Revisión del estado del arte en el manejo del CPNM desde el punto de vista del oncólogo

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My main objectives today

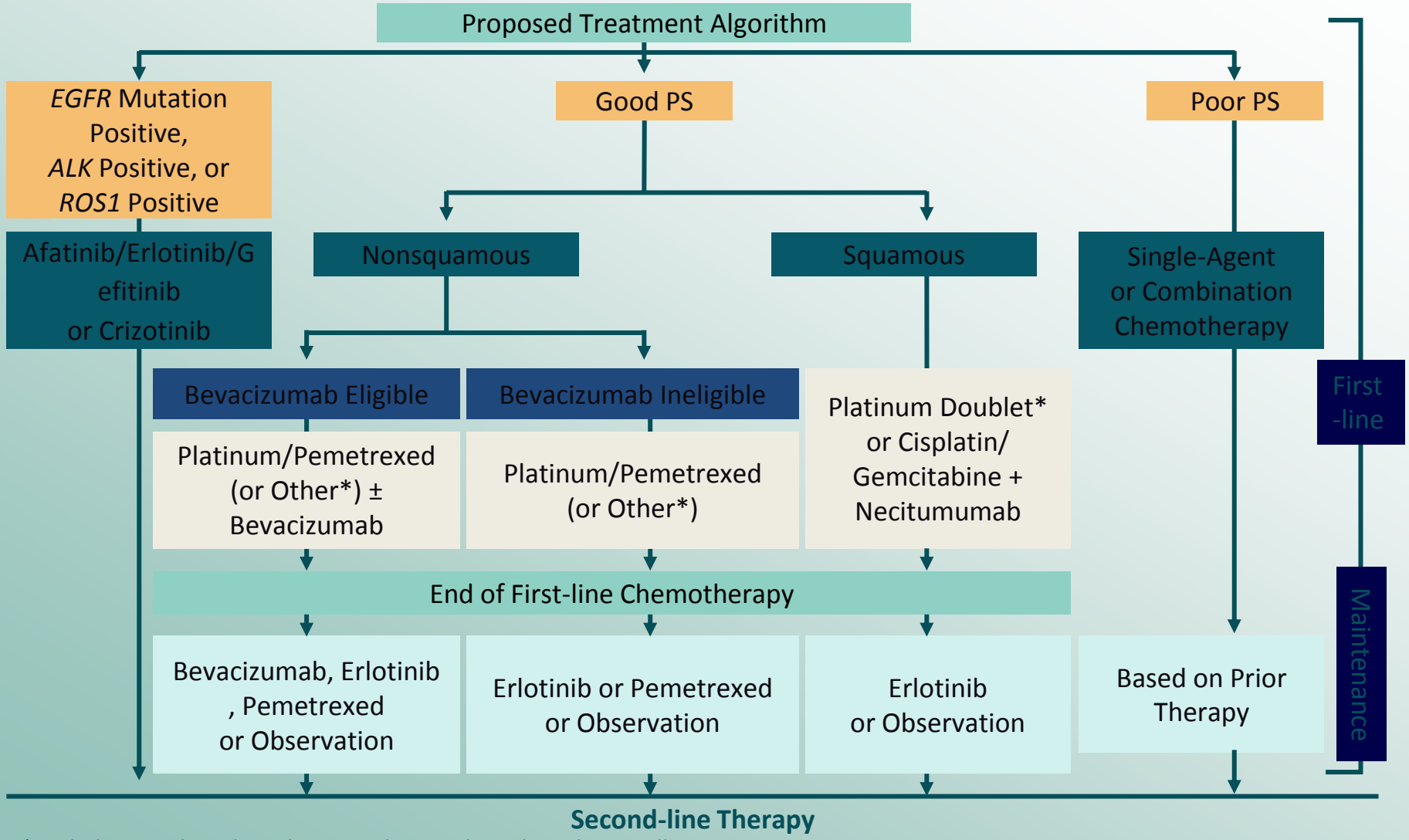
STATE OF THE ART

“The secret of being a bore...

is to tell everything”

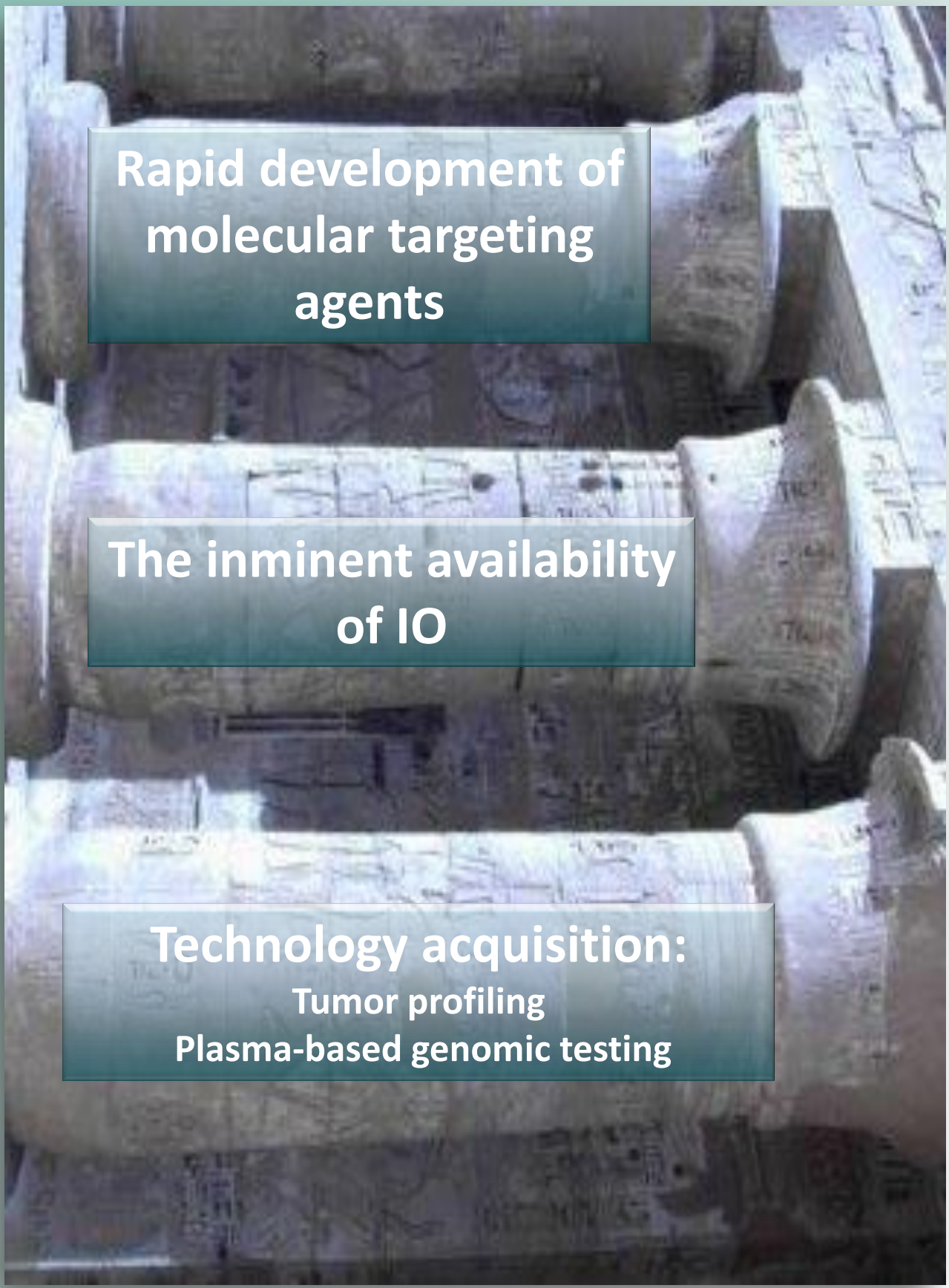
Voltaire

Updated Treatment Algorithm for Advanced-Stage NSCLC (2016)

