# Traitement de 2ème ligne et au-delà des CBNPC sans addiction oncogénique

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# Liens d'intérêt

- Participation à des Advisory Boards : Roche, Genentech, Eli Lilly, Pfizer, Boehringer-Ingelheim, Clovis Oncology, Merck, Bristol-Myers Squibb, Novartis, Pierre Fabre
- Fonds de recherche institutionnels : Roche
- Participation à des symposiums : Eli Lilly, Roche, Astra-Zeneca, Pfizer, Amgen, Boehringer-Ingelheim, Novartis

# Traitement de 2ème ligne et au-delà des CBNPC sans addiction oncogénique

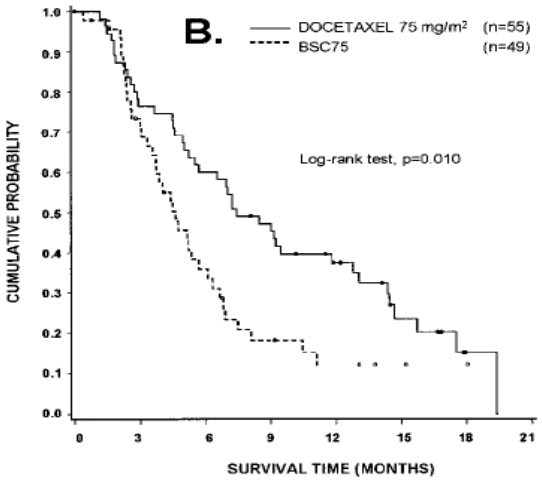
1. **Le passé : les 3 options historiques du traitement de 2ème ligne**
2. **Le présent : les nouvelles options**
   - **Y a t-il une place pour les inhibiteurs de l'EGFR en l'absence de mutation : afatinib dans les carcinomes épidermoïdes**
   - **Inhibition de l'angiogenèse**
   - **La révolution de l'immunothérapie**
3. **Quel algorithme de traitement après la 1ère ligne en 2016 ?**
   - **Cancers épidermoïdes**
   - **Cancers non-épidermoïdes**
   - **Un algorithme très évolutif …**

I

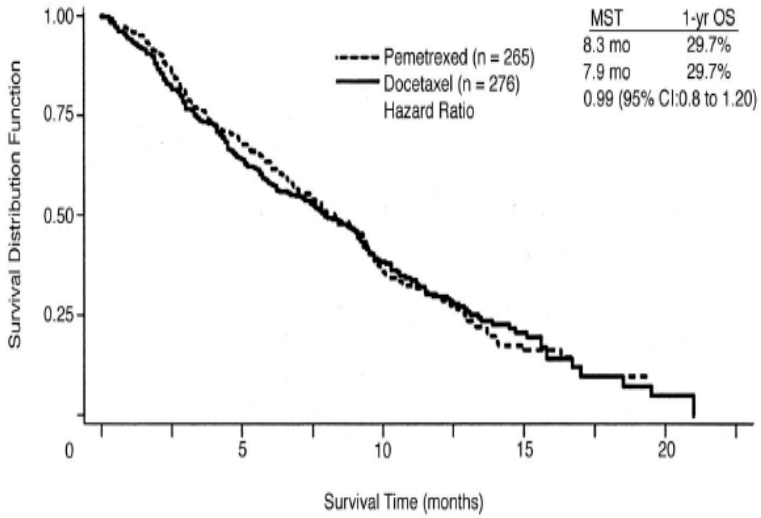
# *Le passé : les trois options "historiques" du traitement de 2ème ligne*

# 2000-2014: The Only Three Available Options in Post-Platinum Setting

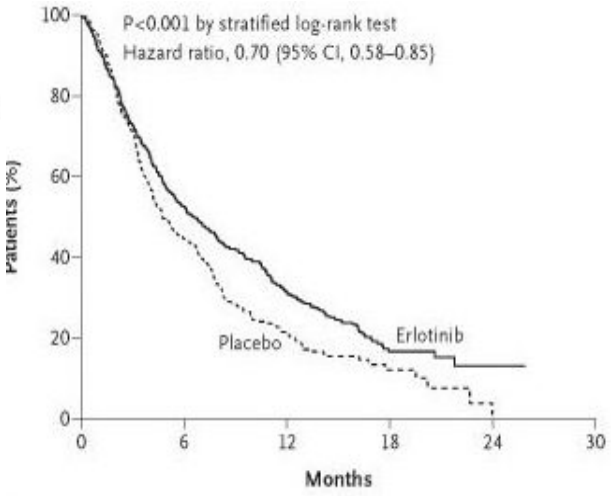
**1999** **2004** **2005**




**Docetaxel *vs* BSC**




**Pemetrexed *vs* docetaxel**




**Erlotinib *vs* placebo**

Shepherd, JCO 2000 ; Hanna, JCO 2004 ; Shepherd, NEJM 2005

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# L'efficacité du traitement "historique" de 2ème ligne est modeste

| | Docetaxel | Pemetrexed | Erlotinib |
|---|---|---|---|
| Taux de réponses, % | 5.0 – 12.0 | 7.1 – 11.8 | 7.9 – 9.0 |
| Médiane SSP, mois | 2.0 – 3.1 | 2.6 – 2.9 | 2.2 – 3.6 |
| Médiane survie, mois | 5.7 – 8.0 | 6.7 – 8.9 | 6.7 – 7.9 |
| Survie à 1 an, % | 28.7 – 37.0 | 29.7 – 38.5 | 31.0 – 35.7 |

Shepherd, et al. JCO 2000; Fossella, et al. JCO 2000; Ramlau, et al. JCO 2006; Paz-Ares, et al. BJC 2008; Kim, et al. Lancet 2008; Krzakowski, et al. JCO 2010; Hanna, et al. JCO 2004, Cullen, et al. Ann Oncol 2008; Shepherd, et al. NEJM 2005; Vamvakas, et al. ASCO 2010, Ciuleanu, et al. IASLC Chicago 2010

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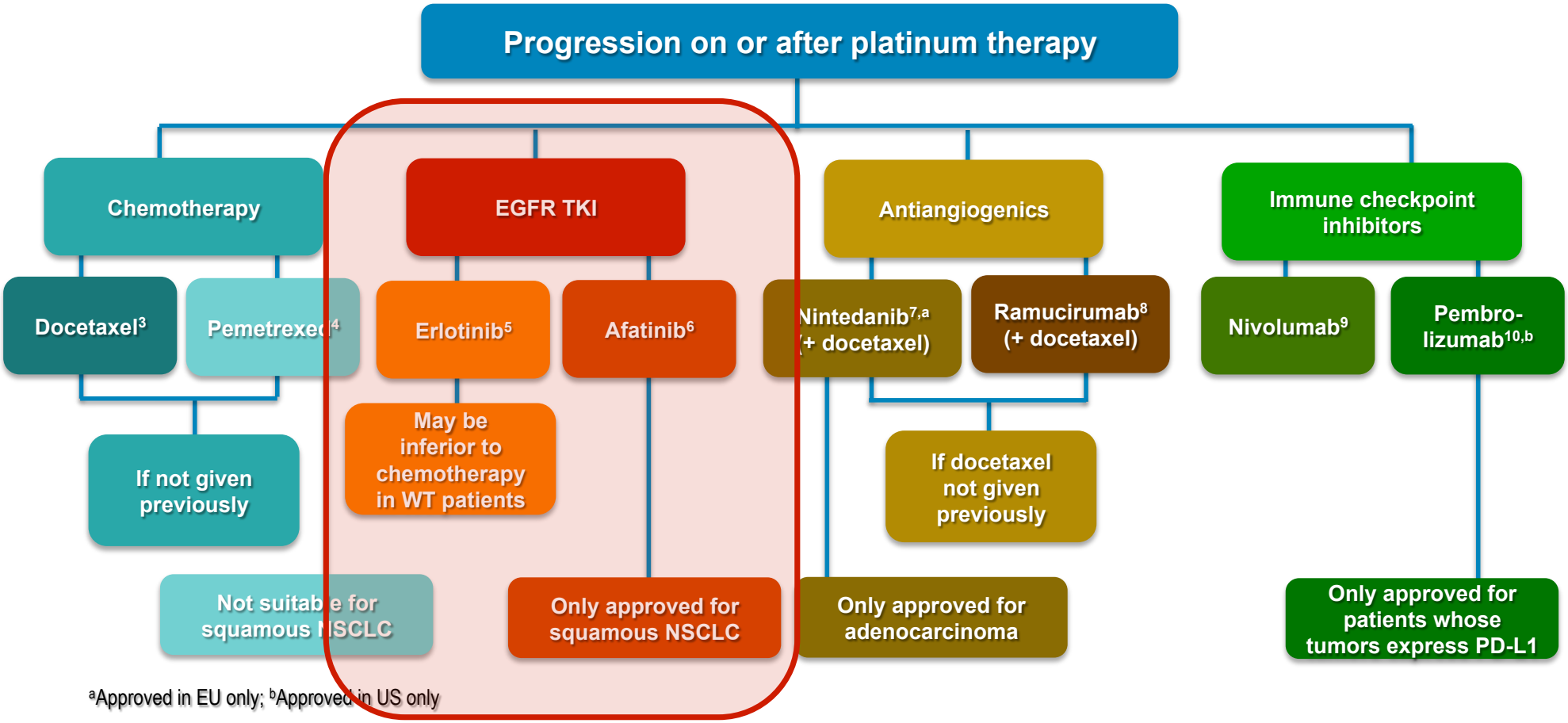
II

# *Le présent : les nouvelles options du traitement de 2ème ligne et au-delà*

# Treatment Options Post-platinum Progression: Overview




[a]Approved in EU only; [b]Approved in US only


1. NCCN Clinical Practice Guidelines for Non-Small Cell Lung Cancer, V.4.2016
2. Reck M et al. *Ann Oncol* 2014;25(Suppl 3):27-39
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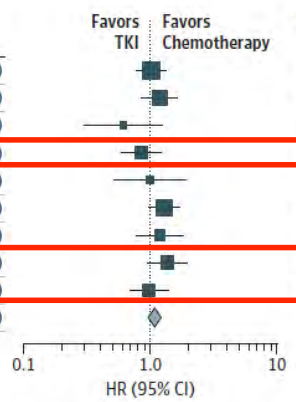
5. Astellas Pharma and Genentech. Tarceva® (erlotinib) prescribing information. June 2015
6. Boehringer Ingelheim. Giotrif® (afatinib) summary of product characteristics. May 2016
7. Boehringer Ingelheim. Vargatef® (nintedanib) summary of product characteristics. March 2015
8. Eli Lilly and Company. Cyramza® (ramucirumab) prescribing information. April 2015
9. Bristol-Myers Squibb. Opdivo® (nivolumab) prescribing information. April 2016
10. Merck & Co., Inc. Keytruda® (pembrolizumab) prescribing information. October 2015

# Chimiothérapie *vs* EGFR TKI en 2ème ligne
# Méta-analyse pour les EGFR "sauvage"

## OS

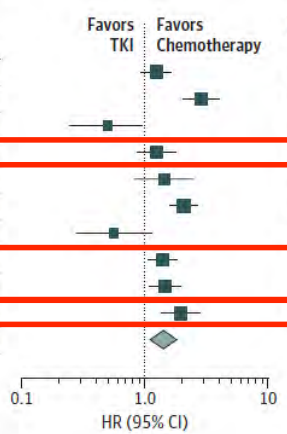
B Overall survival

| Source | No. of Patients With WT *EGFR* TKI | No. of Patients With WT *EGFR* Chemotherapy | HR (95% CI) | Weight, % |
|---|---|---|---|---|
| INTEREST,[12,27] 2008 and 2010 | 119 | 134 | 1.02 (0.78-1.33) | 20.28 |
| IPASS,[5,28] 2009 and 2011 | 91 | 85 | 1.18 (0.86-1.63) | 14.12 |
| ML20322,[29] 2012 | 21 | 15 | 0.62 (0.30-1.24) | 2.87 |
| TITAN,[13] 2012 | 75 | 74 | 0.85 (0.59-1.22) | 10.94 |
| First-SIGNAL,[30] 2012 | 27 | 27 | 1.00 (0.52-1.91) | 3.44 |
| TORCH,[14] 2012 | 119 | 117 | 1.29 (0.97-1.71) | 17.96 |
| CT/06.05,[32] 2013 | 55 | 57 | 1.19 (0.77-1.84) | 7.61 |
| TAILOR,[15] 2013 | 109 | 110 | 1.28 (0.95-1.96) | 11.01 |
| DELTA,[33] 2013 | 109 | 90 | 0.98 (0.69-1.39) | 11.77 |
| Overall: $I^2$=0%; $P$=.496 | 725 | 709 | 1.08 (0.96-1.22) | 100 |

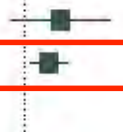



## PFS

| Source | No. of Patients With WT *EGFR* TKI | No. of Patients With WT *EGFR* Chemotherapy | Progression-Free Survival, HR (95% CI) | Weight, % |
|---|---|---|---|---|
| INTEREST,[12,27] 2008 and 2010 | 106 | 123 | 1.24 (0.94-1.64) | 11.57 |
| IPASS,[5,28] 2009 and 2011 | 91 | 85 | 2.85 (2.05-3.98) | 10.90 |
| ML20322,[29] 2012 | 21 | 15 | 0.50 (0.25-0.97) | 6.81 |
| TITAN,[13] 2012 | 75 | 74 | 1.25 (0.88-1.78) | 10.64 |
| First-SIGNAL,[30] 2012 | 27 | 27 | 1.42 (0.82-2.47) | 8.12 |
| TORCH,[14] 2012 | 119 | 117 | 2.07 (1.58-2.71) | 11.67 |
| KCSG-LU08-01,[31] 2012 | 18 | 20 | 0.56 (0.28-1.13) | 6.56 |
| TAILOR,[15] 2013 | 109 | 110 | 1.39 (1.06-1.82) | 11.66 |
| DELTA,[33] 2013 | 109 | 90 | 1.45 (1.09-1.94) | 11.45 |
| CTONG-0806,[34] 2013 | 81 | 76 | 1.96 (1.37-2.78) | 10.62 |
| Overall: $I^2$=79.1%; $P$<.001 | 756 | 737 | 1.41 (1.10-1.81) | 100 |




| Subgroup | No. of Trials | No. of Patients With WT *EGFR* TKI | No. of Patients With WT *EGFR* Chemotherapy | Progression-Free Survival, HR (95% CI) | Heterogeneity Within Subgroups $I^2$, % | Heterogeneity Within Subgroups *P* Value |
|---|---|---|---|---|---|---|
| Line of treatment | | | | | | |
| First[5,14,28-30] | 4 | 258 | 244 | 1.53 (0.87-2.69) | 86.6 | <.001 |
| Second or later[12,13,15,27,31-34] | 6 | 498 | 493 | 1.34 (1.09-1.65) | 55.2 | .048 |
| Subgroup difference: $P$=.58 | | | | | | |




## PFS

Lee, JAMA 2014

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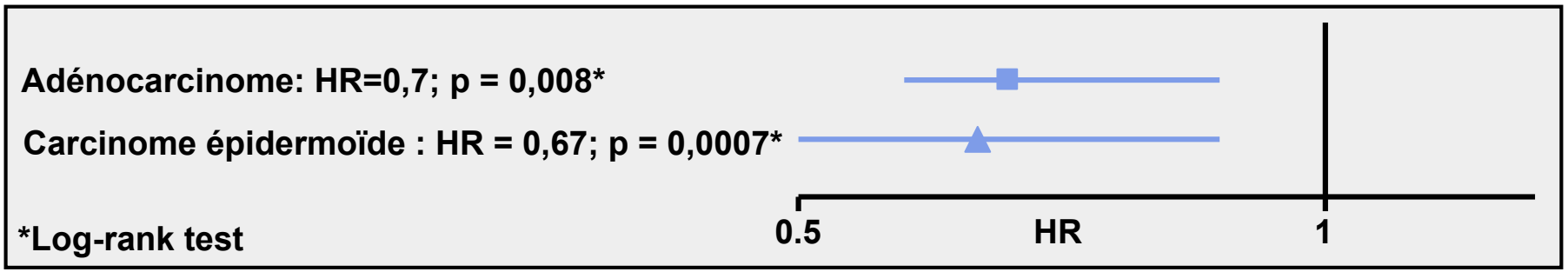
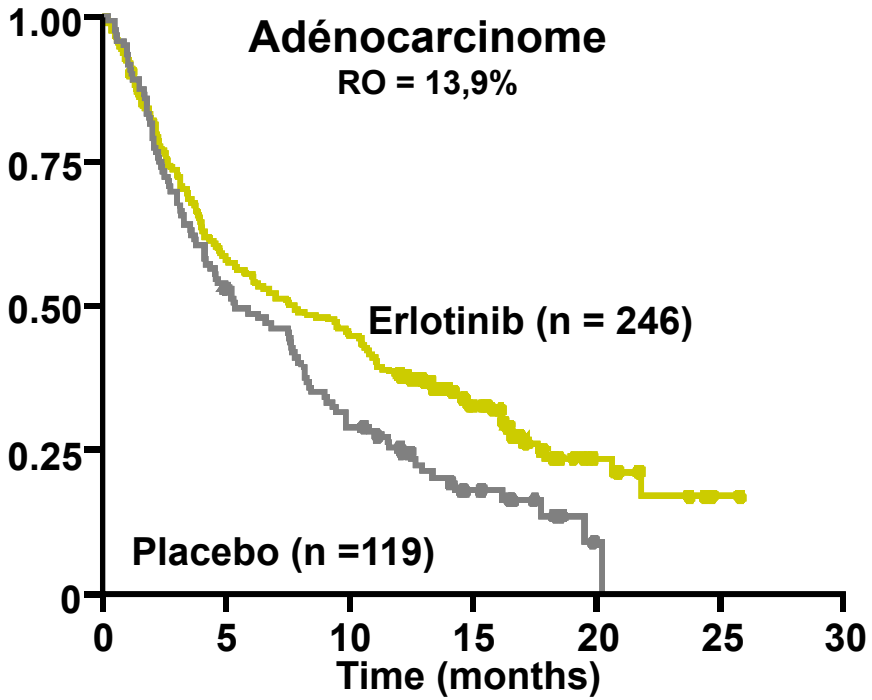
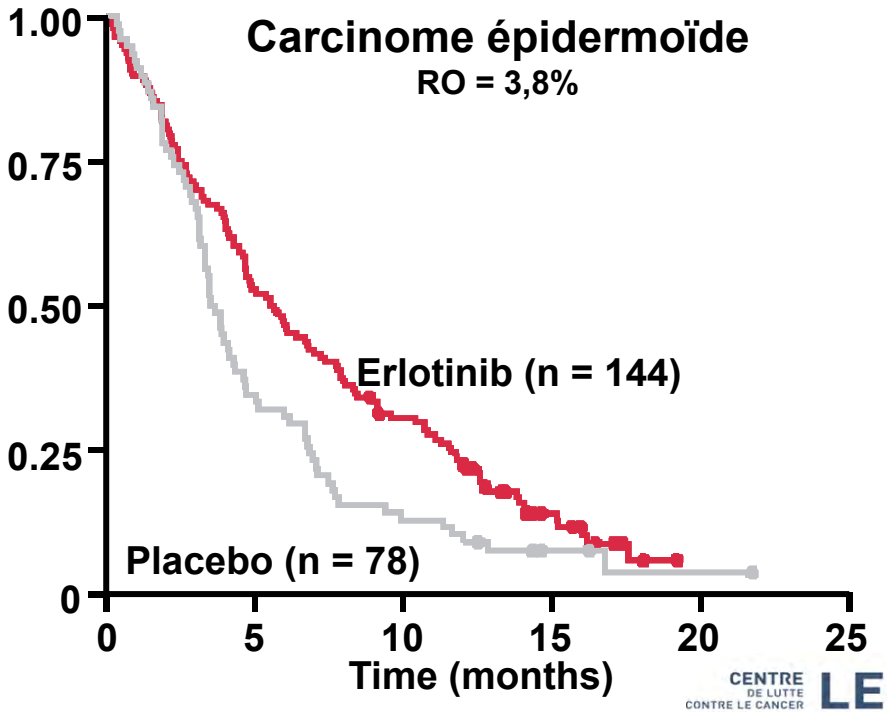
# BR21 : erlotinib *vs* placebo
# Bénéfice de survie en fonction de l'histologie




