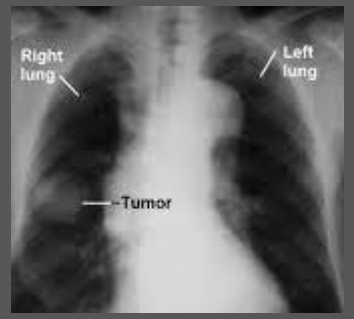
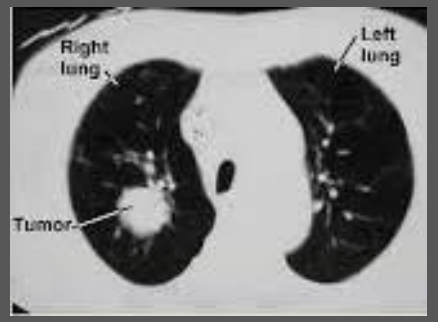


Post-ASCO 2018

Lungekræft



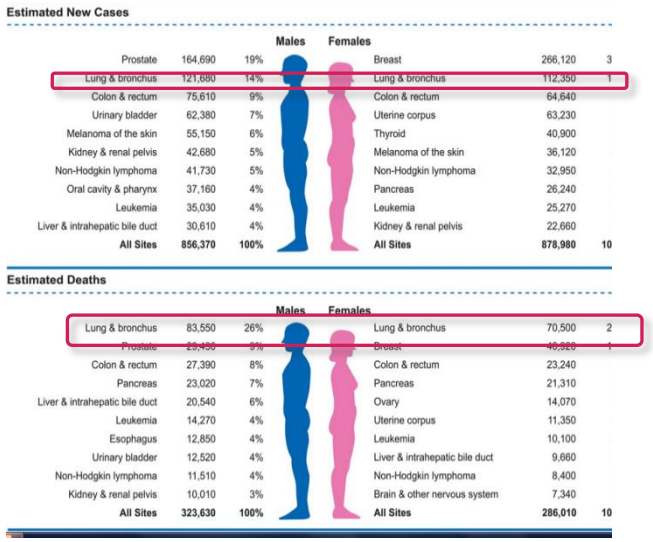
Junior speaker: Jakob Sidenius Johansen, reservelæge, klinisk assistent

Senior speaker: Gitte Persson, overlæge, ph.d.

Herlev Hospital, Onkologisk Afdeling R, Lunge Team

Disclosures

Lungecancer
Lidt statistikker



Estimated New Cases

	Males			Females		
Prostate	164,690	19%		Breast	266,120	3
Lung & bronchus	121,680	14%		Lung & bronchus	112,350	1
Colon & rectum	75,610	9%		Colon & rectum	64,640	
Urinary bladder	62,380	7%		Uterine corpus	63,230	
Melanoma of the skin	55,150	6%		Thyroid	40,900	
Kidney & renal pelvis	42,680	5%		Melanoma of the skin	36,120	
Non-Hodgkin lymphoma	41,730	5%		Non-Hodgkin lymphoma	32,950	
Oral cavity & pharynx	37,160	4%		Pancreas	26,240	
Leukemia	35,030	4%		Leukemia	25,270	
Liver & intrahepatic bile duct	30,610	4%		Kidney & renal pelvis	22,660	
All Sites	**856,370**	**100%**		**All Sites**	**878,980**	**10**

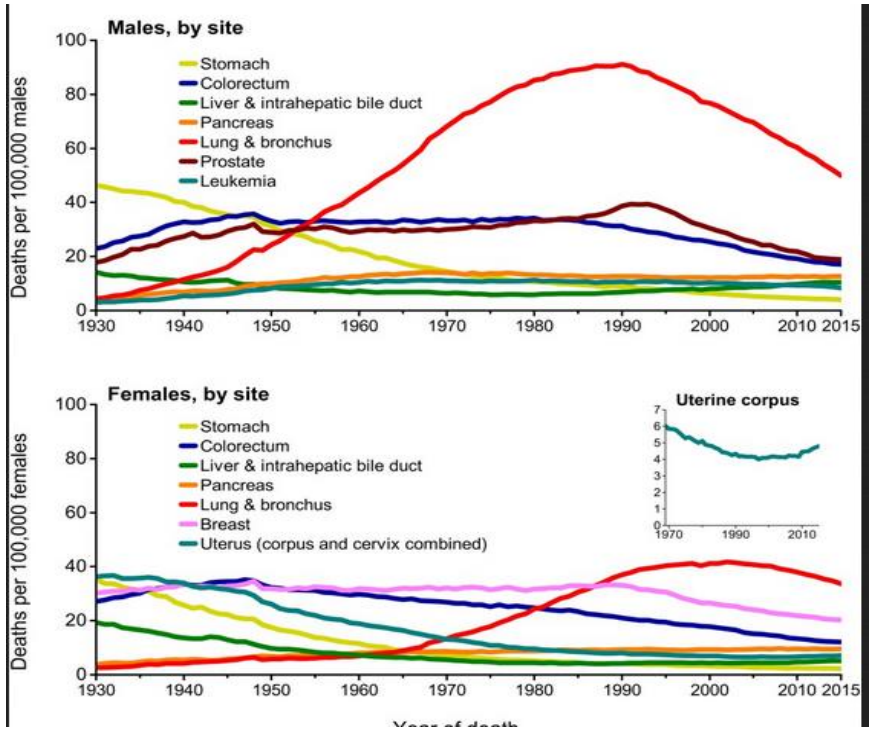
Estimated Deaths

	Males			Females		
Lung & bronchus	83,550	26%		Lung & bronchus	70,500	2
Prostate	29,430	9%		Breast	40,920	1
Colon & rectum	27,390	8%		Colon & rectum	23,240	
Pancreas	23,020	7%		Pancreas	21,310	
Liver & intrahepatic bile duct	20,540	6%		Ovary	14,070	
Leukemia	14,270	4%		Uterine corpus	11,350	
Esophagus	12,850	4%		Leukemia	10,100	
Urinary bladder	12,520	4%		Liver & intrahepatic bile duct	9,660	
Non-Hodgkin lymphoma	11,510	4%		Non-Hodgkin lymphoma	8,400	
Kidney & renal pelvis	10,010	3%		Brain & other nervous system	7,340	
All Sites	**323,630**	**100%**		**All Sites**	**286,010**	**10**

4.600 nye tilfælde årligt i DK, 1,8 mill. i verden

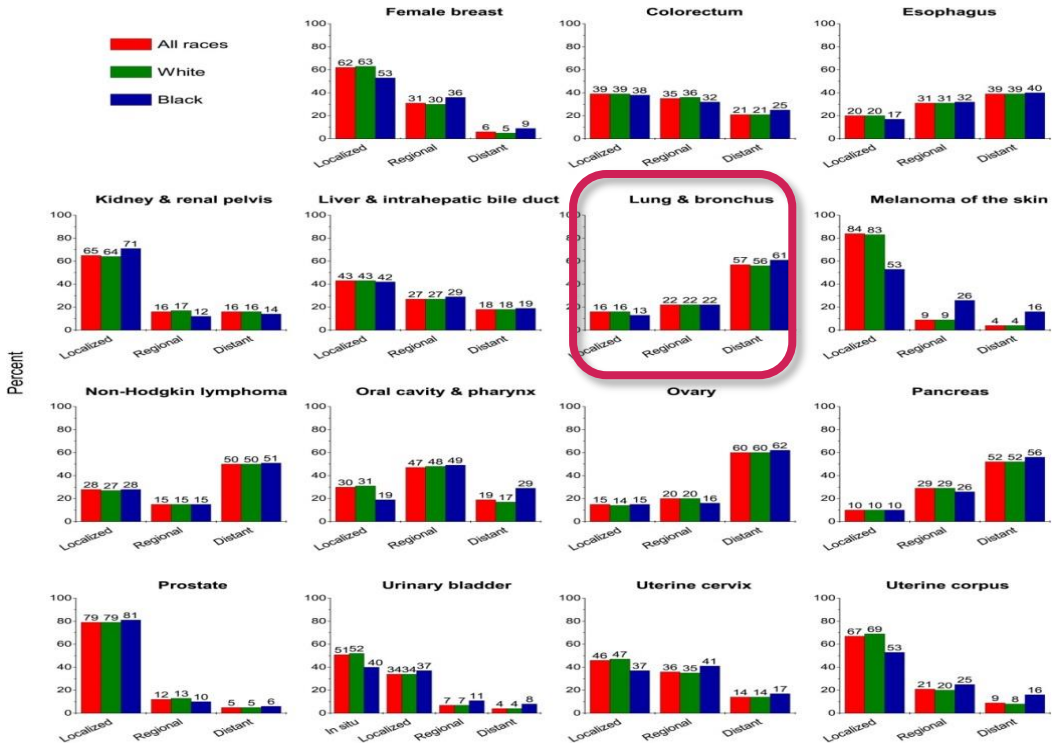
Hyppigste årsag til kræftdødsfald i DK og i verden

Primære årsag er tobaksrygning



Trends i Cancer dødsårsag, USA, 1930-2015

Behandlingsstrategier
Ny vin på nye og gamle flasker

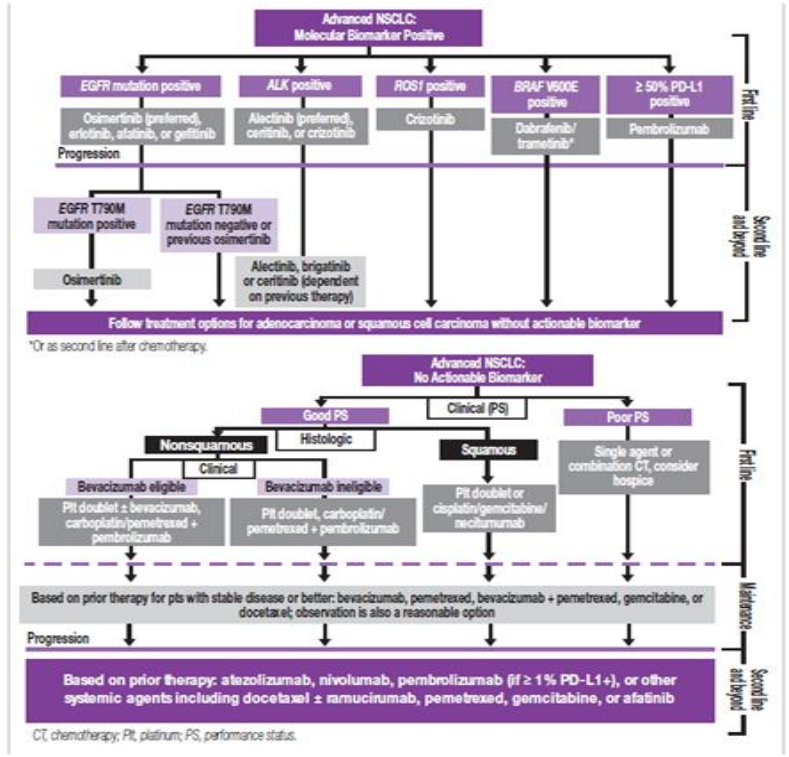


Stadiedistribution, USA, 2007-2013

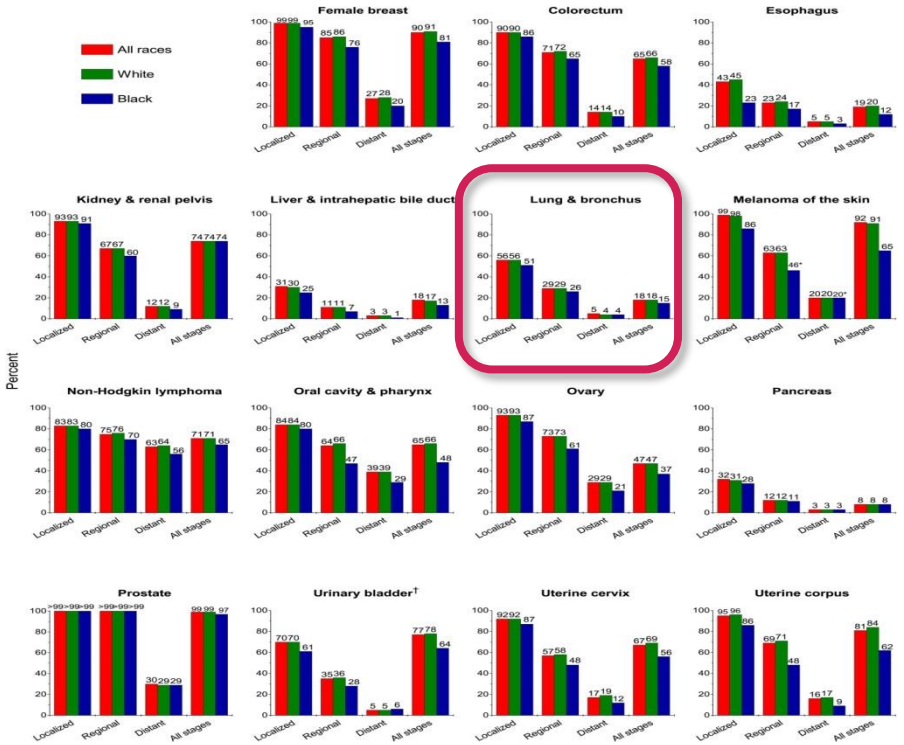
Stadie	Behandling	Overlevelse (5 år)
I	Kirurgi stereotaktisk stråleterapi	77-92%*
II	Kirurgi + adjuverende kemoterapi	53-60%*
III	Konkomitant kemoradioterapi	13-36%*
IV	Immunoterapi Kemoterapi Målrettet terapi Stråleterapi	0-10%*