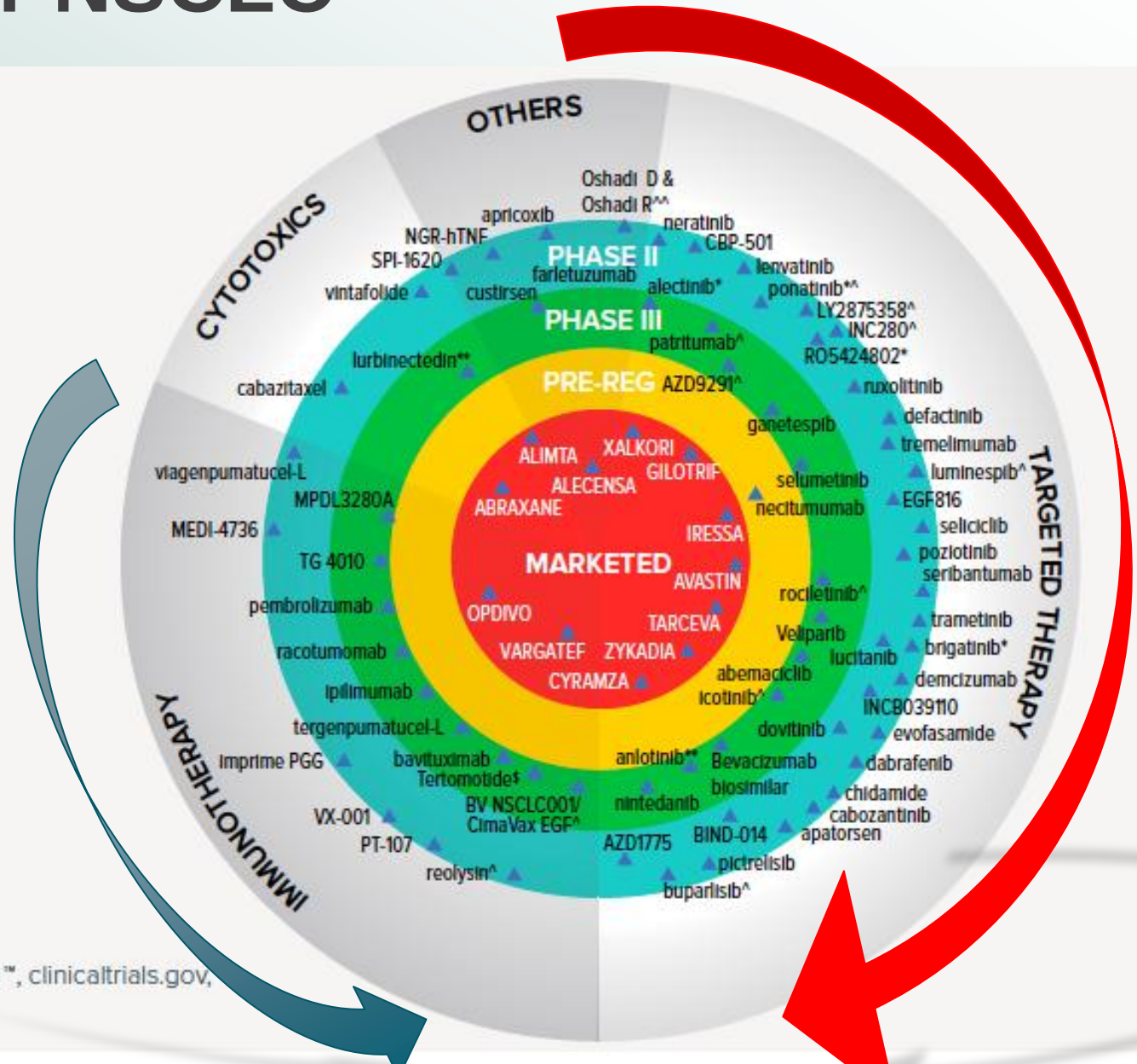


*With docetaxel, paclitaxel, gemcitabine, nab-paclitaxel, vinorelbine.