Shepherd, Tsao, NEJM 2005

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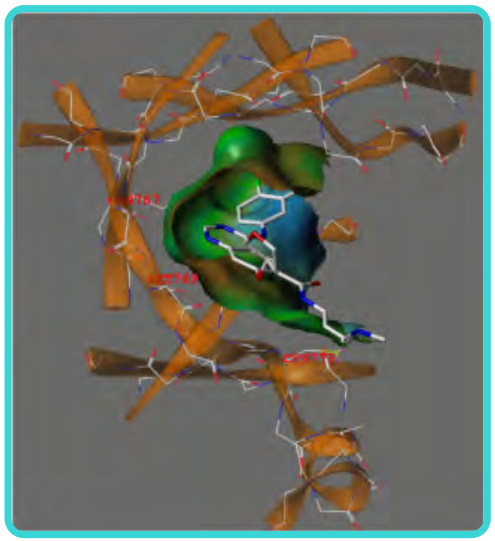
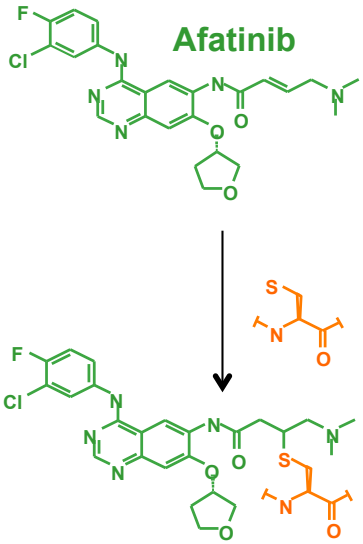
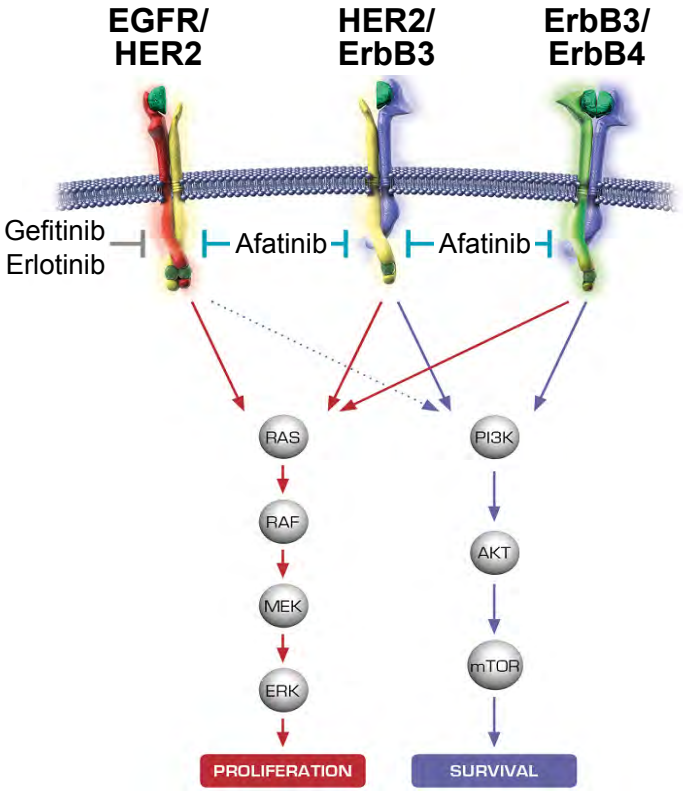
# Afatinib : inhibiteur irréversible de la famille ErbB

**Giotrif covalently binds and irreversibly blocks EGFR, HER2, and ErbB4**






**Afatinib covalently bound**




Targeting EGFR, HER2, and ErbB4 enhances the effect on important and relevant signaling pathways

Data on file. Boehringer Ingelheim.
Li et al. *Oncogene.* 2008;27:4702.
Solca et al. *J Pharmacol Exp Ther*. 2012;343:342.

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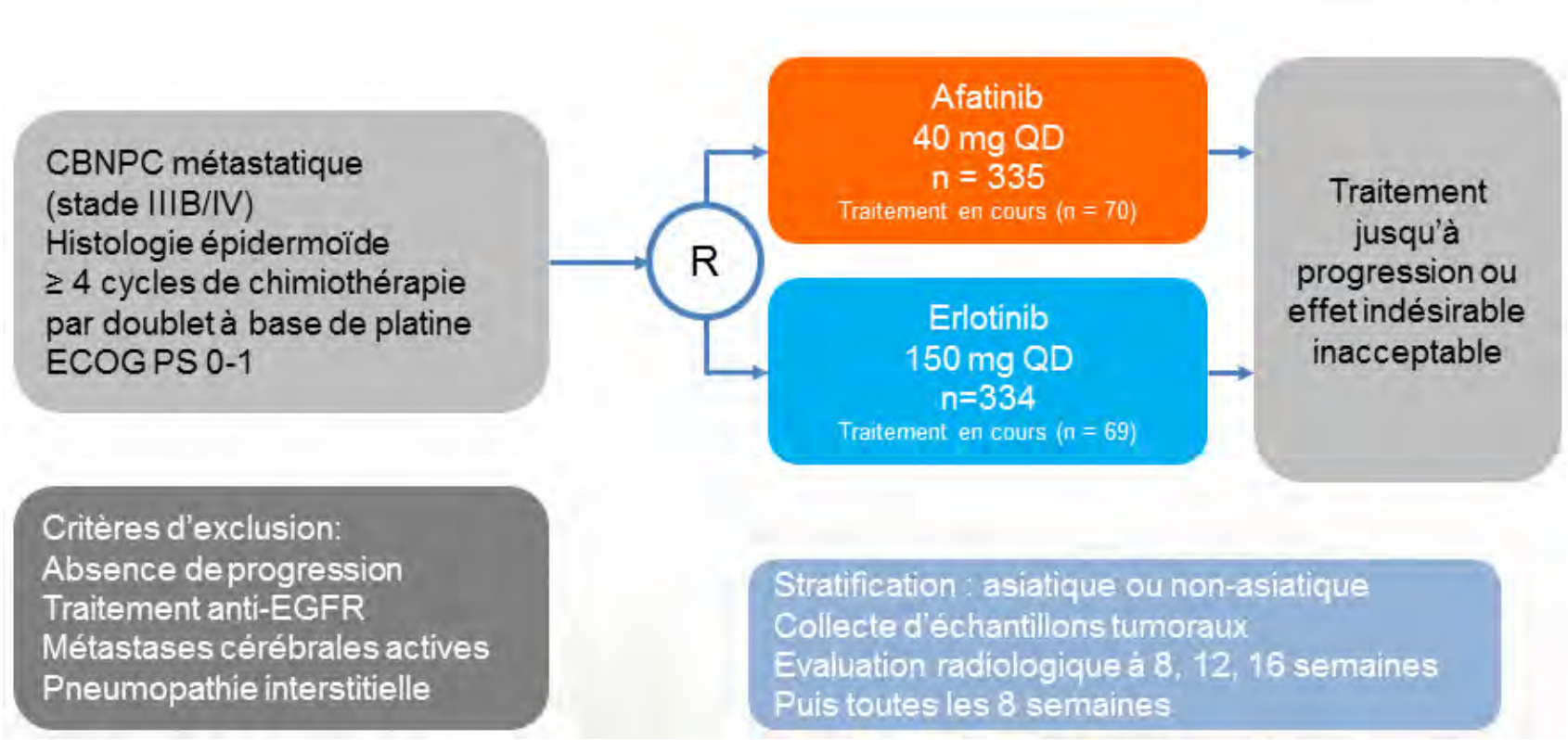
# LUX-Lung 8 : afatinib *vs* erlotinib en 2ème ligne de traitement des cancers épidermoïdes




- **Critère de jugement principal : survie sans progression**
- **Critères secondaires : survie, réponse, contrôle de la maladie, tolérance, QoL**

Soria, Lancet Oncol 2015

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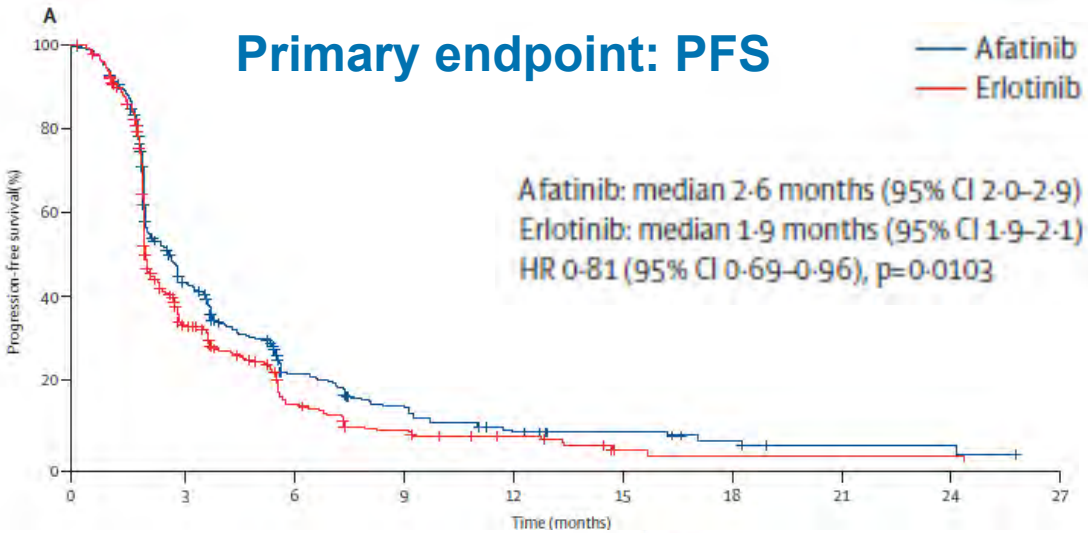
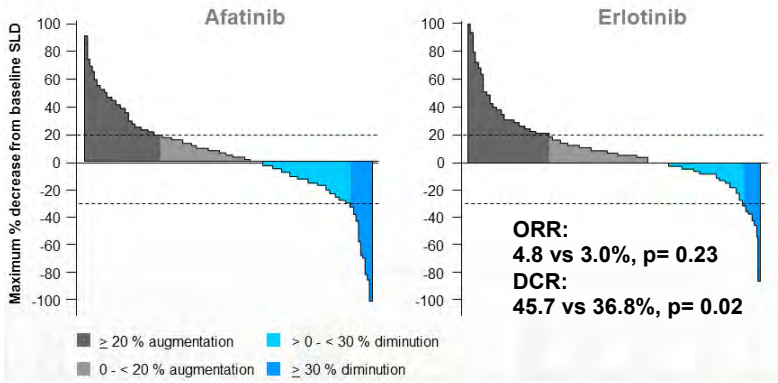
# LUX-Lung 8: Afatinib *vs* Erlotinib in 2nd-Line Treatment of Squamous Lung Cancer

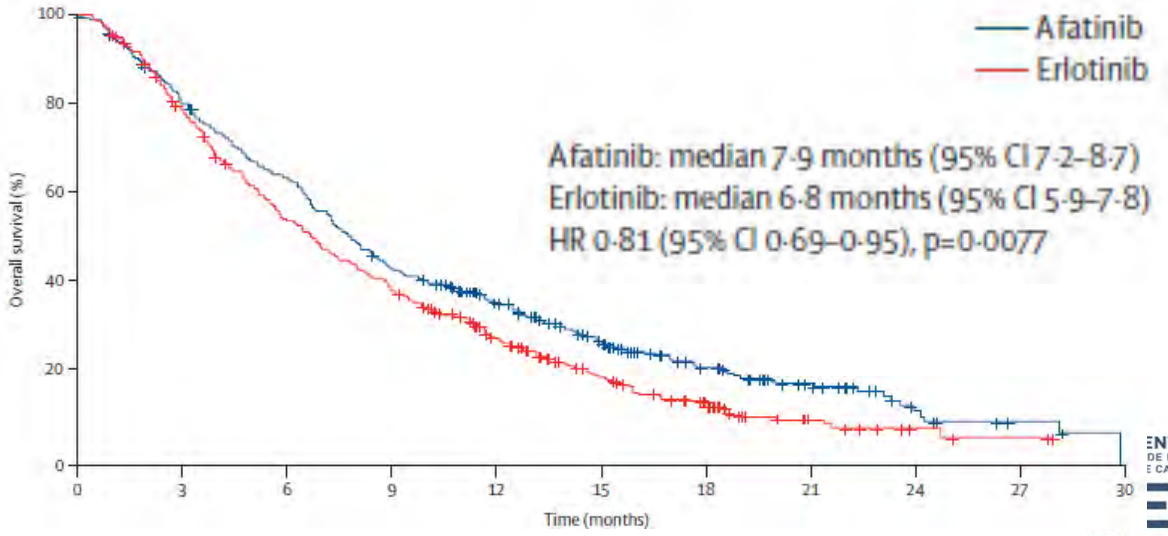
## Primary endpoint: PFS




## Response rate




## Secondary endpoint: OS



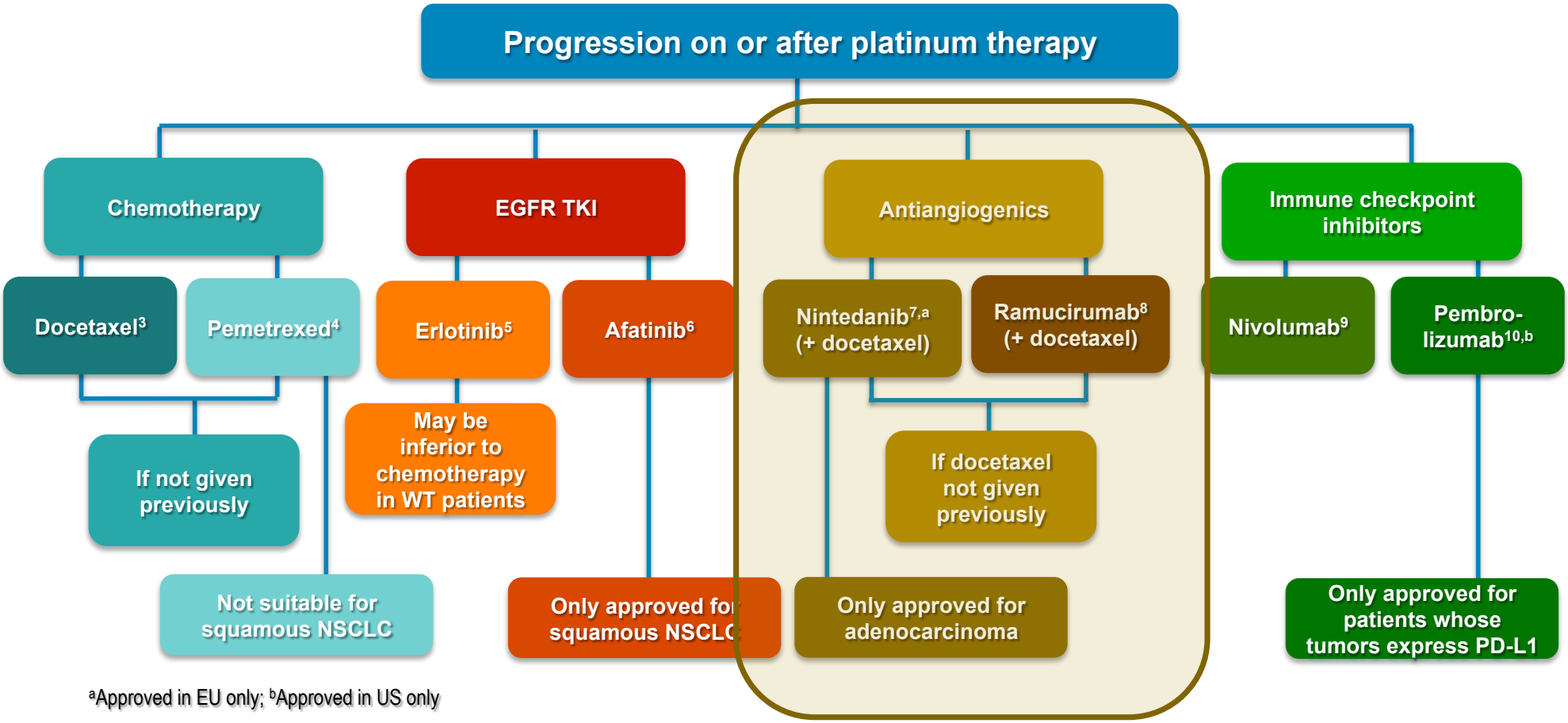

Soria, Lancet Oncol 2015

# LUX-Lung 8 : tolérance

| | Afatinib (n = 329) n (%) | | | Erlotinib (n = 332) n (%) | | |
|---|---|---|---|---|---|---|
| | Tous grades | Grade 3 | Grade 4 | Tous grades | Grade 3 | Grade 4 |
| Total des toxicités | 298 (91) | 75 (23) | 4 (< 1) | 266 (80) | 48 (15) | 1 (< 1) |
| Diarrhée | 218 (66) | 30 (9) | 2 (< 1) | 103 (31) | 7 (2) | 1 (< 1) |
| Rash/Acné | 208 (63) | 18 (6) | | 221 (67) | 30 (9) | |
| Stomatite | 90 (27) | 11 (3) | | 28 (8) | | |
| Fatigue | 44 (13) | 3 (1) | | 43 (13) | 6 (2) | |
| Baisse de l'appétit | 38 (12) | 3 (1) | | 34 (10) | 2 (< 1) | |
| Nausées | 38 (12) | 3 (1) | | 24 (7) | 3 (1) | |
| Paronychie | 35 (11) | 1 (< 1) | | 14 (4) | 1 (< 1) | |
| Prurit | 29 (9) | 1 (< 1) | | 36 (11) | | |
| Sécheresse cutanée | 27 (8) | 2 (< 1) | | 34 (10) | | |
| Vomissements | 25 (8) | 2 (< 1) | | 10 (3) | 2 (< 1) | |

