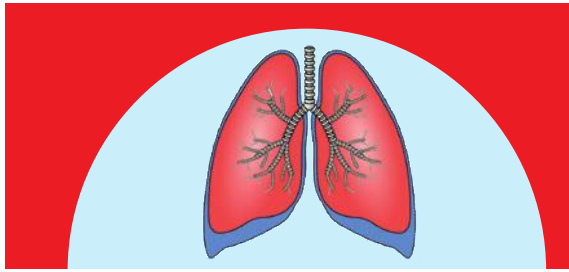
CARCINOMA POLMONARE: QUALI NOVITÀ NEL 2022?



Terapie adiuvanti: targeted therapy e immunoterapia

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Oncologia Medica 2
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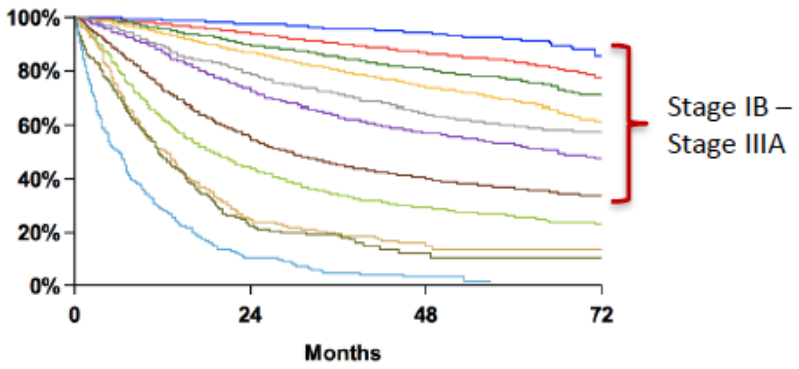
20 Maggio 2022

Il trattamento della malattia precoce

AJCC 8th Edition (2017)



Proposed	Events / N	MST	24 Month	60 Month
IA1	68 / 781	NR	97%	92%
IA2	505 / 3105	NR	94%	83%
IA3	546 / 2417	NR	90%	77%
IB	560 / 1928	NR	87%	68%
IIA	215 / 585	NR	79%	60%
IIB	605 / 1453	66.0	72%	53%
IIIA	2052 / 3200	29.3	55%	36%
IIIB	1551 / 2140	19.0	44%	26%
IIIC	831 / 986	12.6	24%	13%
IVA	336 / 484	11.5	23%	10%
IVB	328 / 398	6.0	10%	0%

CURE

LOCAL TREATMENT

SYSTEMIC TREATMENT

HETEROGENEITY IN STAGE

MICROMETASTASES

HETEROGENEITY IN BIOLOGY

Il carcinoma polmonare in stadio non avanzato: una rivoluzione in corso?

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 16, 2017 VOL. 377 NO. 20

Durvalumab after Chemoradiotherapy in Stage III Non–Small-Cell Lung Cancer

S.J. Antonia, A. Villegas, D. Daniel, D. Vicente, S. Murakami, R. Hui, T. Yokoi, A. Chiappori, K.H. Lee, M. de Wit, B.C. Cho, M. Bourhaba, X. Quantin, T. Tokito, T. Mekhail, D. Planchard, Y.-C. Kim, C.S. Karapetis, S. Hiret, G. Ostoros, K. Kubota, J.E. Gray, L. Paz-Ares, J. de Castro Carpeño, C. Wadsworth, G. Melillo, H. Jiang, Y. Huang, P.A. Dennis, and M. Özgüroğlu, for the PACIFIC Investigators*

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Overall Survival with Durvalumab after Chemoradiotherapy in Stage III NSCLC

S.J. Antonia, A. Villegas, D. Daniel, D. Vicente, S. Murakami, R. Hui, T. Kurata, A. Chiappori, K.H. Lee, M. de Wit, B.C. Cho, M. Bourhaba, X. Quantin, T. Tokito, T. Mekhail, D. Planchard, Y.-C. Kim, C.S. Karapetis, S. Hiret, G. Ostoros, K. Kubota, J.E. Gray, L. Paz-Ares, J. de Castro Carpeño, C. Faivre-Finn, M. Reck, J. Vansteenkiste, D.R. Spigel, C. Wadsworth, G. Melillo, M. Taboada, P.A. Dennis, and M. Özgüroğlu, for the PACIFIC Investigators*

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Osimertinib in Resected *EGFR*-Mutated Non–Small-Cell Lung Cancer

Yi-Long Wu, M.D., Masahiro Tsuboi, M.D., Jie He, M.D., Thomas John, Ph.D., Christian Grohe, M.D., Margarita Majem, M.D., Jonathan W. Goldman, M.D., Konstantin Laktionov, Ph.D., Sang-We Kim, M.D., Ph.D., Terufumi Kato, M.D., Huu-Vinh Vu, M.D., Ph.D., Shun Lu, M.D., Kye-Young Lee, M.D., Ph.D., Charuwan Akewanlop, M.D., Chong-Jen Yu, M.D., Ph.D., Filippo de Marinis, M.D., Laura Bonanno, M.D., Manuel Domine, M.D., Ph.D., Frances A. Shepherd, M.D., Lingmin Zeng, Ph.D., Rachel Hodge, M.Sc., Ajlan Atasoy, M.D., Yuri Rukazenkov, M.D., Ph.D., and Roy S. Herbst, M.D., Ph.D., for the ADAURA Investigators*

PACIFIC e ADAURA: quale rivoluzione?

1- Il ruolo della terapia sistemica nella malattia limitata/localmente avanzata
--> CURE?

2- Cambiamento della gestione multidiscplinare delle neoplasie precoci/localmente avanzate

3- Ruolo caratterizzazione molecolare anche nelle malattie precoci/localmente avanzate

LA RIVOLUZIONE PARTE 2: ADAURA

Adult patients with completely resected stage* IB, II, IIIA EGFRm NSCLC, <u>with or without adjuvant chemotherapy</u>

Key eligibility criteria:

- WHO performance status 0 / 1
- Confirmed primary, non-squamous, non-metastatic NSCLC
- MRI or CT scan of the brain prior to surgery or randomization
- **Prior, post, or planned radiotherapy was not allowed**
- **Complete resection with negative margins (open surgery or VATS allowed; wedge resection or segmentectomy not allowed)†**
- **Adequate lymph node resection**
- **Max. interval between surgery and randomization 10 / 26 weeks without / with adjuvant chemotherapy**
- **Major surgery within 4 weeks of the first dose of study drug was not allowed**

Stratification by:
stage (IB vs II vs IIIA)
EGFRm (Ex19del vs L858R)‡
race (Asian vs non-Asian)

Randomization 1:1 (N=682)

