IL VALORE DELL'INNOVAZIONE:

DALLA VALUTAZIONE ALLA GESTIONE DELLE CRITICITA'

Catanzaro, 20 giugno 2017

Innovazione in oncologia, stato dell'arte e prospettive future: il carcinoma polmonare

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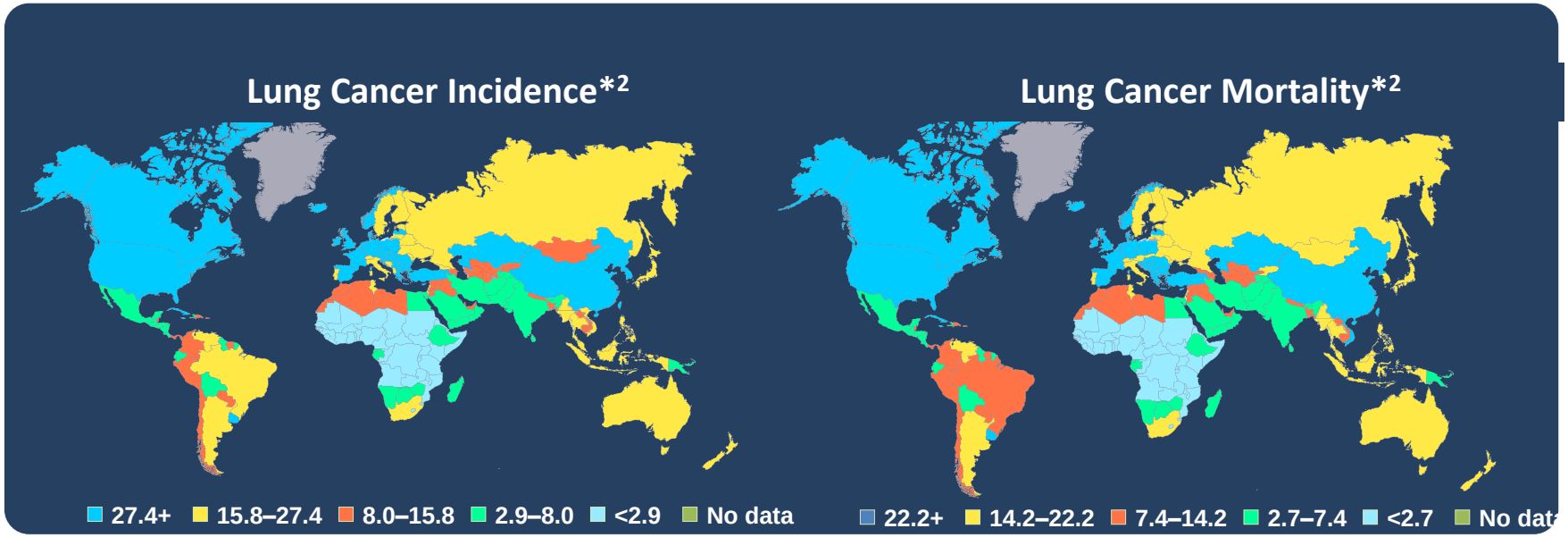
Ospedale «Tiberio Evoli»
Melito di Porto Salvo

Il Tumore del polmone è la prima causa di morte per cancro al mondo[1]

