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28ο ΠΑΝΕΛΛΗΝΙΟ Πνευμονολογικό ΣΥΝΕΔΡΙΟ
12-15 ΔΕΚΕΜΒΡΙΟΥ 2019 | ATHENS HILTON
ΕΛΛΗΝΙΚΗ ΠΝΕΥΜΟΝΟΛΟΓΙΚΗ ΕΤΑΙΡΕΙΑ
HELLENIC THORACIC SOCIETY

Πρόοδος νόσου υπό Ανοσοθεραπεία: Και μετά τι;

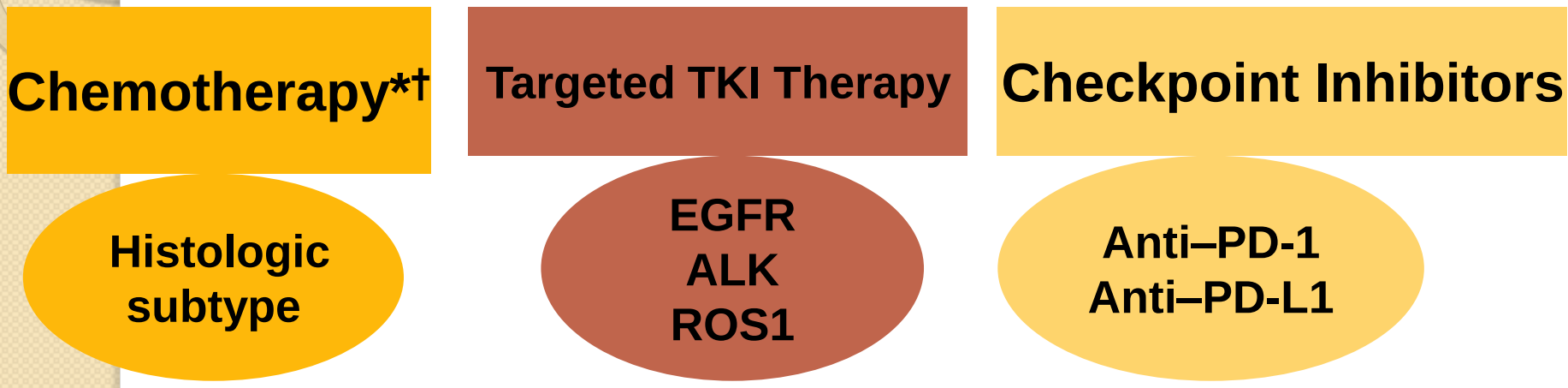
Αγγελική Ράπτη

Συντ. Διευθύντρια

2η Πνευμονολογική Κλινική ΝΝΘΑ

aggeliki.rapti@gmail.com

Personalized Therapy in Advanced-Stage NSCLC: Current Therapeutic Landscape



1970s - today 2000s - today 2015 - today

*± EGFR/VEGF mAbs from 2000s - today.
†± PD-1 mAb from May 2017.

SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE[a,b]
INITIAL SYSTEMIC THERAPY OPTIONS

Adenocarcinoma, Large Cell, NSCLC NOS (PS 0–1)

No contraindications to the addition of pembrolizumab or atezolizumab[c]

Preferred
- **Pembrolizumab/carboplatin/pemetrexed (category 1)[1,2,d]**
- **Pembrolizumab/cisplatin/pemetrexed (category 1)[2,d]**

Other Recommended
- **Atezolizumab/carboplatin/paclitaxel/bevacizumab[e] (category 1)[3,d,f,g,h]**

Useful in Certain Circumstances

Contraindications to the addition of pembrolizumab or atezolizumab[c]
- **Bevacizumab[e]/carboplatin/paclitaxel (category 1)[4,f,g,h]**
- **Bevacizumab[e]/carboplatin/pemetrexed[4,5,f,g,h]**
- **Bevacizumab[e]/cisplatin/pemetrexed[6,f,g,h]**
- **Carboplatin/albumin-bound paclitaxel (category 1)[7]**
- **Carboplatin/docetaxel (category 1)[8]**
- **Carboplatin/etoposide (category 1)[9,10]**
- **Carboplatin/gemcitabine (category 1)[11]**
- **Carboplatin/paclitaxel (category 1)[12]**
- **Carboplatin/pemetrexed (category 1)[13]**
- **Cisplatin/docetaxel (category 1)[8]**
- **Cisplatin/etoposide (category 1)[14]**
- **Cisplatin/gemcitabine (category 1)[12,15]**
- **Cisplatin/paclitaxel (category 1)[16]**
- **Cisplatin/pemetrexed (category 1)[15]**
- **Gemcitabine/docetaxel (category 1)[17]**
- **Gemcitabine/vinorelbine (category 1)[18]**

Adenocarcinoma, Large Cell, NSCLC NOS (PS 2)

Preferred
- **Carboplatin/pemetrexed[13]**

Other Recommended
- **Carboplatin/albumin-bound paclitaxel[20,21]**
- **Carboplatin/docetaxel[8]**
- **Carboplatin/etoposide[9,10]**
- **Carboplatin/gemcitabine[11]**
- **Carboplatin/paclitaxel[12]**

Useful in Certain Circumstances
- **Albumin-bound paclitaxel[19]**
- **Docetaxel[22,23]**
- **Gemcitabine[24-26]**
- **Gemcitabine/docetaxel[17]**
- **Gemcitabine/vinorelbine[18]**
- **Paclitaxel[27-29]**
- **Pemetrexed[30]**

[a] Albumin-bound paclitaxel may be substituted for either paclitaxel or docetaxel in patients who have experienced hypersensitivity reactions after receiving paclitaxel or docetaxel despite premedication, or for patients where the standard premedications (ie, dexamethasone, H2 blockers, H1 blockers) are contraindicated.
[b] Carboplatin-based regimens are often used for patients with comorbidities or those who cannot tolerate cisplatin.
[c] Contraindications for treatment with PD-1/PD-L1 inhibitors may include active or previously documented autoimmune disease and/or current use of immunosuppressive agents or presence of an oncogene, which would predict lack of benefit.
[d] If progression on PD-1/PD-L1 inhibitor, switching to another PD-1/PD-L1 inhibitor is not recommended.
[e] An FDA-approved biosimilar is an appropriate substitute for bevacizumab.
[f] Bevacizumab should be given until progression.
[g] Any regimen with a high risk of thrombocytopenia and the potential risk of bleeding should be used with caution in combination with bevacizumab.
[h] Criteria for treatment with bevacizumab: non-squamous NSCLC, and no recent history of hemoptysis. Bevacizumab should not be given as a single agent, unless as maintenance if initially used with chemotherapy.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE[a,b,i]
INITIAL SYSTEMIC THERAPY OPTIONS

