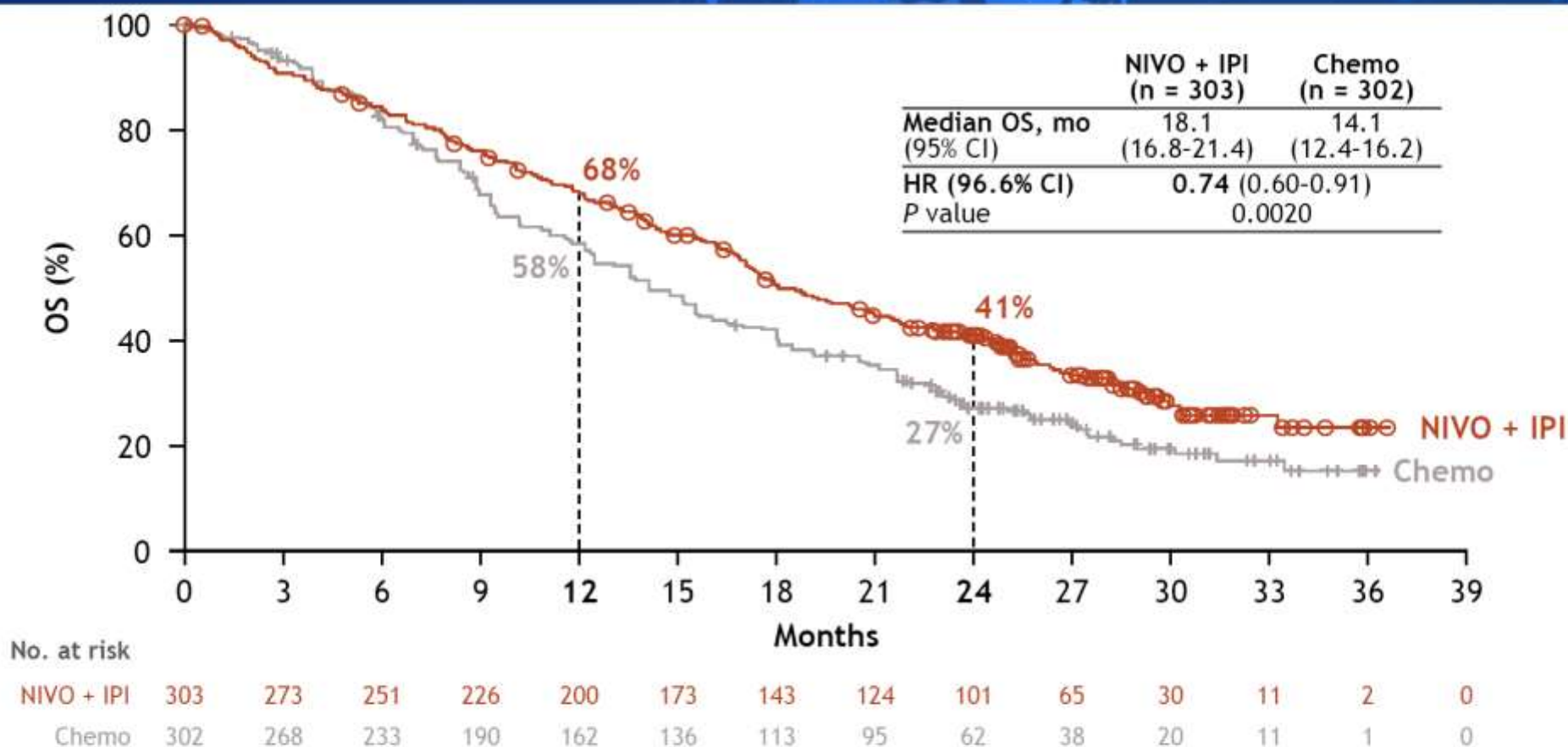
^aNCT02899299; ^bCisplatin (75 mg/m²) or carboplatin (AUC 5) + pemetrexed (500 mg/m²), Q3W for 6 cycles; ^cDetermined by PD-L1 IHC 28-8 pharmDx assay from Dako.