- Osimertinib 80 mg, once daily
- Placebo, once daily

3-yr treatment until recurrence / treatment completion / discontinuation§

<u>Primary endpoint:</u> investigator-assessed DFS in stage II / IIIA (designed for superiority under assumed DFS HR 0.70)

<u>Secondary endpoints:</u>

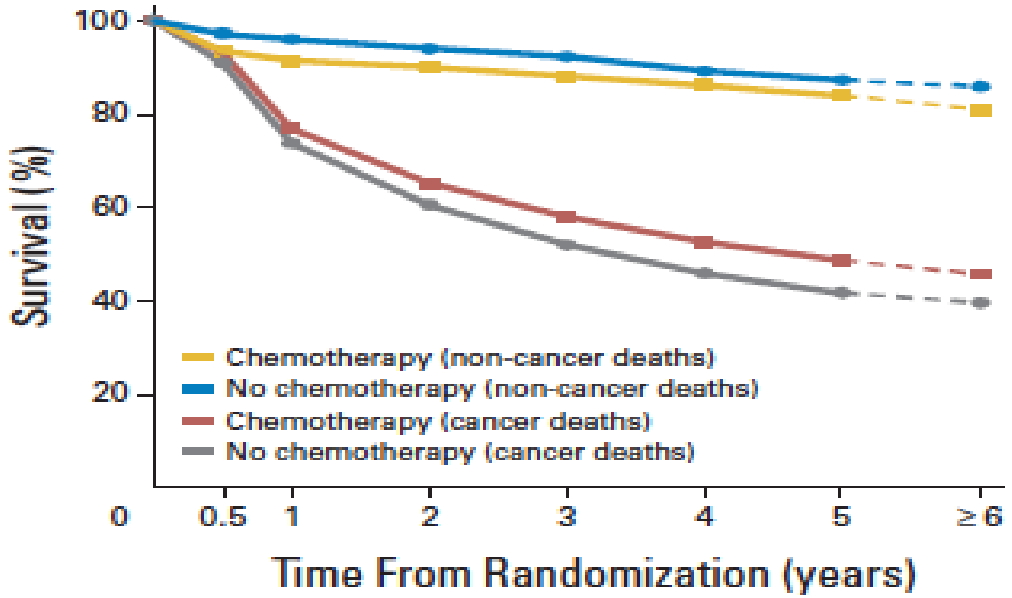
- DFS in the overall population**
- DFS at 2, 3, 4, and 5 yr
- OS
- Safety
- HRQoL

<u>Pre-specified exploratory endpoint:</u>
assessment of site(s) of recurrence, including CNS

- **Following IDMC recommendation, the study was unblinded early due to efficacy; here we report an unplanned interim analysis**
  - **At the time of unblinding the study had completed enrollment and all patients were followed up for at least 1 yr**

La terapia sistemica adiuvante prima di adaura

C



Non-cancer deaths / person years by period	Years 0-3	Years 4-5	Years ≥ 6
Control	88 / 4,353	42 / 1,399	9 / 611
Chemotherapy	141 / 4,635	38 / 1,611	24 / 708
Cancer deaths by period			
Control	878	197	40
Chemotherapy	716	165	52

At 5 years

Absolute reduction in cancer death: **6.9%**

HR 0.83; 95% CI, 0.76 to 0.90; *P* .001

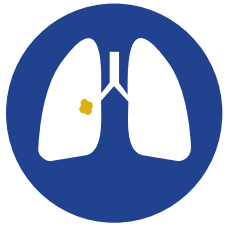
Abs. increase in non cancer death: **1.4%**

HR 1.36; 95% CI, 1.10 to 1.69; *P* .004

Pignon JP et al, JCO 2008

Localized / early stage

Stage IB[10]

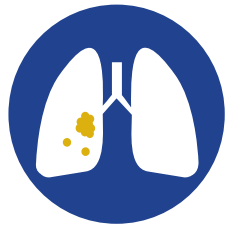


45%

5-yr recurrence / death rates*[6]

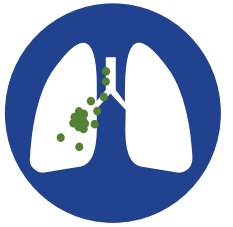
Regional / locally advanced

Stage II[10]



62%

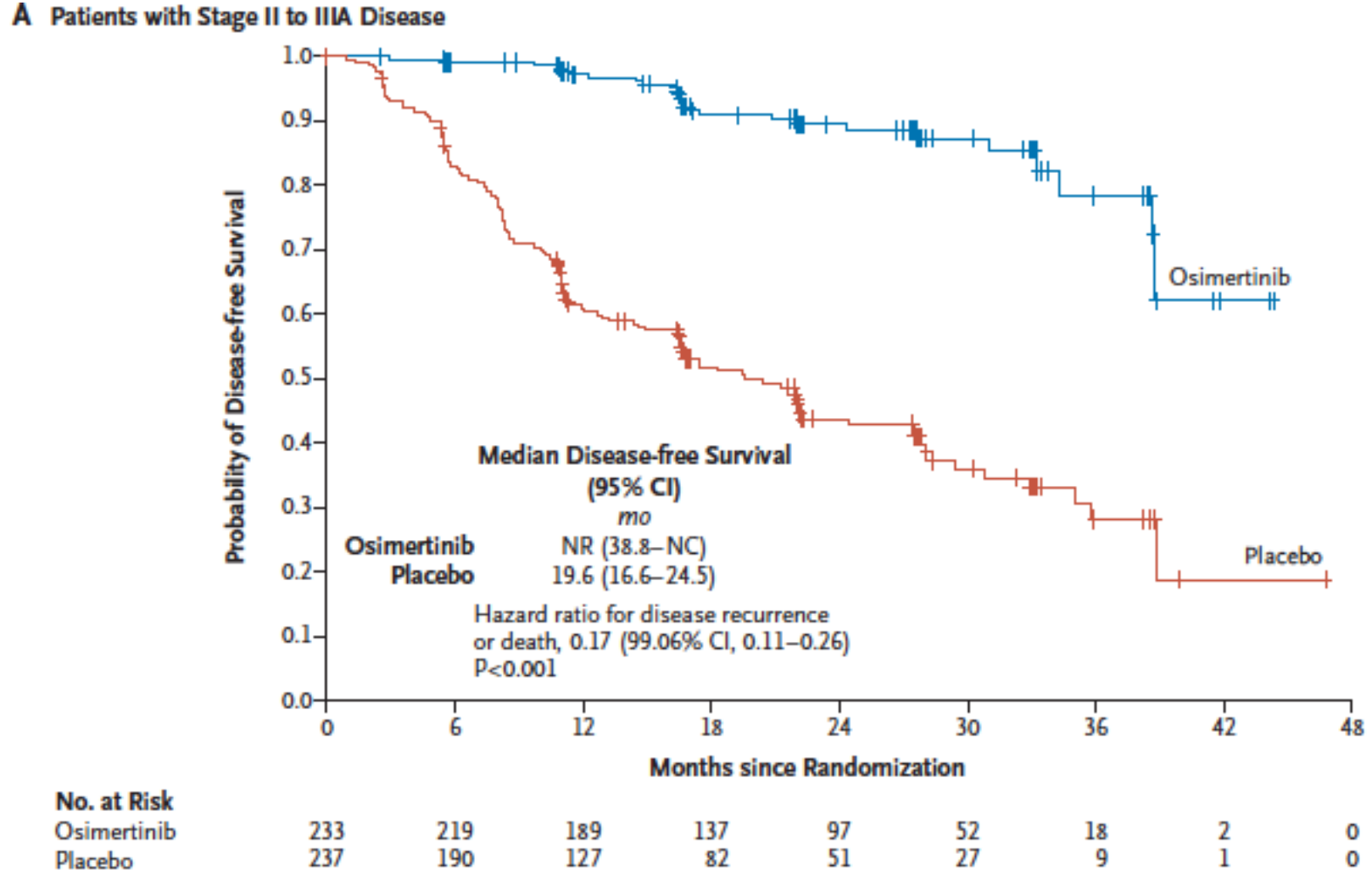
Stage III[10]