Squamous Cell Carcinoma (PS 0–1)

No contraindications to the addition of pembrolizumab[c]

Preferred
- Pembrolizumab/carboplatin/paclitaxel[31,d] (category 1)
- Pembrolizumab/carboplatin/albumin-bound paclitaxel[31,d] (category 1)

Useful in Certain Circumstances

Contraindications to the addition of pembrolizumab[c]
- Carboplatin/albumin-bound paclitaxel (category 1)[7]
- Carboplatin/docetaxel (category 1)[8]
- Carboplatin/gemcitabine (category 1)[11]
- Carboplatin/paclitaxel (category 1)[12]
- Cisplatin/docetaxel (category 1)[8]
- Cisplatin/etoposide (category 1)[14]
- Cisplatin/gemcitabine (category 1)[12,15]
- Cisplatin/paclitaxel (category 1)[16]
- Gemcitabine/docetaxel (category 1)[17]
- Gemcitabine/vinorelbine (category 1)[18]

Squamous Cell Carcinoma (PS 2)

Preferred
- Carboplatin/albumin-bound paclitaxel[20,21]
- Carboplatin/gemcitabine[11]
- Carboplatin/paclitaxel[12]

Other Recommended
- Carboplatin/docetaxel[8]
- Carboplatin/etoposide[9,10]

Useful in Certain Circumstances
- Albumin-bound paclitaxel[19]
- Docetaxel[22,23]
- Gemcitabine[24-26]
- Gemcitabine/docetaxel[17]
- Gemcitabine/vinorelbine[18]
- Paclitaxel[27-29]

[a] Albumin-bound paclitaxel may be substituted for either paclitaxel or docetaxel in patients who have experienced hypersensitivity reactions after receiving paclitaxel or docetaxel despite premedication, or for patients where the standard premedications (ie, dexamethasone, H2 blockers, H1 blockers) are contraindicated.
[b] Carboplatin-based regimens are often used for patients with comorbidities or those who cannot tolerate cisplatin.
[c] Contraindications for treatment with PD-1/PD-L1 inhibitors may include active or previously documented autoimmune disease and/or current use of immunosuppressive agents or presence of an oncogene, which would predict lack of benefit.
[d] If progression on PD-1/PD-L1 inhibitor, switching to another PD-1/PD-L1 inhibitor is not recommended.
[i] Cisplatin/gemcitabine/necitumumab in the first-line setting and afatinib in the second-line setting are not used at NCCN Member Institutions for these indications related to the efficacy and safety of these agents compared to the efficacy and safety of other available agents.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