2020 Presidential Symposium

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Primary endpoint: Overall survival



Minimum follow-up: 22.1 months; median follow-up: 29.7 months.

Subsequent systemic therapy was received by 44% of patients in the NIVO + IPI arm and 41% in the chemo arm; subsequent immunotherapy was received by 3% and 20%, and subsequent chemotherapy by 43% and 32%, respectively.

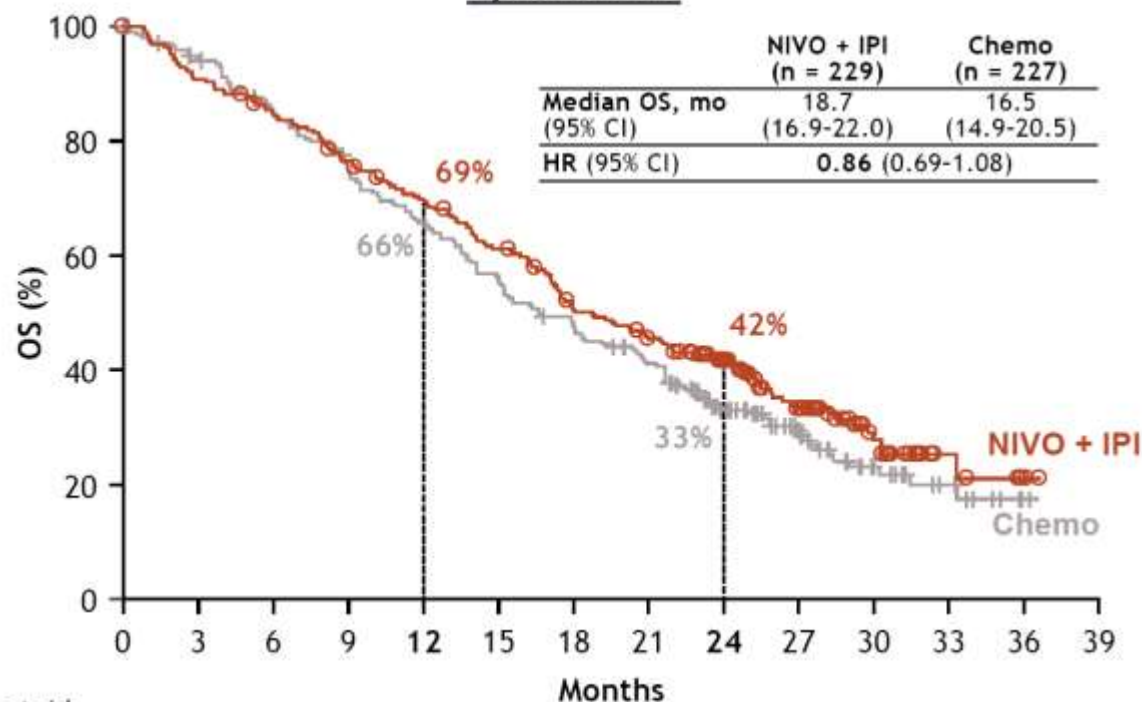


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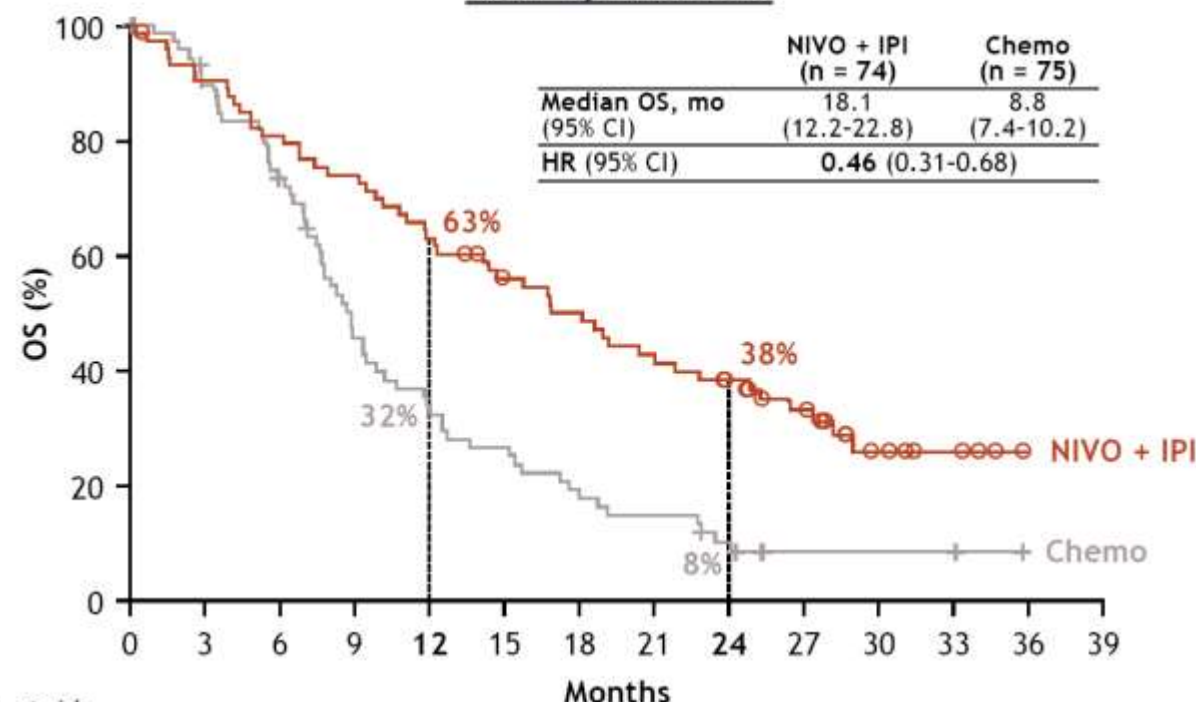
Overall survival by histology^a

Epithelioid



No. at risk														
NIVO + IPI	229	207	192	172	154	135	109	96	77	47	22	6	2	0
Chemo	227	204	182	159	140	118	101	85	57	36	18	9	1	0

Non-epithelioid



No. at risk														
NIVO + IPI	74	66	59	54	46	38	34	28	24	18	8	5	0	0
Chemo	75	64	51	31	22	18	12	10	5	2	2	2	0	0

Minimum follow-up: 22.1 months; median follow-up: 29.7 months.

Patients were stratified by tumor histology: epithelioid vs non-epithelioid.