Soria, Lancet Oncol 2015

# Treatment Options Post-platinum Progression: Overview

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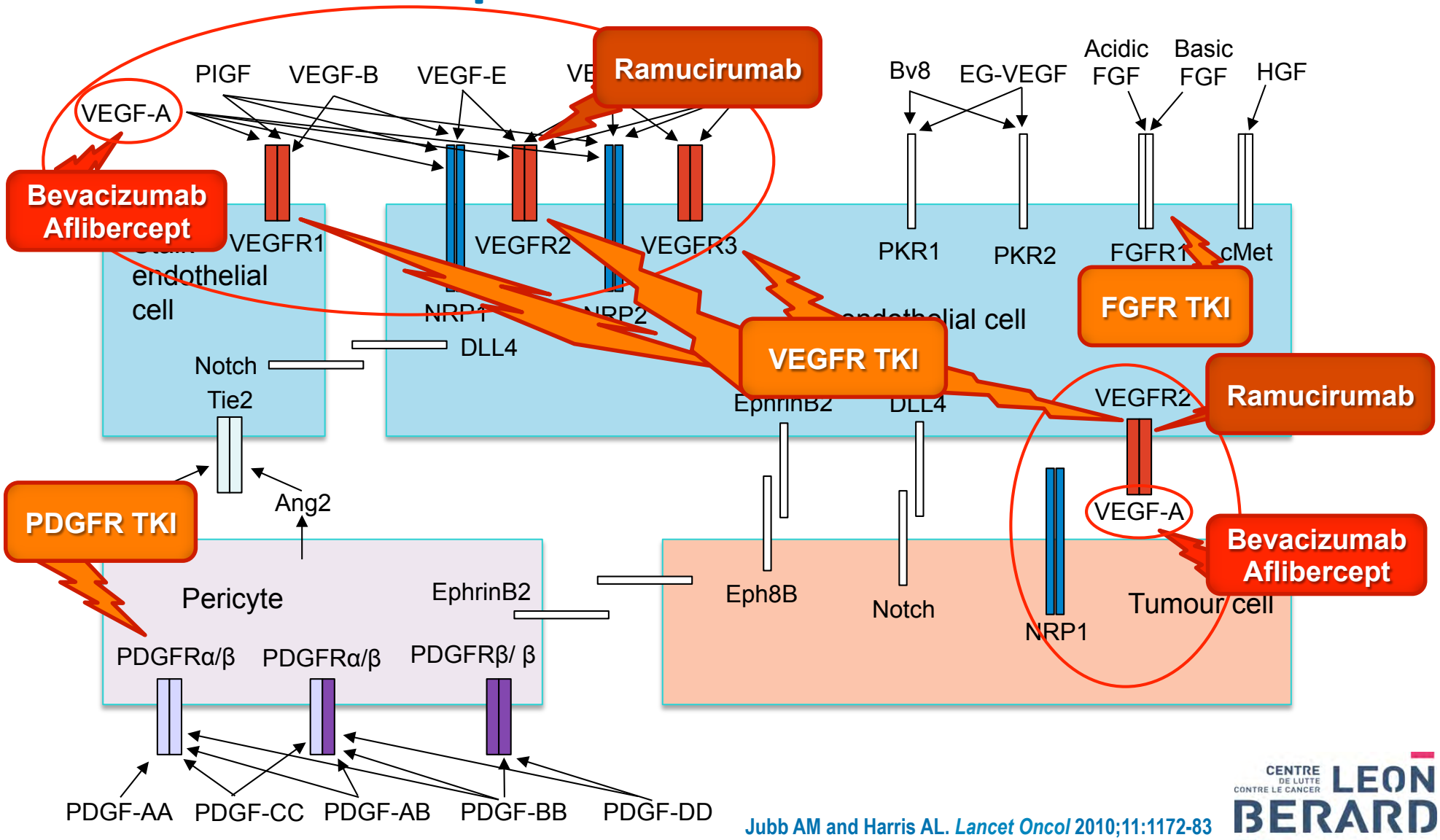
9. Bristol-Myers Squibb. Opdivo® (nivolumab) prescribing information. April 2016
10. Merck & Co., Inc. Keytruda® (pembrolizumab) prescribing information. October 2015

# How to Target Proangiogenic Ligands and Their Receptors




Jubb AM and Harris AL. *Lancet Oncol* 2010;11:1172-83

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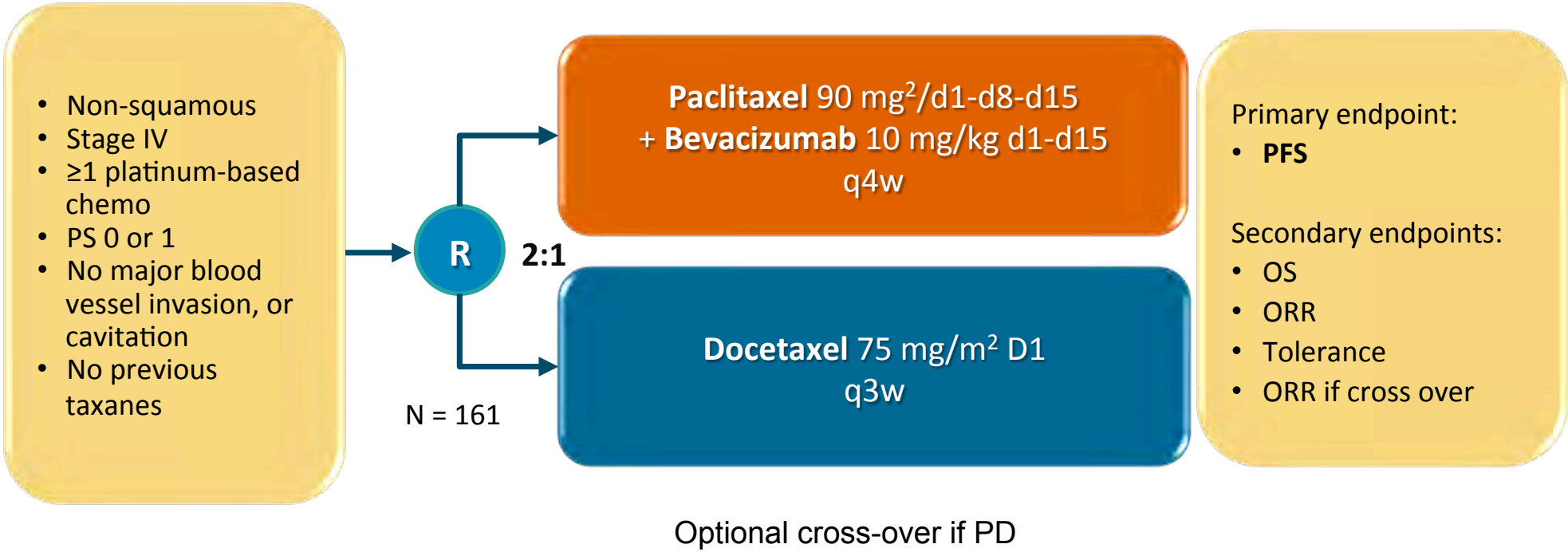
# ULTIMATE Trial (IFCT 11.03)




Cortot A, ASCO 2016

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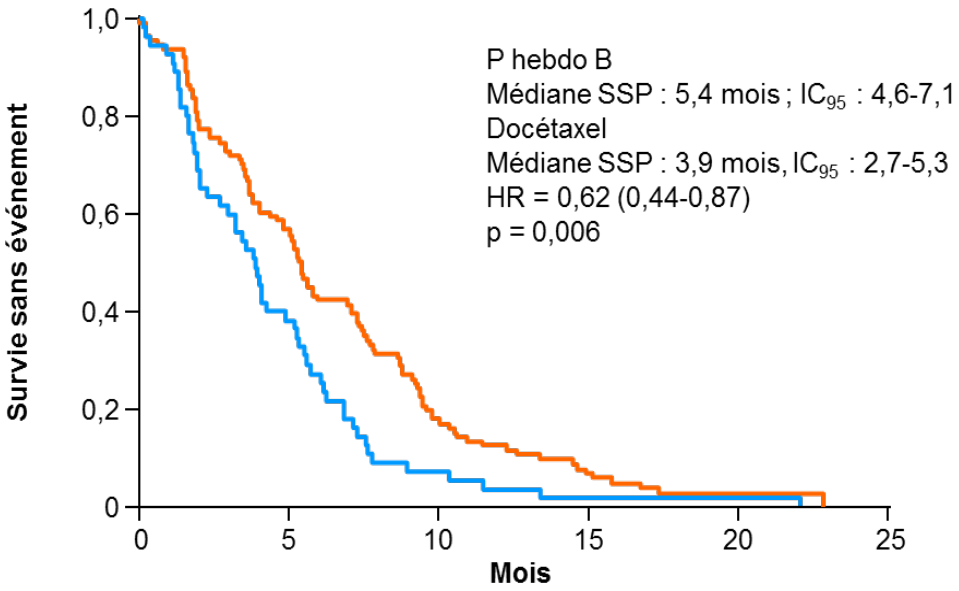
# ULTIMATE (IFCT 11.03)

Survie sans progression




| | Tous grades | | | Grade 3-4 | | |
|---|---|---|---|---|---|---|
| | Docétaxel (n = 55) | P hebdo B (n = 109) | p | Docétaxel (n = 55) | P hebdo B (n = 109) | p |
| Neutropénie fébrile | 7,3 % | 0,9 % | 0,02 | 7,3 % | 0,9 % | 0,02 |
| Neuropathie | 27,3 % | 49,5 % | 0,007 | 0 | 8.3 % | 0,03 |
| Saignements | 1,8 % | 45,0 % | < 0,001 | 0 | 0,9 % | 0,48 |
| Thrombo-embolie | 0 | 7,3 % | 0,04 | 0 | 4,6 % | 0,11 |
| Hypertension | 0 | 20,2 % | < 0,001 | 0 | 7,3 % | 0,04 |
| Protéinurie | 0 | 20,2 % | < 0,001 | 0 | 0 | NA |

Cortot A, ASCO 2016

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# REVEL and LUME Lung 1: Studies Design

- Stage IV after 1 platinum- based chemo +/- maintenance
- Prior Bev allowed
- All histologies
- PS 0 or 1
- No major blood vessel invasion, or cavitation

R 1:1

- ECOG PS 0 *vs* 1
- Gender
- Prior maintenance
- East-Asia vs. ROW

**Ramucirumab** 10 mg/kg
+
**Docetaxel** 75 mg/m² q3wks
N=628

**Placebo**
+
**Docetaxel** 75 mg/m² q3wks
N=625

Primary endpoint:
**OS**

Secondary endpoints:
PFS
ORR
Safety
PROs

- Stage IIIB/IV after 1 platinum- based chemo
- Prior Bev allowed
- All histologies
- PS 0 or 1
- No major blood vessel invasion, or cavitation

R 1:1

- ECOG PS 0 *vs* 1
- Brain mets
- Prior bevacizumab
- Histology

**Nintedanib** 200 mg x2/j, D2-D21
+ **Docetaxel** 75 mg/m² D1
q3 wks
N=655

**Placebo** x 2/j, D2-D21
+ **Docetaxel** 75 mg/m² D1
q3 wks
N=659

Primary endpoint:
**PFS**
Key secondary endpoint: **OS**
Secondary endpoints:
ORR
Tolerance
QoL

Garon, Lancet 2014; Reck, Lancet Oncol 2014

# Cross-Trials Comparison of REVEL, LUME 1 and ULTIMATE

| Study | Primary endpoint | Treatment | N | Response rate | PFS months | HR for PFS 95% CI | OS months | HR for OS 95% CI |
|---|---|---|---|---|---|---|---|---|
| **REVEL** | OS | Doc + Ramucirumab | 628 | 22.9%° | 4.5° | 0.76<br>0.68-0.86 | 10.5 | 0.86<br>0.75-0.98 |
| | | Doc + Placebo | 625 | 13.6%° | 3.0° | | 9.1 | |
| **LUME 1** | PFS | Doc + Nintedanib | 655 | 4.4%* | 3.4* | 0.79<br>0.68-0.92 | 10.1 | 0.94<br>0.83-1.05 |
| | | Doc + Placebo | 659 | 3.3%* | 2.7* | | 9.1 | |
| **ULTIMATE** | PFS | Paclitaxel + bevacizumab | 111 | 22.5%° | 5.4° | 0.62<br>0.44-0.87 | 9.9 | 1.18<br>0.81-1.72 |
| | | Docetaxel | 55 | 5.5%° | 3.9° | | 11.4§ | |

Doc: docetaxel. °: investigator assessed. *: central review; §: cross over for 38% of pts in docetaxel arm

Garon, Lancet 2014; Reck, Lancet Oncol 2014
Cortot, ASCO 2016

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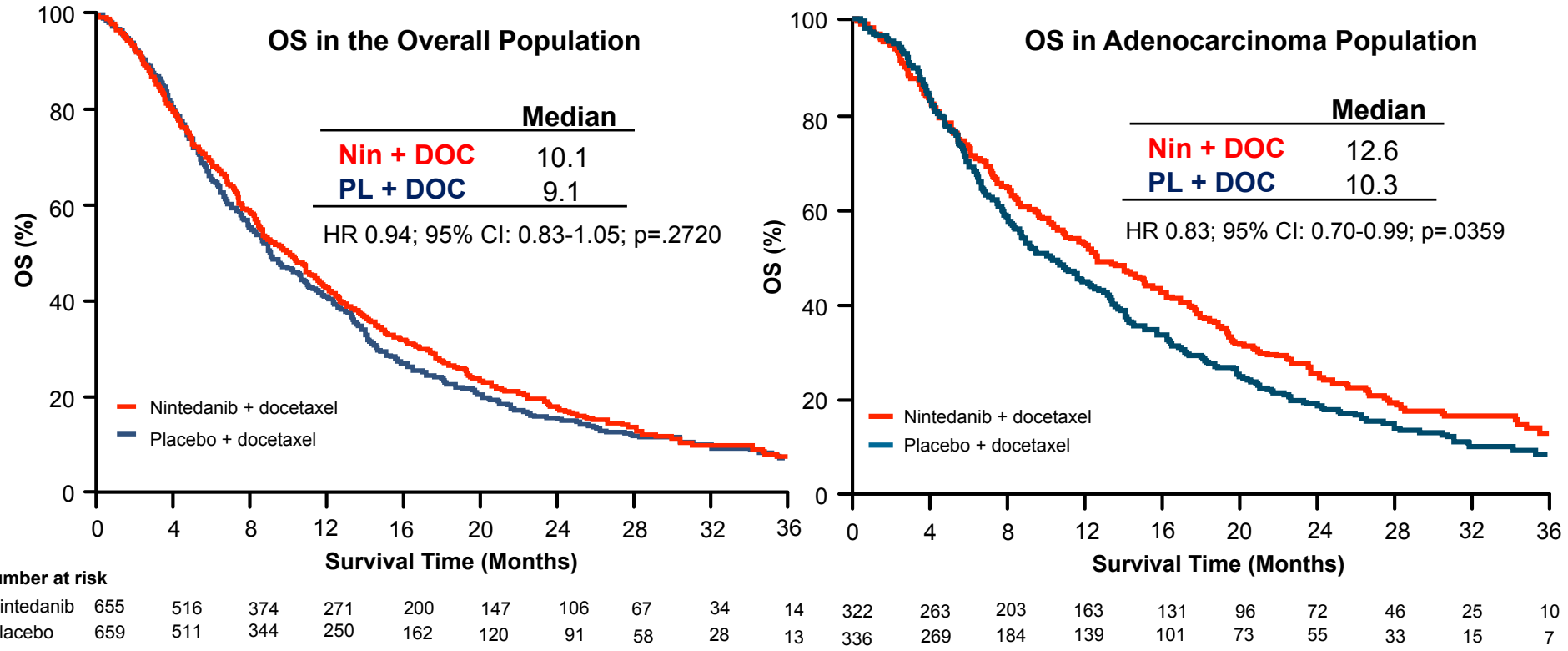
# LUME-1 Trial of Nintedanib in Second Line: Overall Survival