The revolution…2016



Key in-Market and Investigational Agents for NSCLC

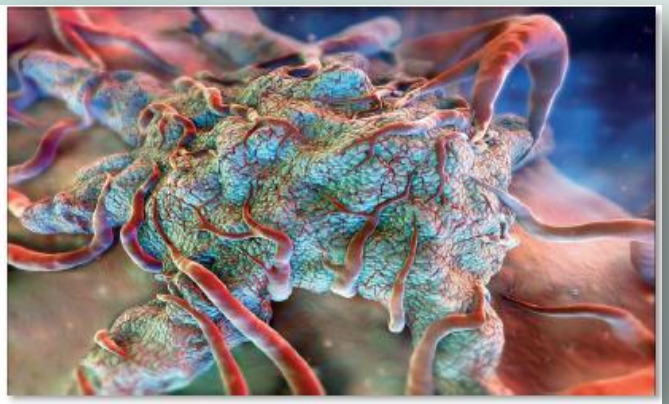


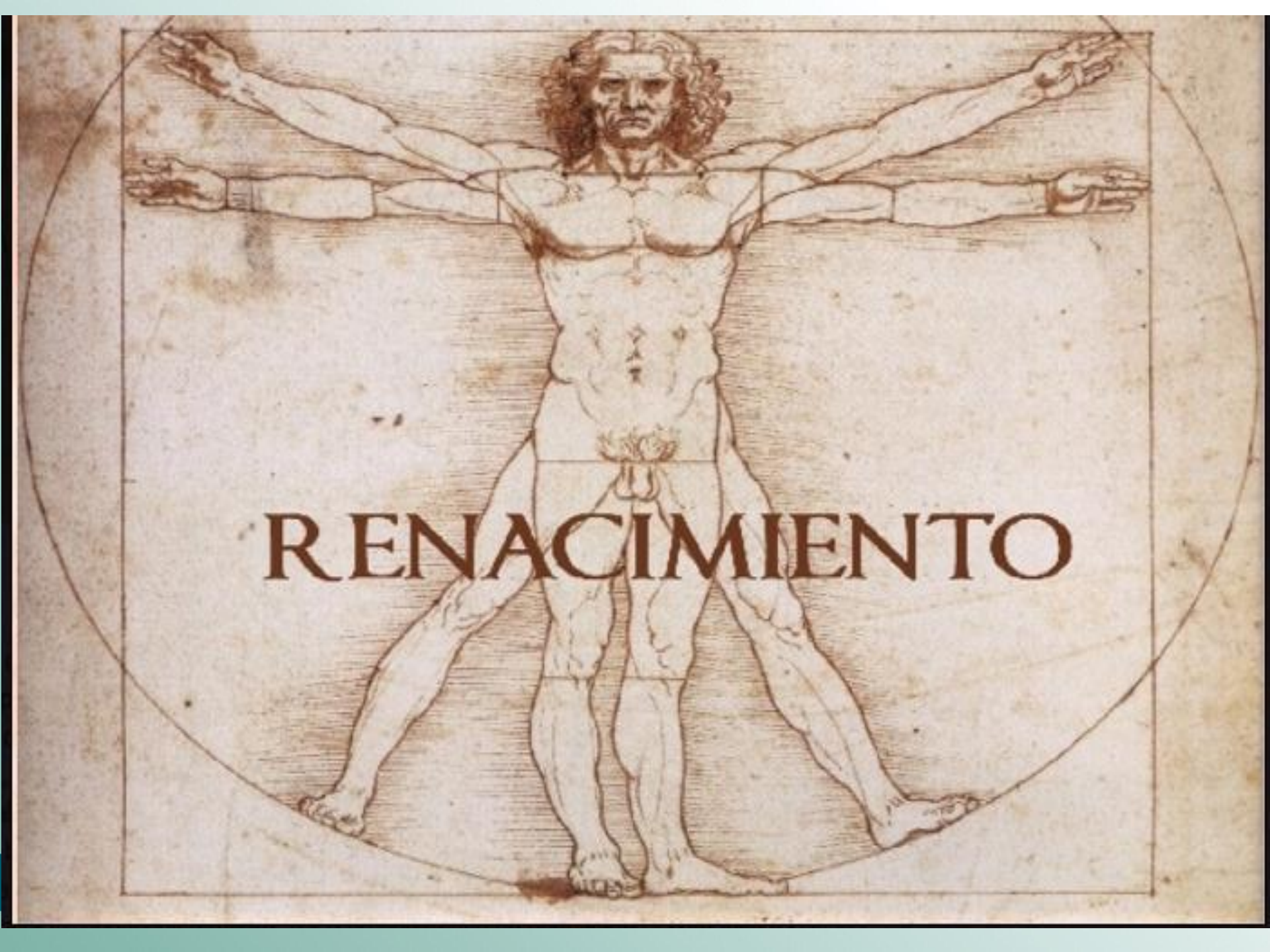
Source: IMS Health R&D Focus ™, clinicaltrials.gov, company websites Dec. 2014

2nd-LINE

ADVANCED NSCLC

- PEMETREXED
- DOCETAXEL
- ERLOTINIB
- NINTEDANIB + DOCETAXEL
- RAMUCIRUMAB + DOCETAXEL
- AFATINIB
- NIVOLUMAB, PEMBRO, ATEZO

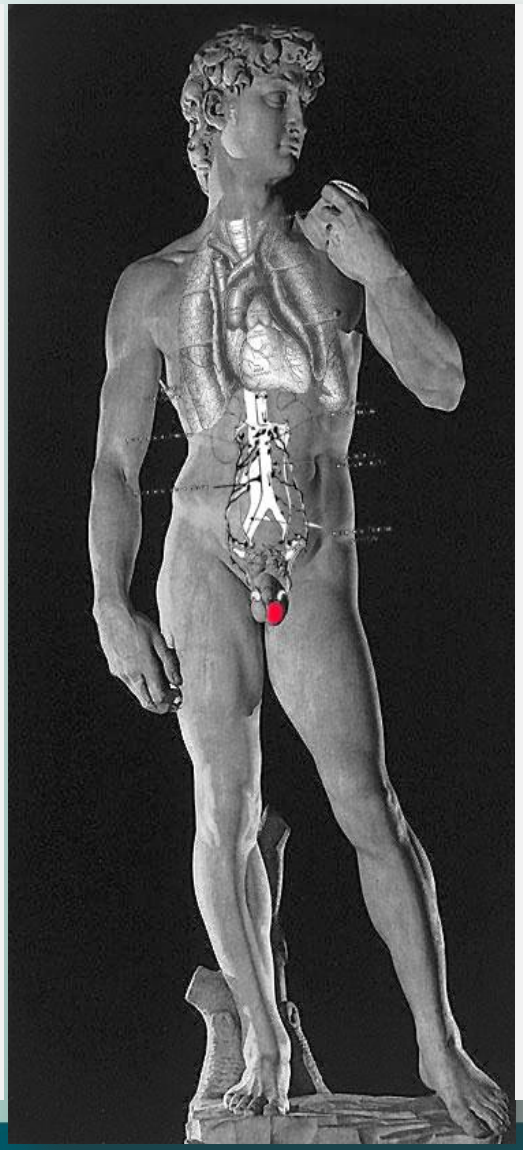



RENACIMIENTO

Lung cancer

TRADITIONAL ONCOLOGY VIEW

A CANCER THAT GROW

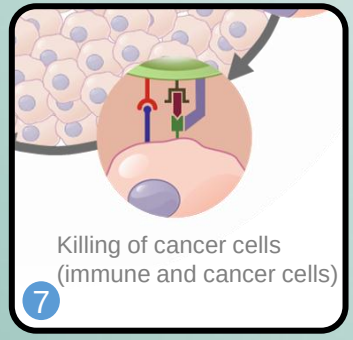


IMMUNO-ONCOLOGY VIEW

A BODY THAT LET A CANCER GROW

Inmune Checkpoint antibodies you need to remember…

TODAY…

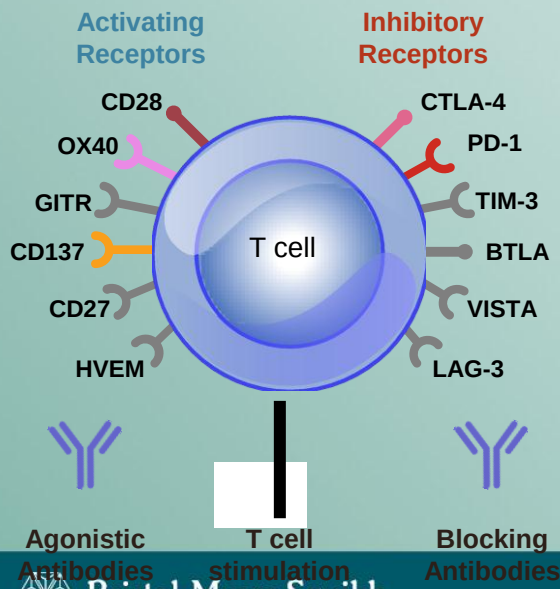


Anti-CTLA-4

CTLA-4 is a major negative regulator of T cell activation and inhibition of CTLA-4 can enhance T cell stimulation, resulting in more potent anti-tumour responses[1]

Ipilimumab
Tremelimumab

T cell targets for modulating activity



Anti-PDL1/PD1

PD-L1 expression on tumour cells and tumour-infiltrating immune cells can inhibit T cell activity via its receptor PD-1, dampening the anti-tumour immune response. Inhibition of PD-L1 or its receptor PD-1 may restore T cell effector function[2]