OS HR (95% CI) for epithelioid vs non-epithelioid were: NIVO + IPI, 0.93 (0.68-1.28); chemo, 0.47 (0.35-0.63).

^aHistology per CRF source.

Studier

Nasjonalt handlingsprogram

Publikasjoner

Studier

Kalender

Kommende møter

Nyheter

▪ Onkologisk forum 2020 12.11.20

Onkologisk forum er i år hel-digitalisert. Norsk lungekreftgruppe vil avholde sitt møte via zoom onsdag 18/11 kl 12-16. Alle er invitert til å delta! [Klikk her for program og innloggingsinformasjon.](#)

▪ Immunterapi også for plateepitelkarsinom med PD-L1 < 50% 26.10.20

[Beslutningsforum](#) vedtok 26.10.20 at pembrolizumab (Keytruda) i kombinasjon med karboplatin og enten paklitaksel eller nab-paklitaksel kan innføres ved førstelinjebehandling av metastatisk plateepitel ikke-småcellet lungekreft for pasienter med PD-L1-uttrykk < 50%.

Dette gjør at alle pasienter med metastatisk ikke-mutert ikke-småcellet lungekreft nå kan få immunterapi i førstelinje, enten som monoterapi (PD-L ≥ 50%), eller i kombinasjon med cellegift.