76%

5-yr recurrence / death rates*[6]

LA RIVOLUZIONE ADAURA



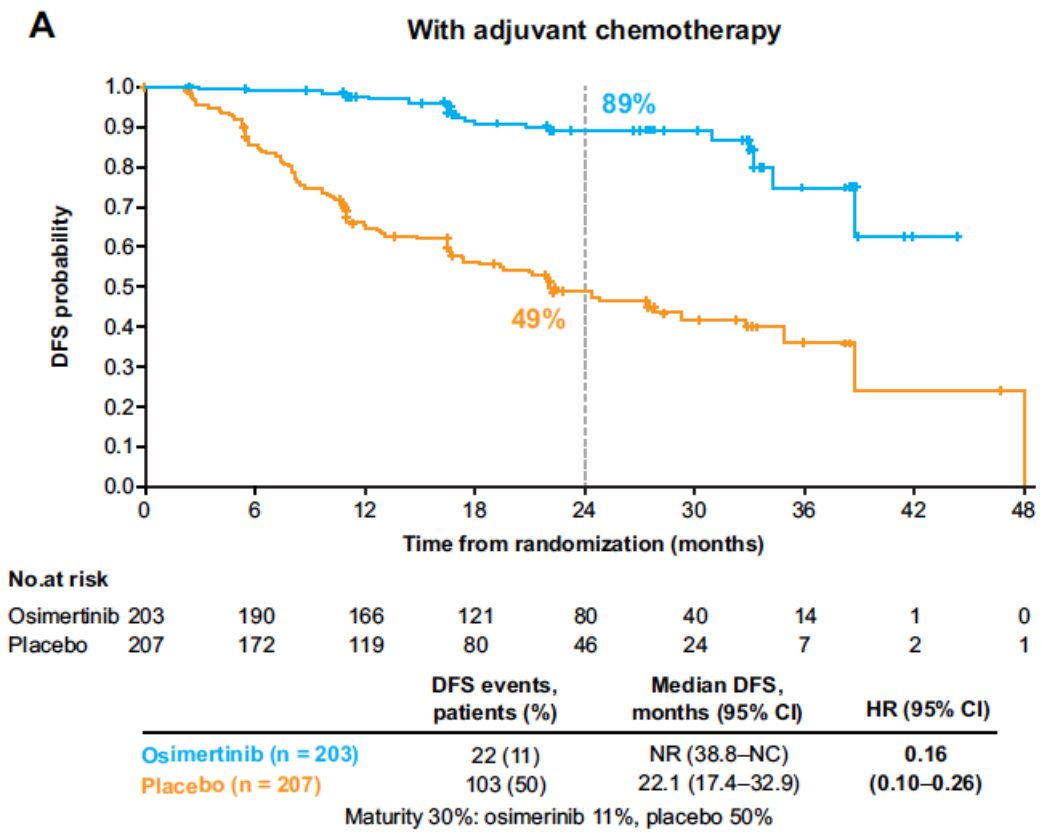
AE of interest:

Diarrhoea (46%), paronychia (25%), dry skin (23%)