**Number at risk**

| | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Nintedanib | 655 | 516 | 374 | 271 | 200 | 147 | 106 | 67 | 34 | 14 | 322 | 263 | 203 | 163 | 131 | 96 | 72 | 46 | 25 | 10 |
| Placebo | 659 | 511 | 344 | 250 | 162 | 120 | 91 | 58 | 28 | 13 | 336 | 269 | 184 | 139 | 101 | 73 | 55 | 33 | 15 | 7 |

Reck M et al. *Lancet Oncol* 2014;15:143-55

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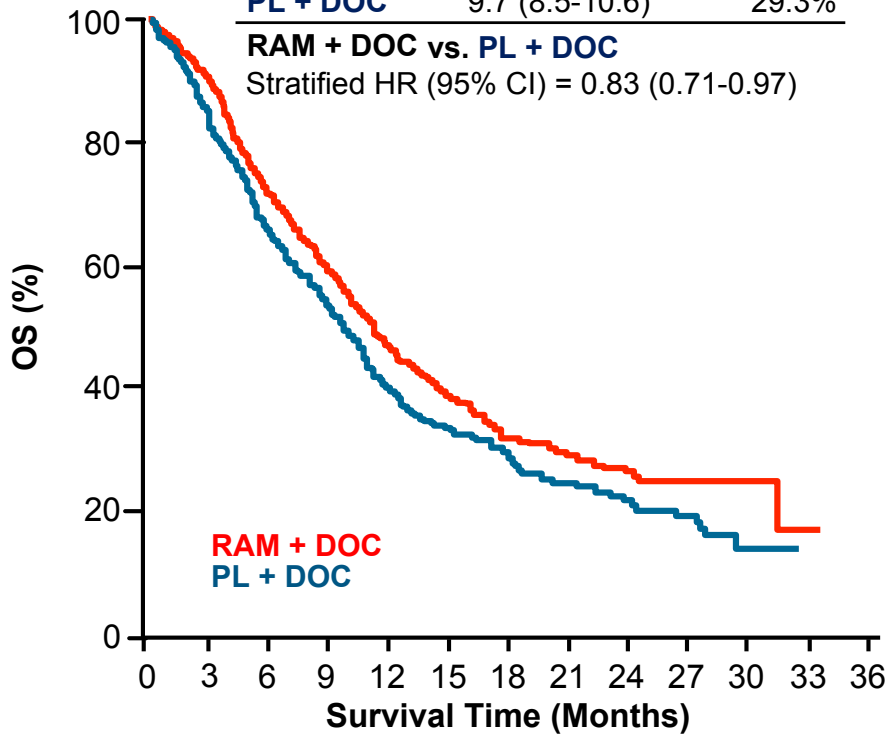
# REVEL Trial of Ramucirumab: OS by Histology

## Nonsquamous OS

| | Median (95% CI) | Censoring Rate |
|---|---|---|
| RAM + DOC | 11.1 (9.9-12.3) | 35.5% |
| PL + DOC | 9.7 (8.5-10.6) | 29.3% |

RAM + DOC vs. PL + DOC
Stratified HR (95% CI) = 0.83 (0.71-0.97)



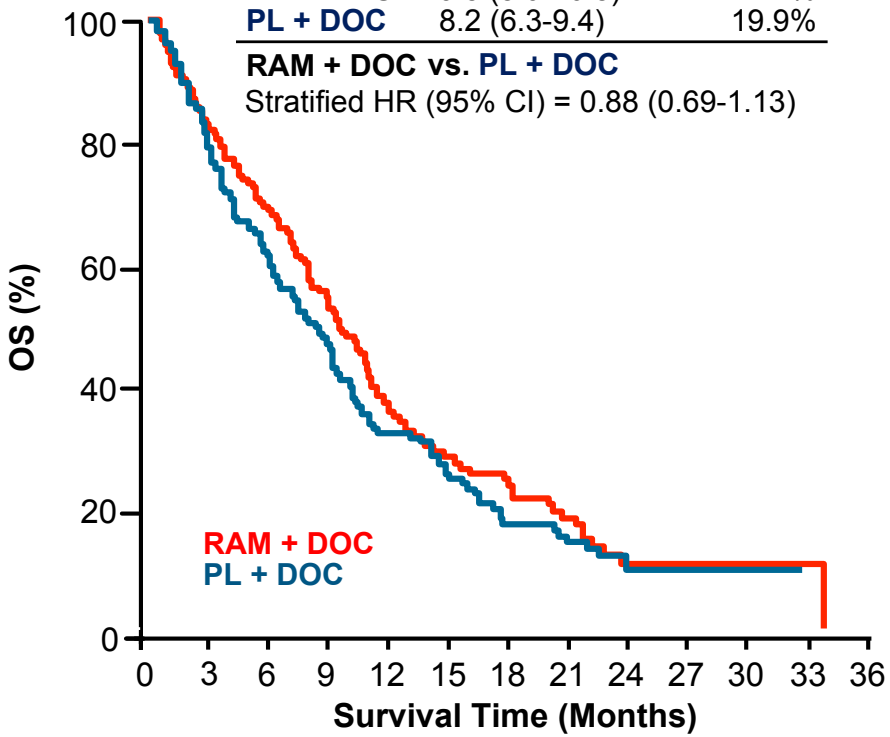

Number at risk

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| RAM + DOC | 465 | 401 | 311 | 251 | 182 | 125 | 80 | 54 | 39 | 21 | 10 | 1 | 0 |
| PL + DOC | 447 | 362 | 282 | 226 | 144 | 94 | 64 | 40 | 27 | 18 | 5 | 0 | 0 |

## Squamous OS

| | Median (95% CI) | Censoring Rate |
|---|---|---|
| RAM + DOC | 9.5 (8.0-10.8) | 21.7% |
| PL + DOC | 8.2 (6.3-9.4) | 19.9% |

RAM + DOC vs. PL + DOC
Stratified HR (95% CI) = 0.88 (0.69-1.13)



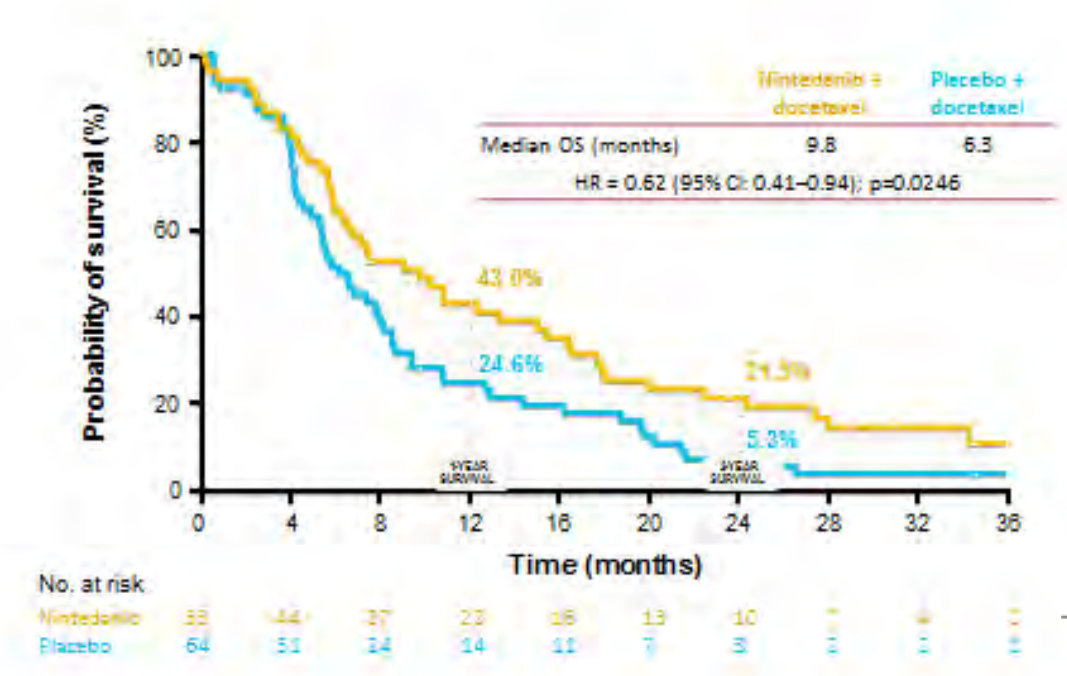

Number at risk

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| RAM + DOC | 157 | 124 | 103 | 78 | 49 | 31 | 23 | 16 | 6 | 2 | 1 | 1 | 0 |
| PL + DOC | 171 | 132 | 99 | 75 | 48 | 31 | 20 | 14 | 8 | 5 | 4 | 0 | 0 |

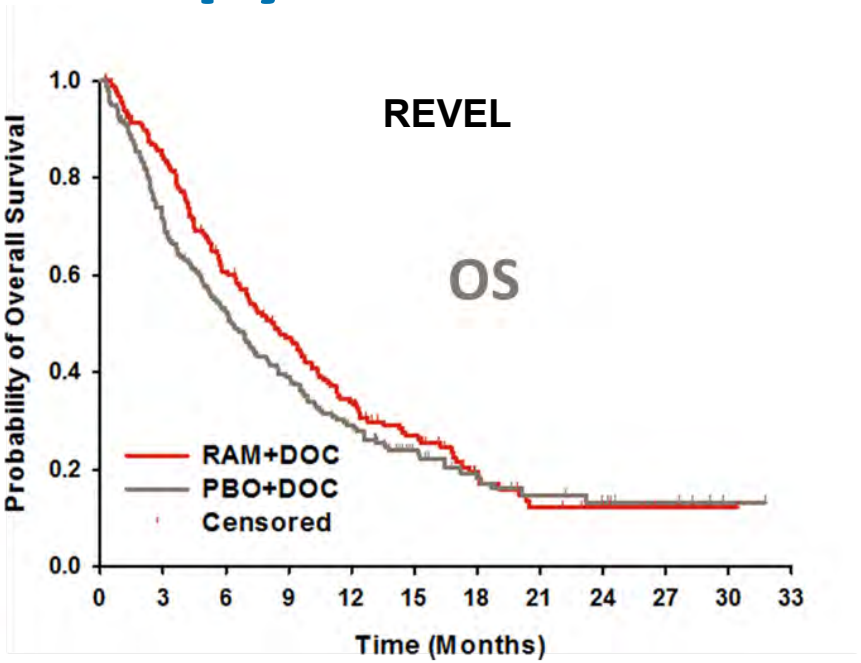
Pérol M et al. *J Clin Oncol* 2014;32(Suppl 5):abstract LBA8006^
Garon EB et al. *Lancet* 2014;384:665-73

CENTRE DE LUTTE CONTRE LE CANCER LEON BERARD

# Angiogenesis Inhibition in Patients Refractory to First-Line Therapy




**LUME-LUNG 1 Trial**




| | N / Events | Median (95% CI) |
|---|---|---|
| RAM+DOC | 178 / 134 | 8.3 (6.6, 9.8) |
| PBO+DOC | 182 / 141 | 6.3 (5.1, 8.0) |

Unstratified HR (95% CI) = 0.86 (0.68, 1.08)

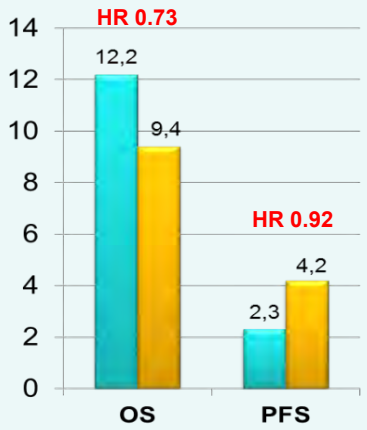
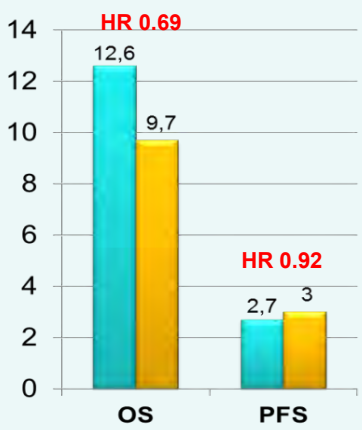
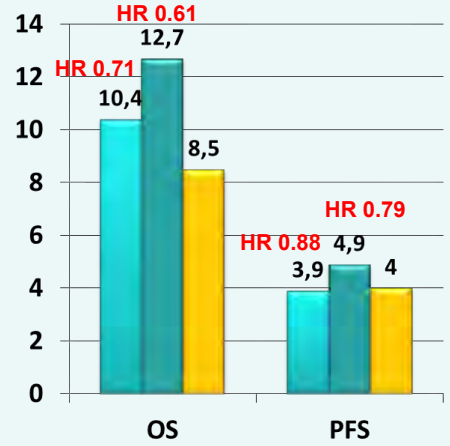
Unstratified *P* = 0.197

Mellemgaard A, et al. Eur J Cancer. 2013;49(suppl. 2):Abstract 3409 and oral presentation; Reck, ASCO 2016

4. Eli Lilly and Company. Alimta® (pemetrexed) prescribing information. Sep 2013
5. Astellas Pharma and Genentech. Tarceva® (erlotinib) prescribing information. June 2015
9. Bristol-Myers Squibb. Opdivo® (nivolumab) prescribing information. April 2016
10. Merck & Co., Inc. Keytruda® (pembrolizumab) prescribing information. October 2015



CENTRE DE LUTTE CONTRE LE CANCER LEON BERARD

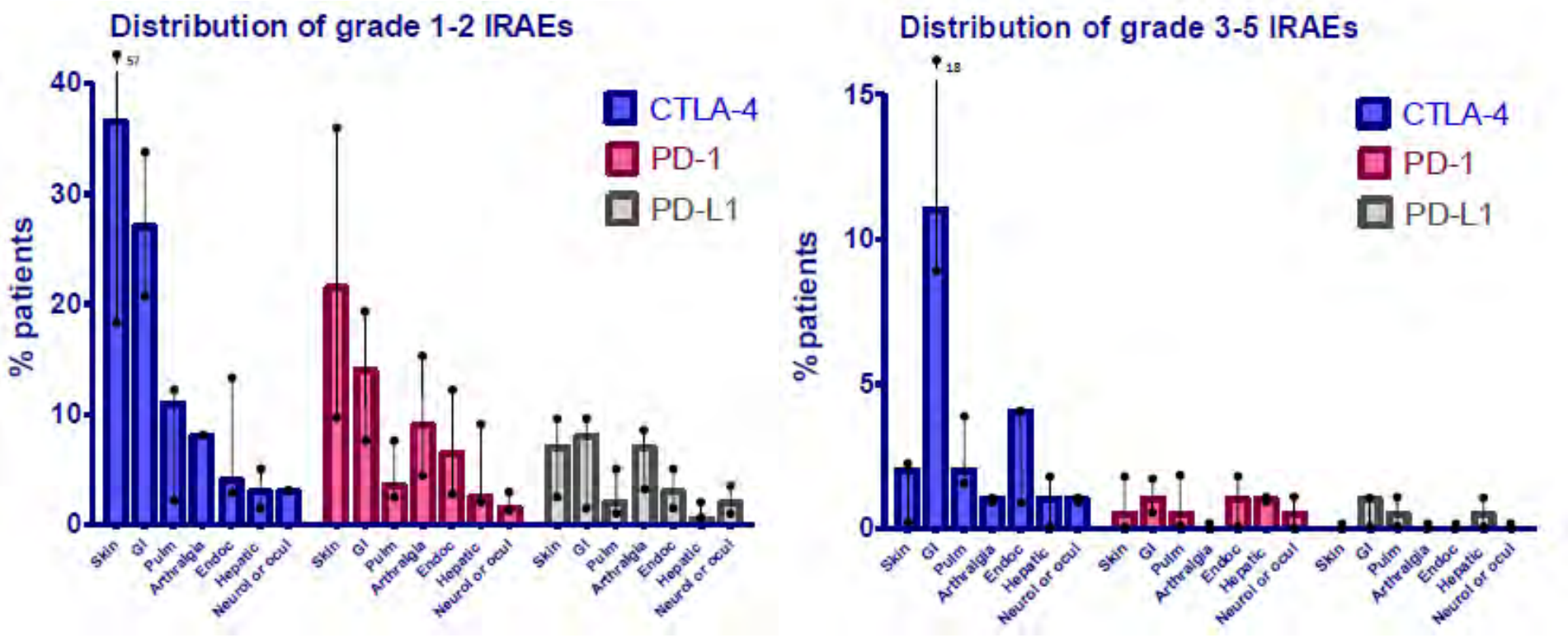
| | CheckMate 057<br>Nivolumab<br>*vs* docetaxel<br>N=582<br><br>Non-Squamous | Données non enregistrées<br>Poplar<br>Atezolizumab<br>*vs* docetaxel<br>N=287<br><br>All histologies | Keynote 010<br>Pembrolizumab<br>*vs* docetaxel<br>N=1034<br><br>All histologies, PDL1≥1% |
|---|---|---|---|
| Histology | Non-Squamous: 100% | Squamous: 34%<br>Non-Squamous: 66% | Squamous: 21%<br>Non-Squamous: 70% |
| OS<br>and PFS<br><br>(HR *vs* docetaxel) |  |  |  |

| | Nivolumab | Docetaxel | Atezolizum. | Docetaxel | Pembro 2 | Pembro 10 | Docetaxel |
|---|---|---|---|---|---|---|---|
| ORR | 20% | 9% | 19% | 12% | 18% | 18% | 9% |
| G3-≥4 AEs | 10% | 54% | 12% | 40% | 13% | 16% | 35% |