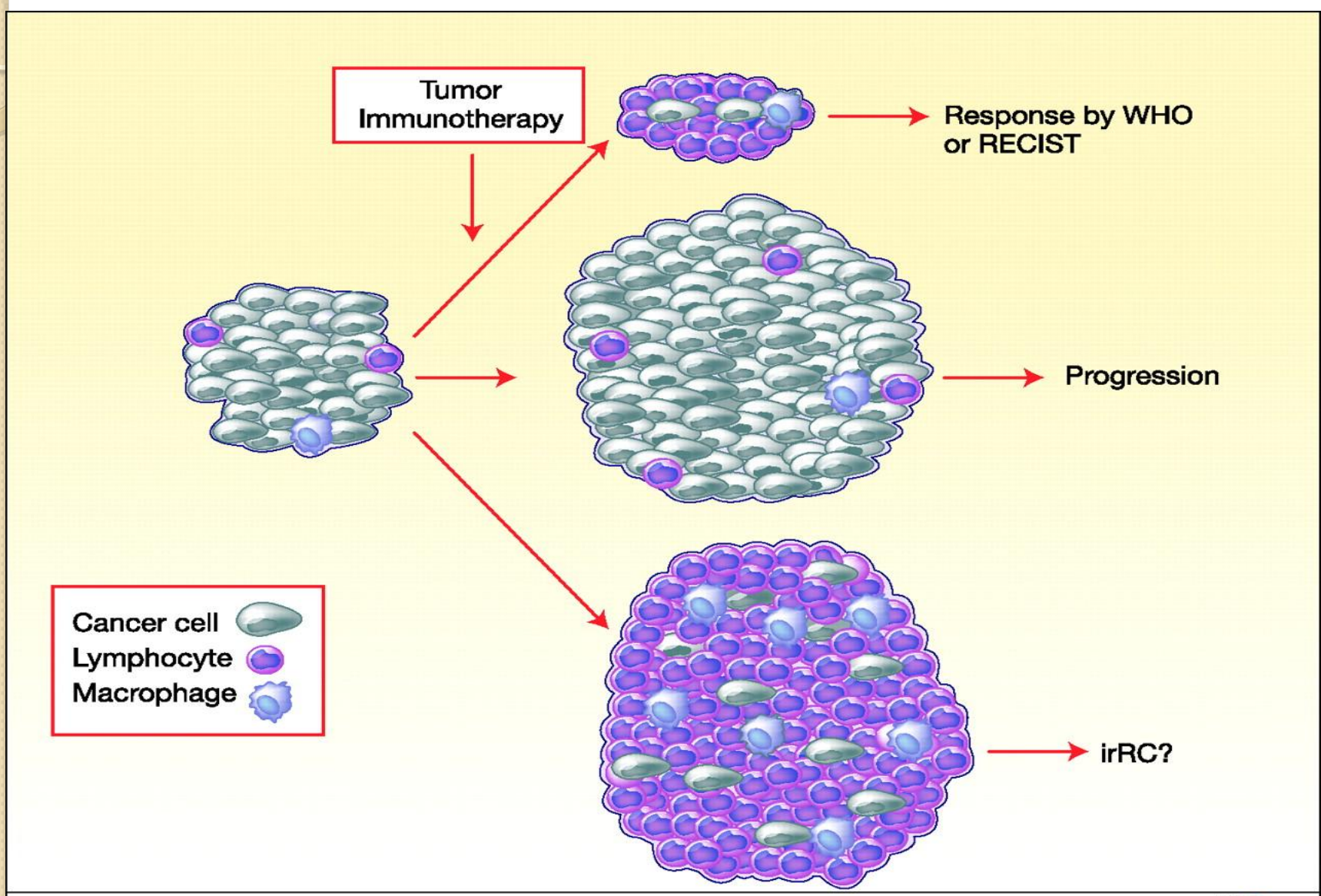
Immune-Related Response Criteria

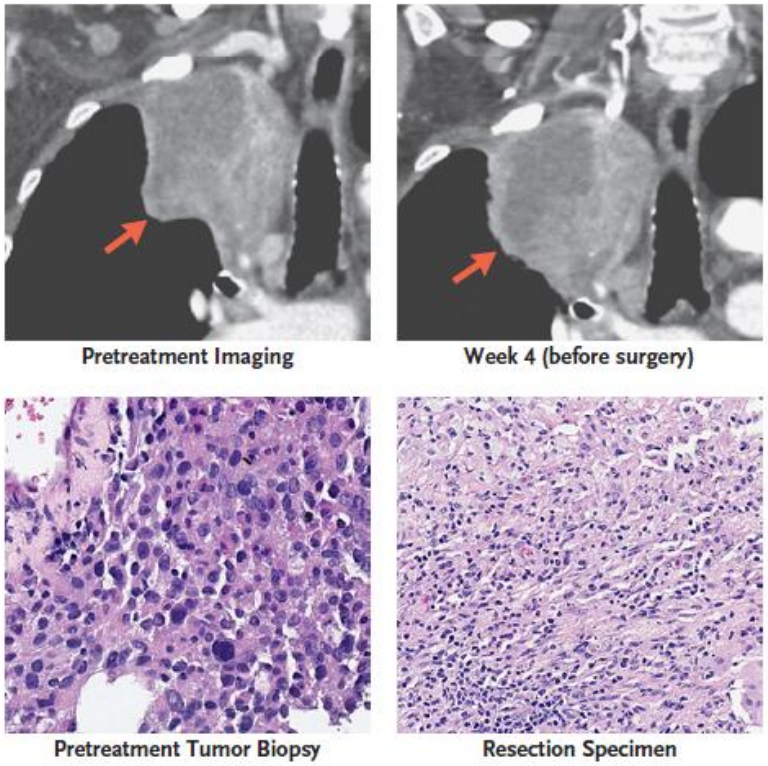
New, measurable lesions (≥ 5 × 5 mm)	Incorporated into tumor burden
New, nonmeasurable lesions (<5 × 5 mm)	Do not define progression (but preclude irCR)
Non-index lesions	Contribute to defining irCR (complete disappearance required)
CR	Disappearance of all lesions in 2 consecutive observations not less than 4 weeks apart
PR	≥ 50% decrease in tumor burden compared with baseline in 2 observations at least 4 weeks apart
SD	Neither a 50% decrease in tumor burden compared with baseline nor a 25% increase compared with nadir can be established
PD	At least 25% increase in tumor burden compared with nadir (at any single time point) in 2 consecutive observations at least 4 weeks apart

irCR = immune-related response criteria; CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease

Hoos A, et al. *J Natl Cancer Inst*. 2010;102:1388-1397[7]; Wolchok JD, et al. *Clin Cancer Res*. 2009;15:7412-7420.[8]