*Detterbeck et al. J Thor Oncol, 11 (9) (2016), pp. 1433-1446

Behandlingsmodaliteter

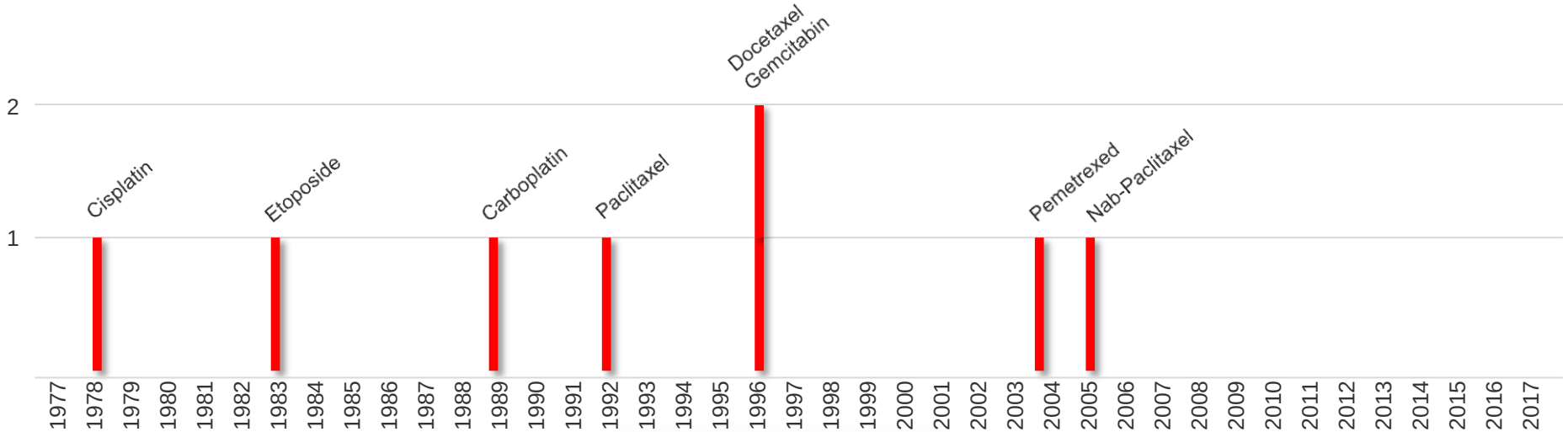


Komplekse behandlingsalgoritmer



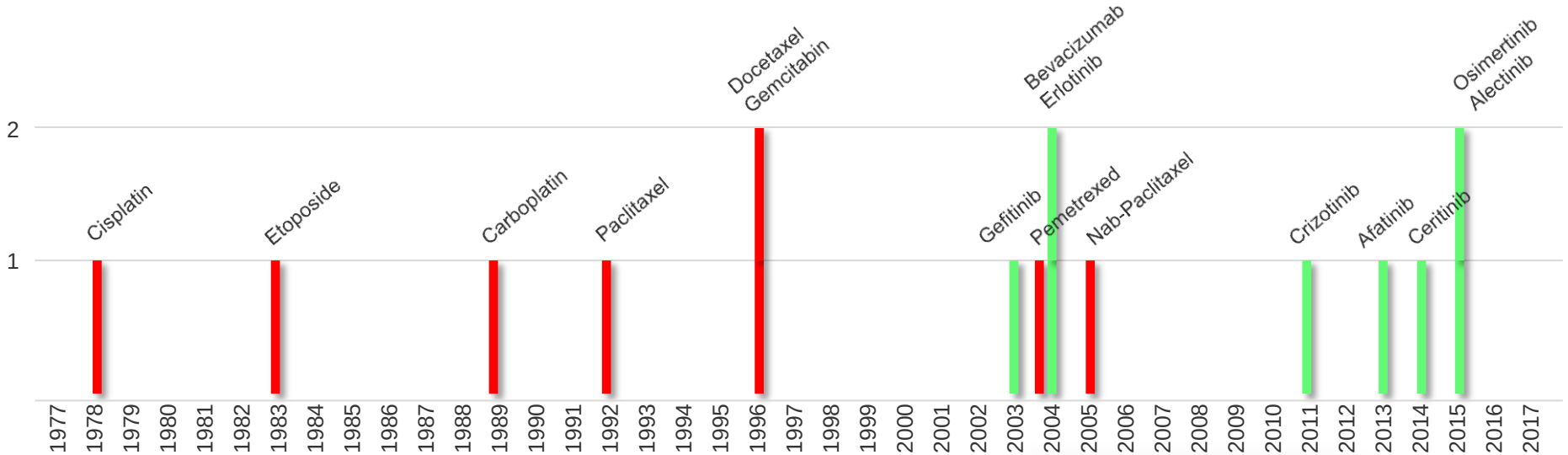
5-års overlevelse og baseline stadie, USA, 2007-2013 (Obs, inden IO)

Kemoterapi, et maraton (1978 – 2005)



Kemoterapi

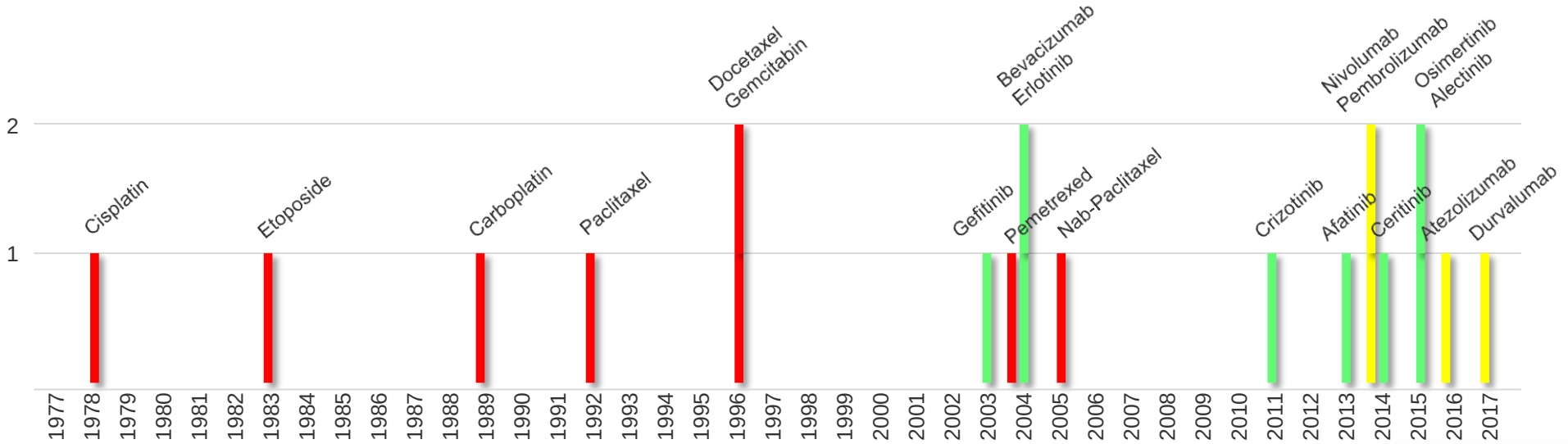
Targeteret behandling, et 3.000 m forhindringsløb (2003-2015)



Kemoterapi

Targeteret behandling (ALKi, EGFR-TKI, VEGFi)

Immunterapi, en 100 m sprint (2014-2017)



Kemoterapi

Targeteret behandling (ALKi, EGFR-TKI, VEGFi)

Immunterapi

Lungecancer studier, ASCO 2018
Udvælgelseskriterier

Fase 3

Primære endpoint: OS

Sekundært endpoint: Safety (QoL)

Klinisk relevant

1. Keynote-042 (Pembrolizumab)

NSCLC, PD-L1 >1%, 1.L, IO-mono, F3

2. NEJ009 (Gefitinib + Platin/Pemetrexed)

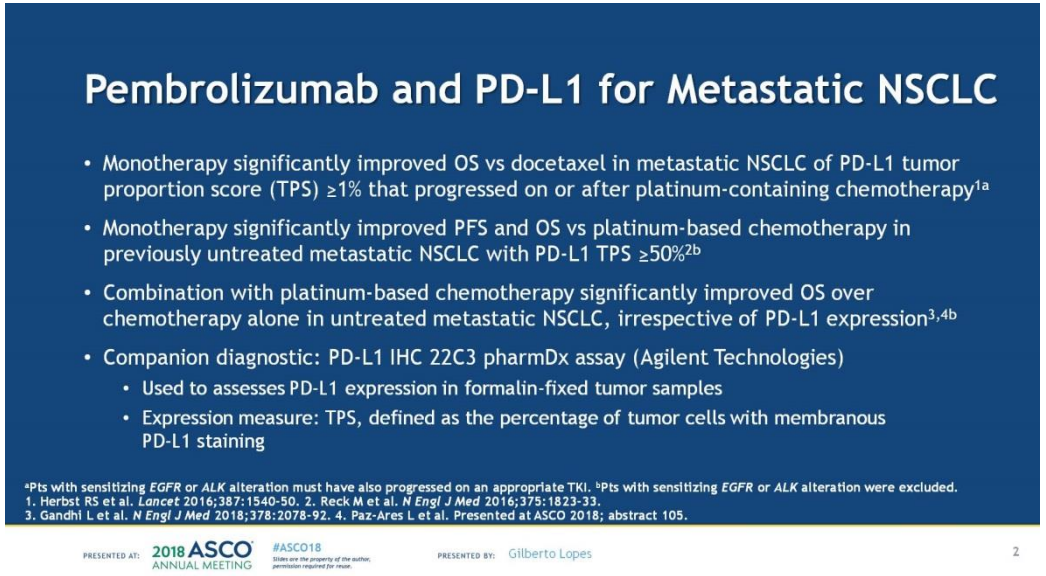
NSCLC, EGFR-mut, 1.L, TT + KT-kombi, F3

3. Baseline Steroids, Review

NSCLC, Retrospektivt, 2-center, Register

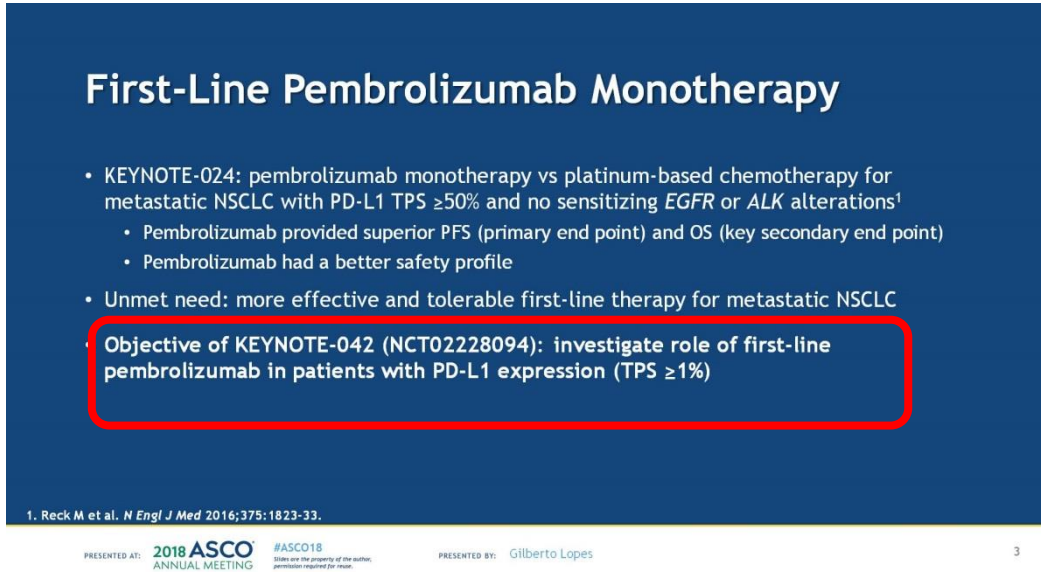
4. Fremtidens højdespringere?