Atezolizumab (anti-PDL1)
Durvalumab (anti-PDL1)
Avelumab (anti-PDL1)
Nivolumab (anti-PD1)
Pembrolizumab (anti-PD1)

Bristol-Myers Squibb

Immuno-Oncology

CTLA-4 = cytotoxic T-lymphocyte-associated protein 4
PD-1 = programmed death 1; PD-L1 = programmed death ligand 1
Please note that atezolizumab has not received regulatory approval in any country yet

1. Mellman, et al. Nature 2011
2. Chen & Mellman. Immunity 2013

CheckMate 017 (NCT01642004) - Study Design

- Stage IIIb/IV SQ NSCLC
- 1 prior platinum doublet-based chemotherapy
- ECOG PS 0–1
- Pre-treatment (archival or fresh) tumor samples required for PD-L1 analysis

N = 272

Randomize 1:1

Nivolumab
3 mg/kg IV Q2W
until PD or
unacceptable toxicity
n = 135

Docetaxel
75 mg/m² IV Q3W
until PD or
unacceptable toxicity
n = 137

- **Primary Endpoint:**
  - OS
- **Additional Endpoints:**
  - Investigator-assessed ORR
  - Investigator-assessed PFS
  - Correlation between PD-L1 expression and efficacy
  - Safety
  - Quality of life (LCSS)

Patients stratified by region and prior paclitaxel use

CheckMate 057 (NCT01673867) Study Design

- Stage IIIB/IV non-SQ NSCLC
- Pre-treatment (archival or recent) tumor samples required for PD-L1
- ECOG PS 0–1
- Failed 1 prior platinum doublet
- Prior maintenance therapy allowed[a]
- Prior TKI therapy allowed for known *ALK* translocation or *EGFR* mutation

N = 582

Randomize 1:1

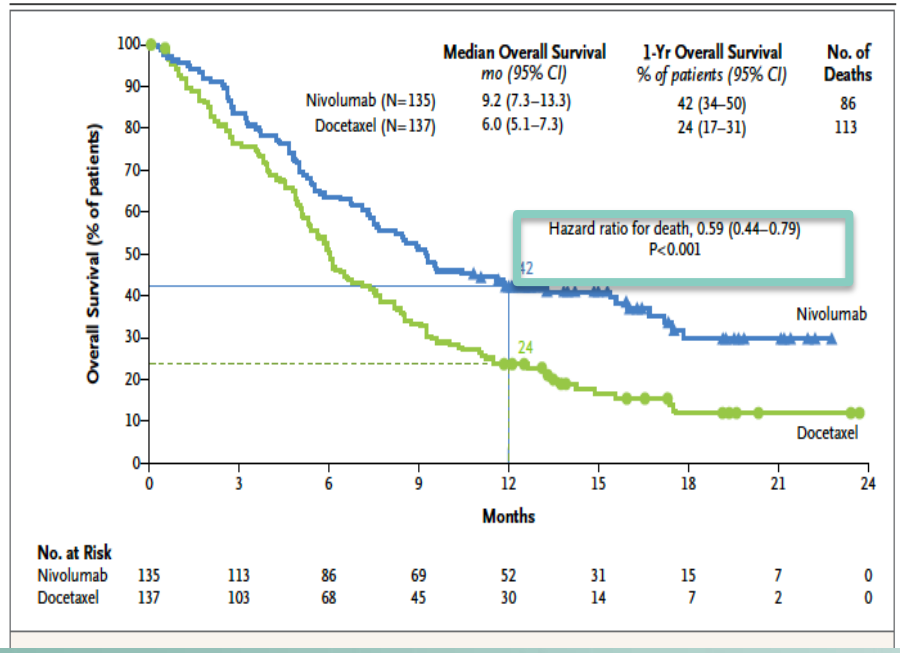
Nivolumab
3 mg/kg IV Q2W
until PD or
unacceptable toxicity
n = 292

Docetaxel
75 mg/m² IV Q3W
until PD or
unacceptable toxicity
n = 290

- **Primary Endpoint**
  - OS
- **Additional Endpoints**
  - ORR[b]
  - PFS[b]
  - Safety
  - Efficacy by tumor PD-L1 expression
  - Quality of life (LCSS)

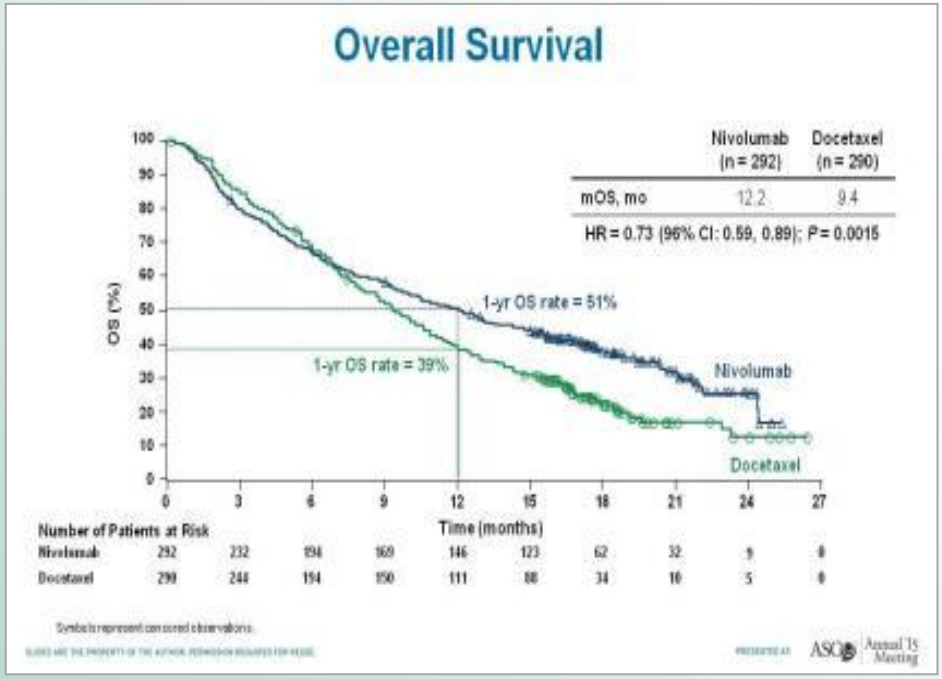
Patients stratified by prior maintenance therapy and line of therapy (second- vs third-line)