pseudoprogression

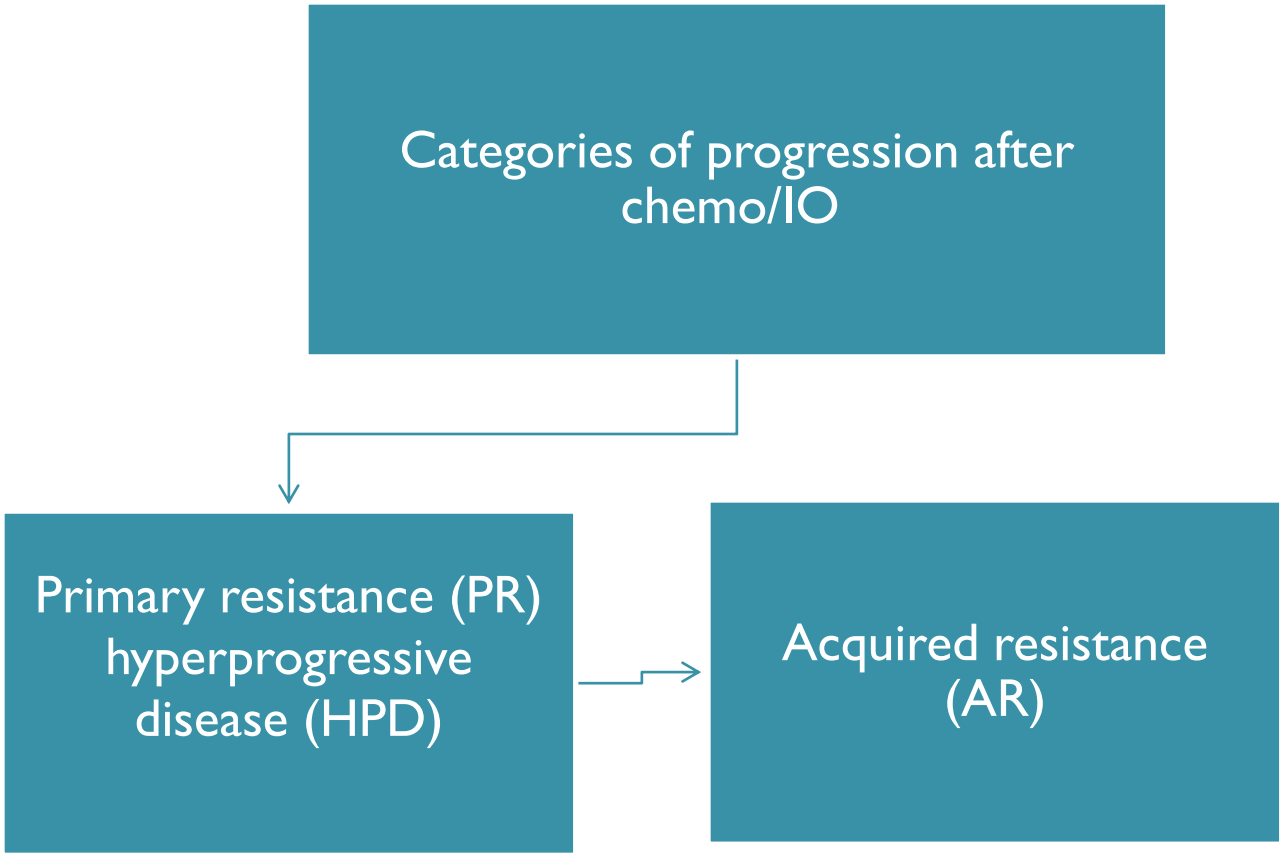




Chest-CT of a 78-year-old female former smoker with stage IIIA lung adeno-ca who received two doses of nivolumab preoperatively

in the post-treatment specimen

there was 90% tumor regression


Categories of progression after chemo/IO
Primary resistance (PR) hyperprogressive disease (HPD)
Acquired resistance (AR)

Primary resistance
Hyperprogressive disease

- disease progression in the first image evaluation

  after treatment initiation

- overexpression of alternative immune checkpoints,

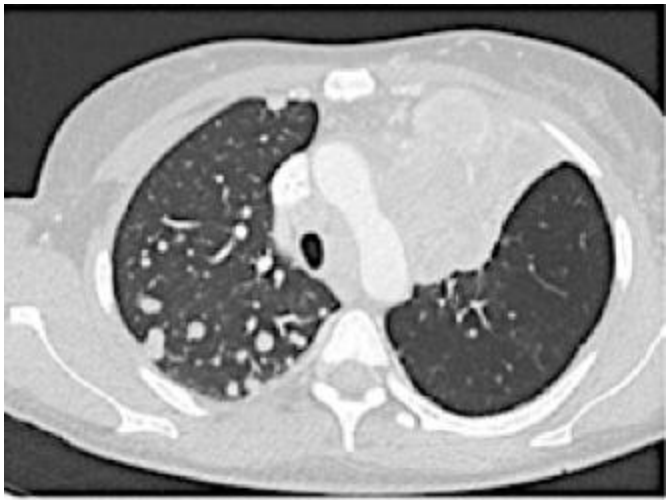
  TIM-3/CTLA-4/ LAG-3/ BTLA

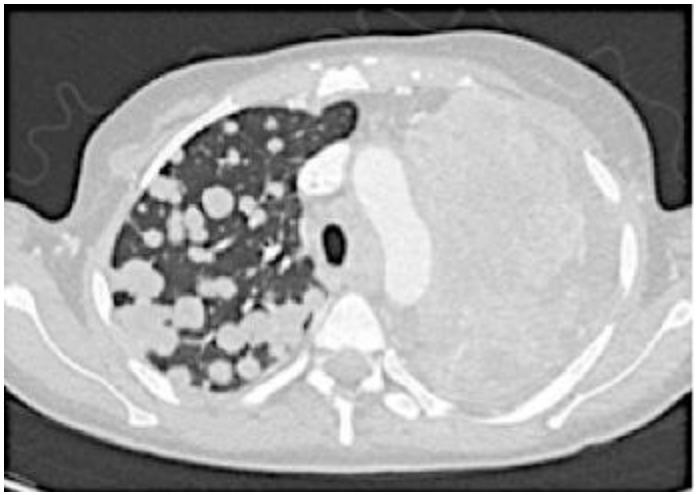
- infiltration of immunosuppressive regulatory T cells

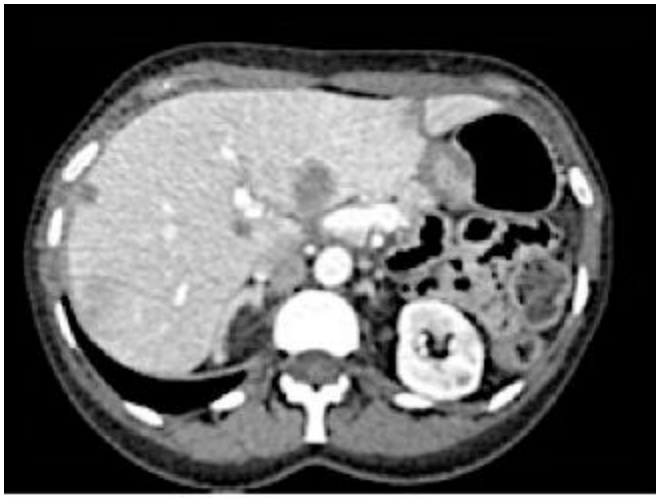
Hyperprogressive disease

- immune-related progression pattern
- acceleration of tumor growth during treatment with PD-1/PD-L1 inhibitors
- the frequency of HPD in patients receiving chemo/IO as first-line treatment has not been determined.