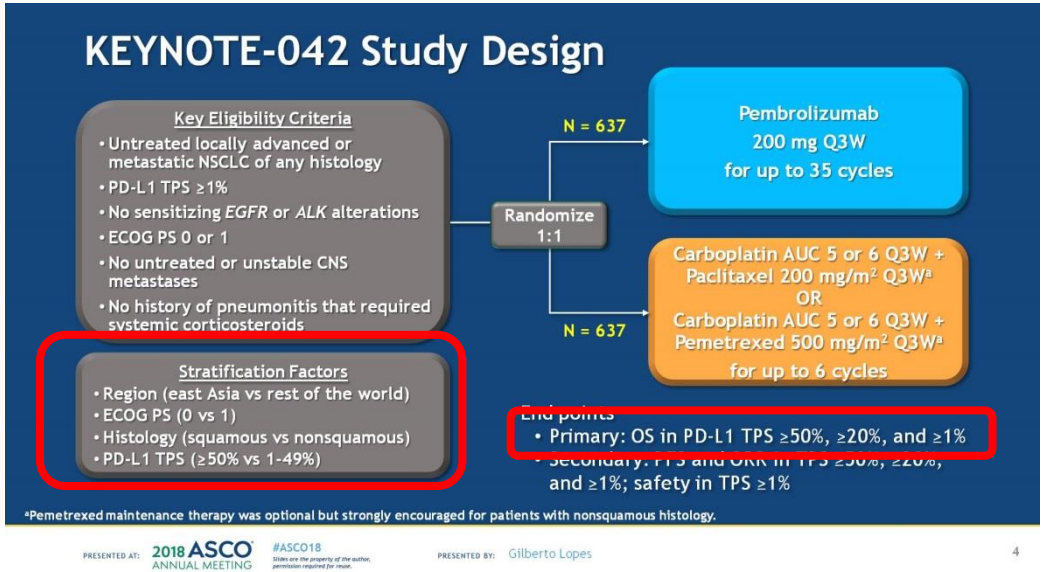
Keynote-042 (Pembrolizumab)
Fase 3, 1. linje til metastatisk NSCLC



KN-010: 2.L mono, IO, F3
KN-024: 1.L mono, IO, F3 -> st. 1.L Pembro
KN-189: 1.L kombi, IO, F3

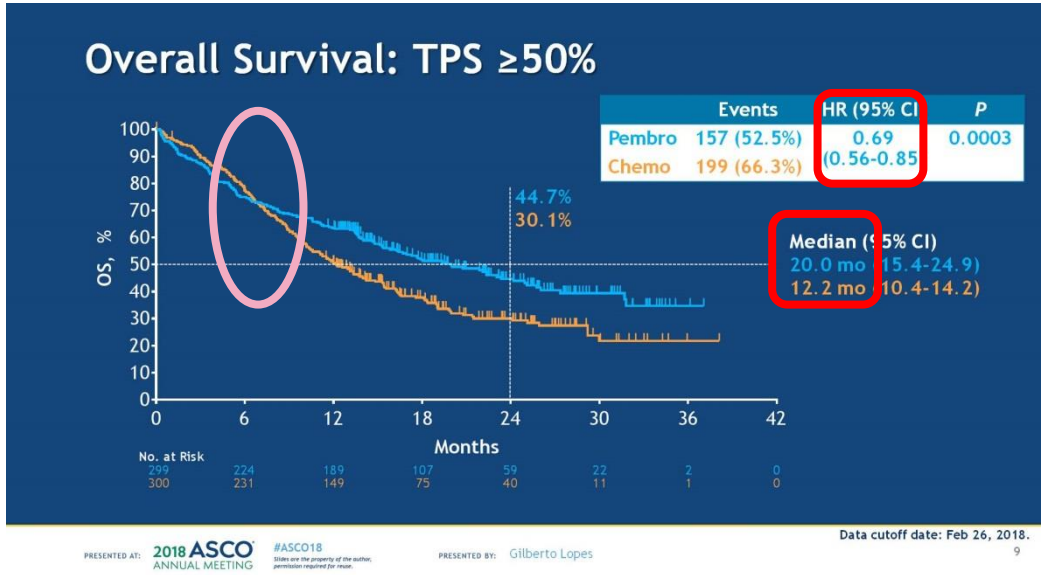
Keynote-042 (Pembrolizumab)
Fase 3, 1. linje til metastatisk NSCLC

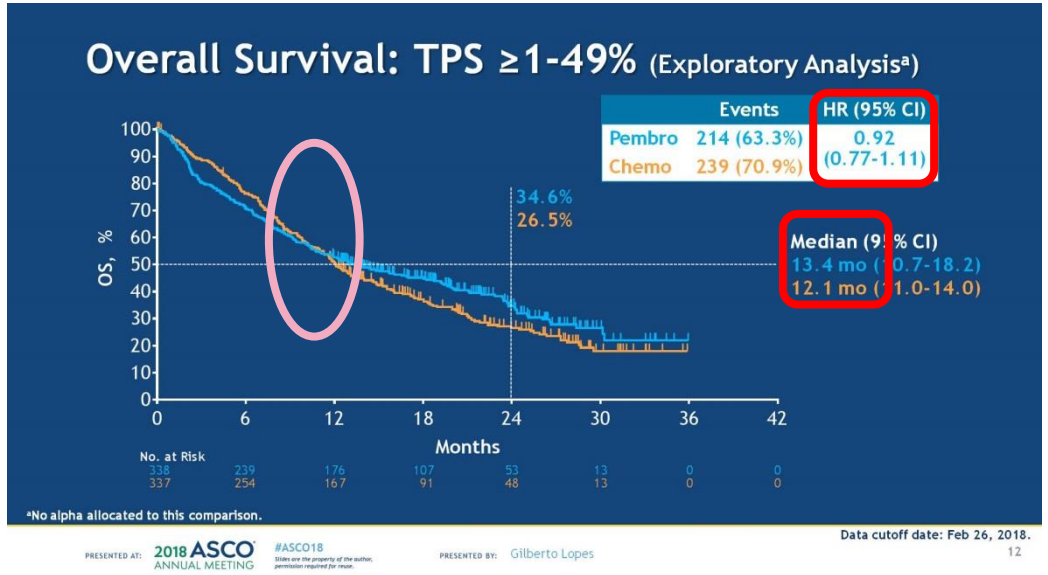




KN-024: fase 3, 1.linje mono IO

Keynote-042 (Pembrolizumab)
Fase 3, 1. linje til metastatisk NSCLC





Hvorfor krydser kurverne først efter 6 mdr?
Hvem har ikke gavn af IO?

One-size doesn't fit all!
De høje TPS løfter kurven.

Keynote-042 (Pembrolizumab)
Fase 3, pallierende 1. linie Immun-monoterapi

Summary of Exposure and Adverse Events: All Treated Patients

	Pembrolizumab (N = 636)	Chemotherapy (N = 615)
No. of doses, median (range)	9 (1-36)	6 (1-42)
Treatment-related AEs	399 (62.7%)	553 (89.9%)
Grade 3-5	113 (17.8%)	252 (41.0%)
Led to death	13 (2.0%)	14 (2.3%)
Led to discontinuation	57 (9.0%)	58 (9.4%)
Immune mediated AEs and infusion reactions[a]	177 (27.8%)	44 (7.2%)
Grade 3-5	51 (8.0%)	9 (1.5%)
Led to death	1 (0.2%)[b]	0

[a]Based on a list of terms specified by the sponsor and considered regardless of attribution to treatment or immune relatedness by the investigator.
[b]Pneumonitis.

Data cutoff date: Feb 26, 2018.

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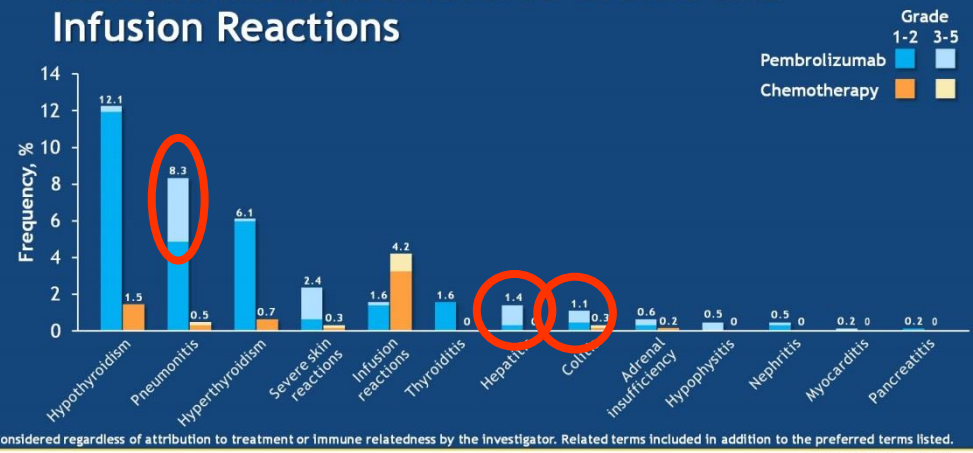
Immune-Mediated Adverse Events and Infusion Reactions



Considered regardless of attribution to treatment or immune relatedness by the investigator. Related terms included in addition to the preferred terms listed.

Data cutoff date: Feb 26, 2018.

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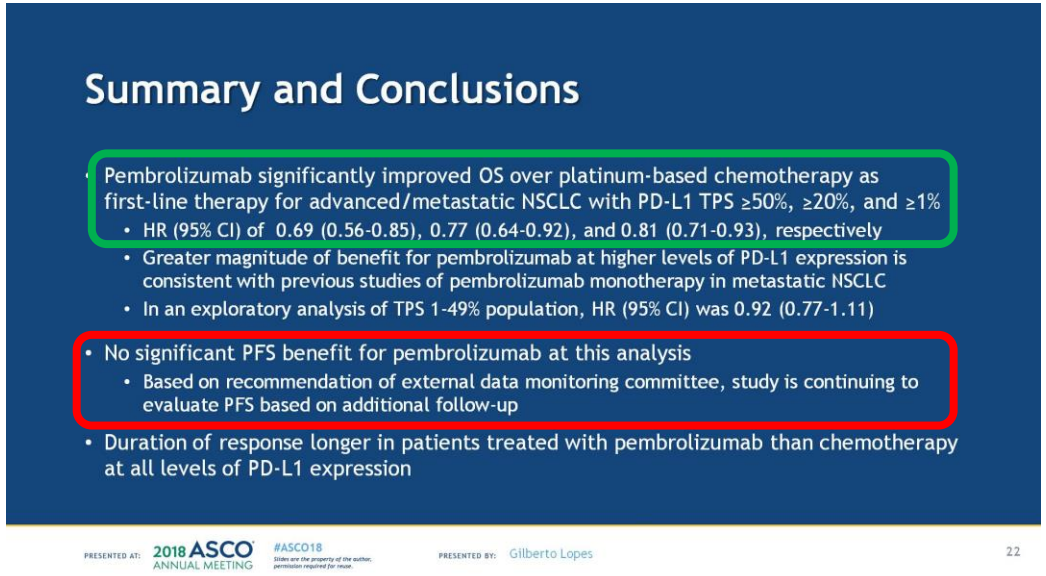
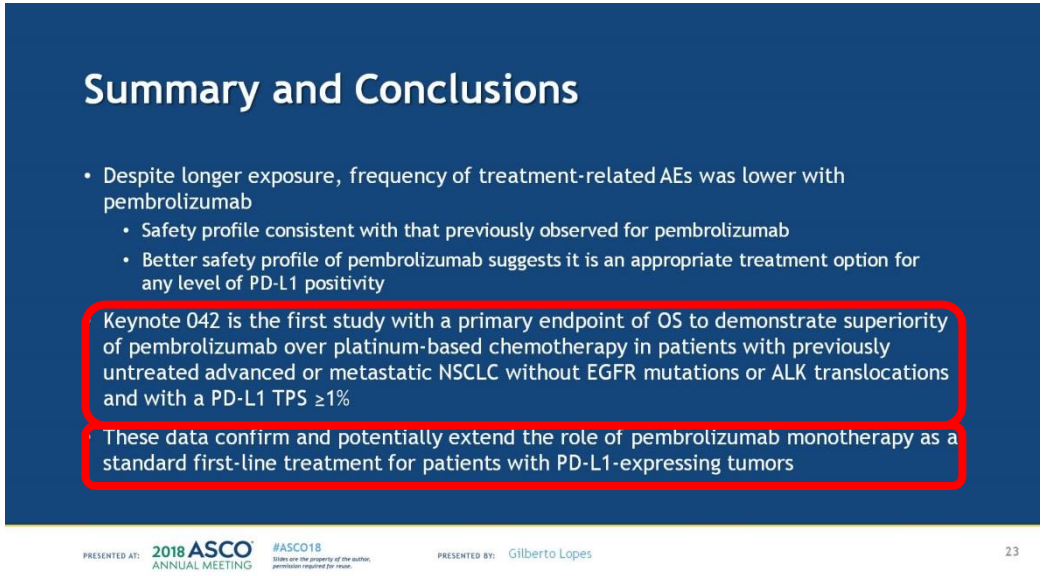
Færre grad 3-5 bivirkninger = bedre QoL