CheckMate 017



Brahmer J et al. N Engl J Med 2015

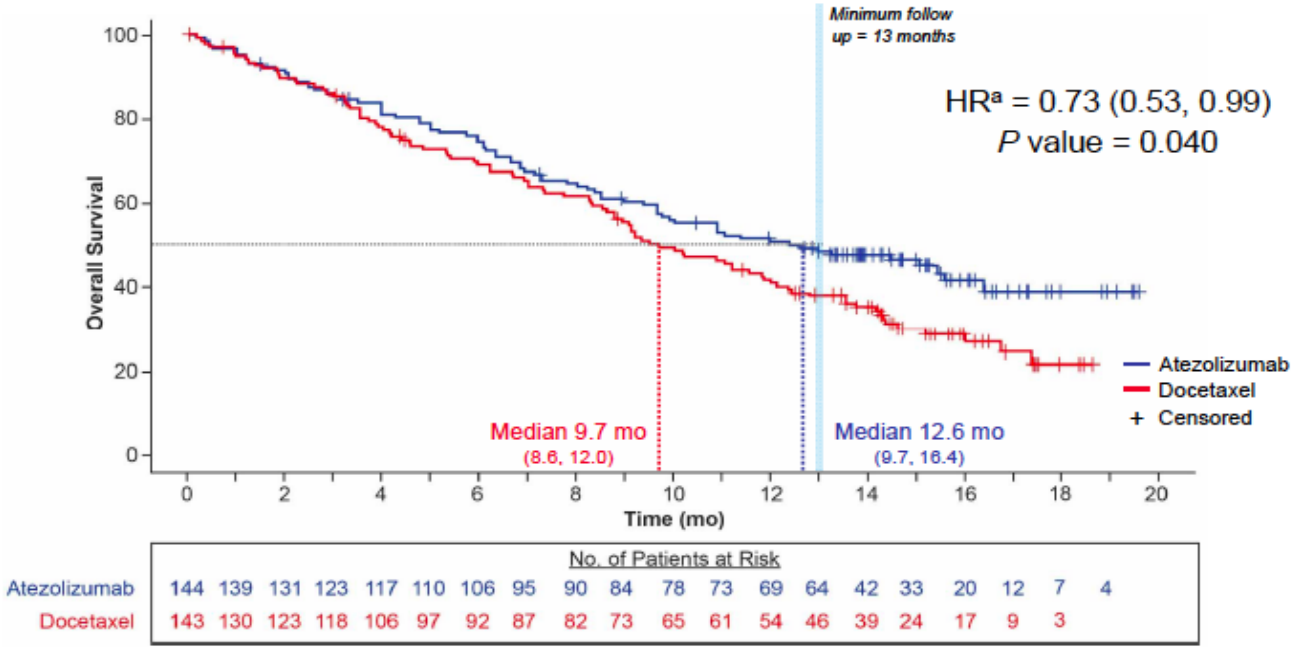
CheckMate 057



Borghaei H, et al. N Engl J Med 2015

ATEZOLIZUMAB

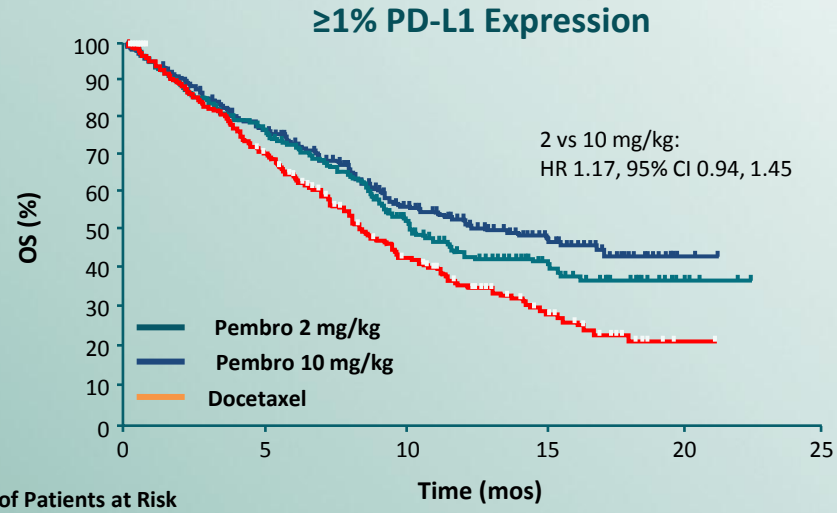
POPLAR: All Patient Efficacy
ITT OS (N = 287)



- **Event/patient ratio: 60%** (54% for atezolizumab, 66% for docetaxel)

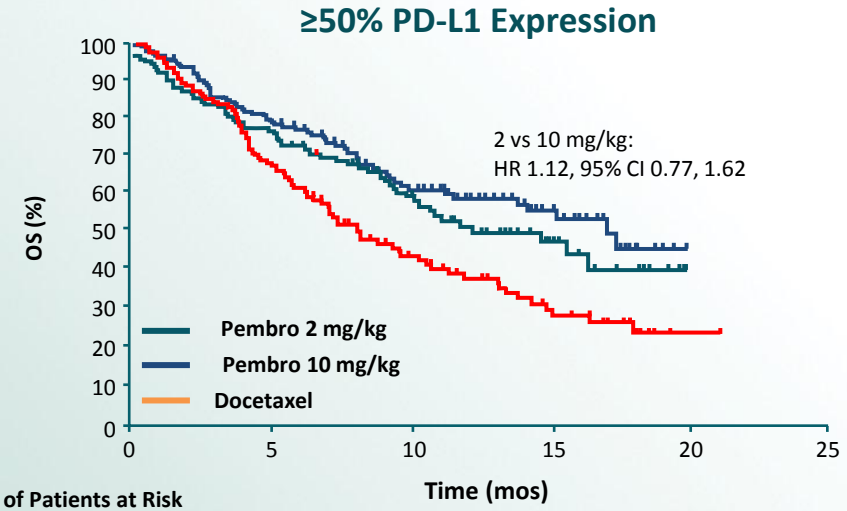
Fehrenbacher L et al. Lancet Oncol 2016

KEYNOTE-010: pembrolizumab
Overall Survival at TPS ≥1% and TPS ≥50%



Number of Patients at Risk						
2 mg/kg	344	259	115	49	12	0
10 mg/kg	346	255	124	56	6	0
Docetaxel	343	212	79	33	1	0

Treatment Arm	Median (95% CI), mo	Rate at 1-yr	HR[a] (95% CI)	*P* value
Pembro 2 mg/kg	10.4 (9.4, 11.9)	43.2%	0.71 (0.58, 0.88)	0.0008
Pembro 10 mg/kg	12.7 (10.0, 17.3)	52.3%	0.61 (0.49, 0.75)	<0.0001
Docetaxel	8.5 (7.5-9.8)	34.6%	–	–



Number of Patients at Risk						
2 mg/kg	139	110	51	20	3	0
10 mg/kg	151	115	60	25	1	0
Docetaxel	152	90	38	19	1	0

Treatment Arm	Median (95% CI), mo	HR[a] (95% CI)	*P* value
Pembro 2 mg/kg	14.9 (10.4, NR)	0.54 (0.38, 0.77)	0.0002
Pembro 10 mg/kg	17.3 (11.8, NR)	0.50 (0.36, 0.70)	<0.0001
Docetaxel	8.2 (6.4, 10.7)		–

[a]Comparison of pembrolizumab vs docetaxel. Analysis cut-off date: September 30, 2015.
HR = hazard ratio; mos = months; NR = not reached; OS = overall survival; PD-L1 = programmed death ligand 1; Pembro = pembrolizumab; TPS = tumor proportion score.
Herbst RS et al. Oral presentation at ESMO Asia 2015.