Brahmer, NEJM 2015; Borghaei, NEJM 2015; Fehrenbacher, Lancet 2016; Smith, ASCO 2016; Herbst, Lancet 2015

CENTRE DE LUTTE CONTRE LE CANCER LEON BERARD

# Comparaison des effets secondaires des anti-CTLA4 et des anti-PD1/PD-L1

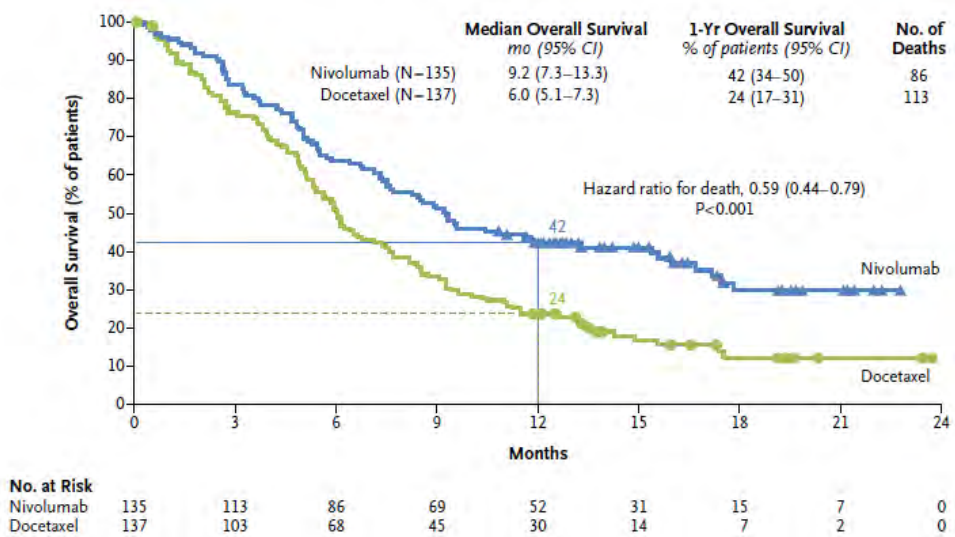


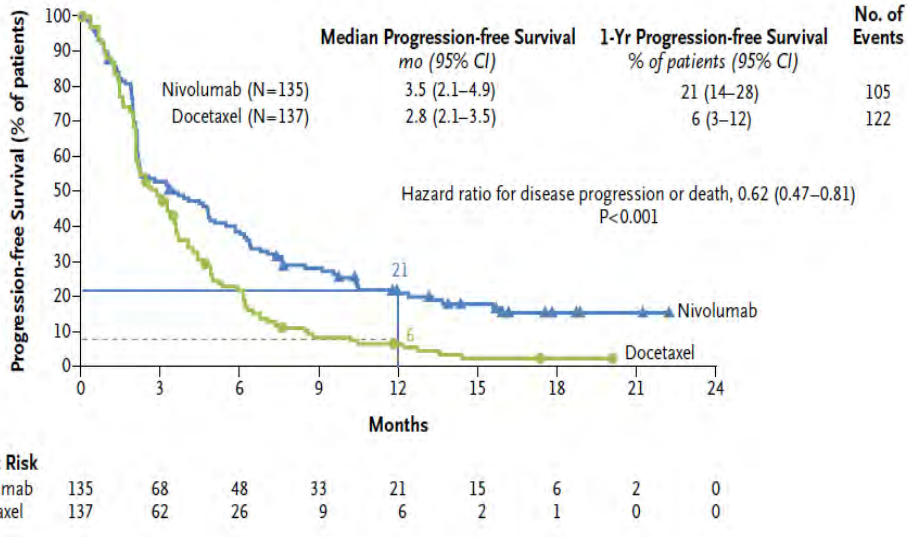

Michot, EJC 2016

CENTRE DE LUTTE CONTRE LE CANCER LEON BERARD

# Nivolumab Phase III Trial Checkmate 017 in 2nd Line of SqCC

| | Nivolumab (n = 135) | Docétaxel (n = 137) |
|---|---|---|
| Âge médian (ans) | 62 | 64 |
| Homme (%) | 82 | 71 |
| ECOG PS 0/1 (%) | 20/79 | 27/73 |
| Métastases cérébrales (%) | 7 | 6 |




Brahmer, NEJM 2015

CENTRE DE LUTTE CONTRE LE CANCER LEON BERARD

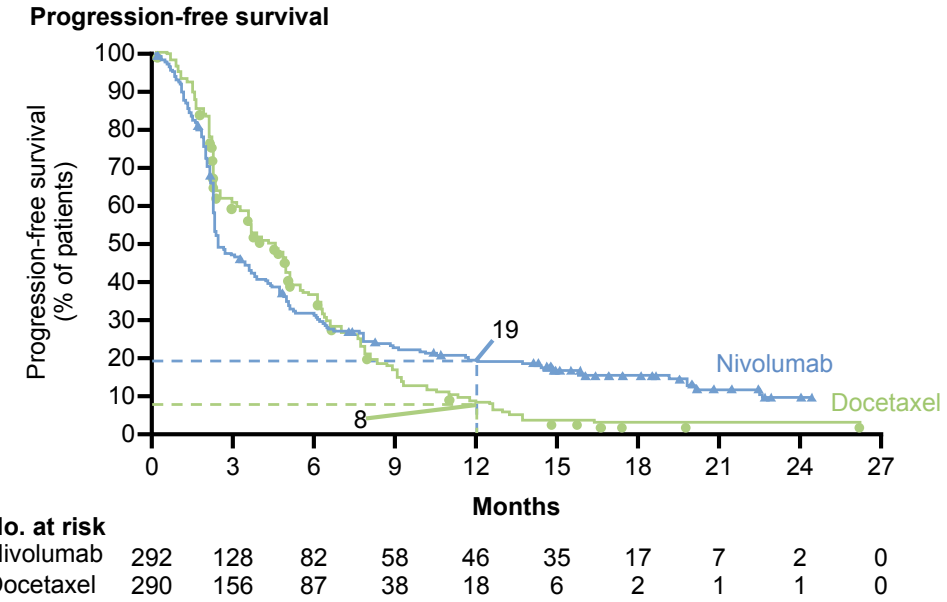
# Phase III CheckMate 057: Nivolumab *vs* Docetaxel in Second-Line Treatment of Adenocarcinoma

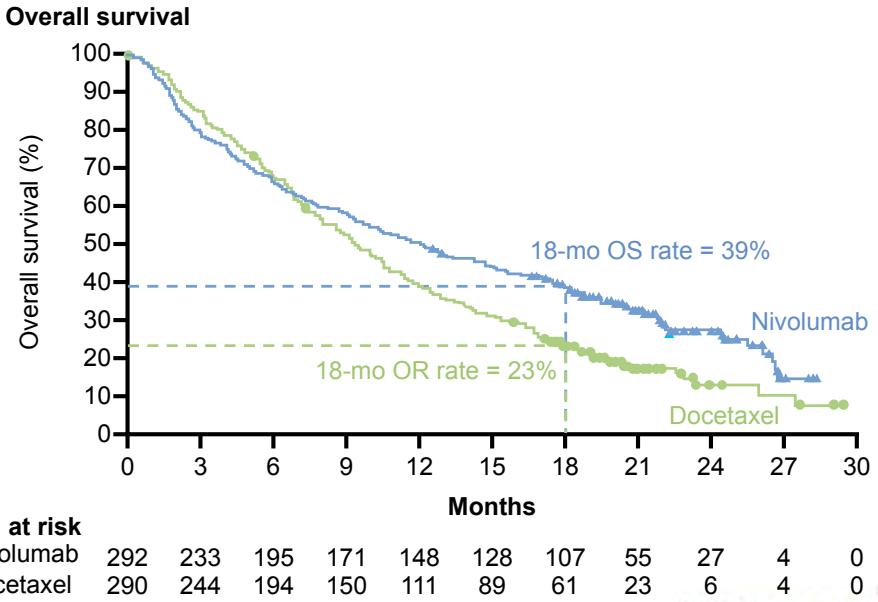
## ORR and PFS

| | Nivolumab (n=292) | Docetaxel (n=290) |
|---|---|---|
| **ORR, %** | 19 | 12 |
| **Median, months** | 2.3 | 4.2 |
| HR 0.92; 95% CI 0.77-1.11; p=0.3932 | | |

## OS

| | Nivolumab (n=292) | Docetaxel (n=290) |
|---|---|---|
| **Median, months** | 12.2 | 9.4 |
| **18-month OS, %** | 39 | 23 |
| HR 0.73; 95%CI 0.59-0.89; p=0.0015 | | |

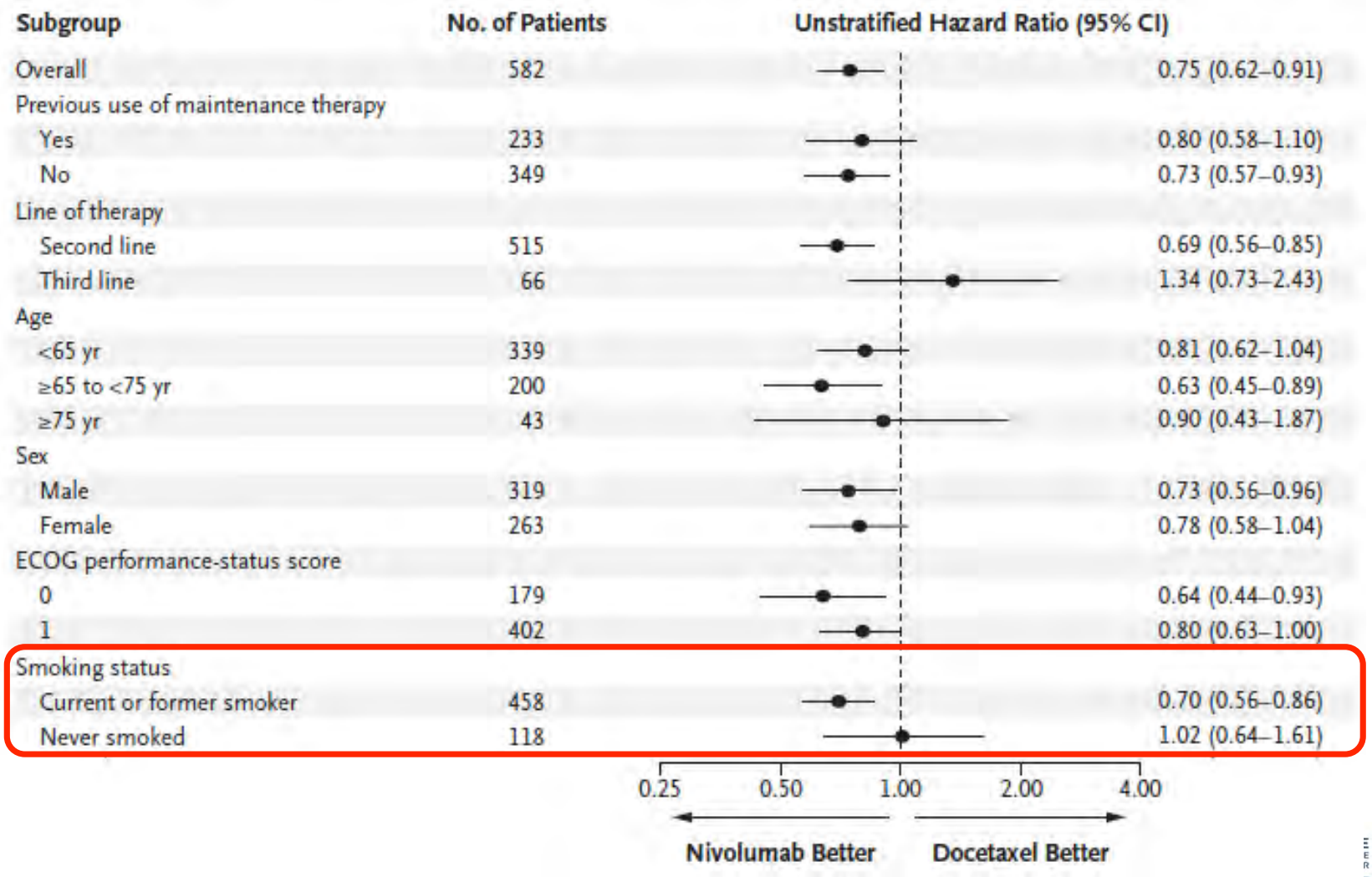



Paz-Ares L et al. *J Clin Oncol* 2015;33(suppl):abstr LBA109;
Borghaei H et al. *N Engl J Med* 2015;373:1627-39

CENTRE DE LUTTE CONTRE LE CANCER LEON BERARD

# Peut-on sélectionner sur les facteurs cliniques ? Checkmate 057

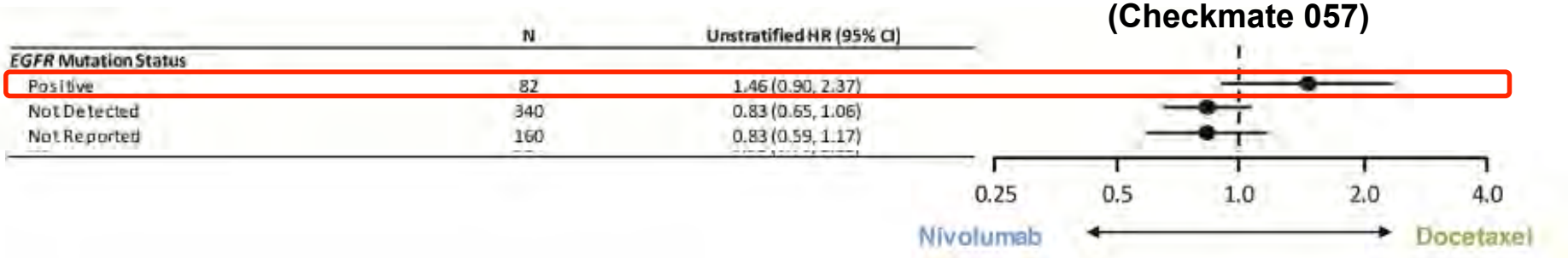



Borghaei, NEJM 2015

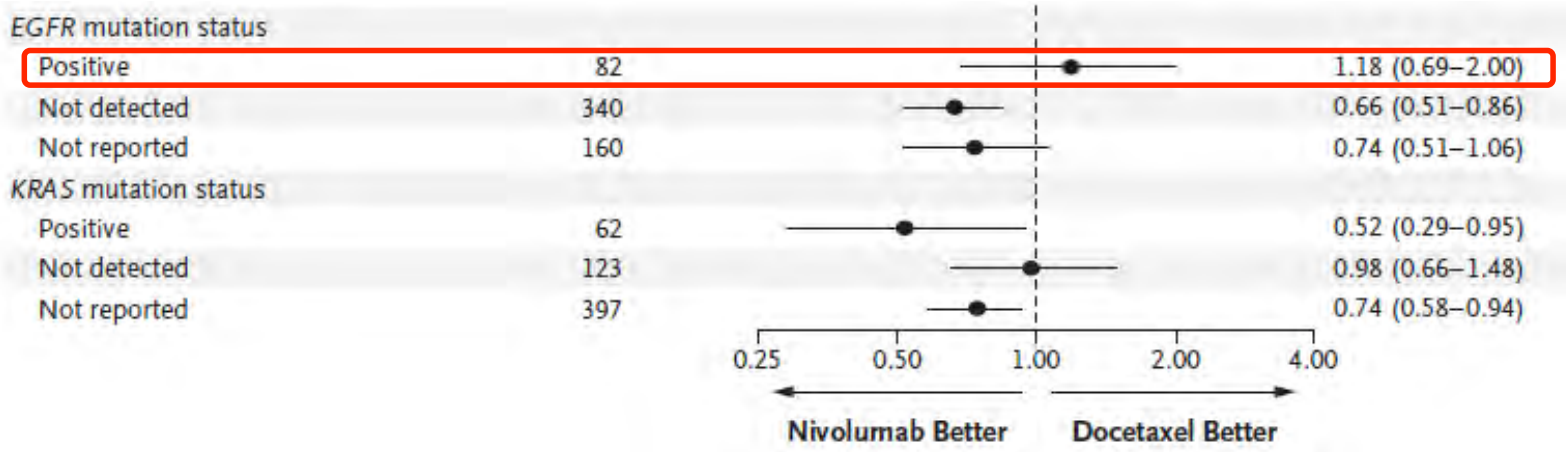
LEON BERARD

# Absence de bénéfice des anti-PD1/docétaxel en présence d'une mutation EGFR

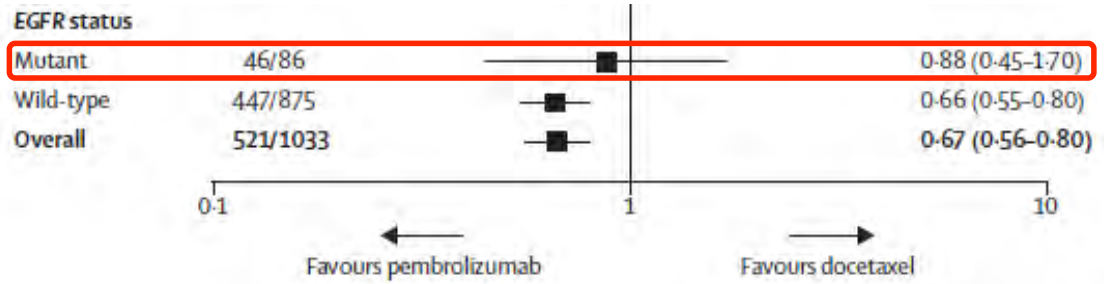
**PFS**
**(Checkmate 057)**




**OS**
**Non-épidermoïde**
**Checkmate 057**




**OS**
**PD-L1>1%**
**Keynote 010**




Borghaei, NEJM 2015, Herbst, Lancet 2016

CENTRE DE LUTTE CONTRE LE CANCER LEON BERARD

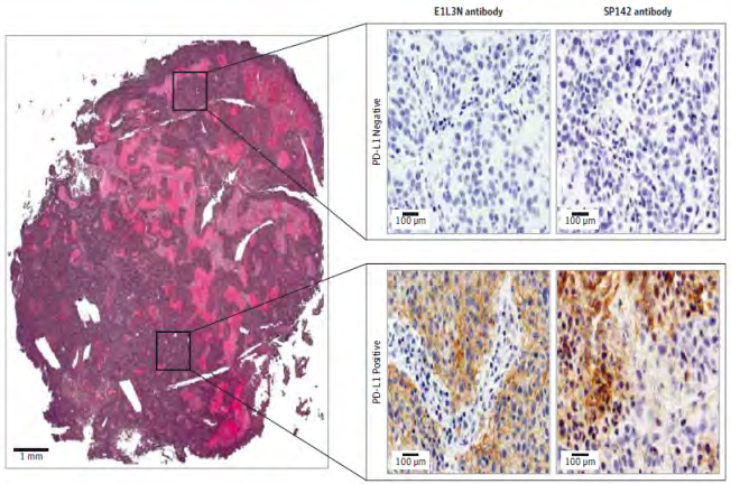
# Complexité de l'évaluation de l'expression de PD-L1 en tant que biomarqueur prédictif