Obs IO-tox: pneumonit, hepatit, colit

Keynote-042 (Pembrolizumab)
Fase 3, 1. linje til metastatisk NSCLC

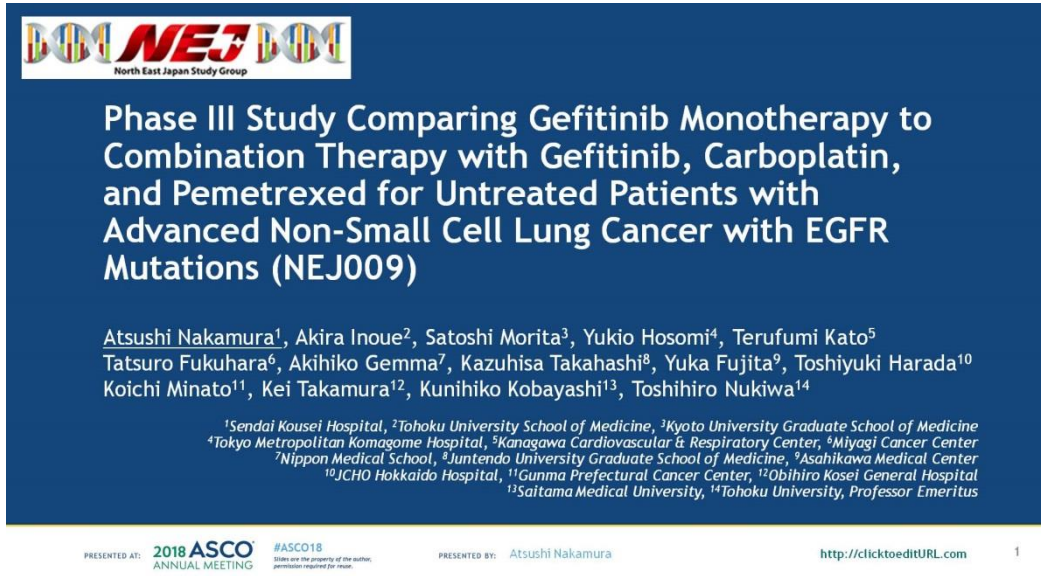


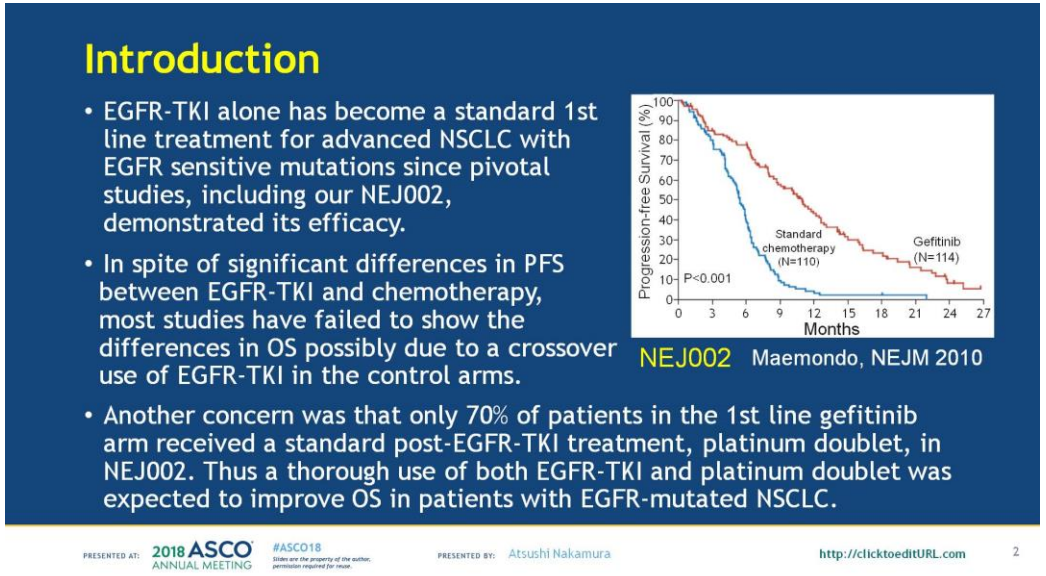


Hos PD-L1>50%: Bedre OS + bedre QoL
= win win
Kun bedre OS ved PD-L1 >50!

Keynote-042 viser bedre OS samt bedre tox (QoL), men det er sandsynligvis PD-L1 >50% Ptt, der løfter kurven

NEJ009 (Gefitinib + Platin + Pemetrexed)
Fase 3, 1. linje til metastatisk EGFR-mut NSCLC

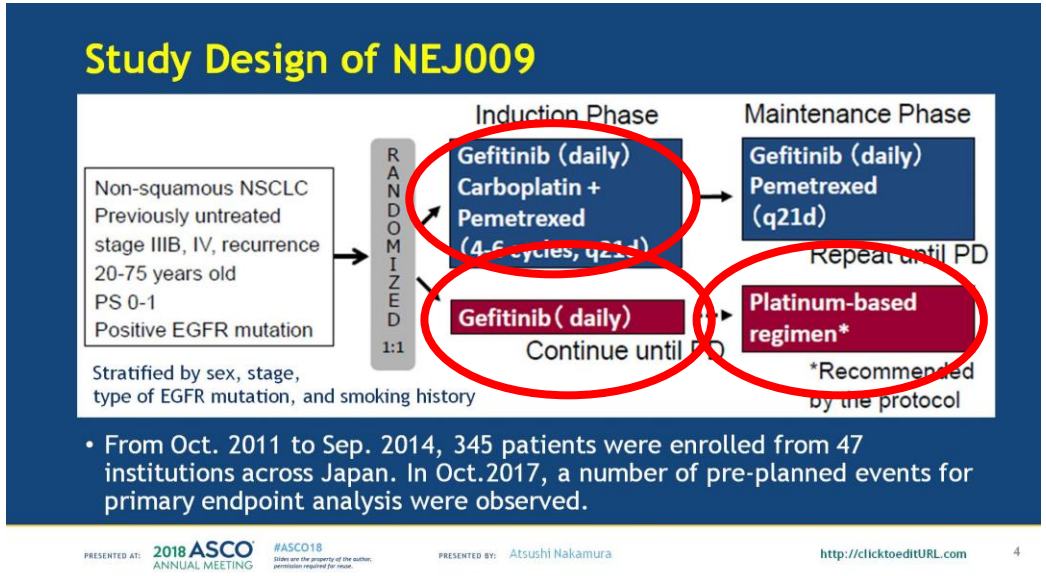


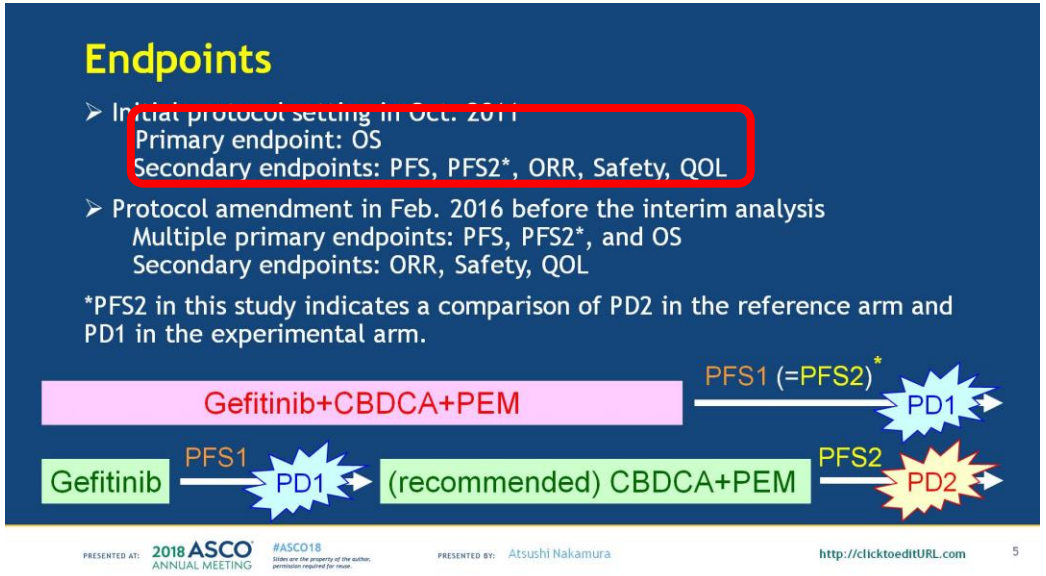


EGFR-TKI (Gefitinib) i kombi med KT (Platin + Pemetrexed)

NEJ002: 1.L mono, TT, F3 PFS ≠ OS

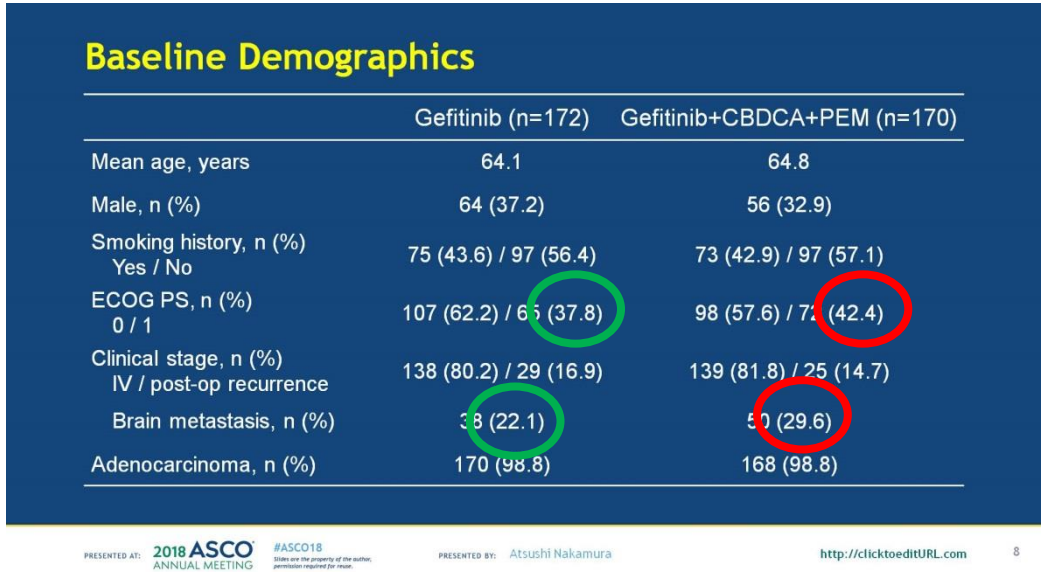
NEJ009 (Gefitinib + Platin + Pemetrexed)
Fase 3, 1. linje til metastatisk EGFR-mut NSCLC





Man bruger hurtigere begge sine våben i kombi-behandling

NEJ009 (Gefitinib + Platin + Pemetrexed)
Fase 3, 1. linje til metastatisk EGFR-mut NSCLC



Baseline Demographics

	Gefitinib (n=172)	Gefitinib+CBDCA+PEM (n=170)
Mean age, years	64.1	64.8
Male, n (%)	64 (37.2)	56 (32.9)
Smoking history, n (%) Yes / No	75 (43.6) / 97 (56.4)	73 (42.9) / 97 (57.1)
ECOG PS, n (%) 0 / 1	107 (62.2) / 65 (37.8)	98 (57.6) / 72 (42.4)
Clinical stage, n (%) IV / post-op recurrence	138 (80.2) / 29 (16.9)	139 (81.8) / 25 (14.7)
Brain metastasis, n (%)	38 (22.1)	50 (29.6)
Adenocarcinoma, n (%)	170 (98.8)	168 (98.8)

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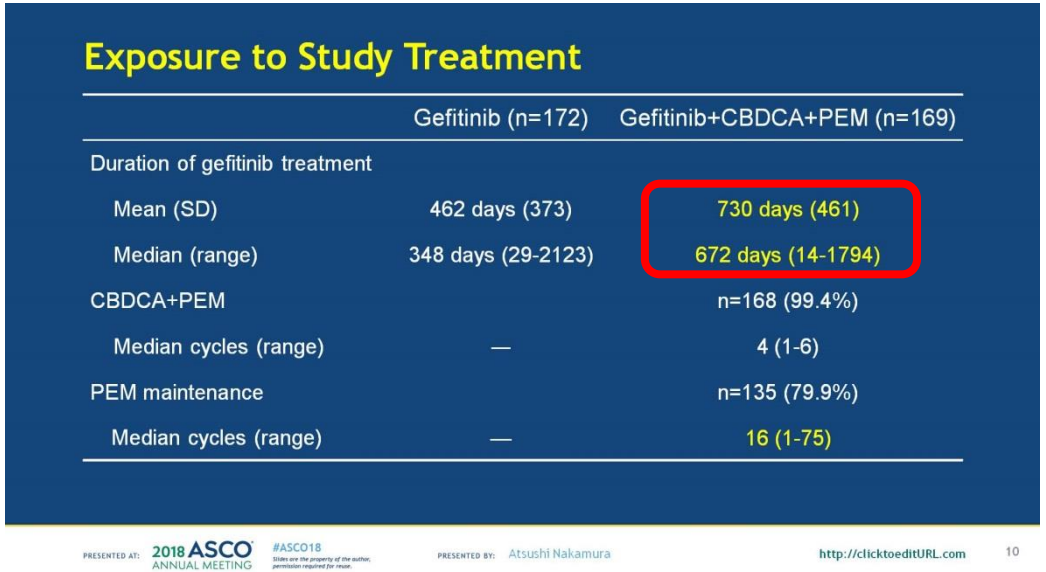

Exposure to Study Treatment

	Gefitinib (n=172)	Gefitinib+CBDCA+PEM (n=169)
Duration of gefitinib treatment		
Mean (SD)	462 days (373)	730 days (461)
Median (range)	348 days (29-2123)	672 days (14-1794)
CBDCA+PEM		n=168 (99.4%)
Median cycles (range)	—	4 (1-6)
PEM maintenance		n=135 (79.9%)
Median cycles (range)	—	16 (1-75)