PHASE III STUDY SHOWED GENENTECH'S CANCER IMMUNOTHERAPY TECENTRIQ™ (ATEZOLIZUMAB) HELPED PEOPLE WITH A SPECIFIC TYPE OF LUNG CANCER LIVE SIGNIFICANTLY LONGER COMPARED TO CHEMOTHERAPY

– TECENTRIQ showed significant improvement in overall survival for people regardless of their PD-L1 status –

– Data will be discussed with global health authorities, including the U.S. Food and Drug Administration (FDA) –

SOUTH SAN FRANCISCO, Calif. – August 31, 2016 – Genentech, a member of the Roche Group (SIX: RO, ROG; OTCQX: RHHBY), today announced positive results for TECENTRIQ from the Phase III study, OAK. The study met its co-primary endpoints and showed a statistically significant and clinically meaningful improvement in overall survival (OS) compared with docetaxel chemotherapy in people with locally advanced or metastatic non-small cell lung cancer (NSCLC) whose disease progressed on or after treatment with platinum-based chemotherapy. Adverse events

Time's up! Conclusions

1. Is Nivolumab the new standard of care for previously treated non-squamous NSCLC?

YES!

- This is a positive randomized Phase III trial with the primary endpoint for all comers. This trial sets a new standard for the treatment of previously treated disease
- There is a particularly long benefit in a select population of patients- even in the absence of clearly defined response
- Nivolumab is significantly less toxic than Docetaxel

PRESENTED AT: ASCO Annual '15 Meeting

If we talk about IO, check your enthusiasm

ONE SIZE DOES NOT FIT ALL

PATIENT SELECTION

Efforts to identify determinants of response

- **PD-L1 Expression** (Tumor or Infiltrating immune cells)[1-5]
- CD8+ Tumor Infiltrating Lymphocytes (**TILs**)[6]
- **Smoking Status**[1-3]
- **Mutation/Neoantigen Burden**[7]

[1]Garon EB, et al. *N Engl J Med.* 2015 [Epub ahead of print]; [2]Herbst RS, et al. *Nature.* 2014;575(7528):563-7; [3]Gettinger SN, et al. *J Clin Oncol.* 2015 Apr 20. pii: JCO.2014.58.3708; [4]Brahmer JR, et al. J Clin Oncol. 32:5s, 2014 (suppl; abstr 8021); [5]Brahmer JR, et al. *N Engl J Med.* 2012;366(26):2455-65; [6]Tumeh PC, et al. *Nature.* 2014;515(7528):568-571.; [7]Rizvi N, et al. *Science.* 2015 Apr 3;348(6230):124-8.

Randomized trials In NSCLC. Main activity data in 2nd line setting

	Doc+Ramucirumab vs Doc *Revel Phase III*	*Doc+Nintedanib vs Doc LumeLung 1 Phase III*	*Afatinib vs Erlotinib Lux-LUNG 8 Phase III*	Nivolumab vs Docetaxel *CheckMate 017 Phase III*	*Nivolumab vs Docetaxel CheckMate 057 Phase III*	*Pembrolizumb vs Docetaxel KeyNote 010 Phase III*	Atezolizumab vs Docetaxel *Poplar Phase II*
ORR	23 vs 14%	4.7% vs 3.6%	5.5% vs 2.8%	20% vs 9%	19% vs 12%	18% vs 18%	15% vs 15%
PFS m	4.5 vs 3	4 vs 2.8	2.6 vs 1.9	3.5 vs 2.8	2.3 vs 4.2	3.9 vs 4 vs 4	2.7 vs 3
OS m	10.4 vs 9.1 9.5 vs 8.2 (SCC)	12.6 vs 10.3 (Non-SCC)	7.9 vs 6.8	9.2 vs 6	12.2 vs 9.4m	10.4-12.7 vs 8.5	12.7 vs 9.7 10.1 vs 8.6 (SCC)
HR OS	0-86 0.883 (SCC)	0.83	0.81	0.59	0.73	0.71-0.61	0.73
HR PDL1-	NA	NA	NA	0.70	0.87	NA	1.09
HR PDL1+	NA	NA	NA	0.50	0.40	0.54-0.50	0.49

Garon GB et al. *Lancet.* 2014. / Soria JC et al. Lancet Oncol 2015 / Bramer J et al. *NEJM.* 2015. / Vansteenkiste J, et al. ECC 2015. / Herbst R. Lancet Oncol 2015

Cross-study comparison is not intended

However… PD-L1 expression is not the perfect biomarker…

- Heterogeneity of expression
- Differences in PD-L1 assays
- Lack of a gold standard for PD-L1 positivity

CHANGING THE STATE OF THE ART…

What about IO in 1st line setting?
Raising the bar

VOLUME 34 · NUMBER 25 · SEPTEMBER 1, 2016

JOURNAL OF CLINICAL ONCOLOGY

EDITORIAL

Moving Programmed Death-1 Inhibitors to the Front Lines in Non–Small-Cell Lung Cancer

MERCK

News Release

Media Contacts: Pamela Eisele (267) 305-3558; Courtney Ronaldo (908) 236-1108

Investor Contacts: Teri Loxam (908) 740-1986; Justin Holko (908) 740-1879

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

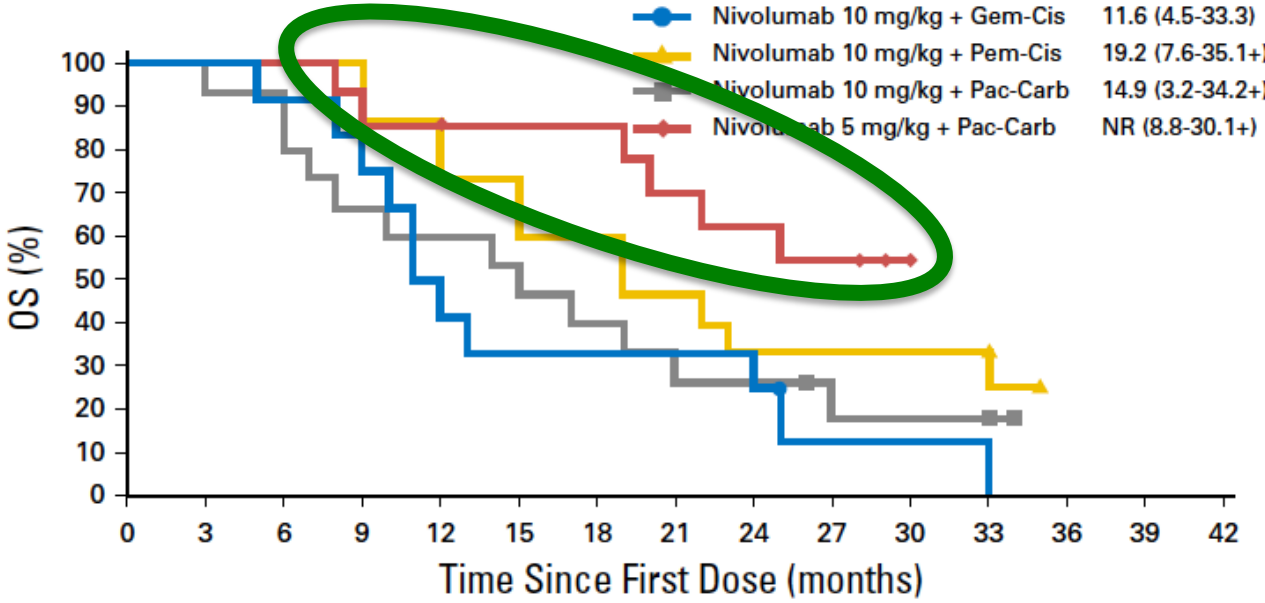
Bristol-Myers Squibb

Bristol-Myers Squibb Announces Top-Line Results from CheckMate -026, a Phase 3 Study of Opdivo (nivolumab) in Treatment-Naïve Patients with Advanced Non-Small Cell Lung Cancer

08/05/2016

Opdivo *did not meet trial primary endpoint of progression-free survival in patients expressing PD-L1 = 5%*

Should we combine IO+CT?