[Handlingsprogrammet](#) er nå oppdatert og denne siste endringen er omtalt.

▪ Bedre prognose for norske lungekreftpasienter 26.10.20

Sammenlignet med våre naboland er prognosen ved lungekreft bedre i Norge, viser en [studie](#) fra Kreftregisteret, omtalt på [forskning.no](#)

▪ Ny neste-linjes behandling for ALK-/EGFR-muterte 21.09.20

[Beslutningsforum](#) besluttet 21. sept. 2020 at [kombinasjonsbehandling med atezolizumab/bevacizumab/paklitaksel/karboplatin](#) kan innføres for pasienter med EGFR- eller ALK-positiv NSCLC som har progrediert etter behandling med EGFR- eller ALK-hemmer. Denne behandlingen skal ikke gis som førstelinjes behandling til pasienter med slike genforandringer, men kun etter progresjon på målrettet behandling. [Handlingsprogrammet](#) er nå oppdatert og er også publisert på HDir sine sider.

▪ Ikke-innførte, EMA-godkjente medikamenter for lungekreft 20.09.20

NLCG oppdaterer fortløpende [en liste](#) over medikamenter som er EMA-godkjente for lungekreft, men ikke tilgjengelige i det offentlige helsevesen.

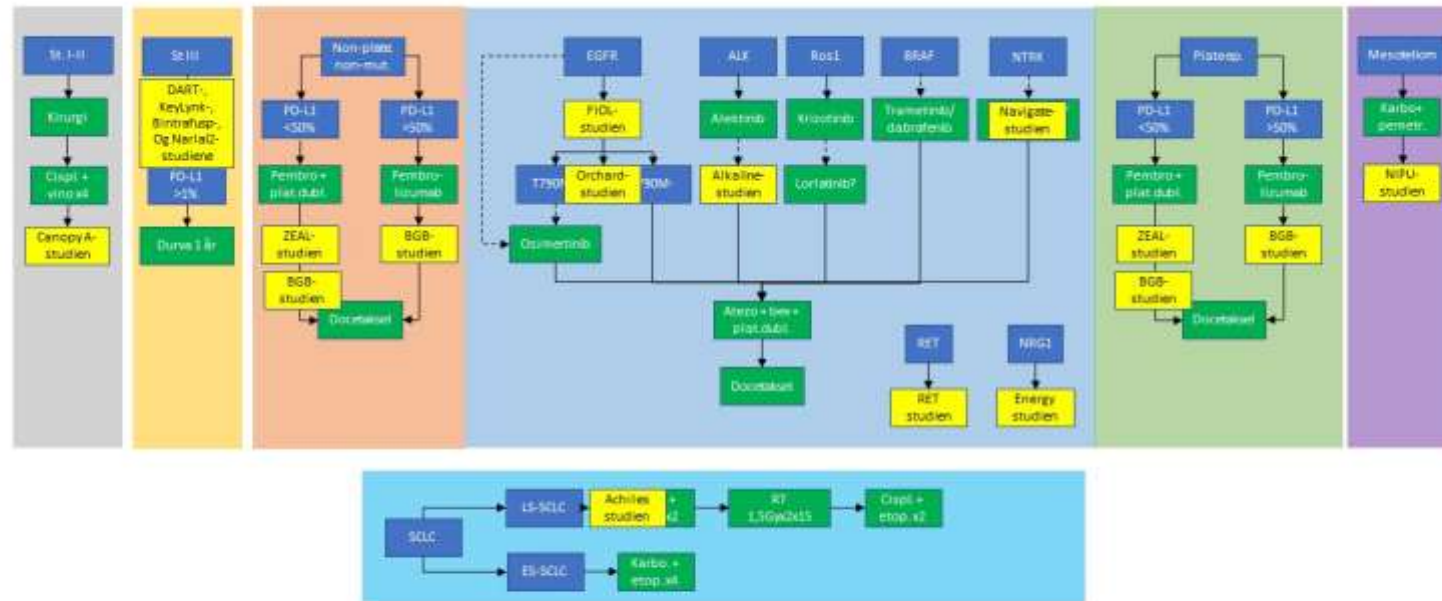
▪ Atezolizumab godkjent i 2. linje for PD-L1 negativt plateepitelkarsinom 31.03.20