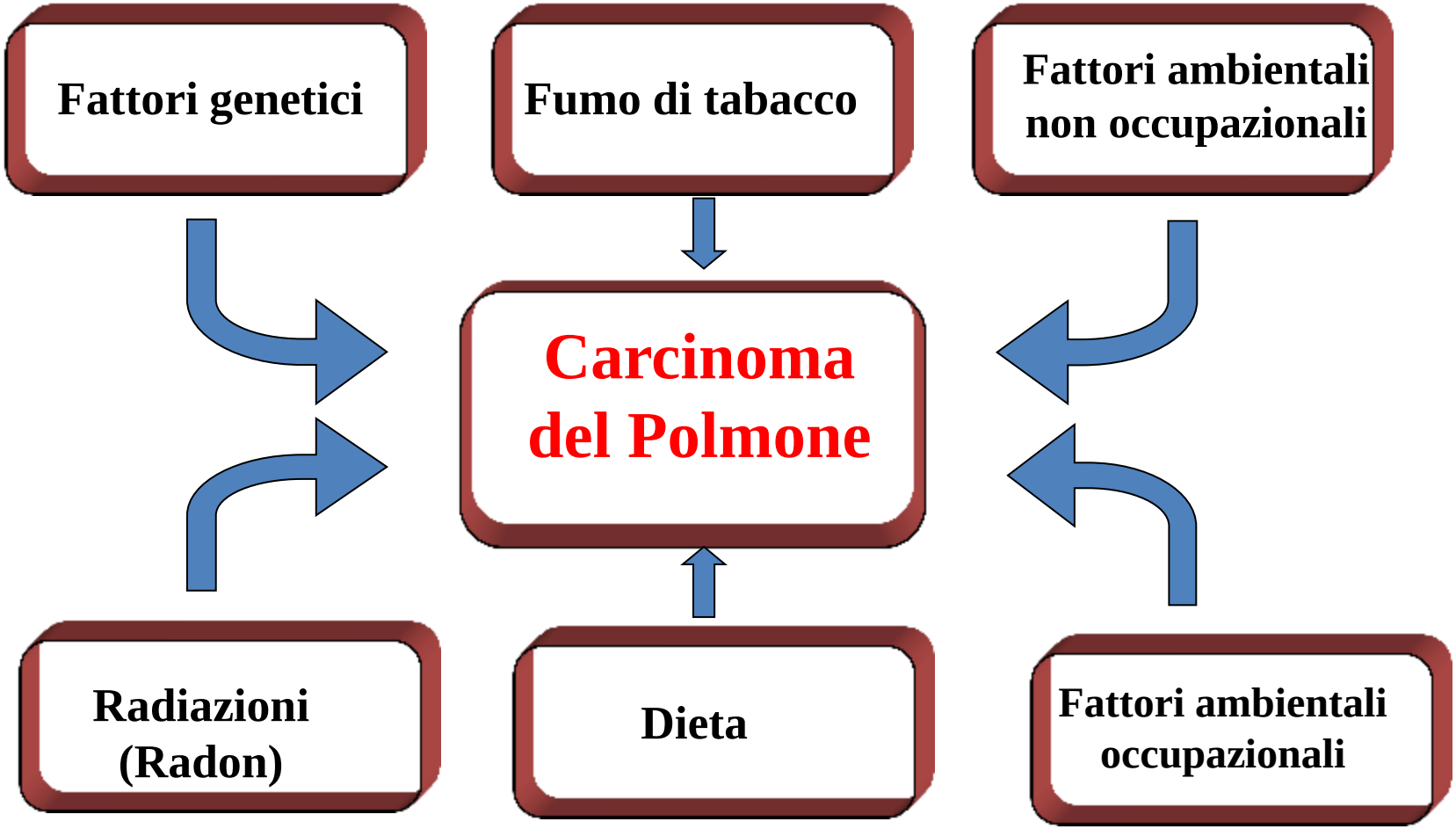


Adapted from GLOBOCAN 2012: Estimated Cancer Incidence, Mortality and Prevalence Worldwide in 2012.

- **In US: ~224.390 nuovi casi e ~158.080 decessi nel 2016[3]**
- **In EU: ~410.220 nuovi casi nel 2012 e ~279.400 decessi nel 2015[1,4]**

GLOBOCAN 2012: Population Fact Sheets. Available at: http://globocan.iarc.fr/Pages/fact_sheets_population.aspx. Accessed August 1, 2016.
GLOBOCAN 2012: Estimated Cancer Incidence, Mortality and Prevalence Worldwide in 2012. Available at: http://globocan.iarc.fr/Pages/Map.aspx. Accessed July 7, 2016.
ACS Lung Cancer Statistics. Available at: http://www.cancer.org/cancer/lungcancer-non-smallcell/detailedguide/non-small-cell-lung-cancer-key-statistics. Accessed July 7, 2016.
Malvezzi M, et al. Ann Oncol. 2015; 26(4):779-786.