3% G1-2 pneumonitis; 7% QT prolongation

Wu Y-L et al, NEJM 2020

L’utilizzo della chemioterapia nello studio ADAURA



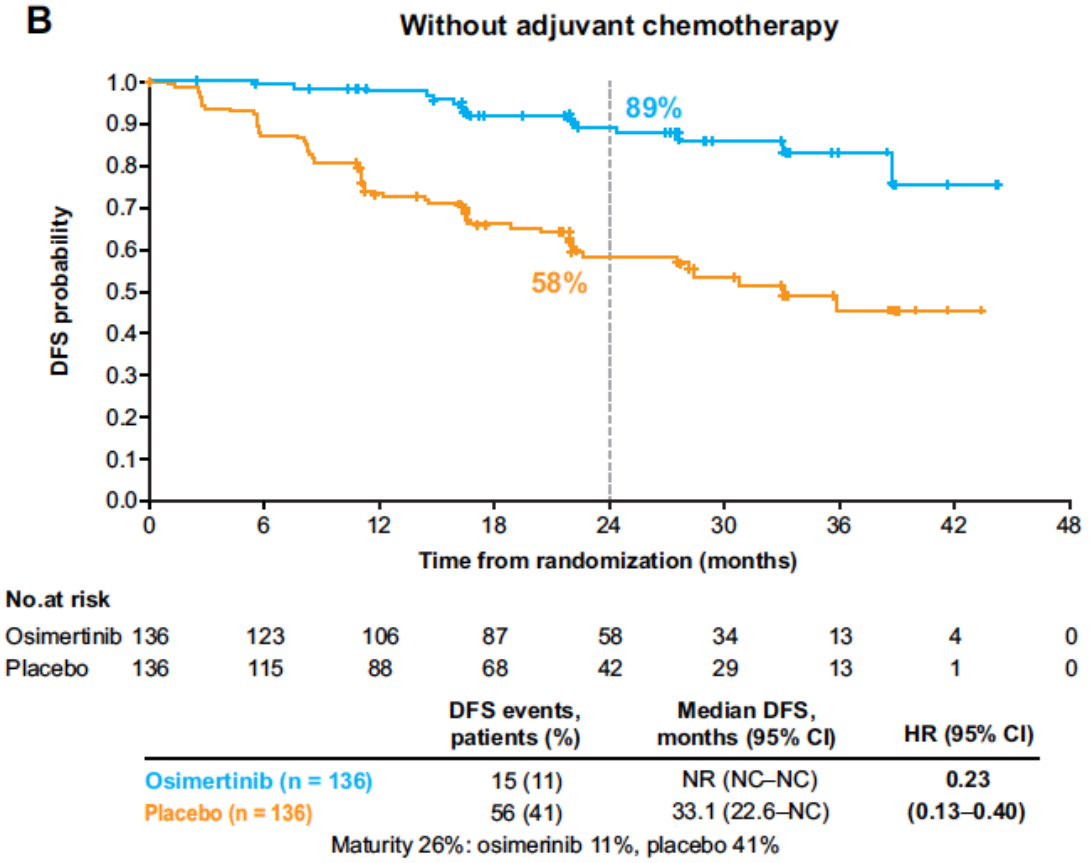


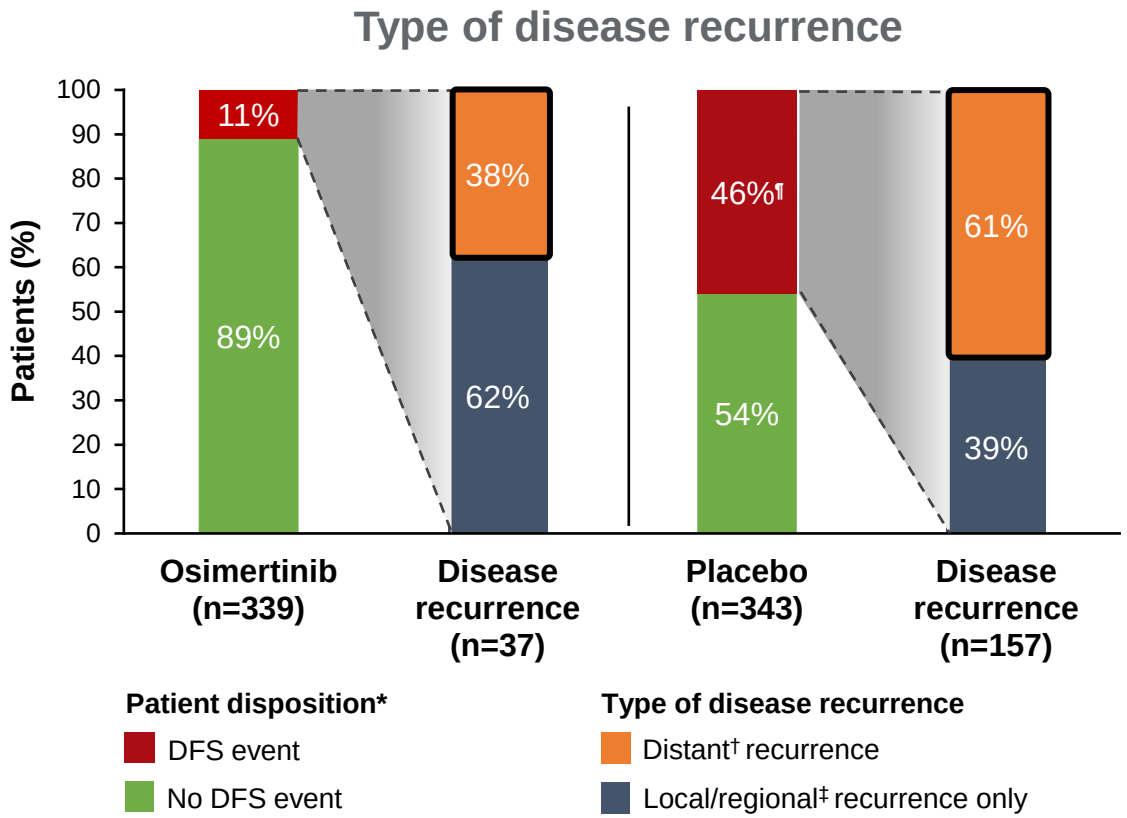
Table 1. Postoperative (Adjuvant) Chemotherapy Use in ADAURA

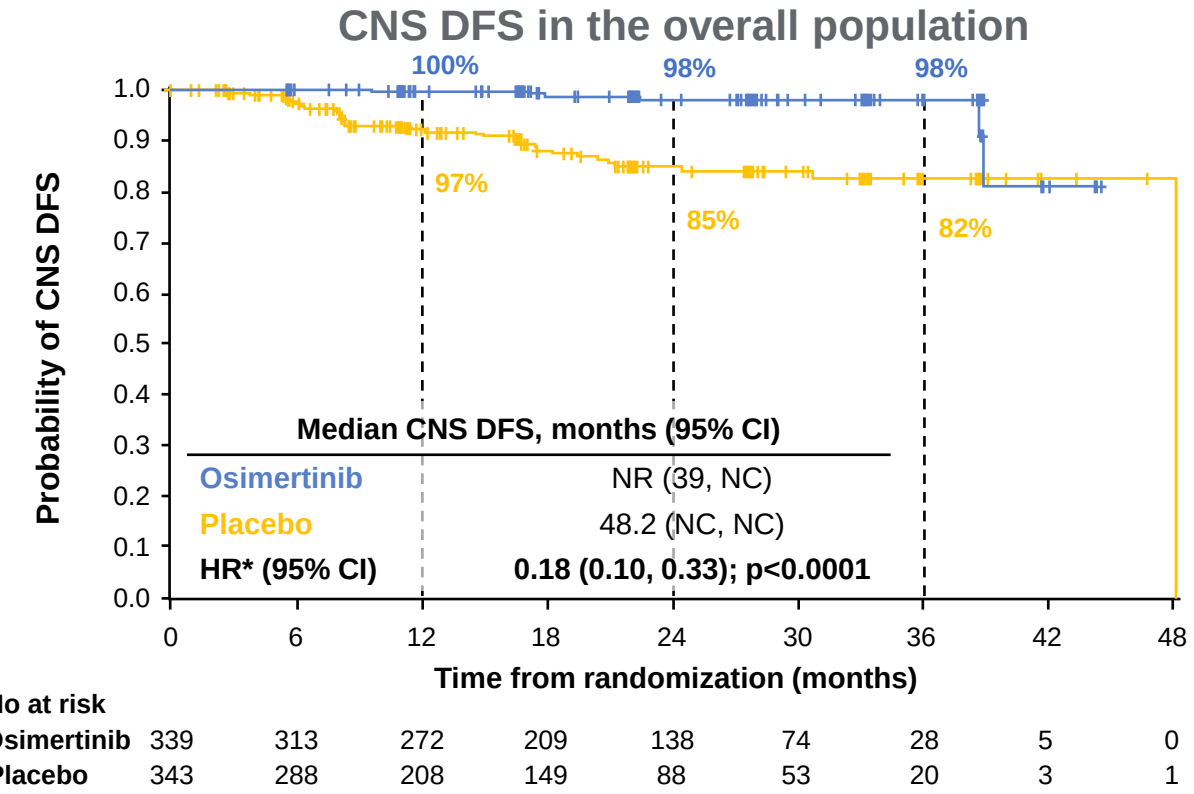
Characteristics	Patients, n	Received Adjuvant Chemotherapy, %
Stage IB	216	26[a]
Stage II	231	71[a]
Stage IIIA	235	80[a]
Aged <70 y	509	66
Aged ≥70 y	173	42
WHO PS 0	434	60
WHO PS 1	248	60
Enrolled in Asia[b]	414	65
Enrolled outside of Asia[c]	268	53
Adjuvant chemotherapy Number of patients who received adjuvant chemotherapy	Patients, n 410[d]	Total, % 60