Group	Median OS, months (range)	1-Year OS, % (95% CI)	2-Year OS, % (95% CI)
Nivolumab 10 mg/kg + Gem-Cis	11.6 (4.5-33.3)	50 (21 to 74)	25 (6 to 50)
Nivolumab 10 mg/kg + Pem-Cis	19.2 (7.6-35.1+)	87 (56 to 96)	33 (12 to 56)
Nivolumab 10 mg/kg + Pac-Carb	14.9 (3.2-34.2+)	60 (32 to 80)	27 (8 to 50)
Nivolumab 5 mg/kg + Pac-Carb	NR (8.8-30.1+)	86 (54 to 96)	62 (32 to 82)

No. at risk															
Nivolumab 10 mg/kg + Gem-Cis	12	12	11	9	6	4	4	4	3	1	1	1	0	0	0
Nivolumab 10 mg/kg + Pem-Cis	15	15	15	14	13	10	9	7	5	5	5	4	0	0	0
Nivolumab 10 mg/kg + Pac-Carb	15	15	14	10	9	7	6	4	4	3	2	1	0	0	0
Nivolumab 5 mg/kg + Pac-Carb	14	14	14	13	12	11	11	9	8	7	1	0	0	0	0

Rizvi N, et al. J Clin Oncol 2016

Should we combine AntiCTL4 plus anti PD-1/PD-L1? CHECKMATE 012

Nivolumab Plus Ipilimumab in First-line NSCLC: Summary of Efficacy

	Nivo 3 Q2W + Ipi 1 Q12W (n = 38)	Nivo 3 Q2W + Ipi 1 Q6W (n = 39)	Nivo 3 Q2W (n = 52)
Confirmed ORR, % (95% CI)	47 (31, 64)	39 (23, 55)	23 (13, 37)
Median duration of response, mo (95% CI)	NR (11.3, NR)	NR (8.4, NR)	NR (5.7, NR)
Median length of follow-up, mo (range)	12.9 (0.9–18.0)	11.8 (1.1–18.2)	14.3 (0.2–30.1)
Best overall response, %			
Complete response	0	0	8
Partial response	47	39	15
Stable disease	32	18	27
Progressive disease	13	28	38
Unable to determine	8	15	12
Median PFS, mo (95% CI)	8.1 (5.6, 13.6)	3.9 (2.6, 13.2)	3.6 (2.3, 6.6)
1-year OS rate, % (95% CI)	NC	69 (52, 81)	73 (59, 83)

NC = not calculated (when >25% of patients are censored); NR = not reached

Combination data based on a February 2016 database lock; monotherapy data based on a March 2015 database lock except for OS data, which are based on an August 2015 database lock

8

- **TOXICITY…gr 3-4: 34-37% combo vs 10% nivo monotherapy**
- **COST….**

EFFICACY WITH NIVO PLUS IPI IS ENHANCED WITH INCREASING PDL-1 EXPRESSION

Nivolumab Plus Ipilimumab in First-line NSCLC: Efficacy by Tumor PD-L1 Expression

	Nivo 3 Q2W + Ipi 1 Q12W	Nivo 3 Q2W + Ipi 1 Q6W	Nivo 3 Q2W
ORR, % (n/N)			
<1% PD-L1	30 (3/10)	0 (0/7)	14 (2/14)
≥1% PD-L1	57 (12/21)	57 (13/23)	28 (9/32)
≥50% PD-L1	100 (6/6)	86 (6/7)	50 (6/12)
Median PFS (95% CI), mo			
<1% PD-L1	4.7 (0.9, NR)	2.4 (1.7, 2.9)	6.6 (2.0, 11.2)
≥1% PD-L1	8.1 (5.6, NR)	10.6 (3.6, NR)	3.5 (2.2, 6.6)
≥50% PD-L1	13.6 (6.4, NR)	NR (7.8, NR)	8.4 (2.2, NR)
1-year OS rate (95% CI), %			
<1% PD-L1	NC	NC	79 (47, 93)
≥1% PD-L1	90 (66, 97)	83 (60, 93)	69 (50, 82)
≥50% PD-L1	NC	100 (100, 100)	83 (48, 96)

NC = not calculated (when >25% of patients are censored); NR = not reached due to high percentage of ongoing response

Combination data based on a February 2016 database lock; monotherapy data based on a March 2015 database lock except for OS data, which are based on an August 2015 database lock

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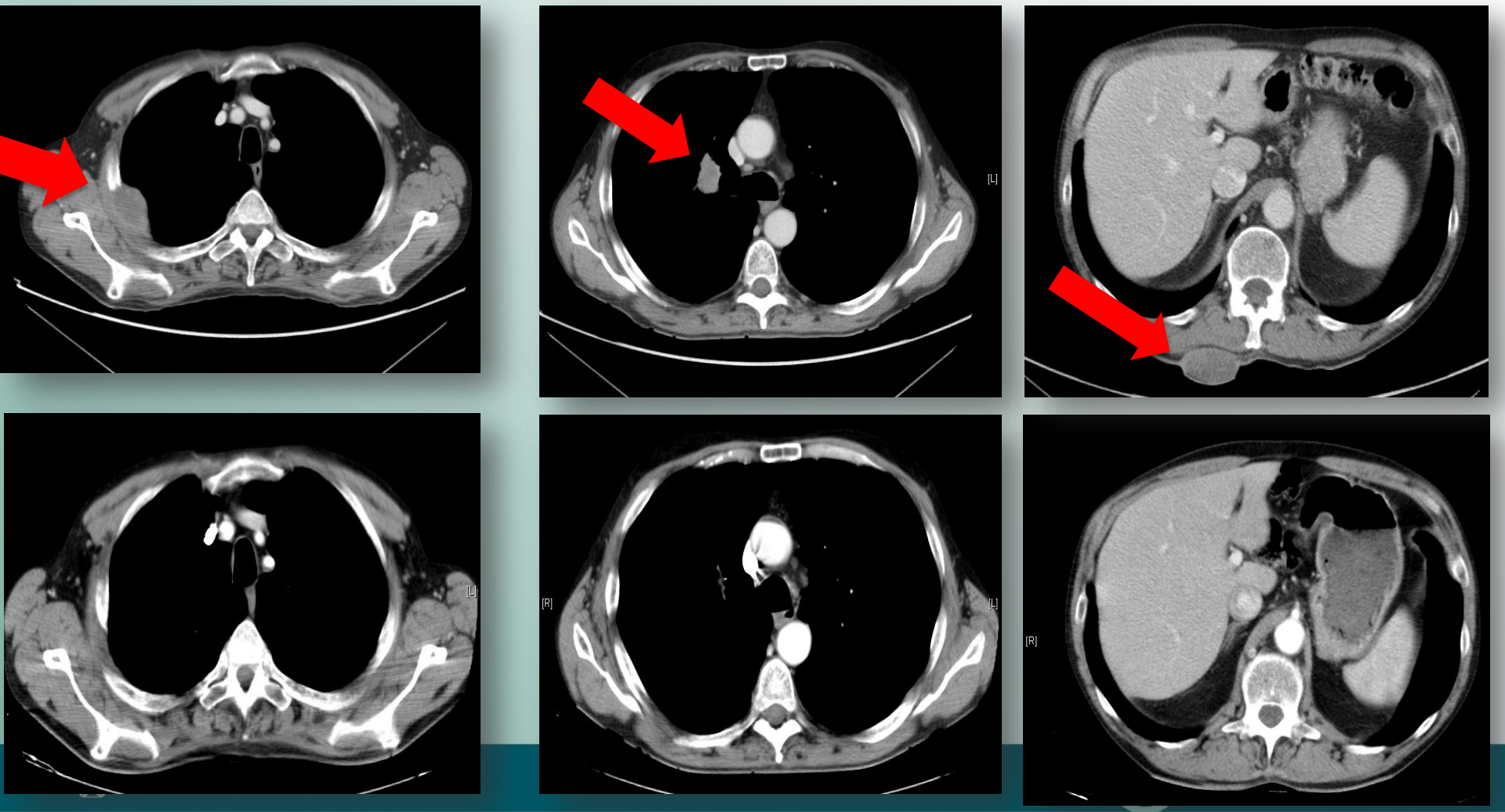
Hellmann et al. ASCO 2016