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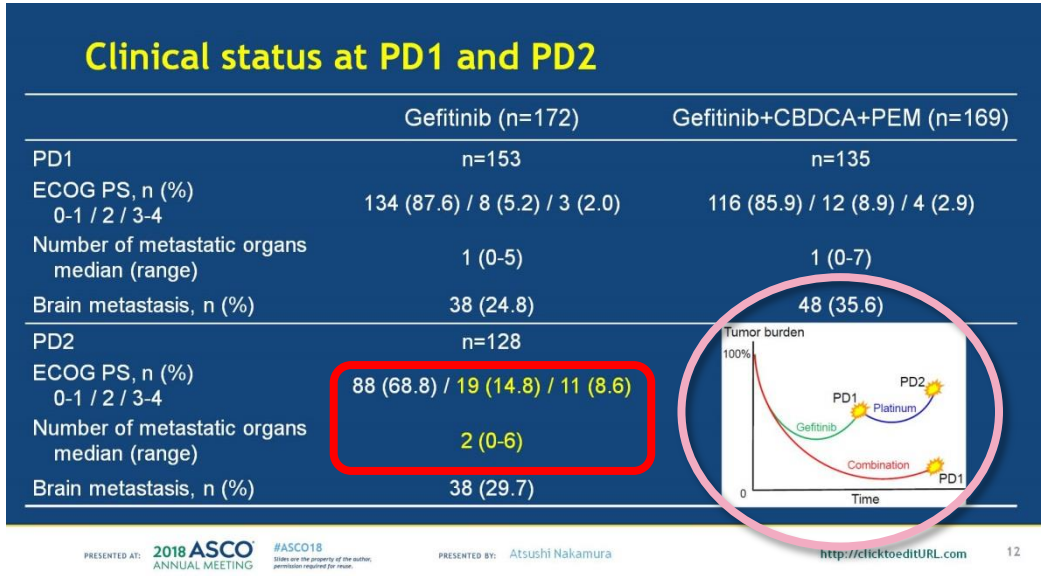
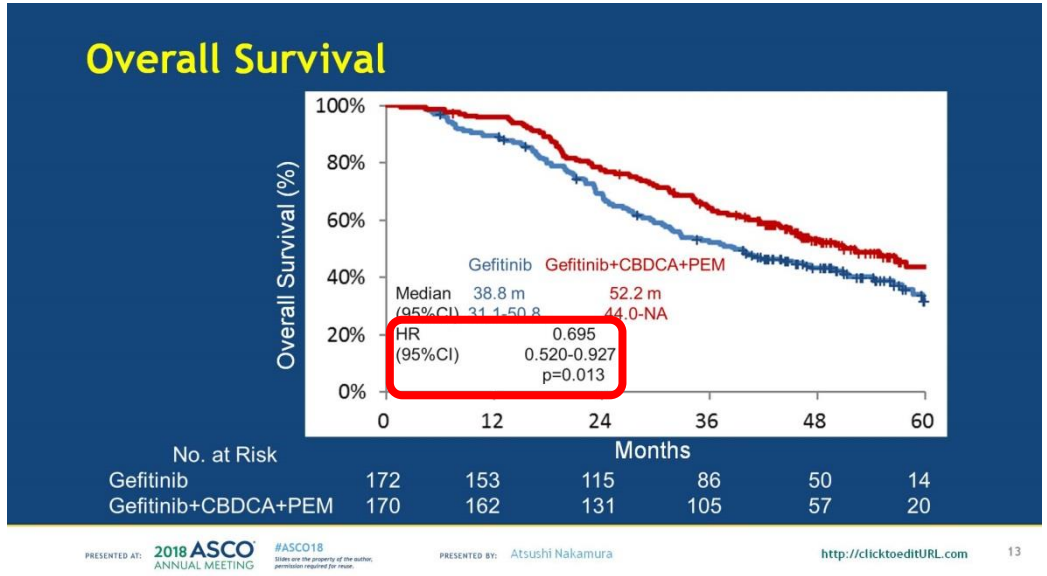
Lidt skæv stratification (PS, Hjernemets), men ok for løfter kontrol-Ptt

Kombi virker markant bedre, pæn synergi (2 + 2 = 5)

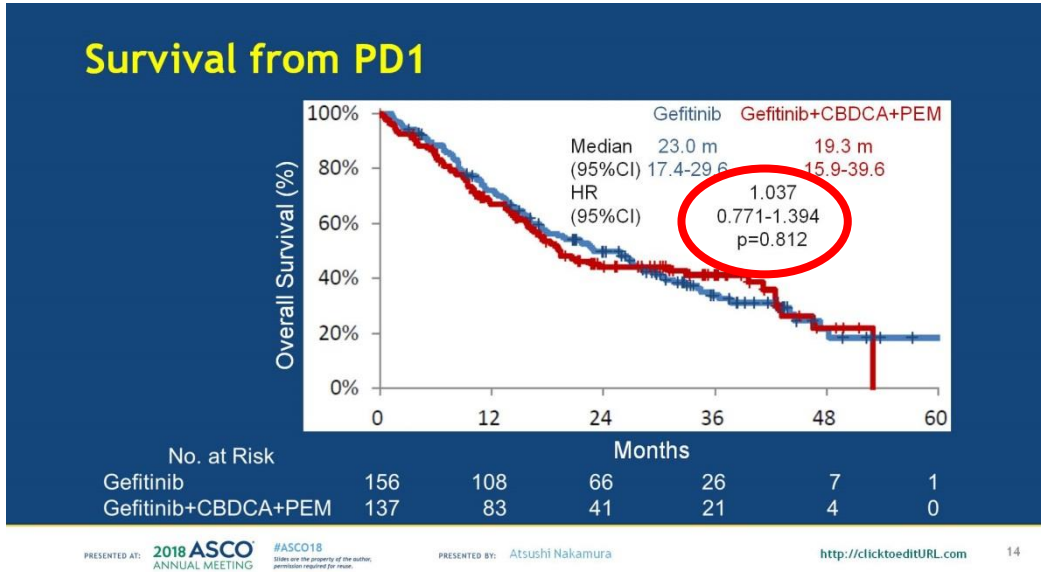
NEJ009 (Gefitinib + Platin + Pemetrexed)
Fase 3, 1. linje til metastatisk EGFR-mut NSCLC

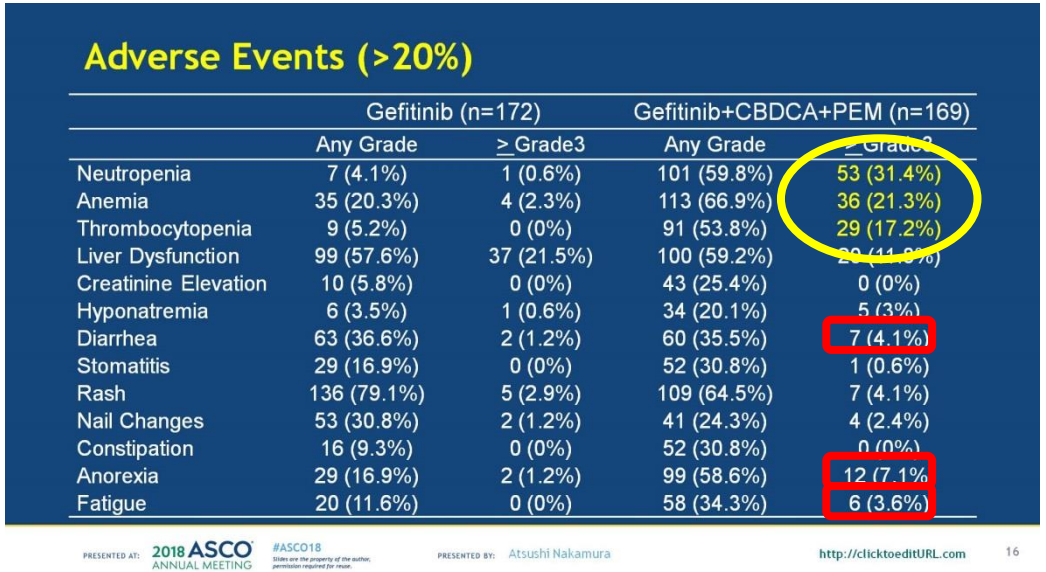




Kæmp det store slag up front
Træd hårdere på speederen i starten!
(Træd hurtigere på bremsen mod slutningen…)

NEJ009 (Gefitinib + Platin + Pemetrexed)
Fase 3, 1. linje til metastatisk EGFR-mut NSCLC

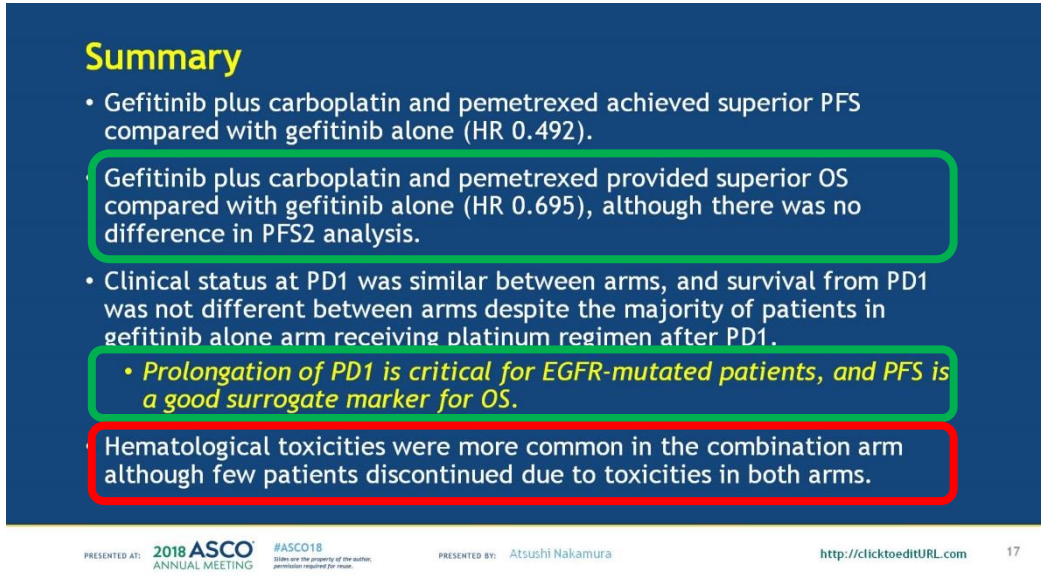


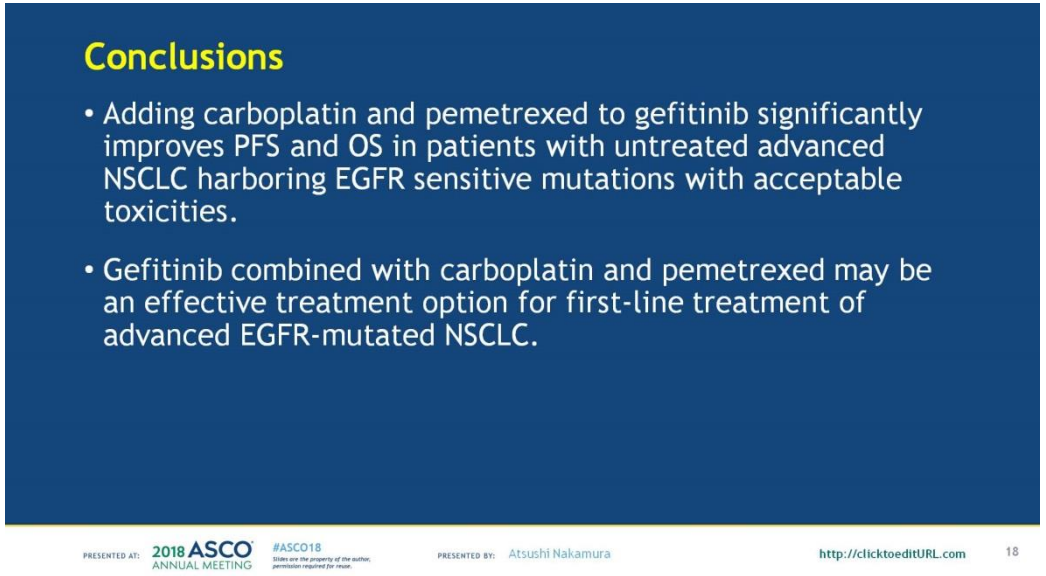


Ammunitionen løber tør hurtigere = Skift fokus til QoL

Kombi-Tox er noget hårdere, men de "værste" påvirker ikke direkte QoL (penier)

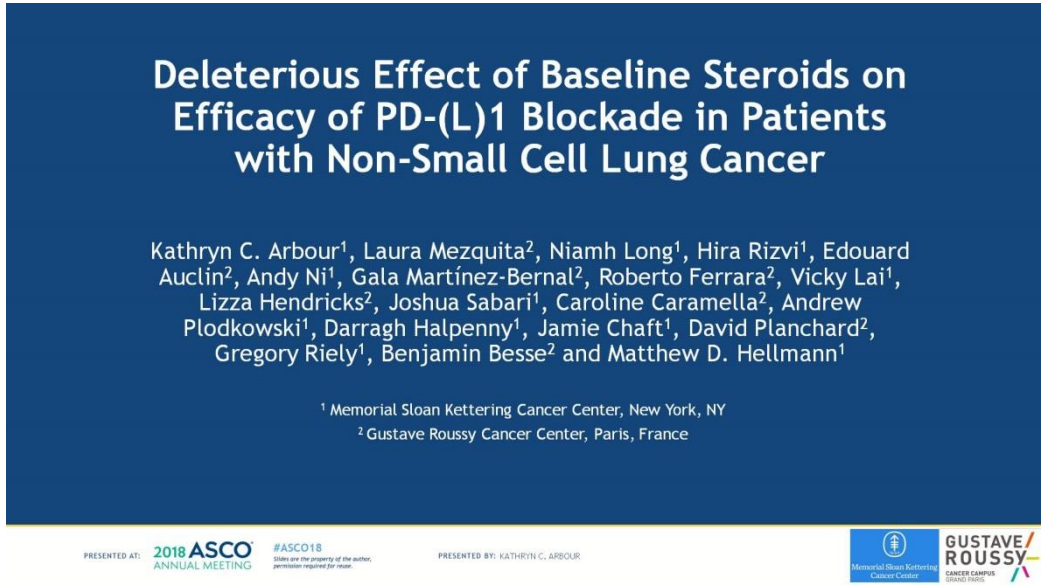
NEJ009 (Gefitinib + Platin + Pemetrexed)
Fase 3, 1. linje til metastatisk EGFR-mut NSCLC