Wu Y-L et al, JTO 2021

Osimertinib e il pattern di recidiva…

- 11% vs 46% of patients had DFS events (disease recurrence or death) with osimertinib vs placebo
- In the osimertinib arm, the majority of patients with recurrence had local / regional recurrence only, with only 38% of patients having metastatic recurrence vs 61% in the placebo arm



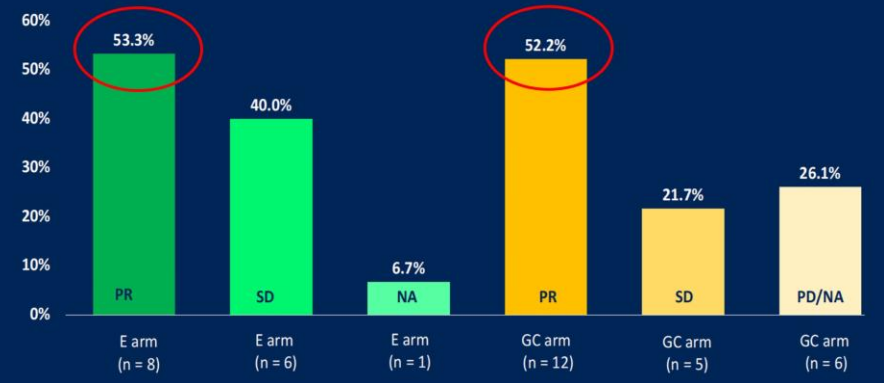


Tsuboi M et al, ESMO 2020

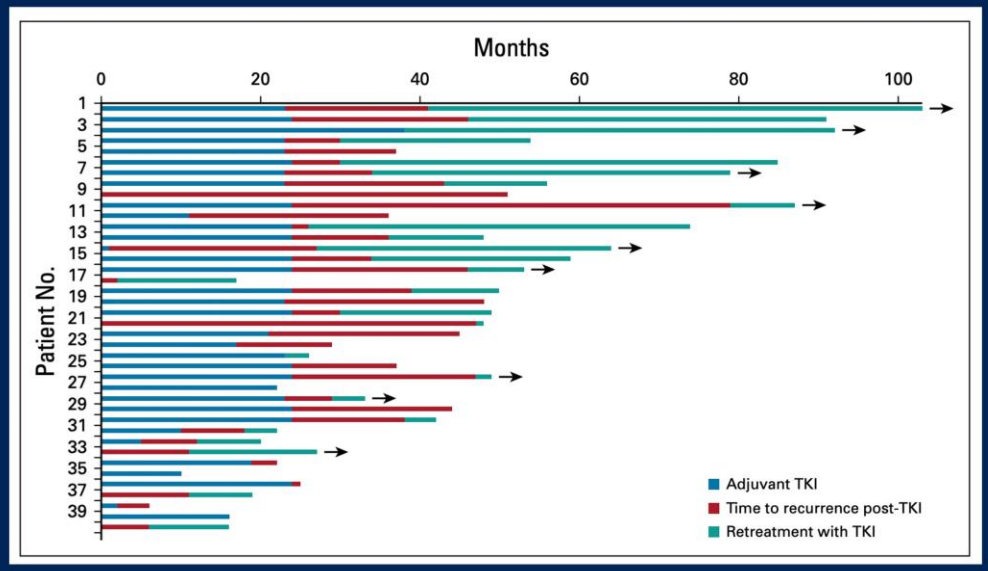
IMPACT, ADJUVANT, RADIANT, SELECT, CTONG 1103…
La lezione dagli studi di adiuvante con inibitori di 1a gen…

EMERGING-CTONG1103

Best response for the subsequent TKIs

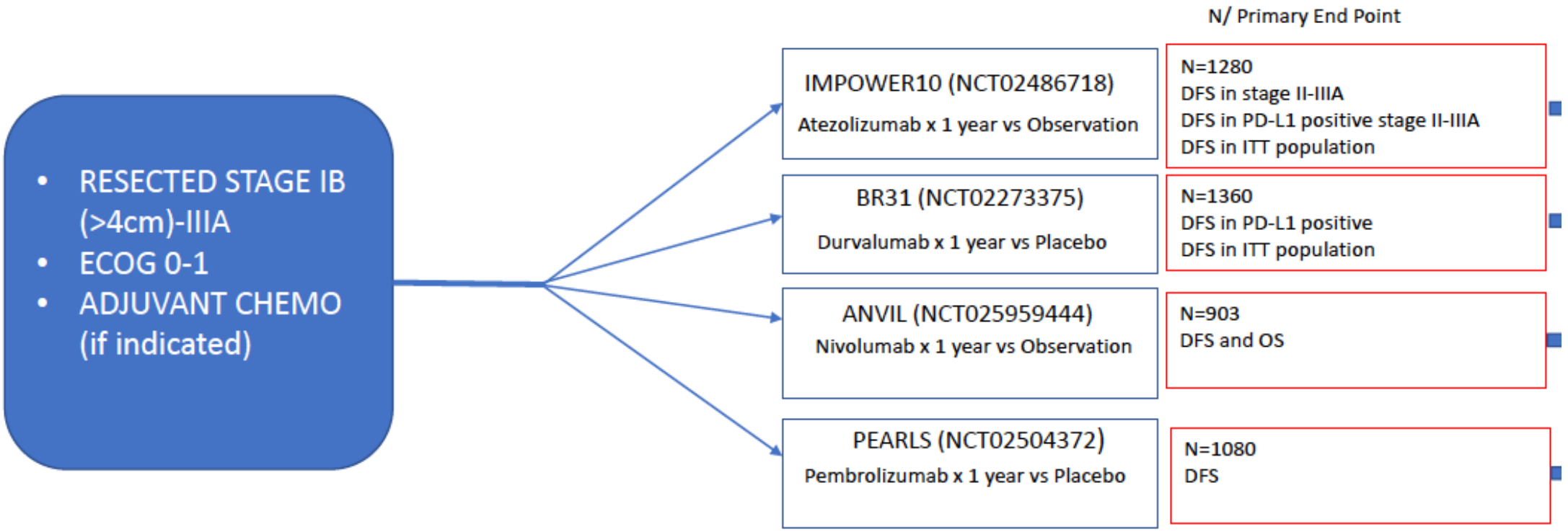


SELECT[1]