FATTORI DI RISCHIO



ALGORITMO DIAGNOSTICO:
CLINICA – LABORATORIO - IMAGING

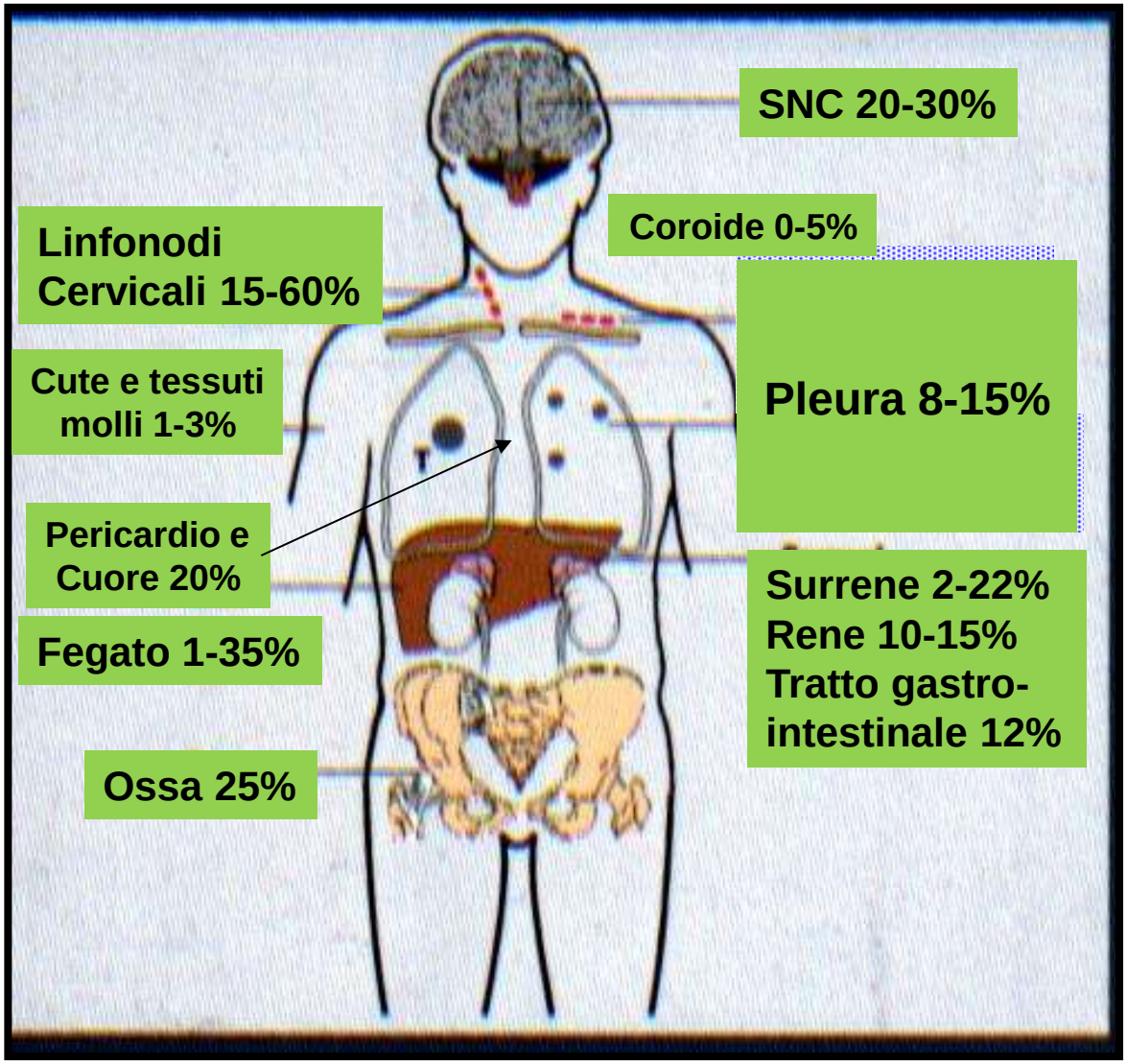
Diagnosi

- Rx Torace
- Citologia espettorato
- Broncoscopia con biopsia e/o citologia
- Agoaspirato TC guidato
- Mediastinoscopia
- Biopsia linfonodi superficiali
- Biopsia lesioni a distanza
- Toracentesi e citologia del versamento pleurico
- VATS: Videotoracoscopia
- Toracotomia