Beslutningsforum vedtok 30.3.20 at PD-L1-hemmeren atezolizumab kan innføres i 2. linje for PD-L1 negativt

Studier

For en oversikt over aktuelle kliniske studier, se www.icgi.net/studieapp

Behandlingsskjema med studiemuligheter for lungekreft/mesoteliom

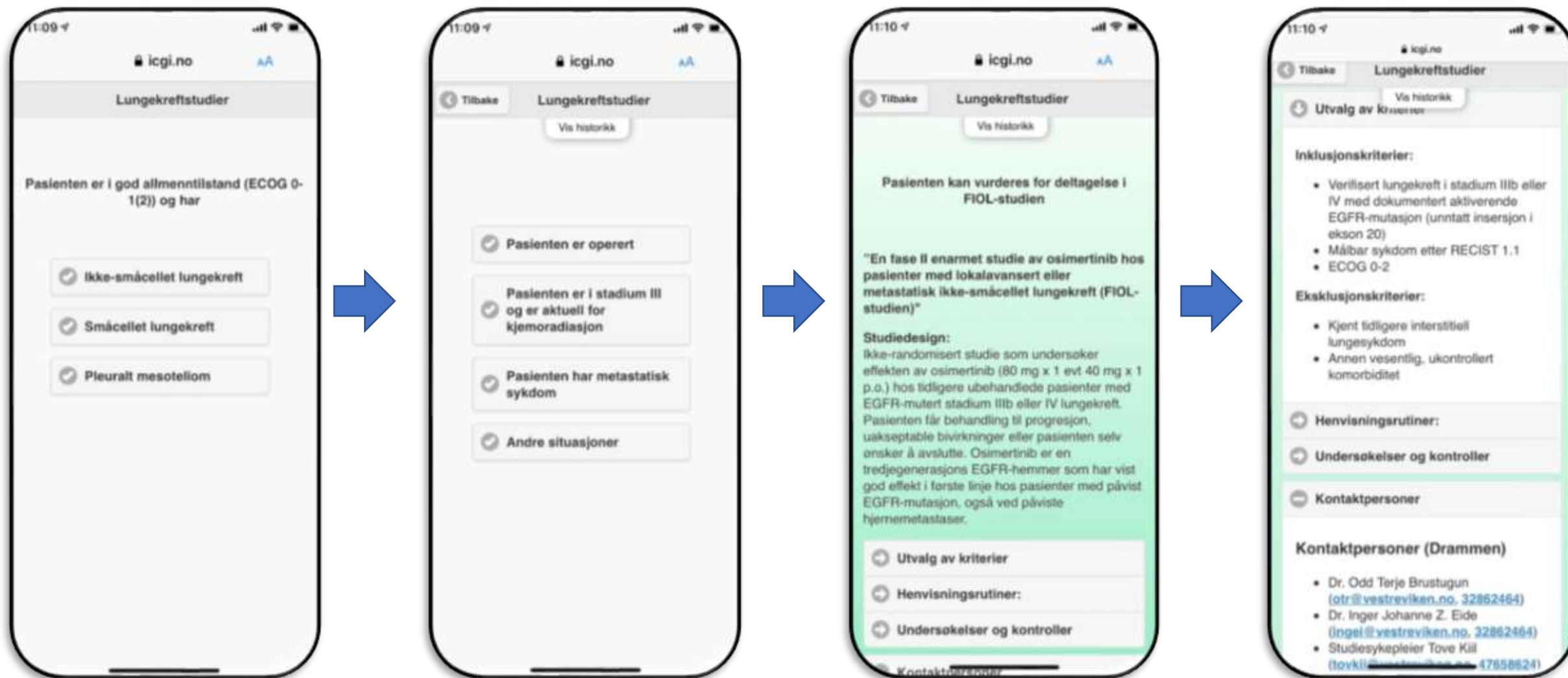


Vurder alltid inklusjon i kliniske studier!