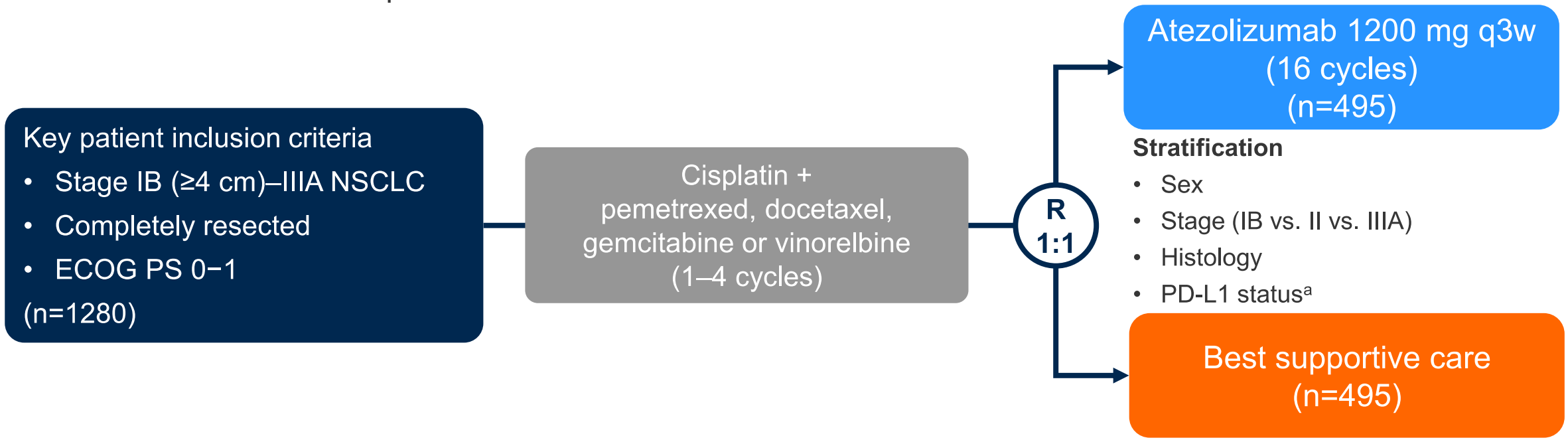
Piotrowska Z, ASCO 2021

L’altra faccia della medaglia: immunoterapia adiuvante



Impower 010

- **Study objective**
  - To evaluate the efficacy and safety of atezolizumab after adjuvant chemotherapy in patients with early stage resected NSCLC in IMpower010



Primary endpoint

- DFS (investigator assessed)

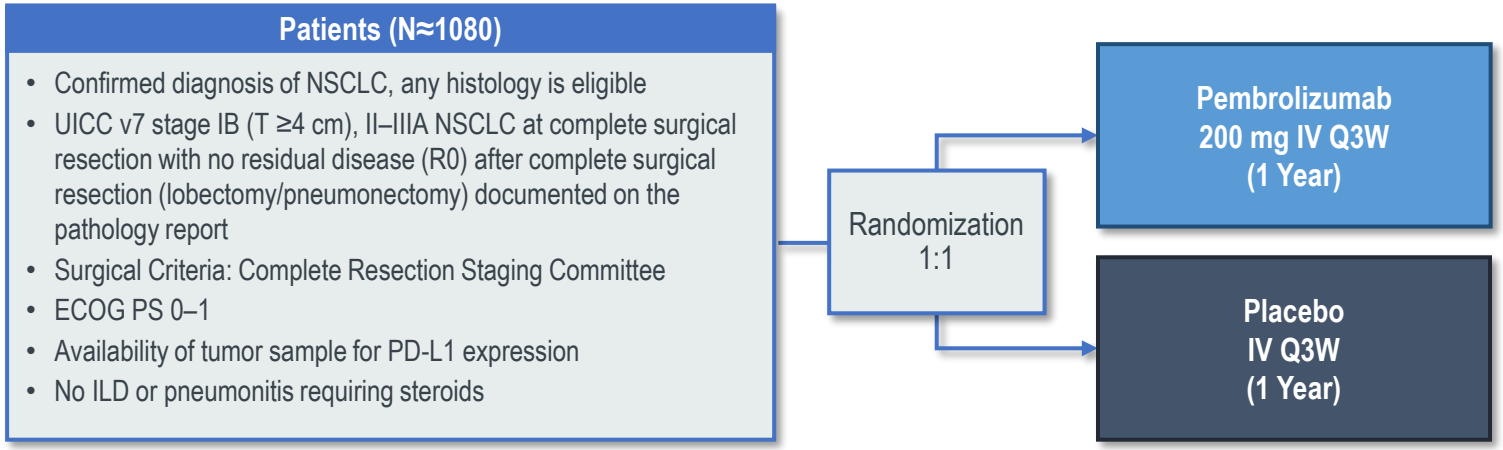
Secondary endpoints

- OS, safety

KEYNOTE-091

Active, not recruiting

Phase 3, randomized, double-blind study of pembrolizumab versus placebo for patients with early-stage or locally advanced NSCLC after resection and standard adjuvant chemotherapy



Stratification Factors

- Stage (IB vs II vs IIIA)
- Adjuvant chemotherapy (No vs Yes)
- PD-L1 status: TPS = 0% vs TPS = 1–49% vs TPS ≥50%
- Regions (Western vs Eastern Europe vs Asia vs rest of the world).