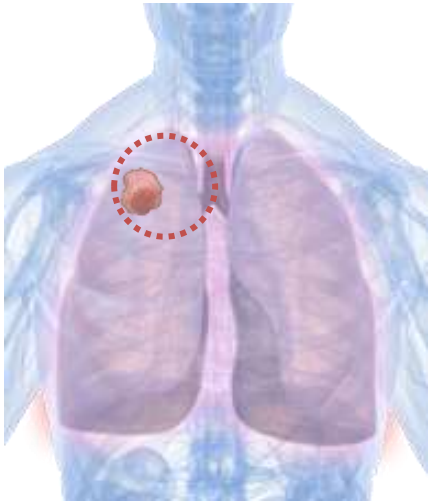
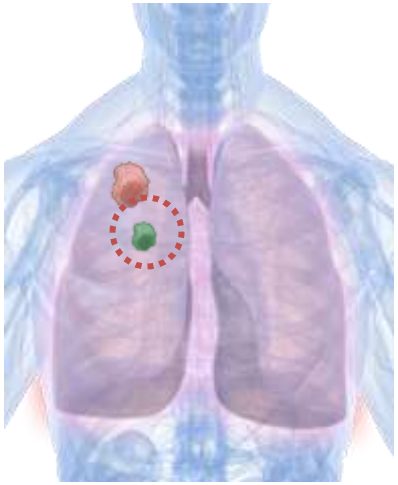
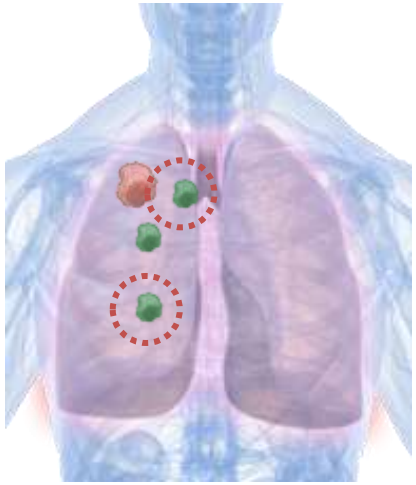
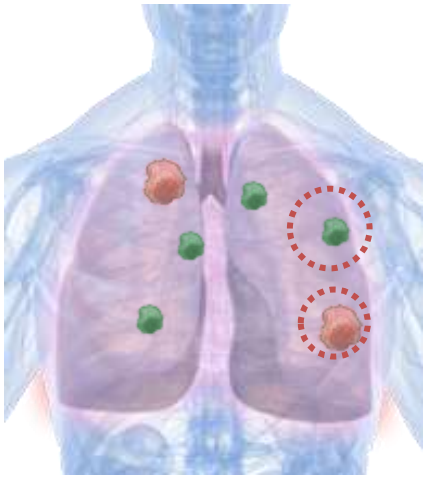
Stadiazione

- TC torace e quadranti sup. addome
- Ecografia addome (epatica)
- TC SNC
- Scintigrafia ossea
- PET