## Biologie de PD-L1

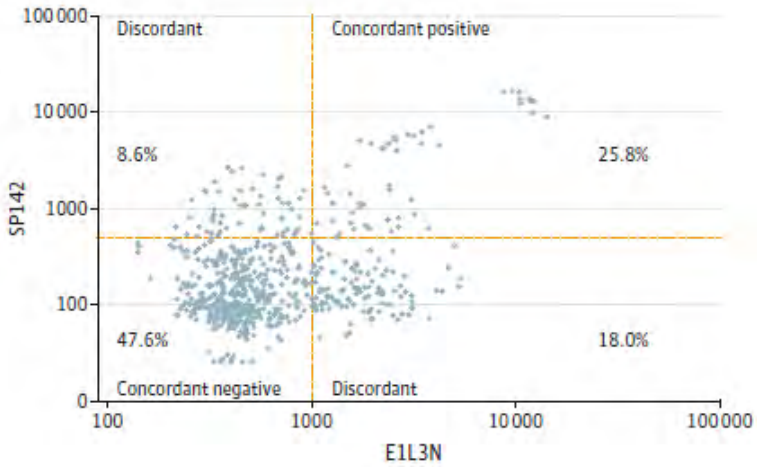
- Hétérogénéité intra-tumorale
- Dynamique d'expression (IFN, traitement)
- Cellules tumorales *vs* cellules immunes
- Expression membranaire vs cytoplasmique

## Test utilisé

- Différents épitopes et anticorps
- Différentes plateformes
- Différents cut-offs
- Reproductibilité inter-observateurs ?




**PD-L1**




## Echantillon tissulaire

- Tumeur primitive *vs* métastase
- Biopsie archivée *vs* biopsie pré-traitement
- Ancienneté du prélèvement
- Représentativité de la biopsie

Adapté d'après Martin Reck, ESMO Asia 2015
McLaughlin, JAMA Oncol 2015

CENTRE DE LUTTE CONTRE LE CANCER LEON BERARD

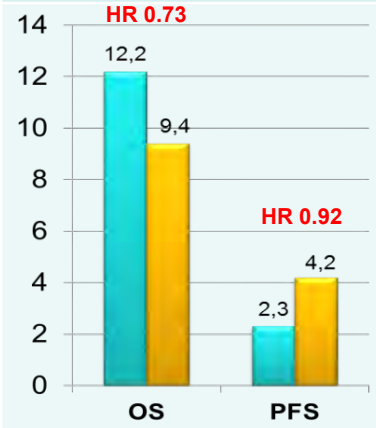
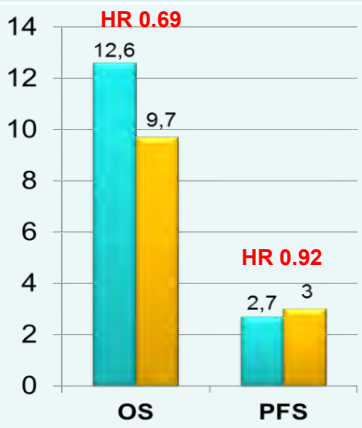
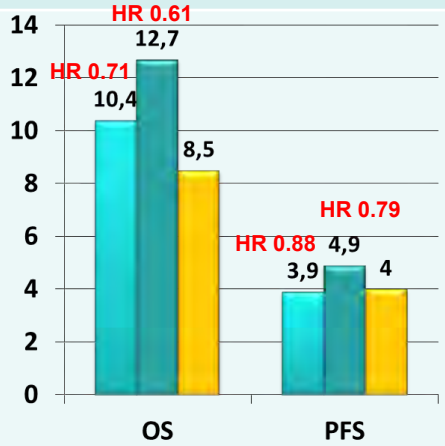
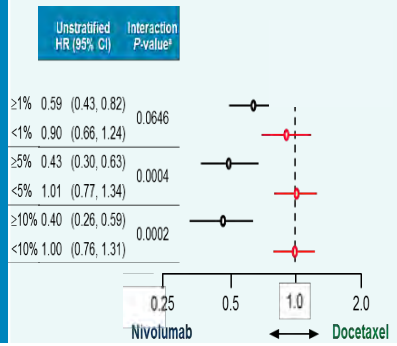
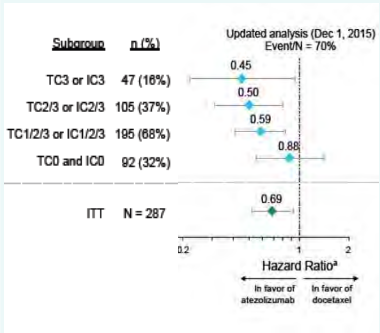
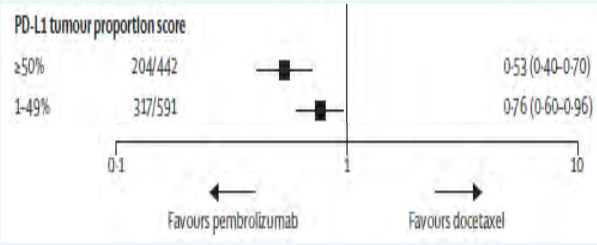
# PD-L1 Expression Analysis

| Agent | Assay | Analysis | Definition of positivity | PD-L1 expression |
|---|---|---|---|---|
| Nivolumab IgG4 (anti-PD-1) [1-4] | Dako automated IHC assay (5H1) Analytically validated | • Archival FFPE | • 1% and 5% cut-off among >100 evaluable tumour cells | • 56%: 1% cut-off<br>• 49%: 5% cut-off<br>• 44%: <1% |
| Pembrolizumab IgG4 (anti-PD-1)[5,6] | Dako automated IHC assay (22C3) | • New tumour biopsy within 60 days prior to first dose of pembrolizumab | • Tumour dependent:<br>- NSCLC<br>PD-L1 (+): Strong (≥50%) and weak staining (1–49%)<br>PD-L1 (–): no staining | • ~25%: ≥50% staining<br>• ~45–70%: ≥1% staining<br>• ~30–55%: <1% |
| Atezolizumab IgG1 (anti-PD-L1)[7,8,9] | Ventana automated clinical research IHC assay (SP 142) | • Archival or fresh FFPE<br>• Tumor cells and immune cells | • PD-L1 (+):<br>IHC 3 (≥10%),<br>IHC 2,3 (≥5%),<br>IHC 1,2,3 (≥1%)<br>• PD-L1 (–):<br>IHC 0 (<1%) | • 11%: IHC 3<br>• 25%: IHC 2 and 3<br>• 49%: IHC 1/2/3<br>• 45%: IHC 0 |
| Durvalumab IgG1 (anti-PD-L1)[10, 11] | Ventana IHC Automated Assay (SP 263) | • Archival FFPE | • ≥ 25% positive tumor cells | • 53% PDL1+<br>• 47% PDL1 - |

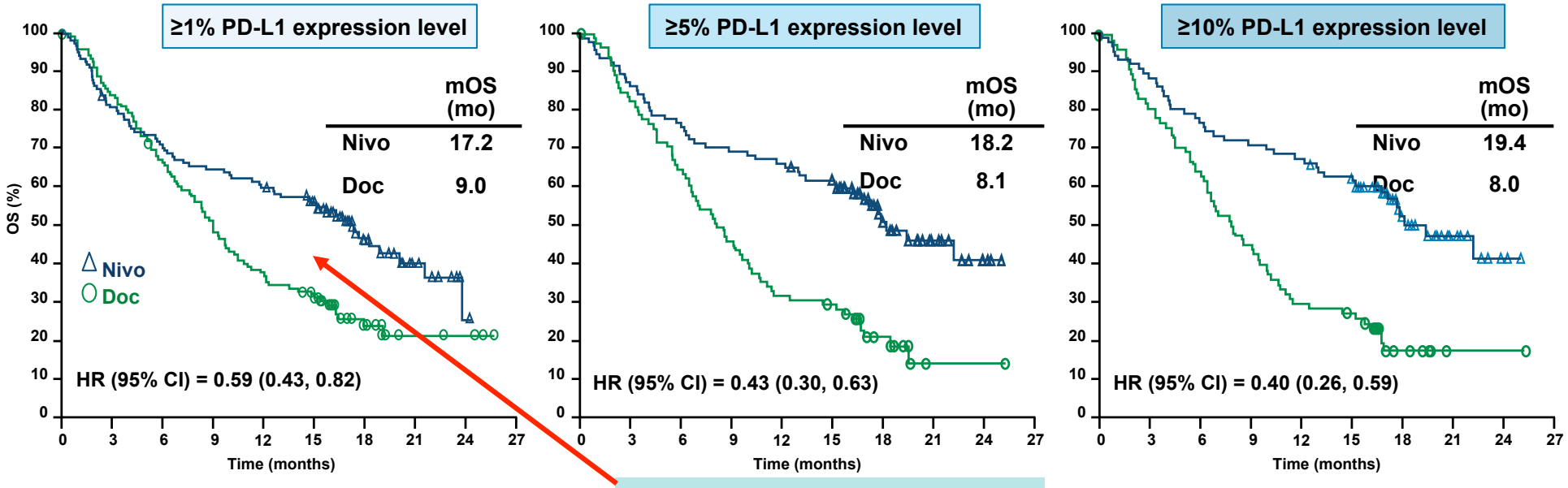
1. Antonia S, et al. Poster presented at WCLC 2013 (Abstract P2.11-035); 2. Brahmer J, et al. Poster 293 presented at ASCO 2014 (Abstract 8112); 3. Gettinger S, et al. Poster presented at ASCO 2014 (Abstract 8024); 4. Topalian S, et al. *N Engl J Med.* 2012;366:2443–2454; 5. Garon E, et al. Poster presented at ASCO 2014 (Abstract 8020); 6. Gandhi L, et al. Oral presentation at AACR 2014 (Abstract CT105); 7. Soria J, et al. Oral presentation at ECC 2013 (Abstract 3408); 8. Rizvi N, et al. Poster presented at ASCO 2014 (Abstract TPS 8123); 9. Soria J, et al. Poster presented at ESMO 2014 (Abstract 1322P); 10. Brahmer J, et al. Poster presented at ASCO 2014 (Abstract 8021), 11. Rizvi, ASCO 2015.

Adapted from Paz-Ares, ESMO 2014

CENTRE DE LUTTE CONTRE LE CANCER LEON BERARD

| | Checkmate 017<br>Nivolumab<br>*vs* docetaxel<br>N=272<br>*Brahmer, NEJM 2015*<br>Squamous | CheckMate 057<br>Nivolumab<br>*vs* docetaxel<br>N=582<br>*Borghaei, NEJM 2015*<br>Non-Squamous | *Not approved in NSCLC*<br>Poplar<br>Atezolizumab<br>*vs* docetaxel<br>N=287<br>*Smith, ASCO 2016*<br>All histologies | Keynote 010<br>Pembrolizumab<br>*vs* docetaxel<br>N=1034<br>*Herbst, Lancet 2015*<br>All histologies, PDL1≥1% |
|---|---|---|---|---|
| Histology | | Non-Squamous: 100% | Squamous: 34%<br>Non-Squamous: 66% | Squamous: 21%<br>Non-Squamous: 70% |
| OS<br>and PFS<br><br>(HR *vs* docetaxel) | |  |  |  |
| | | Nivolumab / Docetaxel | Atezolizum. / Docetaxel | Pembro 2 / Pembro 10 / Docetaxel |
| ORR | | 20% / 9% | 19% / 12% | 18% / 18% / 9% |
| G3-≥4 AEs | | 10% / 54% | 12% / 40% | 13% / 16% / 35% |
| OS by PDL1 status | |  |  |  |

# Checkmate 057: OS by PD-L1 Expression




**PD-L1 = 7%**

Paz-Ares, ASCO 2015

Symbols represent censored observations.

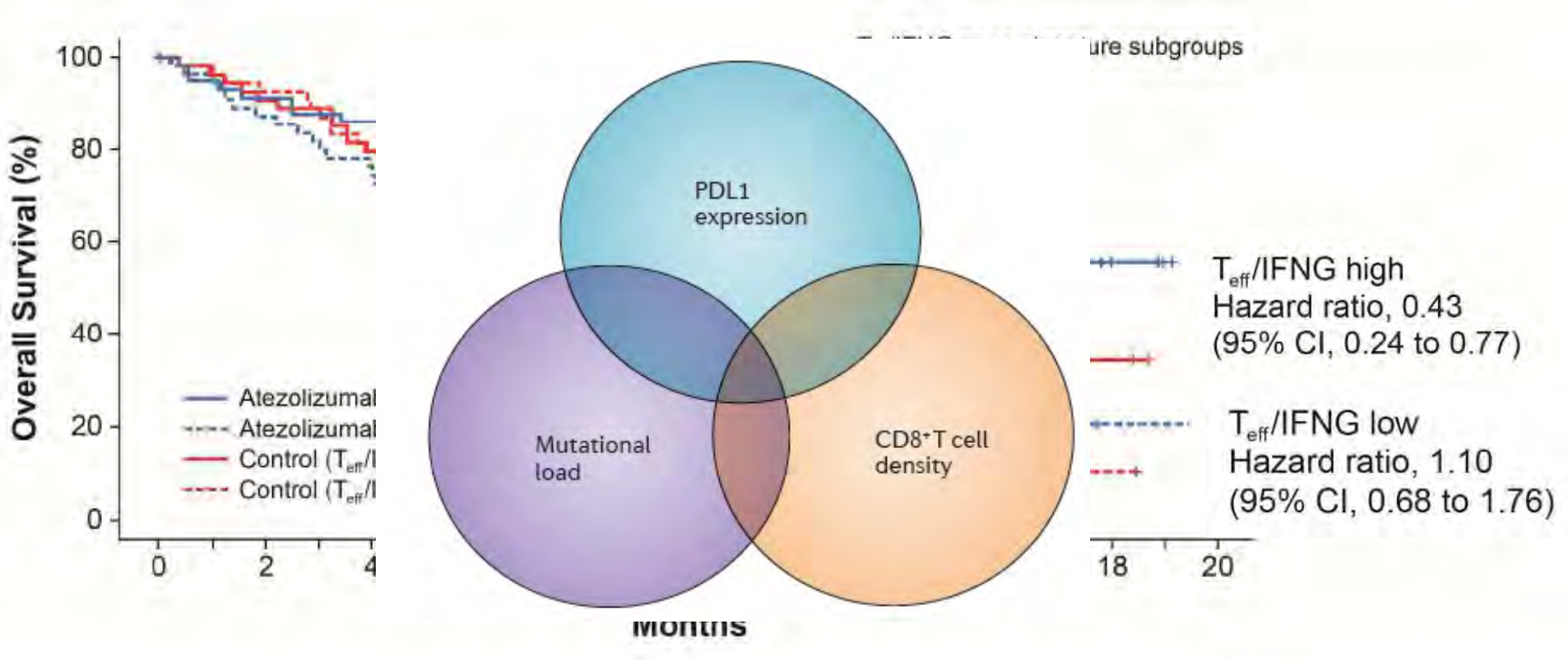
*Données non enregistrées*

BERARD

# Nivolumab vs docetaxel dans les adénocarcinomes
# Impact de l'expression de PDL1 sur le bénéfice de survie

| Niveau d'expression PDL1 (% cellules tumorales exprimant PDL1 – Dako 28.8) | HR non stratifié (IC 95%) Nivolumab *vs* docetaxel (survie globale) |
|---|---|
| < 1% | 0.90 (0.66, 1.24) |
| ≥ 1% | 0.59 (0.43, 0.82) |
| ≥ 1% et < 10% | 1.33 (0.79, 2.24) |
| ≥ 10% et < 50% | 0.61 (0.30, 1.23) |
| > 50% | 0.32 (0.20, 0.53) |