THE QUESTION OF DURATION OF TREATMENT….

Almost CR after 2 cycles of anti PD-1 therapy... common pattern or response

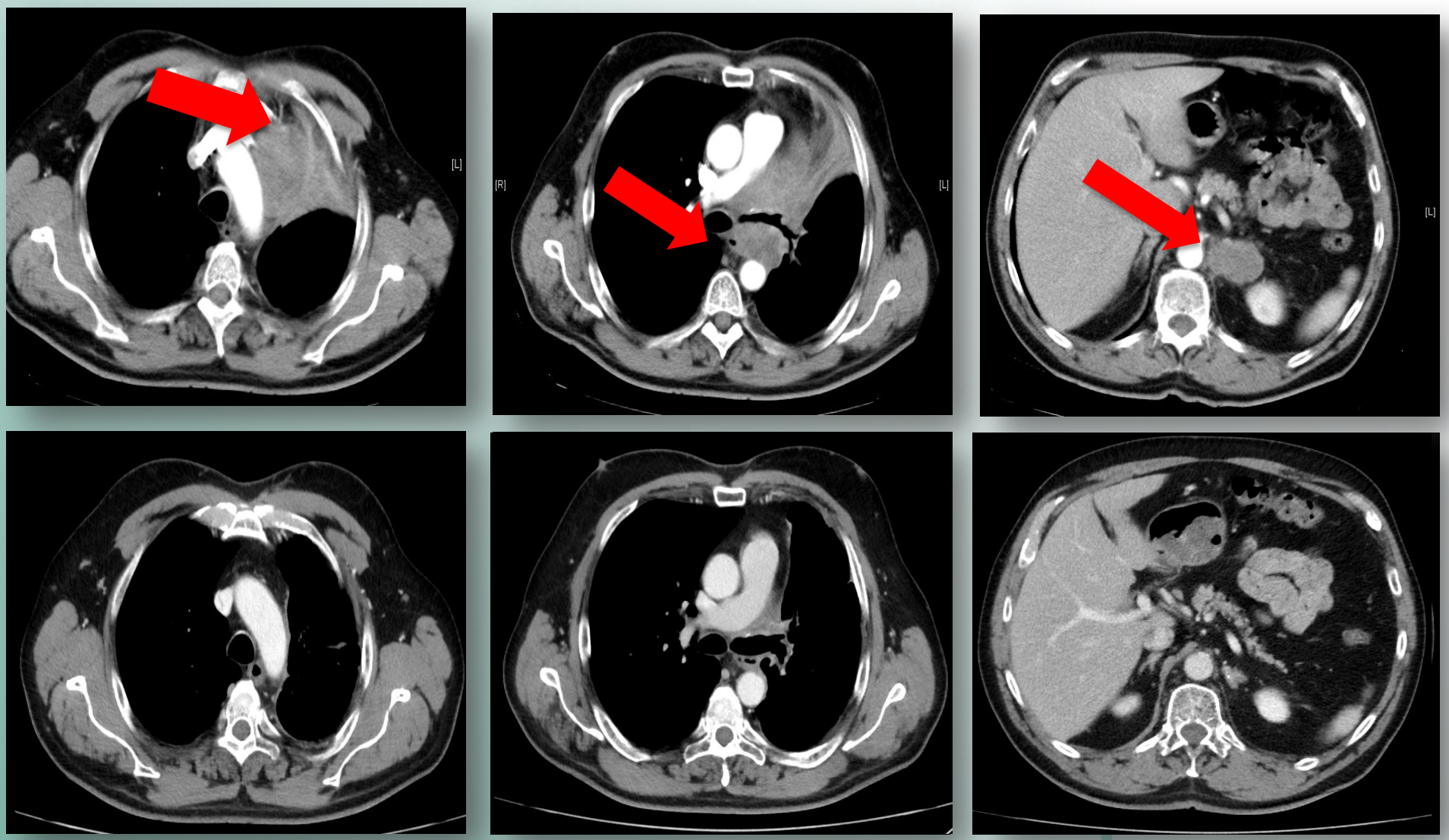


EXCELLENT RESPONSE, QOL AND TOLERABILITY AFTER 2 YEARS…

Which of the following options would you consider?

1. **Continue I-O**
2. **D/C I-O and retreat at progression**
3. **Extend frequency of I-O administration**
4. **Other**

PR after 24 minutes of anti PD-1 infusion….Still PR after 15 months without any treatment…



Some take home messages

IO, THE CHALLENGE

- **IO WORKS…AND IT WORKS REALLY WELL**
- **Patient selection for therapy: IT´S AN URGENT ISSUE**
- **Toxicity management:**
  - Physician education
  - Patient education
  - Early recognition and consideration
- **Economical toxicity…**

Los que se enamoran de la práctica sin la teoría son como los pilotos sin timón ni brújula, que nunca podrán saber a dónde van.

Leonardo Da Vinci,1452-1519.
Pintor, escultor e inventor italiano.

- **PREGUNTA 1: ¿cuántos de los que estáis hoy presentes sois escépticos con respecto al valor del tratamiento con inmunoterapia en cáncer de pulmón?**

- **PREGUNTA 2: ¿Qué opción terapéutica consideraría más apropiada para un paciente diagnosticado de CNMP estadio IV, histología escamosa, ECOG 1 en progresión a un doblete de platino:**
  - Docetaxel
  - Docetaxel+Ramucirumab
  - IO
  - Mejor tratamiento de soporte

- **PREGUNTA 3: ¿tenemos suficiente evidencia para recomendar el uso de inmunoterapia en función de los biomarcadores disponibles?**