Metastasi a distanza



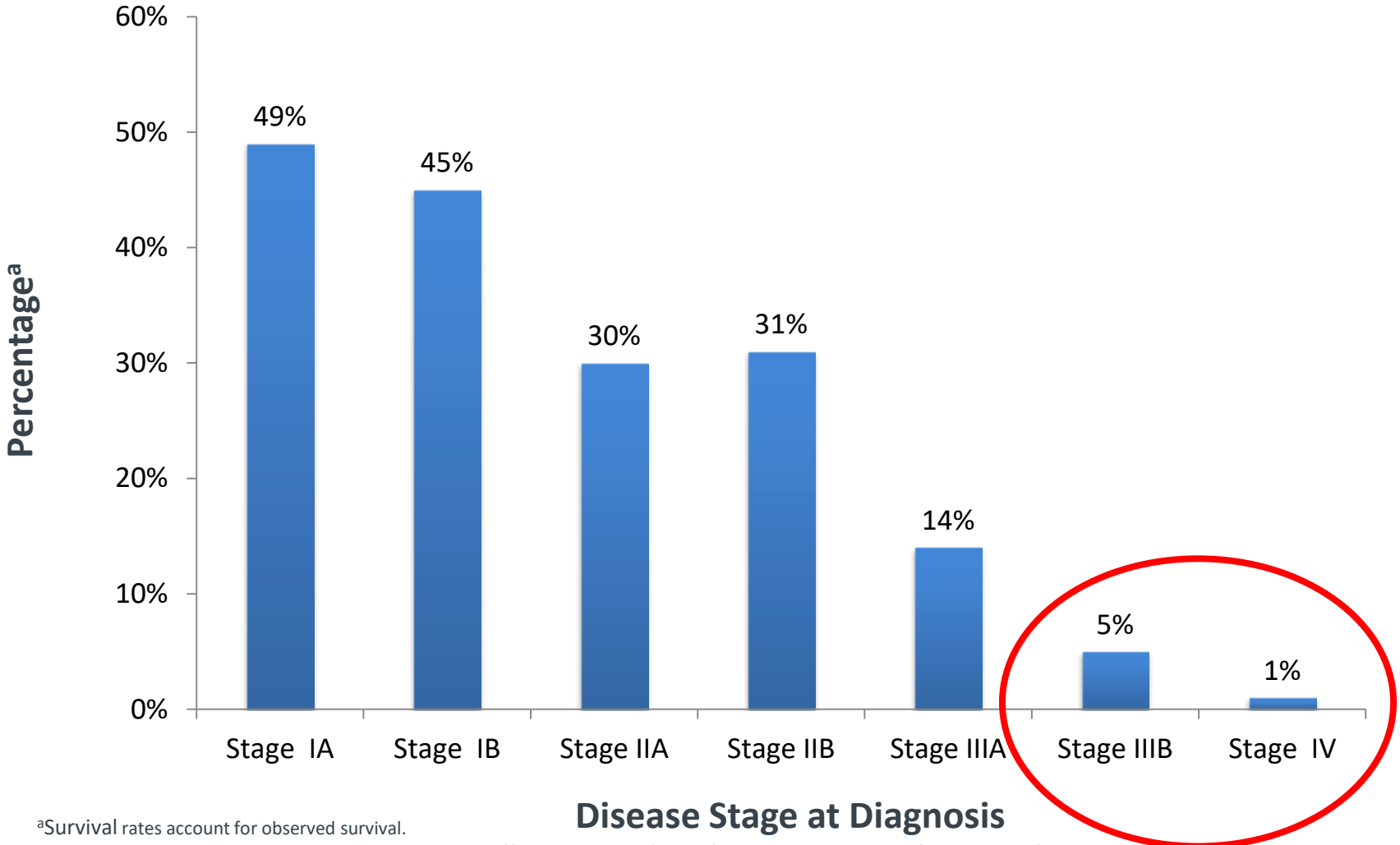
Nella maggior parte dei pazienti il NSCLC viene diagnosticato in fase avanzata

16% of patients		22% of patients	57% of patients
Stage I	**Stage II**	**Stage III**	**Stage IV**
			
Primary tumor	**Lymph node metastases**	**Lymph node metastases**	**Metastatic tumor**
Il cancro è 3-5 cm nel polmone e non si è diffuso.	**Il cancro è di 3-5 cm con metastasi linfo-nodali localizzate o è di 5-7 cm.**	**può essere diffuso allo sterno, alla pleura, al cuore o ai vasi sanguigni principali.**	**può essere diffuso in linfonodi lontani, nel polmone controlate-rale, o in altri organi.**

Adapted From National Cancer Institute. Non-Small Cell Lung Cancer Treatment(PDQ®).
Abbreviations and reference can be found in the speaker notes.