# Prise en compte de l'existence d'une réponse immunitaire anti-tumorale




P. Schmid et al., ECC 2015, Abstr 3017
Fehrenbacher, Lancet 2016

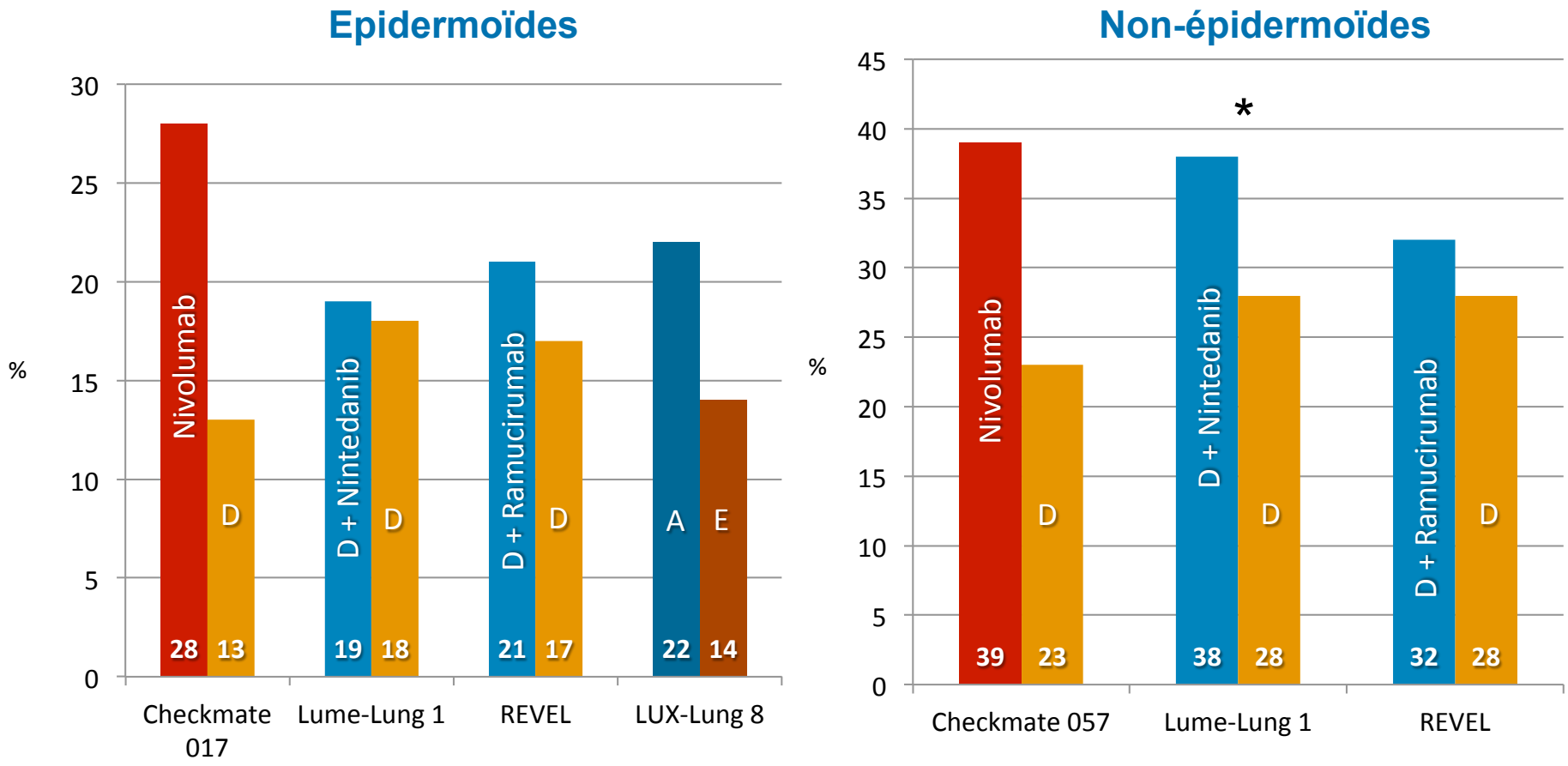
*Données non enregistrées*

CENTRE DE LUTTE CONTRE LE CANCER LEON BERARD

# IV

# *Quel algorithme thérapeutique après la 1ère ligne en 2016 ?*

# Les essais de phase III en seconde ligne
# Survie à 18 mois







* : adénocarcinomes seulement
D : docetaxel; A : afatinib ; E : erlotinib

Brahmer, NEJM 2015; Reck, Lancet Oncol 2014; Garon, Lancet 2014;
Soria, Lancet Oncol 2015; Borghaei H et al. *N Engl J Med* 2015;373:1627-39

*Données non enregistrées*

CENTRE DE LUTTE CONTRE LE CANCER LEON BERARD

# Decision-Making Factors

## Patient characteristics

- Age
- Gender
- Ethnicity
- ECOG PS
- Comorbidities
- CI to immune CP inhibitors
- Smoking status

## Disease characteristics

- Histology
- Mutational status
- Metastases
- Brain metastases
- Eligibility to anti-angiogenic agents
- PDL1 expression (standardization ?)

## Treatment considerations

- Prior treatments received
- Response to 1st line
- Specific toxicity considerations
- Corticosteroids
- Doctor / patient preference
- Cost

# Taux de réponses en cas de CBNPC n'exprimant pas PD-L1

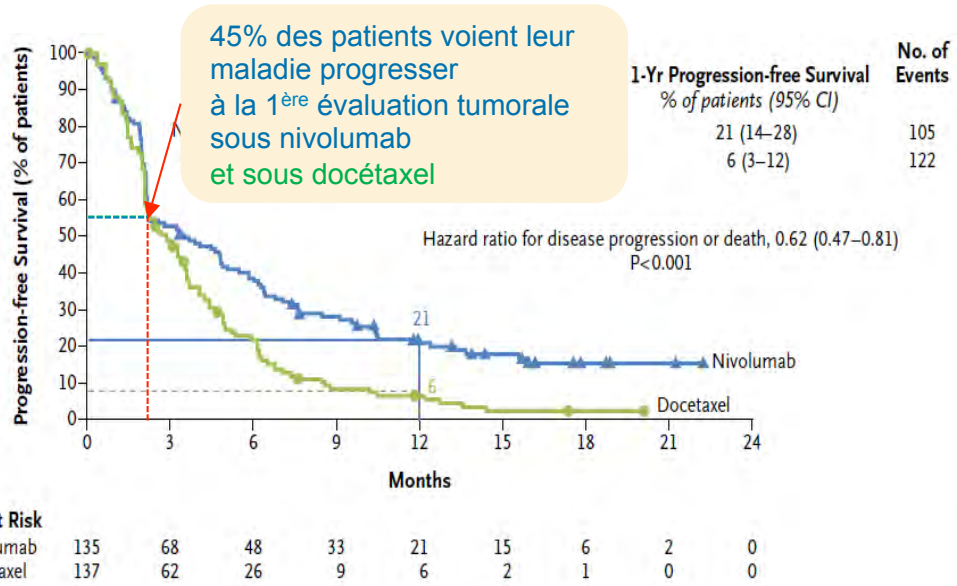
| Anticorps | Histologie | Test | Définition PD-L1 - | Taux de réponses |
|---|---|---|---|---|
| Nivolumab (Checkmate 017) | Epidermoïdes | Dako 28.8 | <1% | 17% |
| Nivolumab (Checkmate 057) | Non-épidermoïdes | Dako 28.8 | <1% | 9% |
| Atezolizumab (Poplar) | Toutes histologies | Ventana SP142 | TC0 + IC0 | 7.8% |
| Durvalumab (phase I) | Toutes histologies | Ventana SP263 | <25% | 5% |
| Pembrolizumab (phase I) | Toutes histologies | Dako 22C3 | <1% | 8.1% |
| Avelumab (phase Ib) | Toutes histologies | Non précisé | <1% | 10% |

Brahmer, NEJM 2015; Borghaei H et al. *N Engl J Med* 2015;373:1627-39; Fehrenbacher; Lancet 2016; Garon, NEJM 2015; Rebelatto, ASCO 2015; Herbst, Lancet 2015

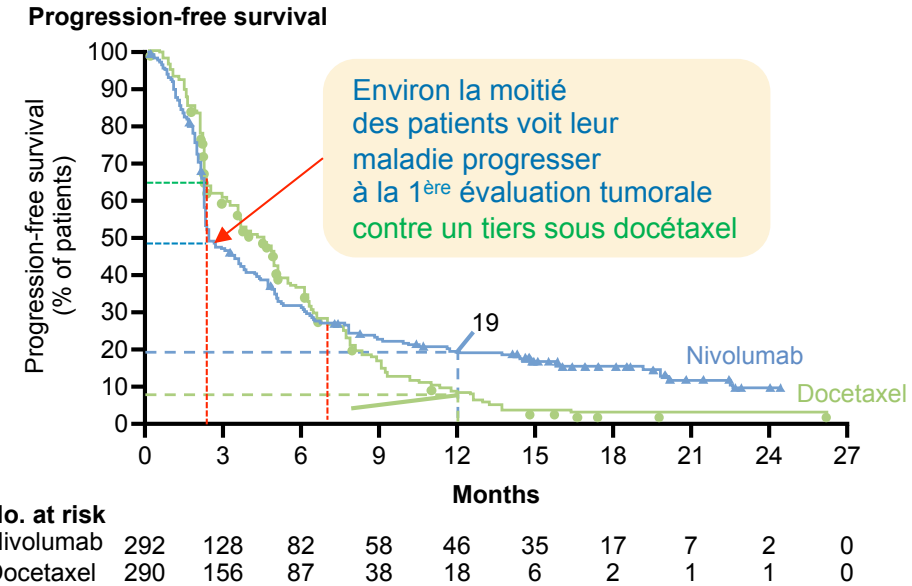
CENTRE DE LUTTE CONTRE LE CANCER LEON BERARD

# Nivolumab *versus* docétaxel en 2ème ligne
# Réponse et survie sans progression

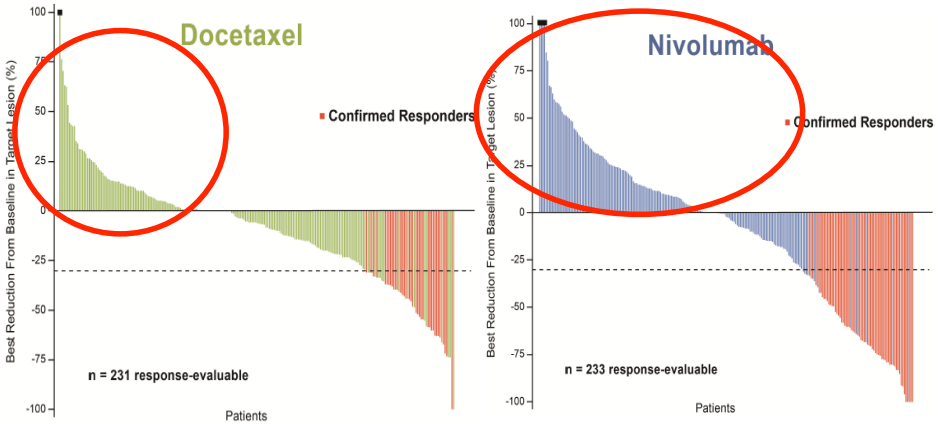
## Epidermoïdes




## Non épidermoïdes



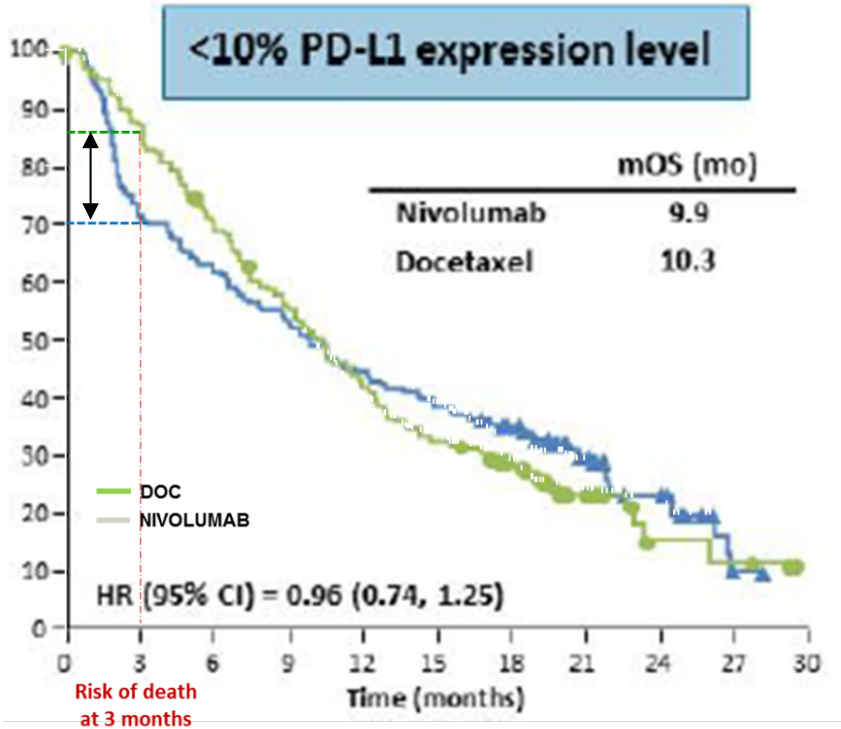

| | Checkmate 017 Epidermoïdes | Checkmate 057 Non-épidermoïdes |
|---|---|---|
| Traitement systémique post-nivolumab, % pts | 36% | 42% |



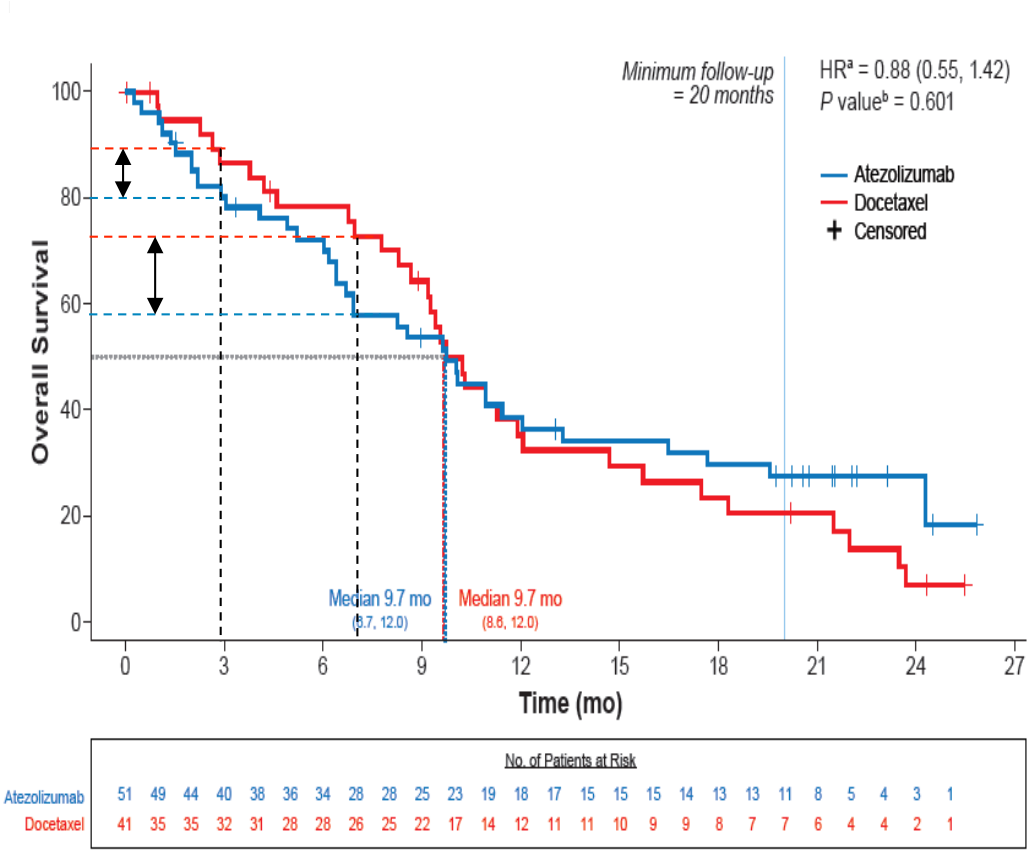

Brahmer J et al., *N Engl J Med* 2015 ; Borghaei H et al. , *N Engl J Med* 2015

# Nivolumab *versus* Docetaxel in 2nd Line Non-Sq NSCLC in PD-L1<10% patients
# Atezolizumab *versus* Docetaxel in 2nd Line NSCLC in TC0 and IC0 patients

## Risk of Early Death




**Checkmate 057 (nivolumab)**
**Non-squamous NSCLC**
**<10% PD-L1 level**




**Poplar (atezolizumab)**
**NSCLC, all histologies**
**PD-L1: TC0 and IC0**

Borghaei H et al. , *N Engl J Med* 2015; Smith, ASCO 2016

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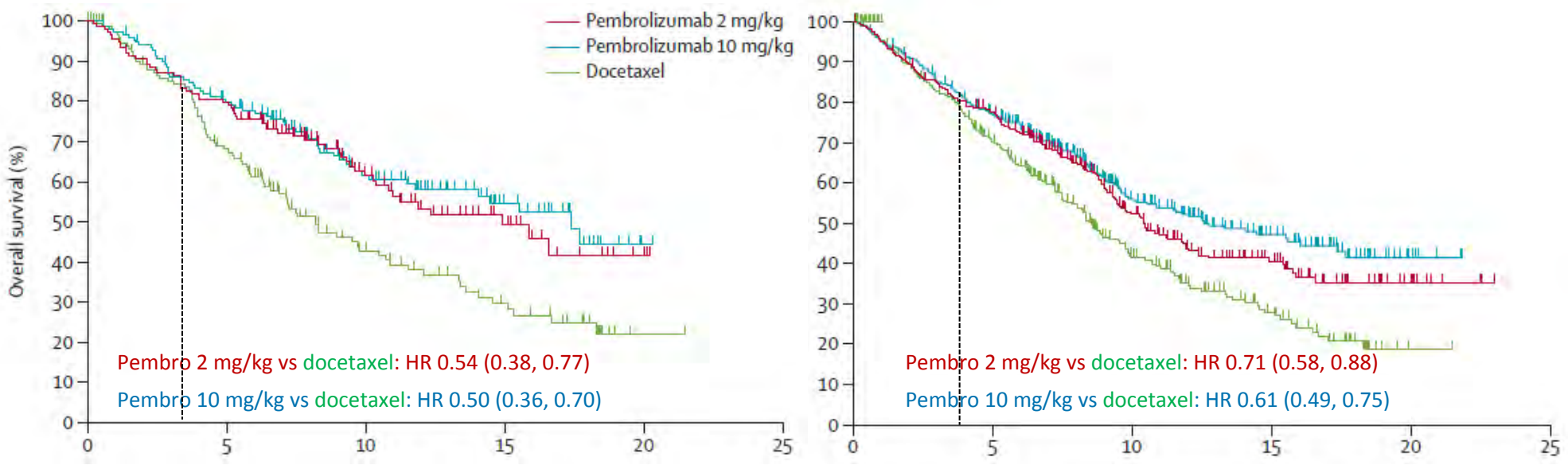
# Keynote 010: Pembrolizumab *vs.* Docetaxel Overall Survival (PD-L1>1%, Dako 22C3 Assay)




**PDL1 ≥ 50%**

**PDL1 ≥ 1%**

Herbst, Lancet 2015

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# Doit-on sélectionner les patients pour un traitement par anti-PD1/PD-L1 en 2ème ligne ?