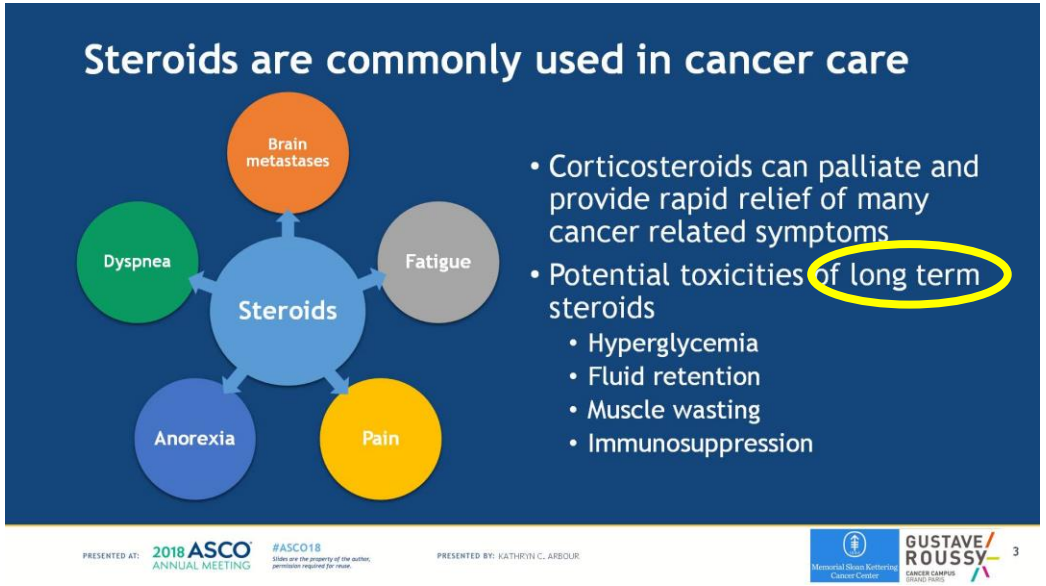




NEJ009: OS-gevinst
og acceptabel tox (QoL)

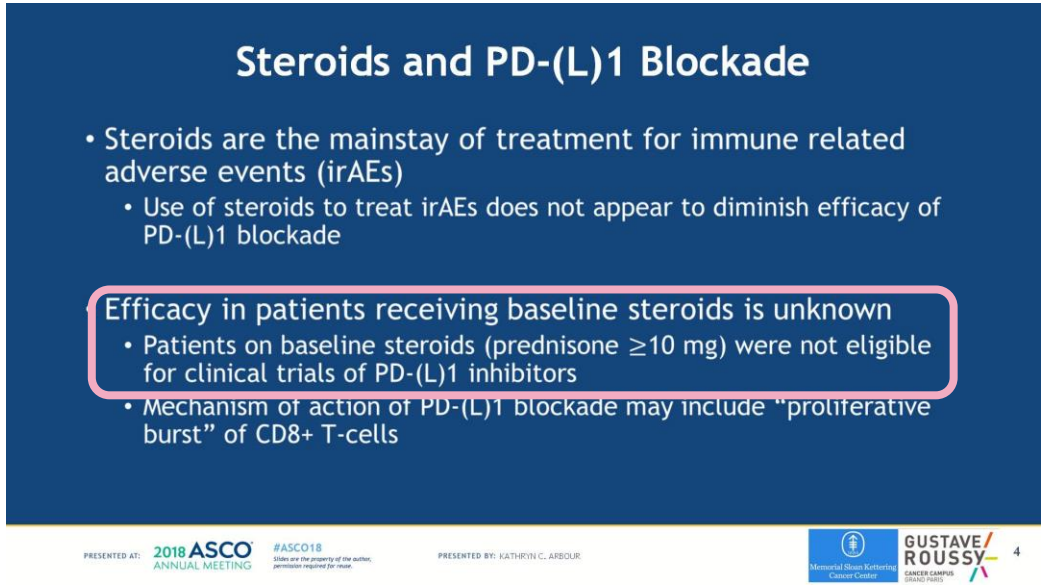
Baseline steroider inden Immunterapi
Retrospektivt, to-center, register-studie

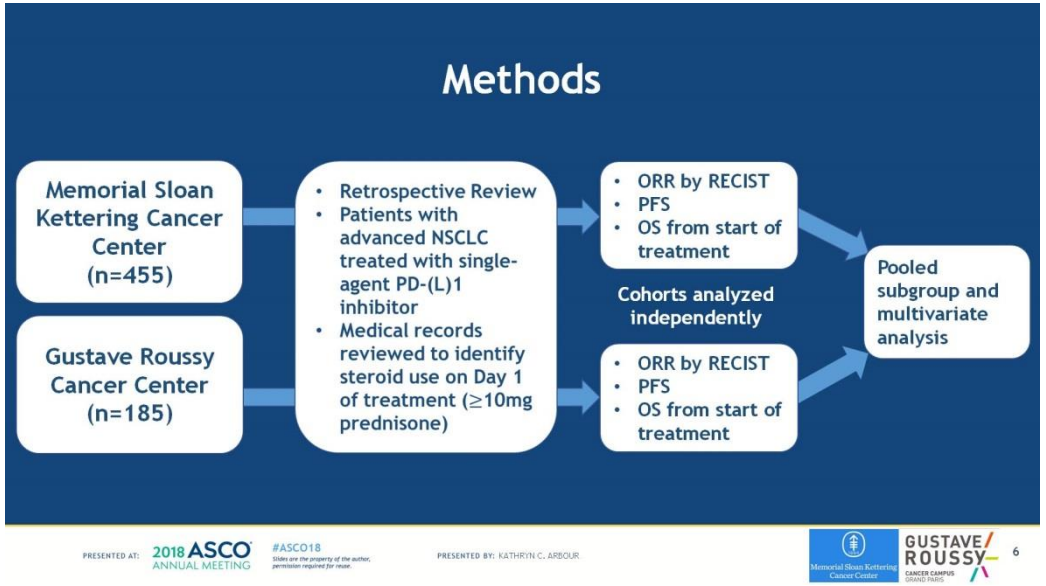




Wonder-drug hos KT-Ptt, men hvad med IO-Ptt?

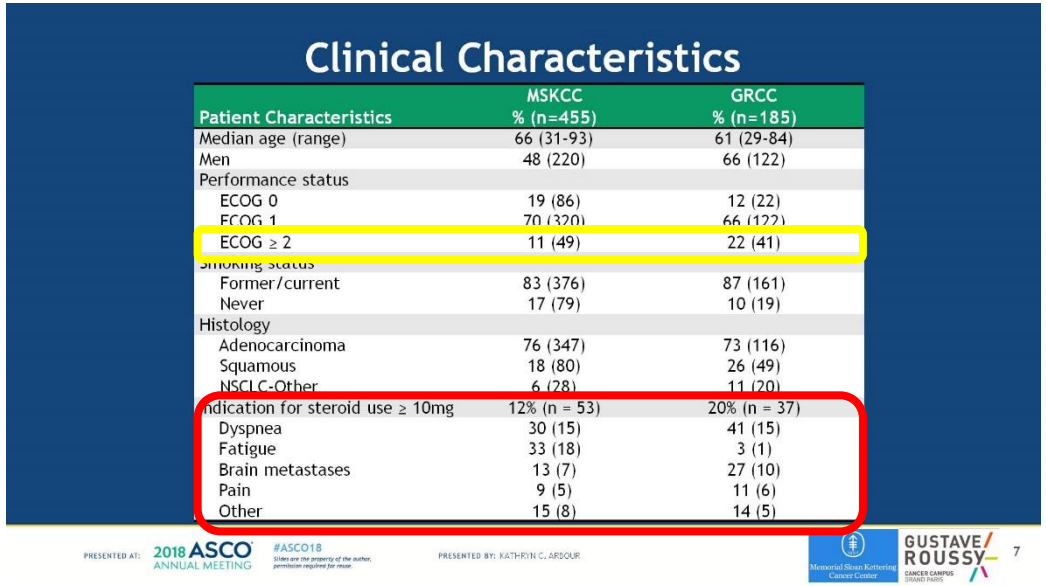
Baseline steroider inden immunterapi
Retrospektivt, to-center, register-studie

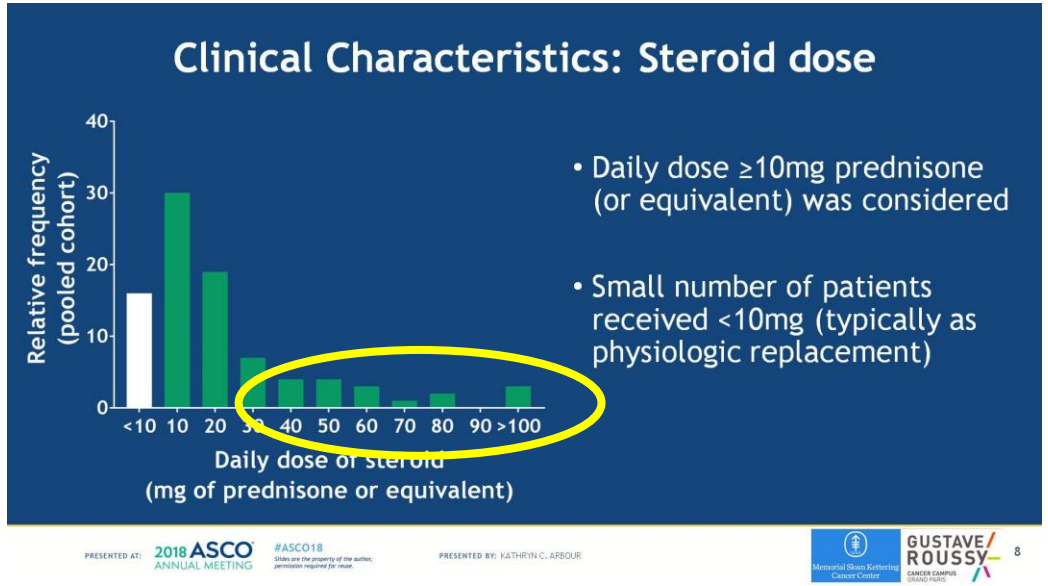




Er steroid-forbrug en prediktor for OS?
- er alle IO-studierne så biased?

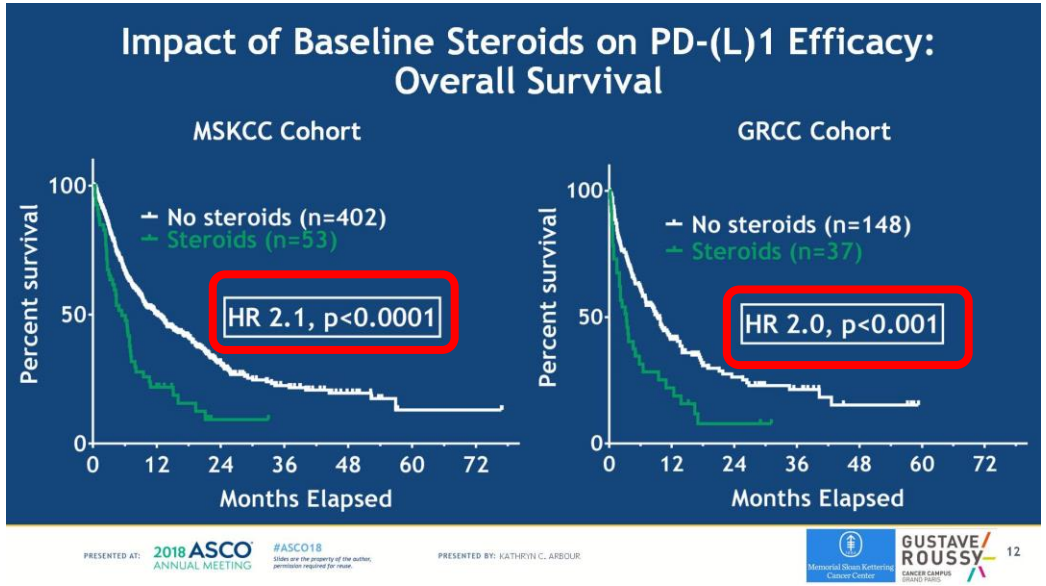
Baseline steroider inden immunterapi
Retrospektivt, to-center, register-studie

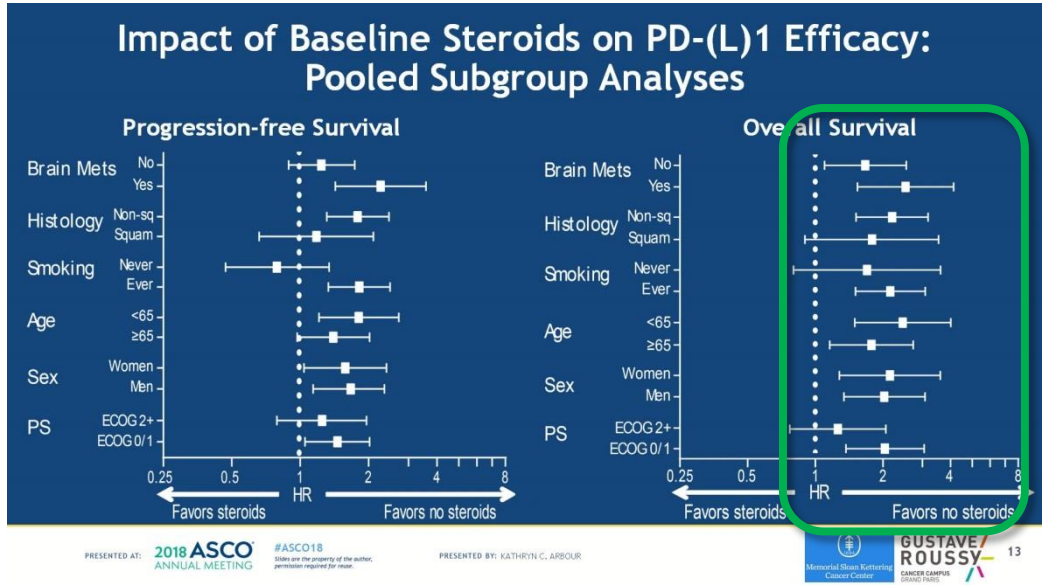




Er steroider ved baseline en driver for dårlig OS, eller blot en "passenger" markør?