Primary End Points

- DFS (all patients)
- DFS (TPS ≥50%)

Secondary End Points

- OS
- LCSS (lung cancer specific survival)

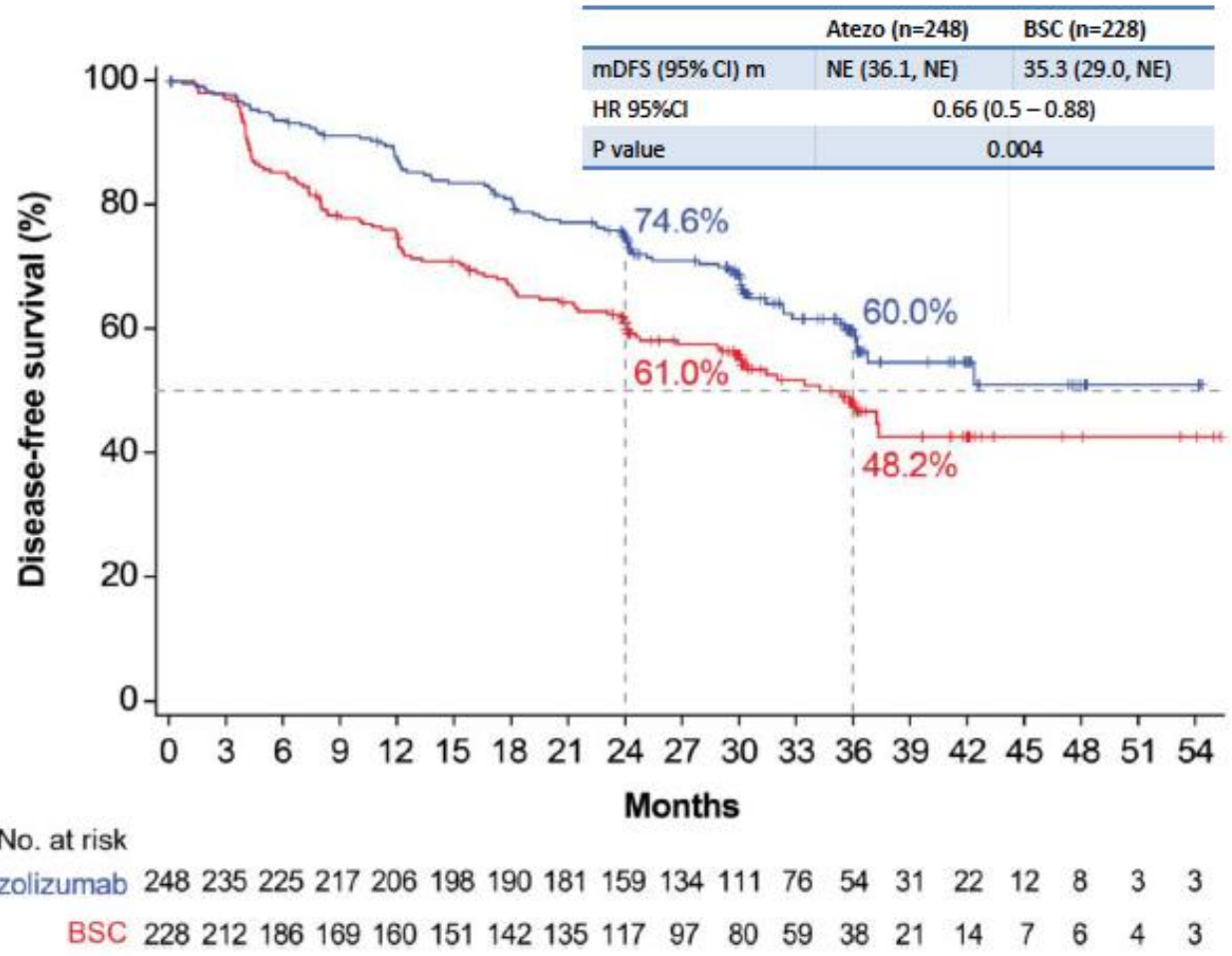
Estimated primary completion: August 19, 2021[a]

[a]Subject to change.

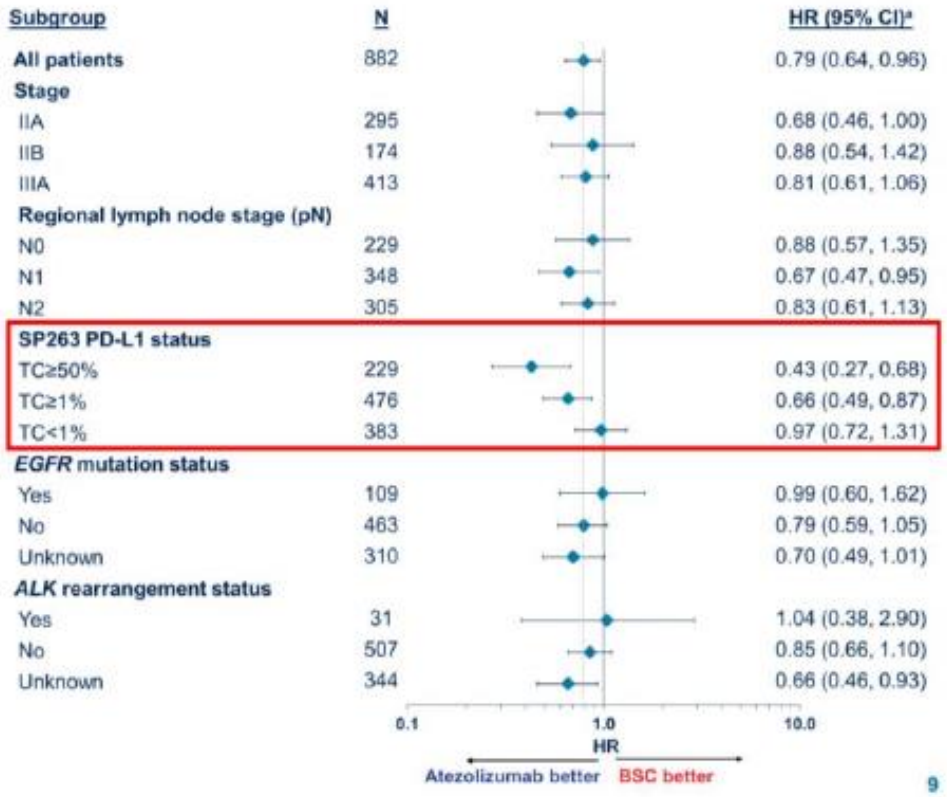
Clinicaltrials.gov website. https://clinicaltrials.gov/ct2/show/NCT02504372. February 24, 2021.

IMPOWER 010

Stage II-IIIA, PDL1 ≥ 1% (SP263) [54.6%]