Hyperprogression







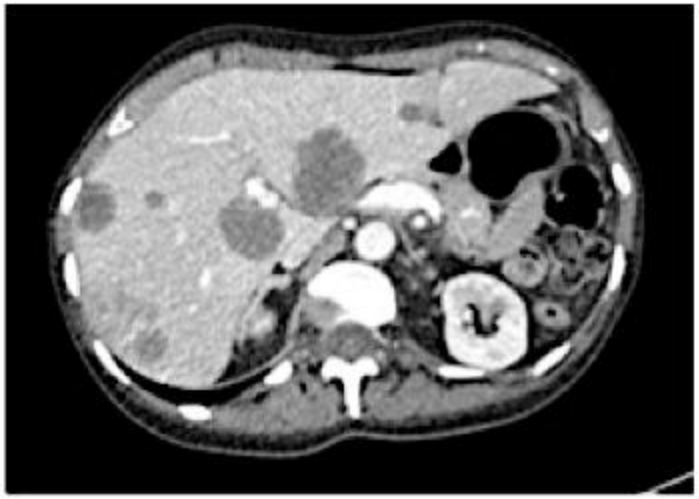
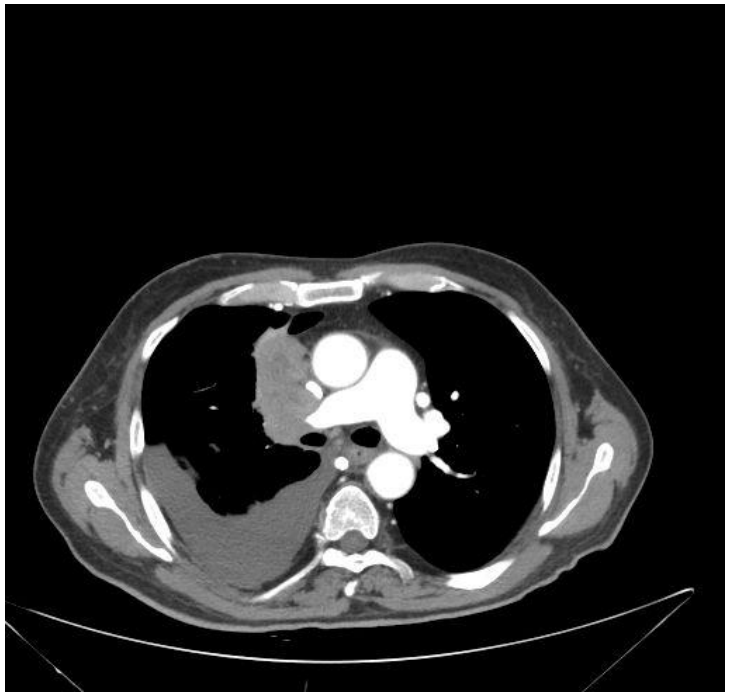


TABLE **Disease Progression of Hyperprogressive Disease**

Study	Definition	Frequency
Kato et al[12]	Time-to-treatment failure < 2 months; > 50% increase in tumor load compared with baseline; and > 2-fold increase in the rate of progression.	8%
Ferrara et al[10]	Progression defined by RECIST in the first evaluation. • Increase in tumor growth rate > 1.5	14%

RECIST = Response Evaluation Criteria in Solid Tumors.

NSCLC
Γυναίκα 55 ετών



adeno-ca stage IV

- EGFR-ALK-BRAF (-)
- PS 0
- PDL-1 >1%

- cisplatin/pemetrexed
  pembrolizumab

8 μήνες μετά ⟹ PD

Currently, patients with NSCLC PD-L1 of 1% or greater who progress after treatment with checkpoint inhibitors/chemotherapy **do not have standard second-line systemic treatment options.**

Treatment options after progression to chemotherapy/immunotherapy

- Single-agent chemotherapy
- Docetaxel with antiangiogenic agent
- Clinical trial
- Nivolumab, Atezolizumab

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Non-Small Cell Lung Cancer

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ADENOCARCINOMA, LARGE CELL, NSCLC NOS

INITIAL SYSTEMIC THERAPY

PS 0–2 → Systemic therapy[nnn] → Tumor response evaluation[nnn]

Tumor response evaluation[nnn] → Progression

Progression → PS 0–2 →

SUBSEQUENT THERAPY[nnn]

Preferred (no previous IO):
Systemic immune checkpoint inhibitors[c,uu,ppp]
Nivolumab (category 1)
or pembrolizumab (category 1)[qqq]
or atezolizumab (category 1)
or
Other Recommended (no previous IO or previous IO):[aaa]
Docetaxel or pemetrexed or gemcitabine
or ramucirumab + docetaxel

→ Progression[ppp,sss]