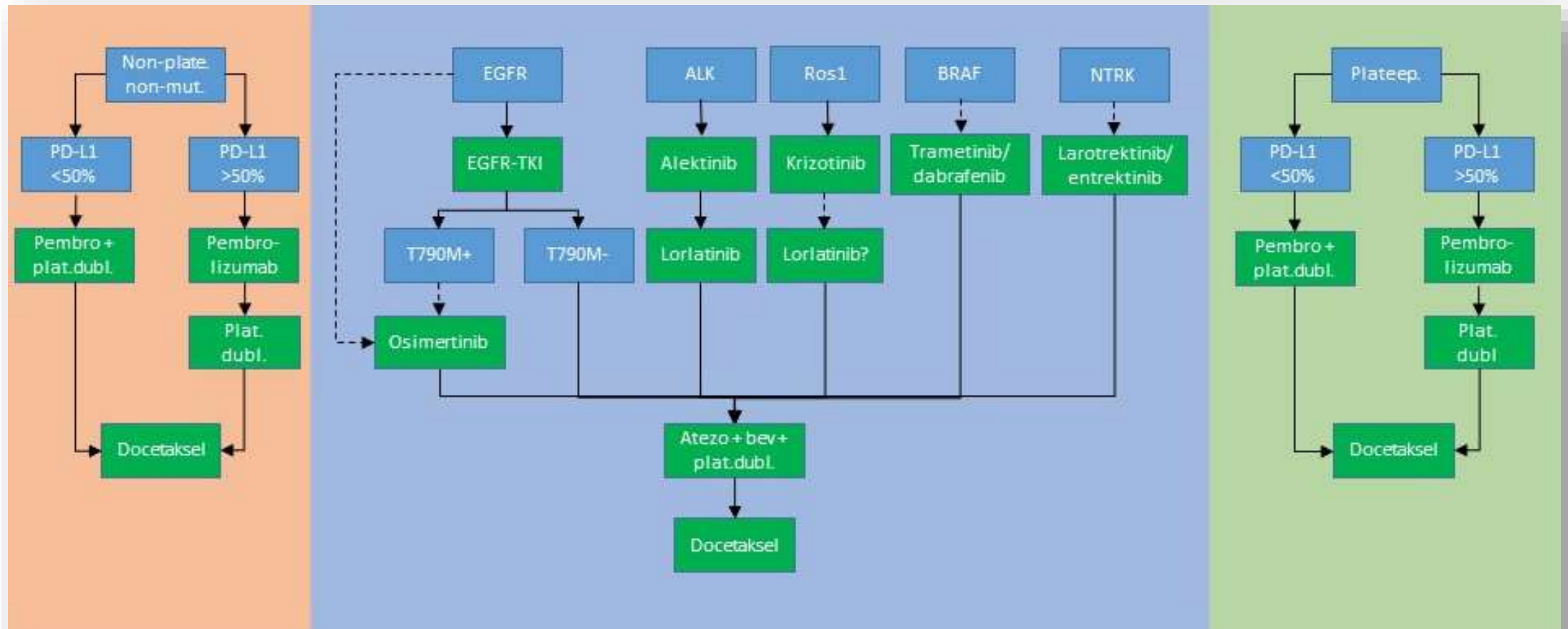
Protokoller (utprøver-initierte studier):

Dåpende studier

Lungekreft-studieapp: icgi.net/studieapp



Behandlingsalgoritme, NSCLC



Vurdèr alltid inklusjon i kliniske studier!