- **Problématique de l'extrapolation des résultats des essais cliniques à la pratique quotidienne**
  - **"screenfailure" = 45 à 50% dans les essais de phase III**
  - **Sélection d'une population de patients à maladie relativement stable (délai du screening = 28 jours), PS 0-1, sans métastase cérébrale …**
- **Carcinomes épidermoïdes**
  - **nivolumab = standard de traitement sauf contre-indication à l'immunothérapie**
  - **ou pembrolizumab si PD-L1≥ 1%**

# Doit-on sélectionner les patients pour un traitement par anti-PD1/PD-L1 en 2ème ligne ?

- **Carcinomes non-épidermoïdes**
  - **l'option anti-PD1/PD-L1 peut être délétère chez certains patients**
    - **non-rattrapage par traitement ultérieur chez > 50% patients**
    - **options thérapeutiques alternatives en 2ème ligne, à plus haute probabilité d'efficacité (contrôle) chez certains patients**
    - **impact sur la séquence thérapeutique : activité des anti-PD1/PD-L1 indépendante de la ligne de traitement**
  - **Sélection des patients ?**
    - **impact négatif de l'absence de tabagisme ou d'une mutation EGFR**
    - **nécessité d'une standardisation pour l'expression de PDL1**
    - **corrélation niveau d'expression de PD-L1 - amplitude du bénéfice de survie**
    - **valeur prédictive négative imparfaite : possibilité de réponses si PDL1 <1% mais risque de décès précoce plus élevé**

# 2016: Proposal for Treatment Algorithm

## Disease progression after platinum-based doublet

Decision-making factors

### Non-squamous Carcinoma

Consider rebiopsy: EGFR and ALK status if unknown, PDL1 expression

***Wild-type EGFR*** and no ***ALK rearrangement***

Co-morbidities, CI to immunotherapy, corticosteroids
Eligibility to anti-angiogenic agents

CI to immune CP inhibitors
And/or rapid disease progression
And/or no PD-L1 expression

PD-L1 + (cut-off?)
No CI to immune CP inhibitors

**2nd line**

Docetaxel + nintedanib
Docetaxel + ramucirumab
Docetaxel or pemetrexed
if CI to anti-angiogenic agent

Nivolumab
or pembrolizumab (PDL1≥1%)

**3rd line**

Erlotinib
Nivolumab if no CI to CP inhibitor

Docetaxel + nintedanib
Docetaxel + ramucirumab
Docetaxel or pemetrexed
if CI to anti-angiogenic agent

### Squamous Carcinoma

**2nd line**

Nivolumab
or pembrolizumab
(PDL1≥1%)
if no CI to immune
checkpoints inhibitors

**3rd line**

Docetaxel ± ramucirumab
Erlotinib or afatinib

# 2016: Proposal for Treatment Algorithm in France

## Disease progression after platinum-based doublet

**Decision-making factors**

### Non-squamous Carcinoma

Consider rebiopsy: EGFR and ALK status if unknown, PDL1 expression

*Wild-type EGFR* and no *ALK rearrangement*

Co-morbidities, CI to immunotherapy, corticosteroids
Eligibility to anti-angiogenic agents

| | |
|---|---|
| CI to immune CP inhibitors<br>And/or rapid disease progression<br>And/or no PD-L1 expression | PD-L1 + (cut-off?)<br>No CI to immune CP inhibitors |

**2nd line**

| | |
|---|---|
| Docetaxel or pemetrexed | Nivolumab<br>or pembrolizumab (PDL1≥1%) |

**3rd line**

| | |
|---|---|
| Erlotinib<br>Nivolumab if no CI to CP inhibitor | Docetaxel or pemetrexed |

### Squamous Carcinoma

**2nd line**

Nivolumab
or pembrolizumab
(PDL1≥1%)
if no CI to immune
checkpoints inhibitors

**3rd line**

Docetaxel
Erlotinib or afatinib

CENTRE DE LUTTE CONTRE LE CANCER LEON BERARD

# Développement en monothérapie de 1ère ligne
# Essais de phase III

| Agent | Etude | Indication | Comparateur | N | Endpoint |
|---|---|---|---|---|---|

**Merck's KEYTRUDA® (pembrolizumab) Demonstrates Superior Progression-Free and Overall Survival Compared to Chemotherapy as First-Line Treatment in Patients with Advanced Non-Small Cell Lung Cancer**

**KEYNOTE-024 Studied Patients Whose Tumors Expressed High Levels of PD-L1**

**16 juin 2016**

5 August 2016

BMS announced today that CheckMate -026 did not meet its primary endpoint of progression-free survival in patients with previously untreated advanced non-small cell lung cancer (NSCLC) whose tumors expressed PD-L1 at = 5%

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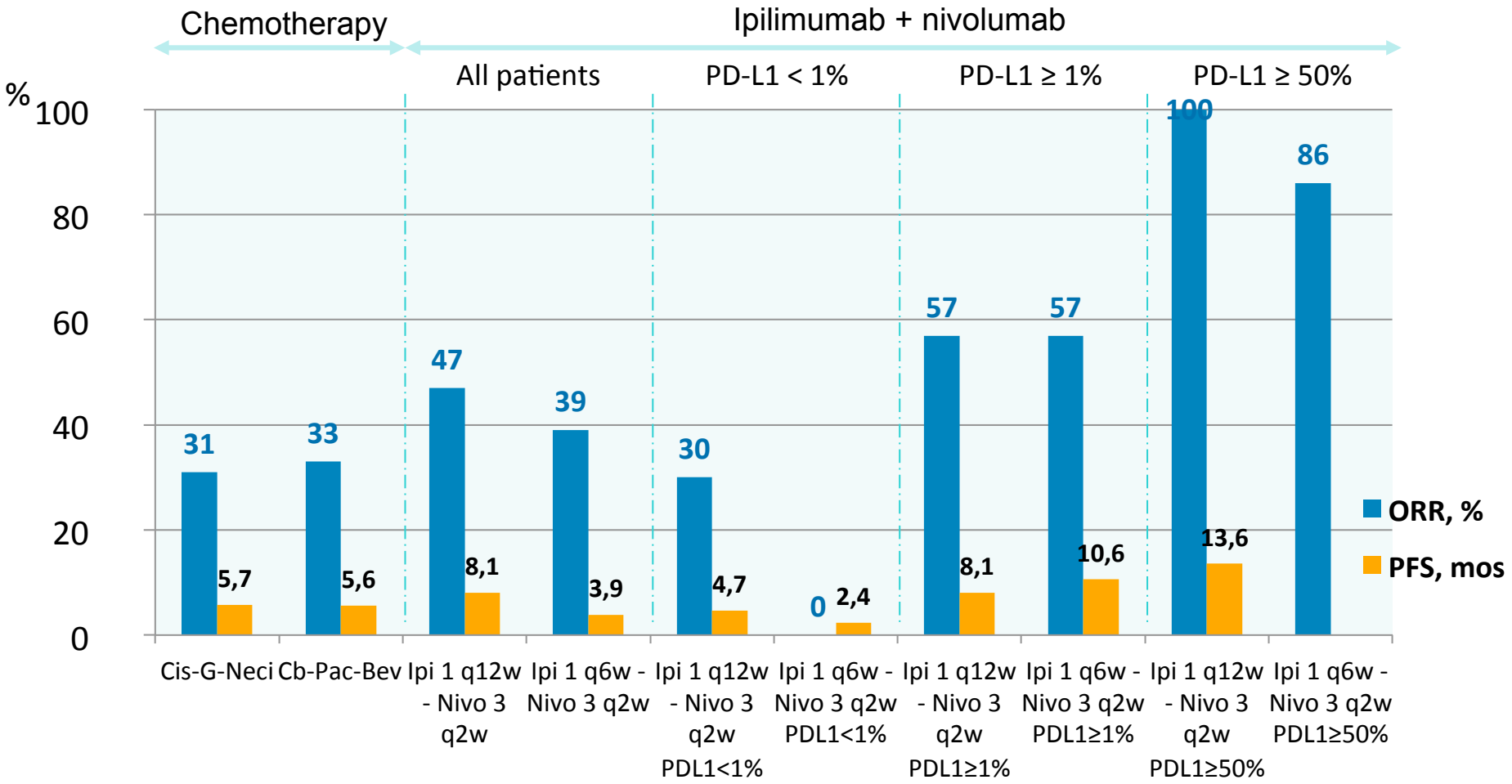
# First-Line Treatment of Advanced NSCLC
# Present and Future …




Thatcher, Lancet Oncol 2015; Patel, JCO 2013; Hellman, ASCO 2016

*Données non enregistrées*

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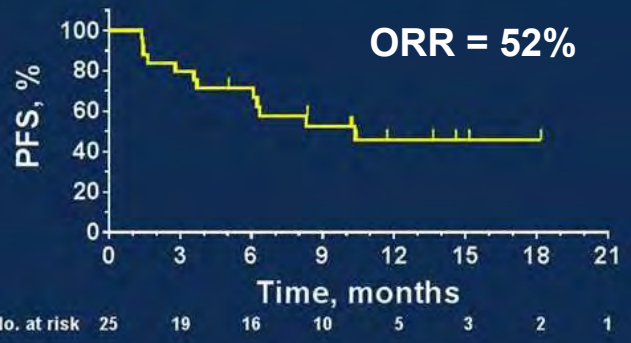
# Keynote 021: PFS and OS

## COHORT A

Carbo-paclitaxel + pembro

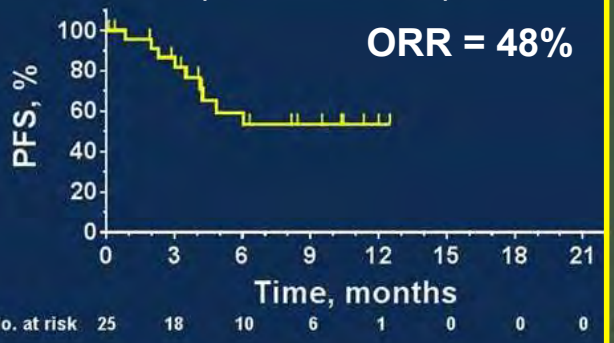
ORR = 52%




## COHORT B

Carbo-paclitaxel -bev+ pembro

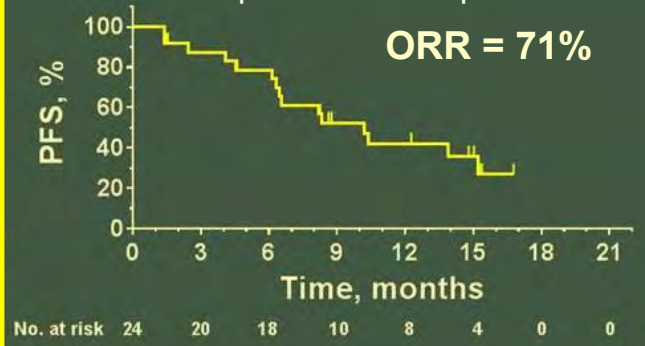
ORR = 48%



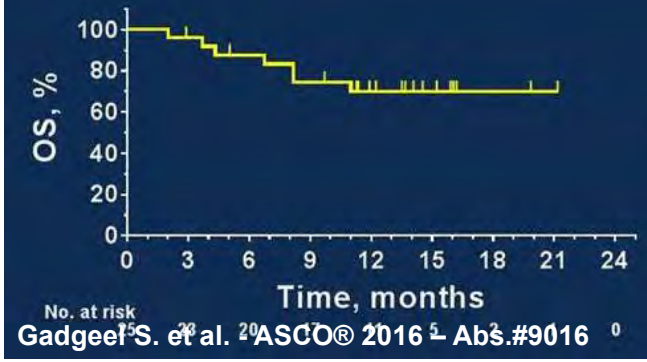

## COHORT C

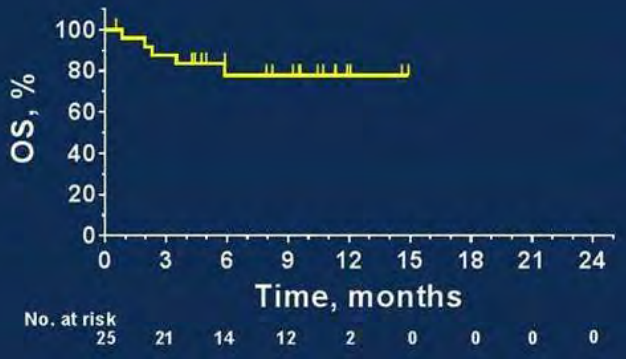
Carbo-pemetrexed + pembro

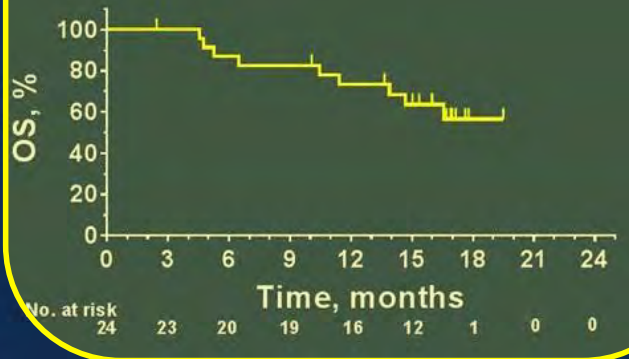
ORR = 71%




| Population | Cohort A n | Cohort A No. of events, n (%) | Cohort A PFS, months, median (95% CI) | Cohort B n | Cohort B No. of events, n (%) | Cohort B PFS, months, median (95% CI) | Cohort C n | Cohort C No. of events, n (%) | Cohort C PFS, months, median (95% CI) |
|---|---|---|---|---|---|---|---|---|---|
| Total | 25 | 12 (48) | 10.3 (3.7-NR) | 25 | 9 (36) | NR (4.1-NR) | 24 | 15 (63) | 10.2 (6.3-15.2) |




Gadgeel S. et al. ASCO® 2016 – Abs.#9016

# ESMO 2016
# Session présidentielle, 9/10/2016

- **OAK : atezolizumab vs docetaxel en 2ème ou 3ème ligne avec stratification sur statut PD-L1**
- **Keynote 024 : pembrolizumab vs chimiothérapie de 1ère ligne (PD-L1 ≥ 50%)**
- **Checkmate 026 : nivolumab vs chimiothérapie de 1ère ligne (PD-L1 ≥ 5%)**
- **Keynote 021, part II Cohort G : carboplatine-pemetrexed ± pembrolizumab (phase IIR)**

# → 2017-2018

| Facteurs décisionnels | Carcinome non-épidermoïde – Recherche biomarqueurs + expression PDL1 | | | | Carcinome épidermoïde – Expression PDL1 | | |
|---|---|---|---|---|---|---|---|
| | *EGFR* Mut+ | *ALK* + | *EGFR* sauvage, *ALK* – *PDL1* -/+ | *EGFR* sauvage, *ALK* – *PDL1* ++/+++ | PDL1 -/+ | | PDL1 ++/+ ++ |
| | Tout PS | Tout PS | PS 0-1 | PS 2 ou > 75 ans | PS 0-1 | PS 2 ou > 75 ans | PS 0-1 |
| | | | Co-morbidités Eligibilité bevacizumab ou immunothérapie | | Co-morbidités Eligibilité immunothérapie | | |
| Induction | Gefitinib Erlotinib Afatinib ± bevacizumab | Crizotinib ou Alectinib | Doublet à base de platine ± bevacizumab | Doublet à base de carboplatine ou monothérapie ± bevacizumab | Doublet à base de platine sauf pem. | Doublet /carbopl. ou monottt sauf pem. | Anti-PD1/ PDL1 |
| Maintenance | Gefitinib Erlotinib Afatinib ± bevacizumab | Crizotinib ou Alectinib | Bevacizumab Pemetrexed | Bevacizumab si utilisé en induction | | | Anti-PD1/ PDL1 |
| 2ème L | T790M + Osimertinib<br>T790M – Chimiothérapie | Céritinib ou Alectinib | *PDL1 – vs PDL1 +* Nivolumab/Atezolizumab Pembrolizumab si PDL1+ Docetaxel ± anti-angiogénique | | PDL1 – vs PDL1 + Nivo/Atezolizumab Pembrolizumab (PDL1+) Docetaxel ± anti-angiogénique | | Chimioth Combo ? |
| | | | | Chimioth. Combo ? | | | |


Sales growth of approved checkpoint inhibitors
Global quarterly sales (USD million)
1'200
1'000
800
600
400
200
0
Opdivo
Keytruda
Yervoy
Q2/2011
Q3/2011
Q4/2011
Q1/2012
Q2/2012
Q3/2012
Q4/2012
Q1/2013
Q2/2013
Q3/2013
Q4/2013
Q1/2014
Q2/2014
Q3/2014
Q4/2014
Q1/2015
Q2/2015
Q3/2015
Q4/2015
Q1/2016