Progression → PS 3–4 →

Best supportive care
See NCCN Guidelines for Palliative Care

Progression → See Subsequent Therapy, above

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Non-Small Cell Lung Cancer

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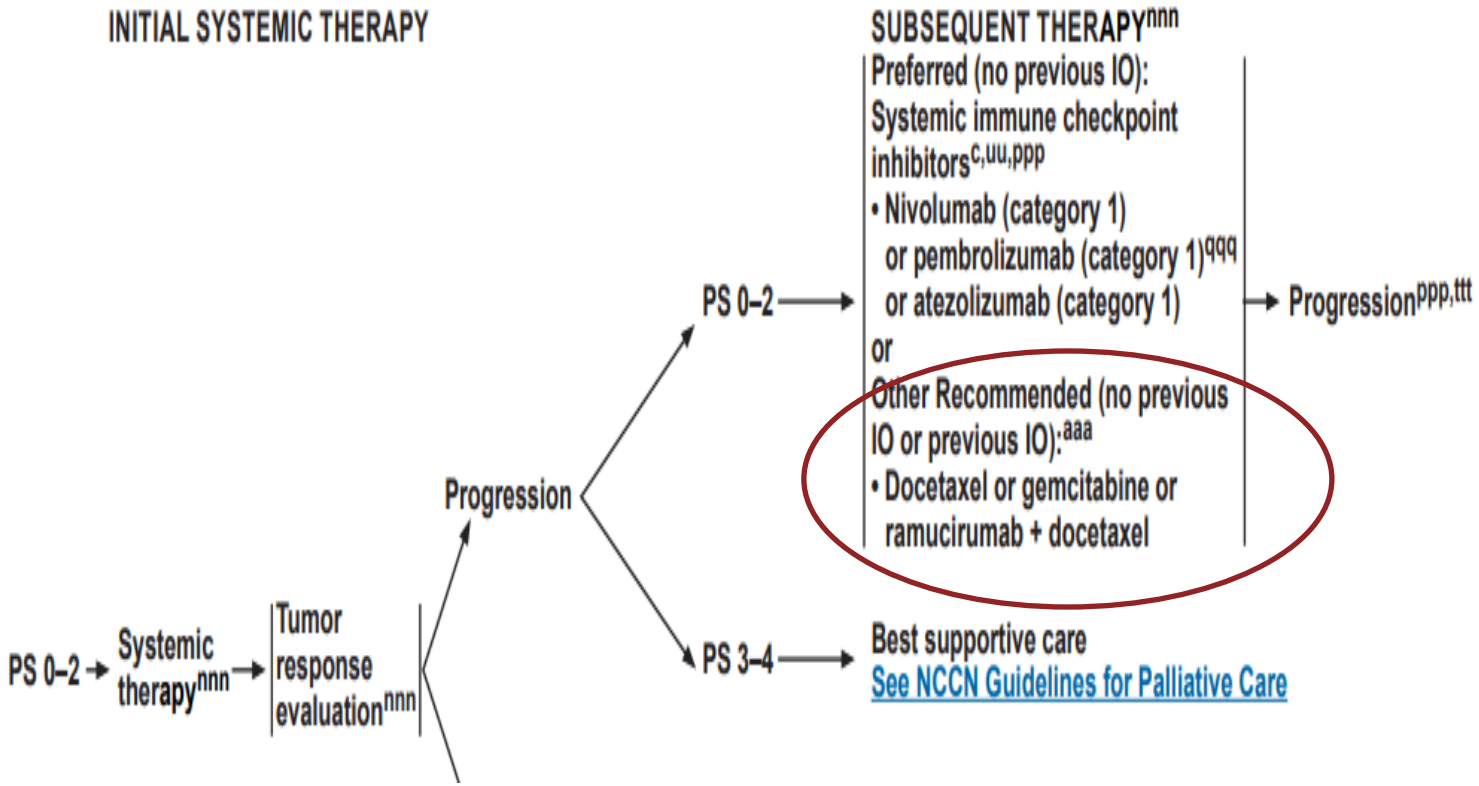
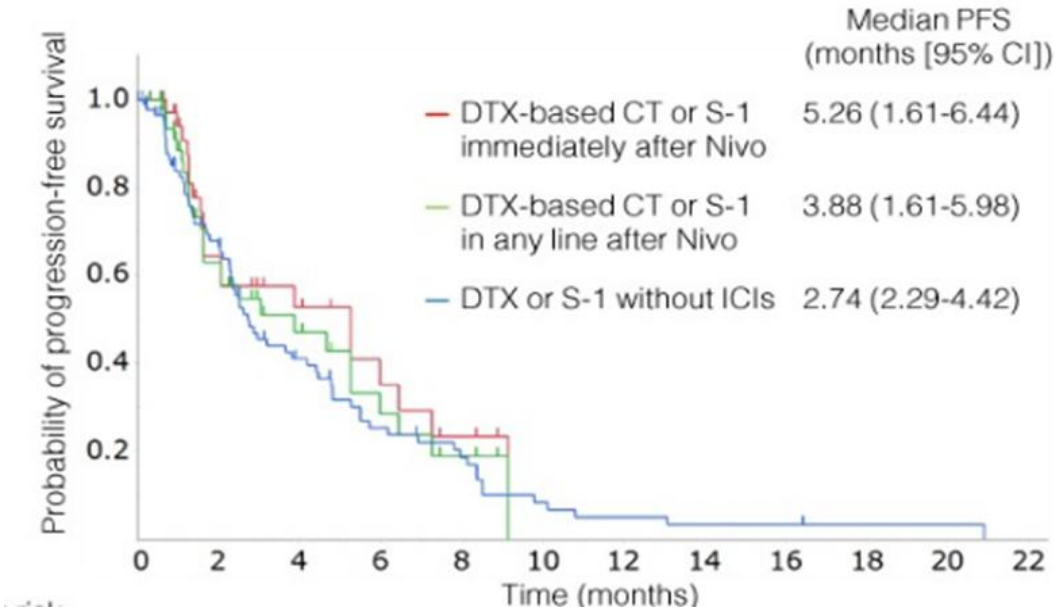
SQUAMOUS CELL CARCINOMA



Thorac Cancer. 2019 May; 10(5): 1141–1148.
Published online 2019 Mar 26. doi: 10.1111/1759-7714.13055
PMCID: PMC6501000
PMID: 30913364

Efficacy of subsequent docetaxel +/− ramucirumab and S-1 after nivolumab for patients with advanced non-small cell lung cancer

Nobumasa Tamura, [1] Hidehito Horinouchi, [1] Katsutoshi Sekine, [1] Yuji Matsumoto, [1] Shuji Murakami, [1] Yasushi Goto, [1] Shintaro Kanda, [1] Yutaka Fujiwara, [1] Noboru Yamamoto, [1] and Yuichiro Ohe [1]



Clinical and Translational Oncology

September 2019, Volume 21, Issue 9, pp 1270–1279 | Cite as

Efficacy of nintedanib and docetaxel in patients with advanced lung adenocarcinoma treated with first-line chemotherapy and second-line immunotherapy in the nintedanib NPU program

Authors Authors and affiliations

J. Corral, M. Majem, D. Rodríguez-Abreu, E. Carcereny, Á. A. Cortes, M. Llorente, J. M. López Picazo, Y. García, M. Domine, M P. López Criado

ORR of 36% and a DCR of 82%.