Baseline steroider inden immunterapi
Retrospektivt, to-center, register-studie





Nedsætter baseline steroider IO-effekten, eller er det blot en prædiktor?

Signalet er tydeligt, men årsagen uklar

Baseline steroider inden immunterapi
Retrospektivt, to-center, register-studie

Impact of Baseline Steroids on PD-(L)1 Efficacy: Multivariate Analysis

Patient characteristics	ORR Odds Ratio (95% CI)	p-value	PFS Hazard Ratio (95% CI)	p-value	OS Hazard Ratio (95% CI)	p-value
Smoking status (never vs ever)	0.33 (0.15-0.74)	0.007	1.64 (1.30-2.04)	<0.001	1.03 (0.81-1.33)	0.78
Performance status (ECOG ≥2 vs 0/1)	0.29 (0.11-0.75)	0.11	1.97 (1.55-2.50)	<0.001	2.29 (1.75-2.98)	<0.001
History of brain metastases (yes vs no)	0.88 (0.52-1.49)	0.6	1.16 (0.96-1.41)	0.1	1.37 (1.11-1.7)	0.003
Steroid use (yes vs no)	0.42 (0.17-1.01)	0.053	1.31 (1.03-1.67)	0.03	1.66 (1.28-2.16)	<0.001

PRESENTED AT: 2018 ASCO ANNUAL MEETING #ASCO18 PRESENTED BY: KATHRYN C. ARBOUR 14

Baseline steroids and PD-(L)1 Efficacy: Conclusions

- Baseline steroid use when starting PD-(L)1 blockade is associated with inferior outcomes (PFS and OS)
  - Effect may be predictive and/or prognostic
- Prudent use of steroids in patients for whom PD-(L)1 blockade is planned should be considered
  - Consideration of non-steroid alternatives for management of cancer symptoms
  - Medically necessary steroids (e.g. brain metastases) should NOT be avoided
- Implications for patients receiving chemo + PD-(L)1 is uncertain

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Øget opmærksomhed på pn steroid ved IO-start.
Altid steroid ved hjernemetastaser!

Hvad er fremtidens højdespringere?

IO kombineret med RT

A 8510 F2, NSCLC, stadie III (NICOLAS)
1L: IO (Nivolumab) + KT (Platin/dublet) + RT

A 9023 F2, NSCLC, stage IV (PEMBRO-RT)
1L: IO (Pembrolizumab) + SBRT

PACIFIC F3, NSCLC, stadie III
Adj: IO (Durvalumab) + RT

Neo-adj IO/TKI (+KT) før OP

A 8521 F2 NSCLC, stage IIIa (NADIM-SLCG)
Neoadj: IO (Nivolumab) + KT (Platin/Paclitaxel)

A 8532 F2, NSCLC, stage Ib – IIIa
Neoadj: IO (Atezolizumab) + KT (Platin/Paclitaxel)

A 8541 F2, NSCLC, stage Ib-IIIb (LCMC3)
Neoadj: IO (Atezolizumab) mono

A 8544 F2, NSCLC, EGFR+, stage III (ASCENT)
Neoadj: TT (Afatinib) + KT(Platin/Pemetrexed) + RT

Hvem er fremtidens højdespringere?
Hvilke Fase 2/3 studier kommer over baren?

KT + IO kombi

A 105 F3, NSCLC, stage IV (Keynote-407)
1L: IO (Pembrolizumab) + KT (Platin/Taxan)

A 9001 F3, NSCLC, stage IV, PDL1 <1 (Checkmate 227)
1L: IO (Nivolumab) + KT (Platin/Dublet)

A 9026 F2, NSCLC, stage IIIb/IV (Keynote-021)
1L: IO (Pembrolizumab) + KT (Platin/Pemetrexed)

LBA 9000 F3, NSCLC, stage IV (IMPOWER 131)
1L: IO (Atezolizumab) + KT (Platin/Taxan)

SCLC

A 8575 F2, SCLC, ED
2L: IO (Pembrolizumab) + KT (Paclitaxel)

Hvad bringer fremtiden?

Nu og nær fremtid

- ✓ PD-L1 >50%: 1.L IO (Pembrolizumab) (KN-024)
- ✓ PD-L1 1-49%: 1.L IO + KT kombi (KN-189)
- ✓ Adjuverende IO efter konkomitant KT + RT (PACIFIC)

Inden for de næste 5 år

- ✓ Implementering af TMB, IO-dublet (PD-(L)1 + CTLA-4) til TMB high
- ✓ Neoadjuverende IO før OP
- ✓ Konkomitant IO + KT + RT
- ✓ Kombinationbehandling til st. IV IO + KT + RT

Hvad bringer fremtiden?

Uafklarede spørgsmål

- ✓Hvordan behandles PD-L1 <1% bedst?
- ✓Hvilken kemo ”backbone” er bedst i kombi med IO?
- ✓Korrekt rækkefølge af KT, RT, IO, TT og OP?
- ✓Steroider samtidigt med IO?
- ✓Hvad med SCLC?

Tak

Dorte Nielsen

Professor, overlæge, dr.med.

Herlev Hospital, Onkologisk Afd.

Peter Michael Vestlev

Overlæge

Lægelig leder i SKA

Gitte Persson

Overlæge, ph.d.

Herlev Hospital, Onkologisk Afd.

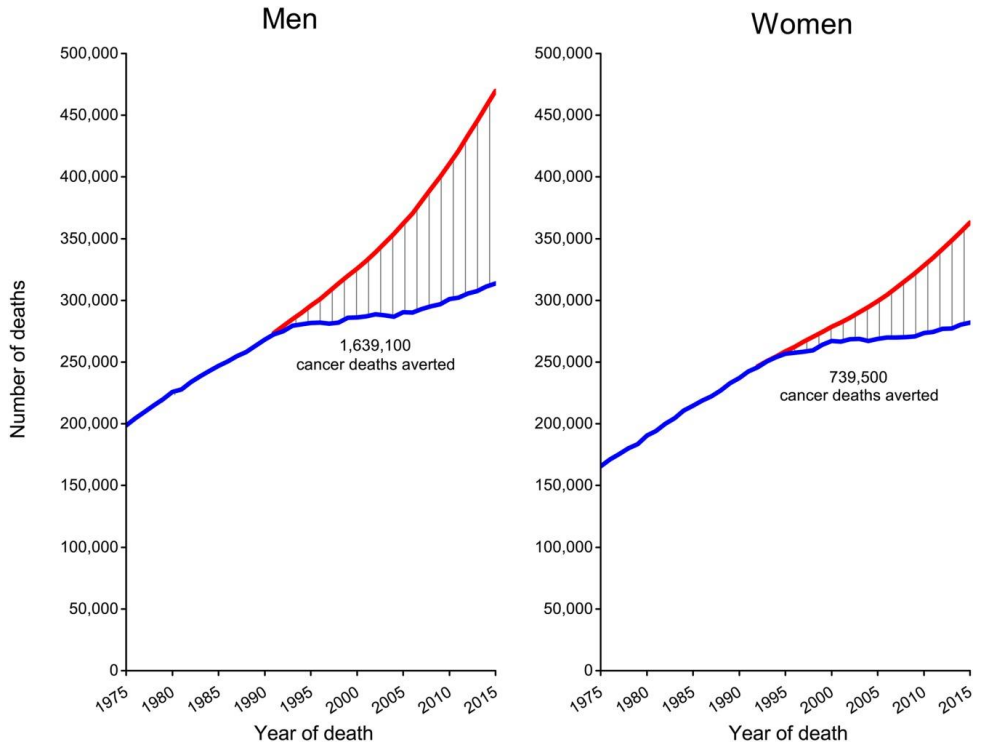
Lunge Team

Tak

SKA - Sammenslutningen af **K**ræft**A**fdelinger

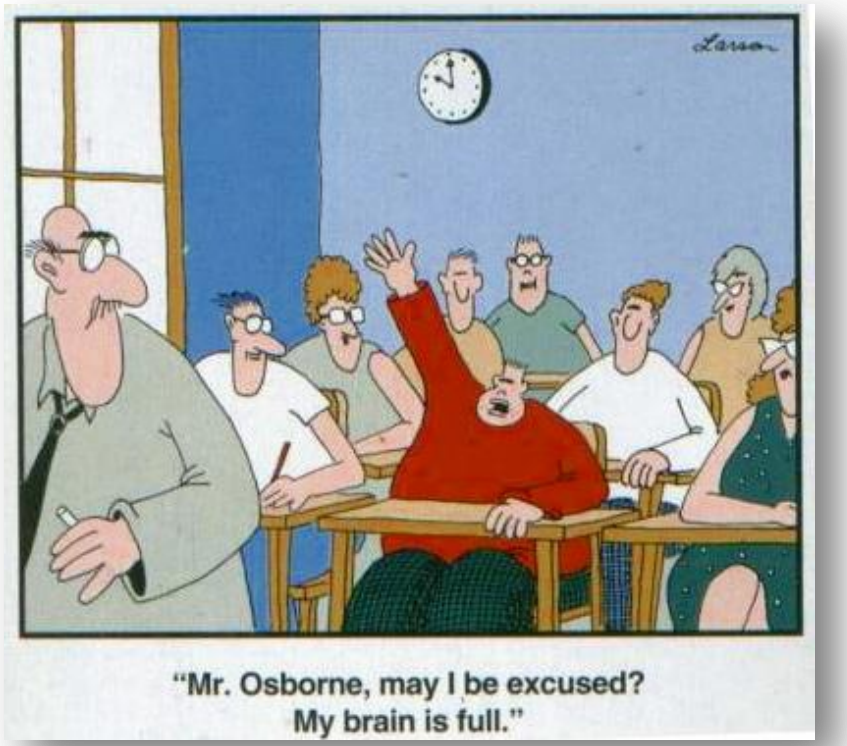
abbvie

SAVE SKA og post-ASCO 2019



Antal undgåede cancer –relaterede dødfald USA, 1991-2015

Spørgsmål?



REGION

Post-ASCO

Lungekræft

Gitte Fredberg Persson, overlæge ph.d.
Jakob Johansen, klinisk assistent
Kræftafdelingen på Herlev Hospital

Stadie	Behandling	Overlevelse (5 år)	Nye behandlinger på vej
I	Kirurgi stereotaktisk stråleterapi	77-92%*	
II	Kirurgi + forebyggende kemoterapi	53-60%*	Neoadj immunterapi (adj?)
III	Stråleterapi + kemoterapi	13-36%*	Immunterapi + KT+RT
IV	Immunoterapi Kemoterapi Målrettet terapi Strålebehandling	0-10%*	IO baseret kombinationsbehandling

*Detterbeck et al. J Thor Oncol, 11 (9) (2016), pp. 1433-1446

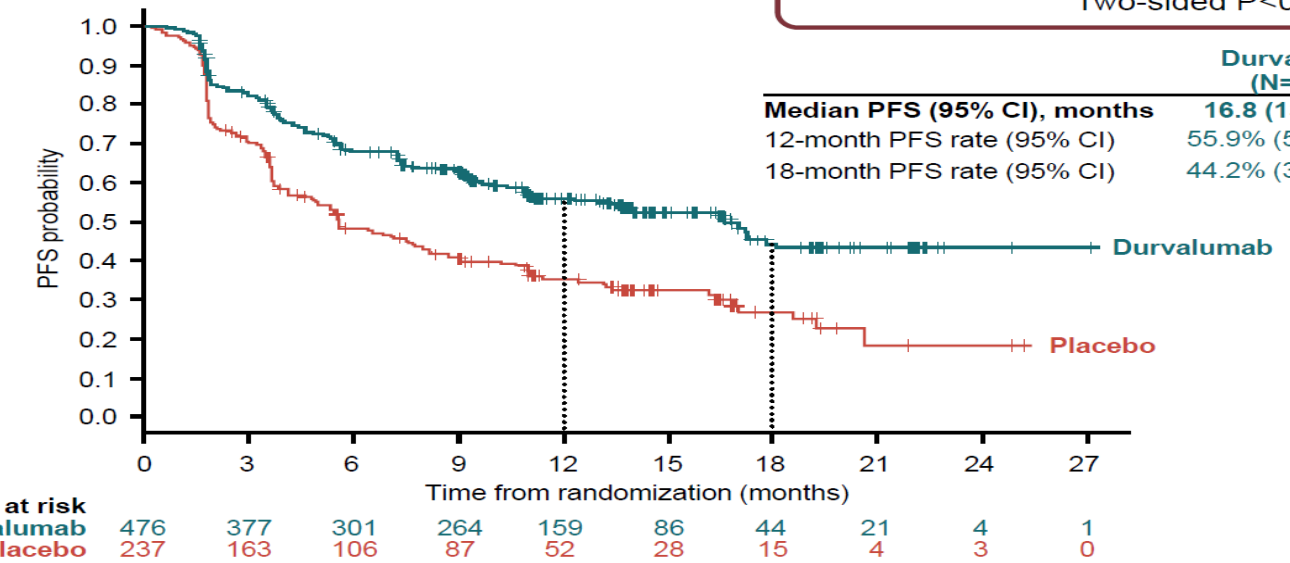
PACIFIC
adj. Durvalumab efter KRT til LA-NSCLC