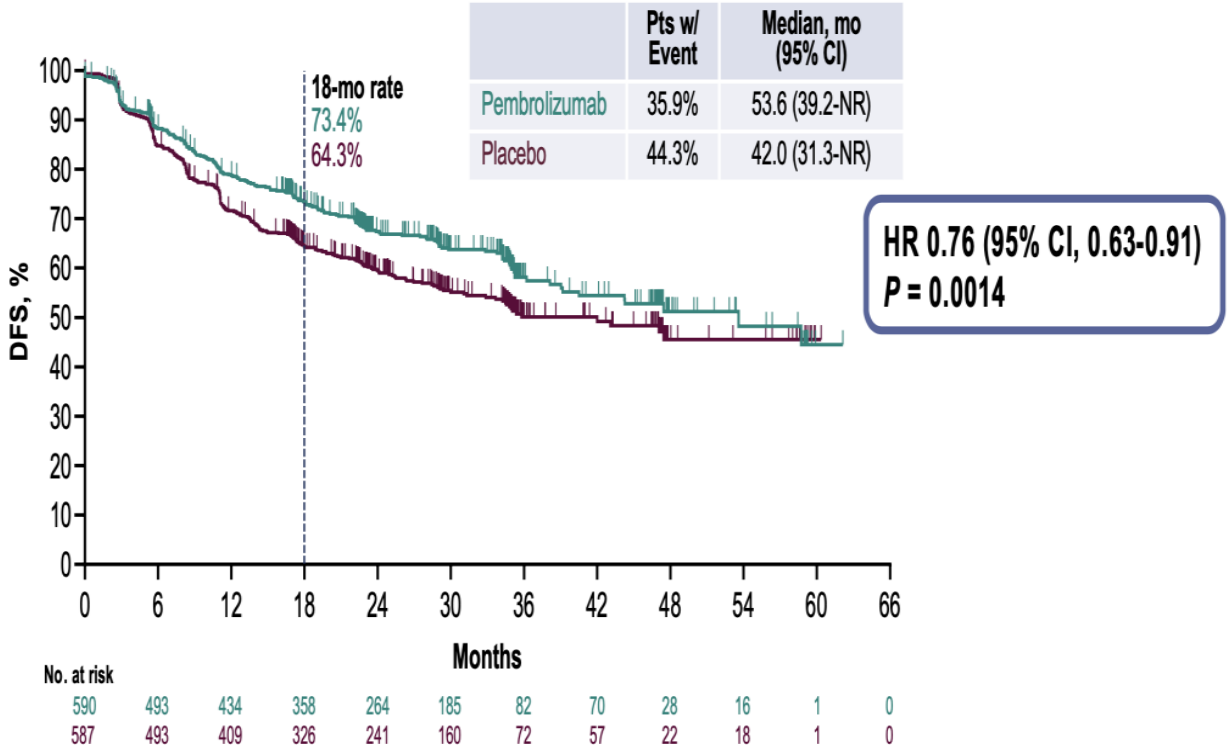
DFS in key subgroups (all-randomized)



OS data immature at this interim DFS analysis

Wakelee H A, ASCO 2021
Felip E et al, Lancet 2021

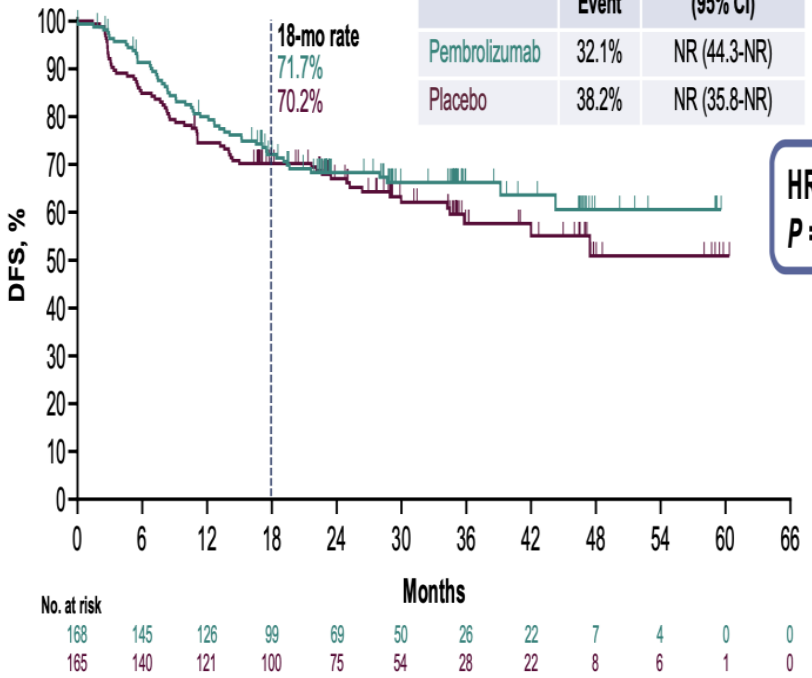
DFS, Overall Population



	Pts w/ Event	Median, mo (95% CI)
Pembrolizumab	35.9%	53.6 (39.2-NR)
Placebo	44.3%	42.0 (31.3-NR)

HR 0.76 (95% CI, 0.63-0.91)
P = 0.0014

DFS, PD-L1 TPS ≥50% Population



	Pts w/ Event	Median, mo (95% CI)
Pembrolizumab	32.1%	NR (44.3-NR)
Placebo	38.2%	NR (35.8-NR)

HR 0.82 (95% CI, 0.57-1.18)
P = 0.14

Received adjuvant chemotherapy		
Yes	506 (85.8%)	504 (85.9%)
No	84 (14.2%)	83 (14.1%)
PD-L1 TPS		
<1%	233 (39.5%)	232 (39.5%)
1-49%	189 (32.0%)	190 (32.4%)
≥50%	168 (28.5%)	165 (28.1%)

[c] 2 (0.3%) participants in the placebo group had stage IV disease.

Paz-Ares L et al, ESMO VIRTUAL PLENARY March 22

Immunoterapia e pattern di recidiva

Site of relapse, n (%)	Atezolizumab (n=156)	BSC (n=203)
Locoregional only	59 (37.8)	75 (36.9)
Distant only	67 (42.9)	82 (40.4)
CNS	16 (10.3)	29 (14.3)
Bone/bone marrow	14 (9.0)	14 (6.9)
Contralateral lung	10 (6.4)	16 (7.9)
Liver	10 (6.4)	8 (3.9)
Lymph node	8 (5.1)	11 (5.4)
Ipsilateral lung	6 (3.8)	8 (3.9)
Subcutaneous tissue	1 (0.6)	2 (1.0)
Other	16 (10.3)	15 (7.4)

Site of relapse, n (%)	Atezolizumab (n=156)	BSC (n=203)
Locoregional and distant	27 (17.3)	38 (18.7)
Bone/bone marrow	11 (7.1)	8 (3.9)
Contralateral lung	7 (4.5)	10 (4.9)
Liver	6 (3.8)	4 (2.0)
Lymph node	5 (3.2)	9 (4.4)
Ipsilateral lung	5 (3.2)	1 (0.5)
CNS	3 (1.9)	6 (3.0)
Subcutaneous tissue	1 (0.6)	0
Other	6 (3.8)	13 (6.4)

Felip E et al, ESMO 2021

Le prospettive future per la terapia adiuvante:

1- miglior definizione del rischio di recidiva negli stadi I (II)
(ADAURA 2)

2- possibile ruolo altre terapie targeted
(ALINA, ALCHEMIST, LIBRETTO 432…. More on perioperative treatment!)

3- Studio dei biomarcatori e ruolo della terapia neaodiuvante
(MRD, MERMAID 1-2)