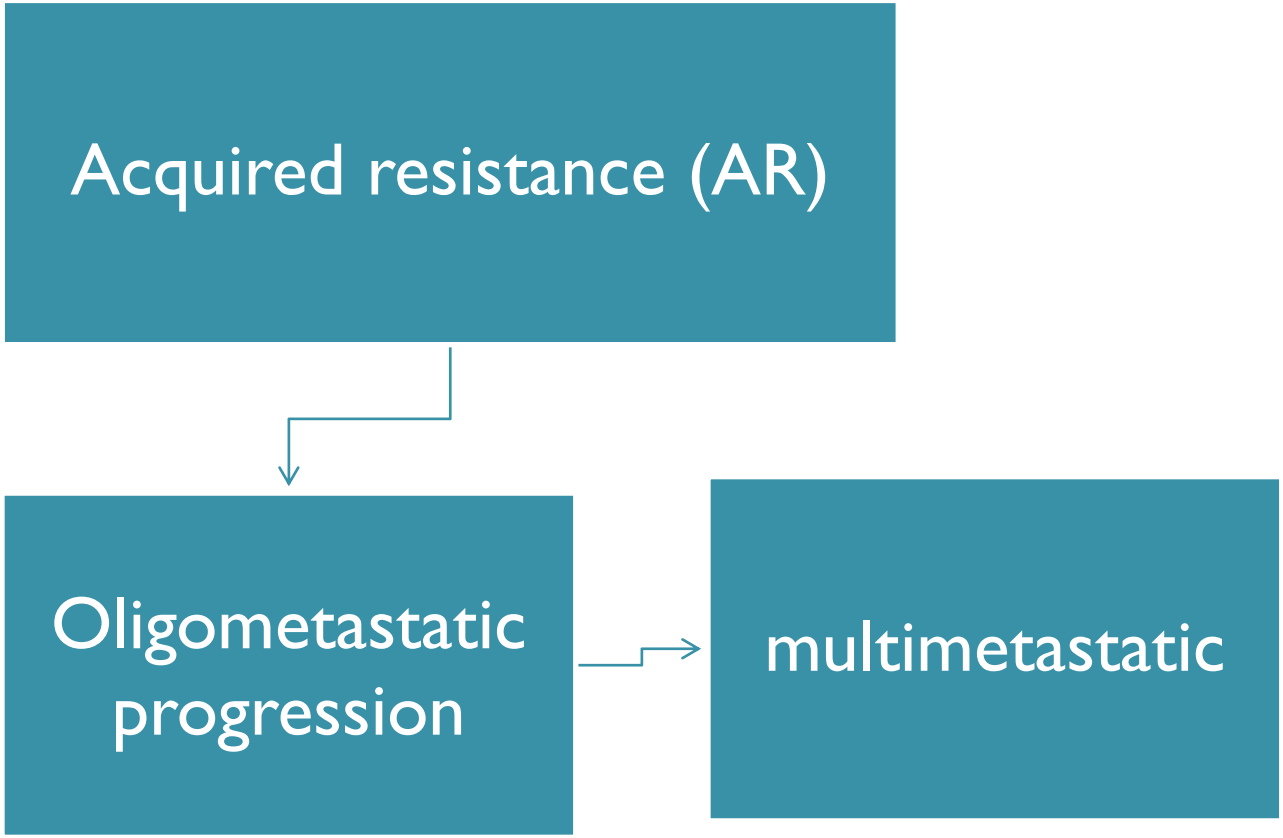
Increased Response Rates to Salvage Chemotherapy Administered after PD-1/PD-L1 Inhibitors in Patients with Non-Small Cell Lung Cancer.

J Thorac Oncol. 2018; 13(1):106-111 (ISSN: 1556-1380)

Park SE; Lee SH; Ahn JS; Ahn MJ; Park K; Sun JM

- ORRs in the group of patients treated with platinum-based combination chemotherapy after IO compared to before IO, 66.7% vs 39.5% (*P* = .03)

- ORRs for patients receiving nonplatinum monotherapies were 46.9% vs 25%


Acquired resistance (AR)
Oligometastatic progression
multimetastatic

Clinical Features and Management of Acquired Resistance to PD-1 Axis Inhibitors in 26 Patients With Advanced Non–Small Cell Lung Cancer

Scott N. Gettinger MD, Anna Wurtz BS, Sarah B. Goldberg MD, David Rimm MD, PhD, Kurt Schalper MD, PhD, Susan Kaech PhD, Paula Kavathas PhD, Anne Chiang MD, PhD, Rogerio Lilenbaum MD, Daniel Zelterman PhD, Katerina Politi PhD, Roy S. Herbst MD,

2-year survival rate 92% (95% confidence interval: 0.77–1).

- 26 patients
- 23 patients (88%) had recu (35%) sites of disease.
- 14 continued PD-1 inhibitor therapy
- 3 were re-challenged with the same PD-1 inhibitor after holiday (2 responded)
- 15 received local therapy to site(s) of AR
- 11 continued PD-1 inhibitor after local therapy
-

www.impactjournals.com/oncotarget/ Oncotarget, 2018, Vol. 9, (No. 4), pp: 4375-4384

Research Paper

Clinical and molecular features of innate and acquired resistance to anti-PD-1/PD-L1 therapy in lung cancer

Shalin Shah[1,*], Kevin Wood[2,*], Brian Labadie[2], Brian Won[2], Ryan Brisson[2], Theodore Karrison[3], Thomas Hensing[2], Mark Kozloff[2], Riyue Bao[4], Jyoti D. Patel[2] and Jason J. Luke[2]

- 60.6% progression of previously existing lesions
- 66.7% progression in a unique disease site
- 30% the progression was diffuse

www.impactjournals.com/oncotarget/ Oncotarget, 2018, Vol. 9, (No. 4), pp: 4375-4384

Research Paper

Clinical and molecular features of innate and acquired resistance to anti-PD-1/PD-L1 therapy in lung cancer