MADRID 2017 ESMO congress

PFS by BICR (Primary Endpoint; ITT)

Stratified hazard ratio, 0.52 (95% CI, 0.42–0.65)
Two-sided P<0.0001

	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)

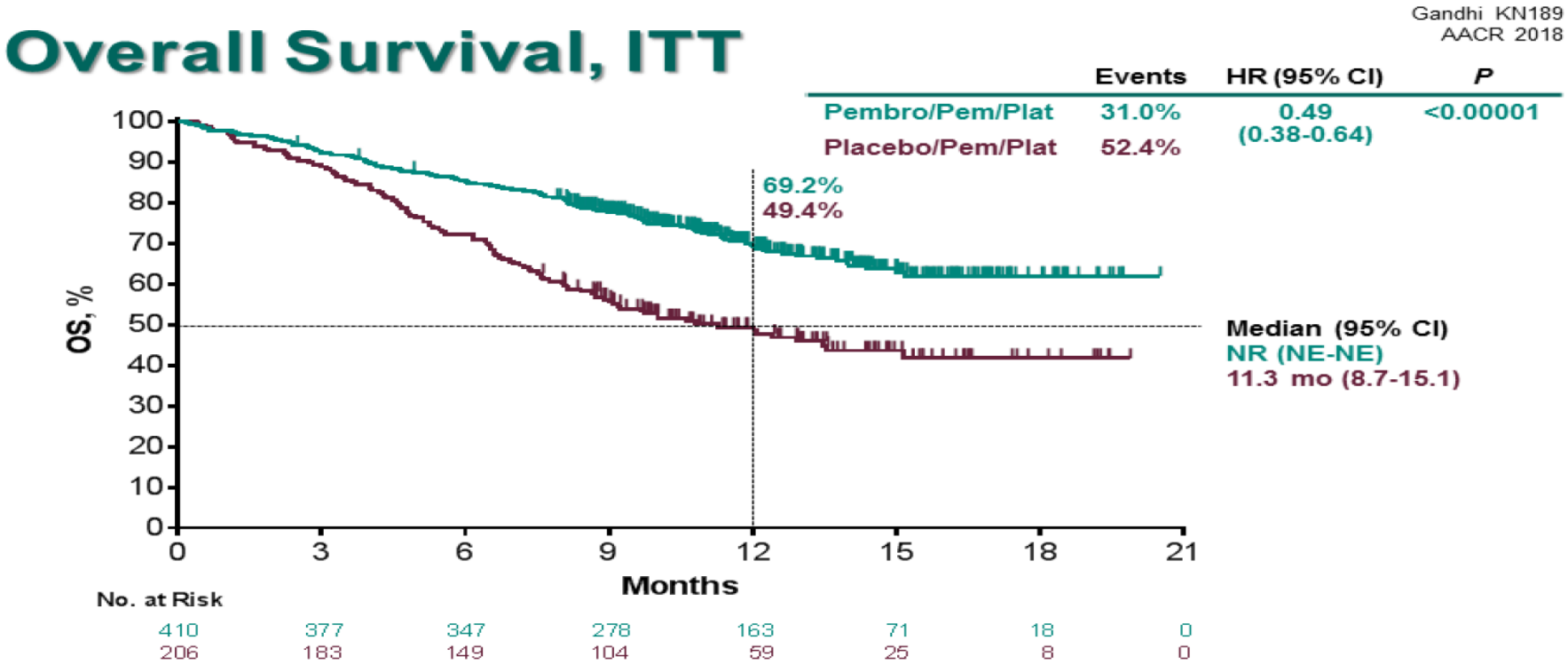


No. at risk										
Durvalumab	476	377	301	264	159	86	44	21	4	1
Placebo	237	163	106	87	52	28	15	4	3	0

BICR, blinded independent central review; CI, confidence interval; ITT, intention-to-treat; PFS, progression-free survival

N Engl J Med. 2017 Nov 16;377(20):1919-1929

Keynote 189
Kemo- og immunterapi til stadie IV NSCLC

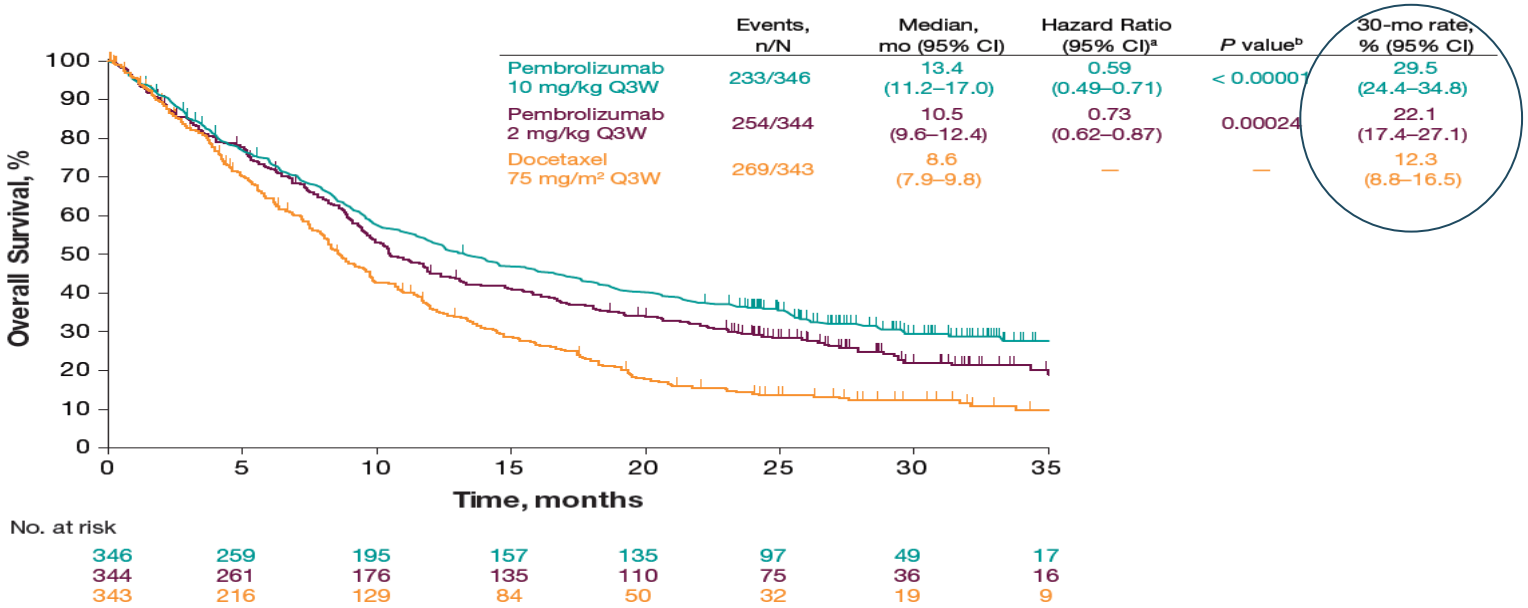


N Engl J Med. 2018 Apr

Keynote001
Fordoblet langtidsoverlevelse (3 år)

Overall Survival

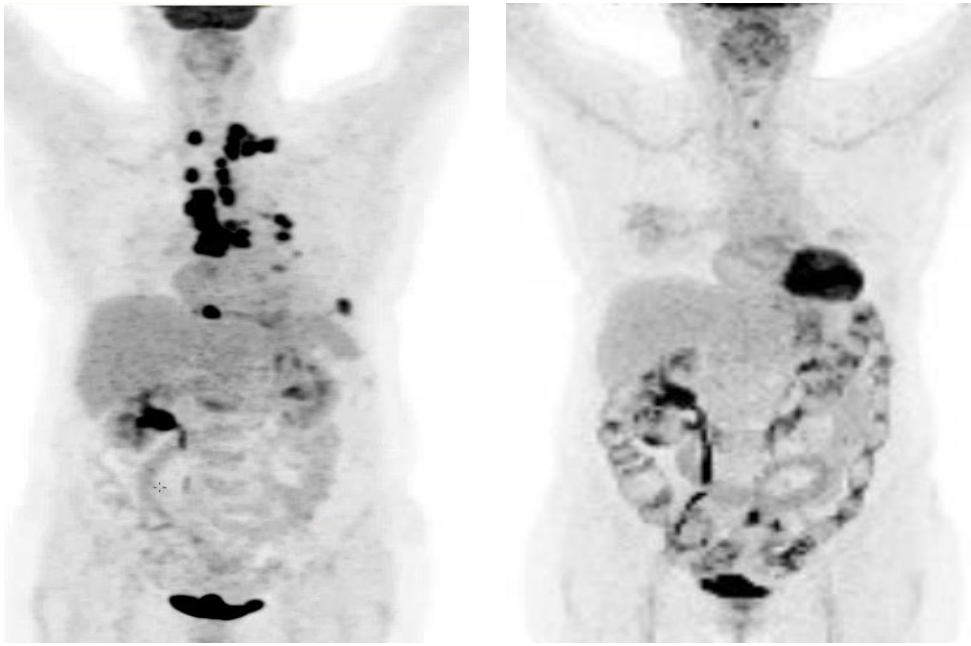
Figure 2. Kaplan-Meier Estimates of OS



	Events, n/N	Median, mo (95% CI)	Hazard Ratio (95% CI)[a]	*P* value[b]	30-mo rate, % (95% CI)
Pembrolizumab 10 mg/kg Q3W	233/346	13.4 (11.2–17.0)	0.59 (0.49–0.71)	< 0.00001	29.5 (24.4–34.8)
Pembrolizumab 2 mg/kg Q3W	254/344	10.5 (9.6–12.4)	0.73 (0.62–0.87)	0.00024	22.1 (17.4–27.1)
Docetaxel 75 mg/m² Q3W	269/343	8.6 (7.9–9.8)	—	—	12.3 (8.8–16.5)

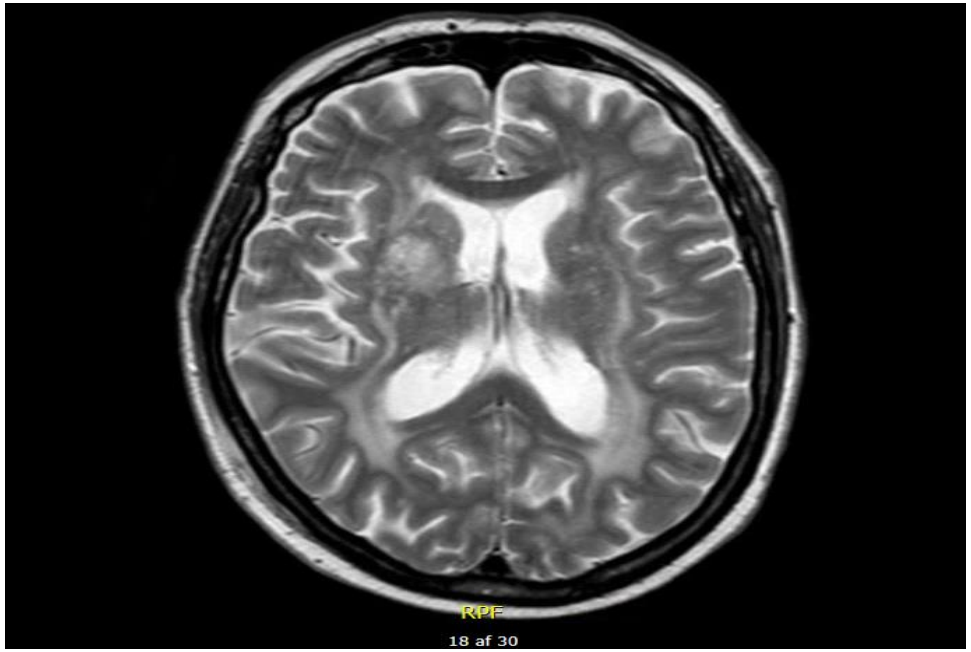
Case
Fantastisk effekt

- 67 årig kvinde med adenokarcinom i venstre lunge
- Jan 2017, helhjernebestråling og 4 serier kemoterapi → stabile forhold
- Maj 2017, progression. Starter PD-1 hæmmer
- Nov 17, resterer kun svulst i venstre lunge, strålebehandles
- Feb 2018, ingen tegn til restsygdom (fraset synkron c. thyroidea)



Patient historie
Alvorlige bivirkninger

- Marts 18, indlægges efter krampeanfald. MR af hjernen viser subakut infarkt og stråleføIger.
- April 18, udskrives til genoptræning. Tilstanden forværres, tilskrives senfølger efter stråleterapi og blodpropper.
- Overflyttes til hospice af familien
- Maj 18, starter behandling med binyrebarkhormon på mistanke om immunudløst hjernebetændelse
- Betydelig bedring



Konklusion

- De fleste patienter med NSCLC i god PS skal have PD-(L)1 hæmmer i fremtiden
- Neoadjuvant, adjuvant, konkomitant,1. linje
- Kombination med CTLA-4 hæmmere, KT, RT, operation,