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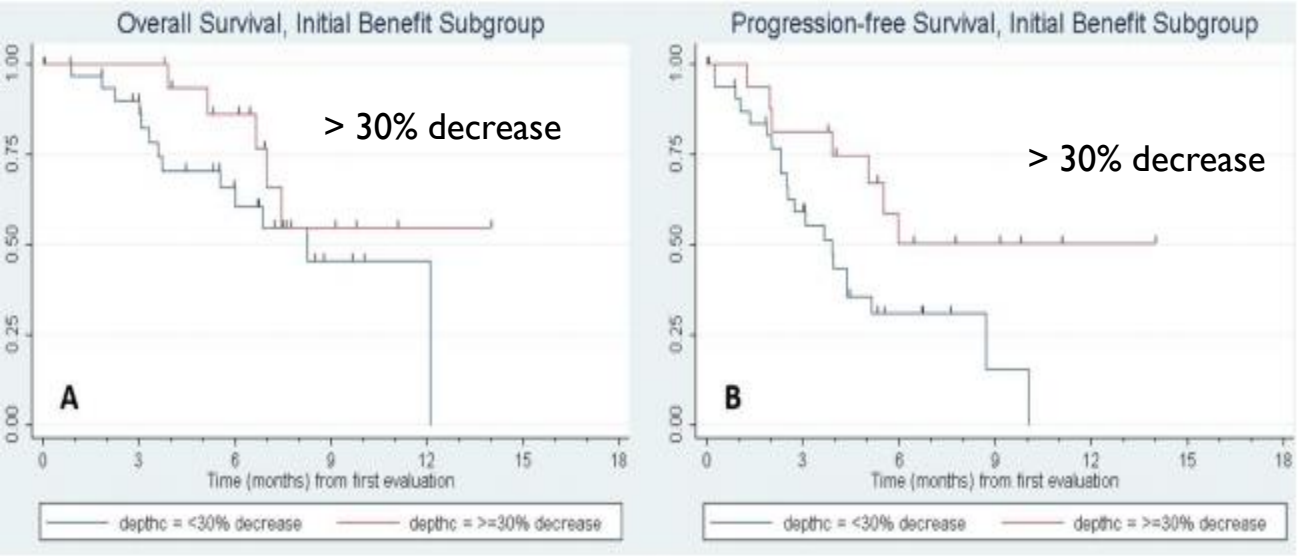


NIH U.S. National Library of Medicine

ClinicalTrials.gov

First line Pembrolizumab Alone or in Combination with Pemetrexed and Carboplatin in Induction/Maintenance or Postprogression in Treating patients with stage IV Non-Small Cell Lung Cancer

Study Design

Study Type :	Interventional (Clinical Trial)
Estimated Enrollment :	846 participants
Allocation:	Randomized
Intervention Model:	Parallel Assignment
Masking:	None (Open Label)
Primary Purpose:	Treatment

NIH U.S. National Library of Medicine

ClinicalTrials.gov

First line Pembrolizumab Alone or in Combination with Pemetrexed and Carboplatin in Induction/Maintenance or Postprogression in Treating patients with stage IV Non-Small Cell Lung Cancer

This phase III trial studies whether :

- pembrolizumab alone as a first-line treatment, followed by pemetrexed and carboplatin with or without pembrolizumab after disease progression is superior to
- induction with pembrolizumab, pemetrexed and carboplatin followed by pembrolizumab and pemetrexed maintenance

PRIMARY OBJECTIVES:
overall survival

Conclusion

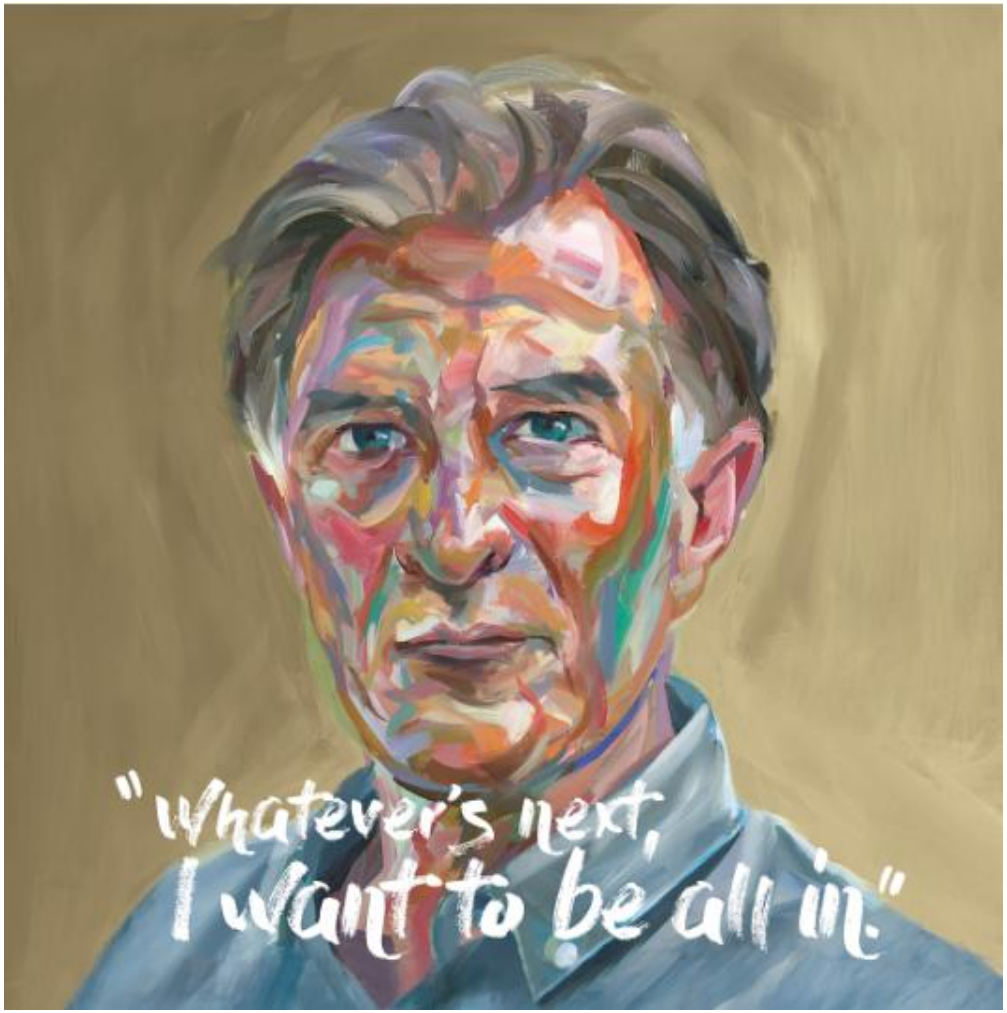
- Second-line treatment after progression on chemo/IO in PD-L1–positive NSCLC has not yet been established.

- Treatment decisions depend on the time to treatment failure and affected sites

  - chemotherapy with or without antiangiogenic agent
  - local therapy
  - or reintroduction of immunotherapy

  enrollment in a clinical trial

Πρόοδος νόσου υπό Ανοσοθεραπεία : Και μετά τι;


"Whatever's next,
I want to be all in."