NSCLC: prognosi infausta in stadio avanzato

Sopravvivenza a 5 anni dalla diagnosi

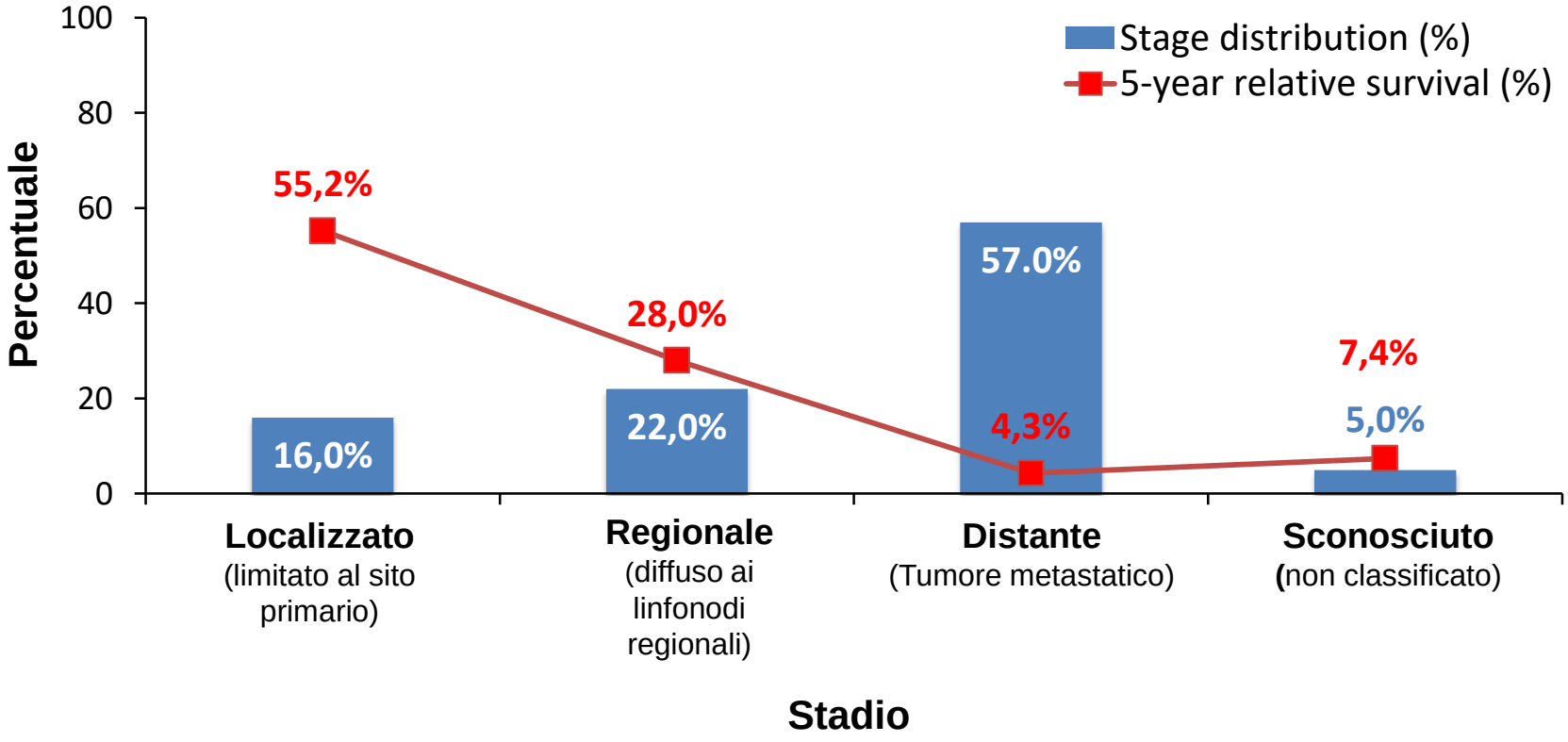


[a]Survival rates account for observed survival.

1. American Cancer Society. NSCLC survival by stage. http://www.cancer.org/cancer/lungcancer-non-smallcell/detailedguide/non-small-cell-lung-cancer-survival-rates. Accessed October 29, 2015.

Tumore polmonare negli USA: rapporto tra stadio di malattia alla diagnosi e sopravvivenza a 5 anni

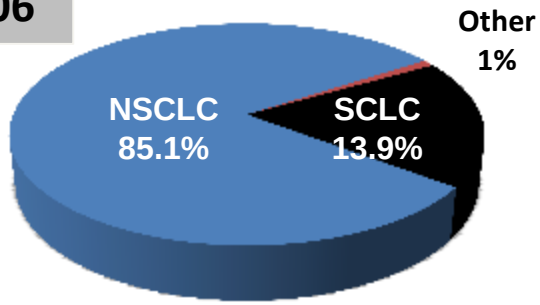
Riferimento dello studio 2006/12



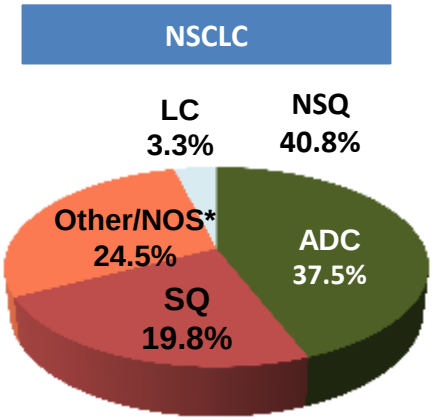
Adapted from Surveillance, Epidemiology, and End Results Program (SEER) Stat Fact Sheets: Lung and Bronchus Cancer.
Reference can be found in the speaker notes.

Esistono diverse sotto-popolazioni di NSCLC

Prima del 2006



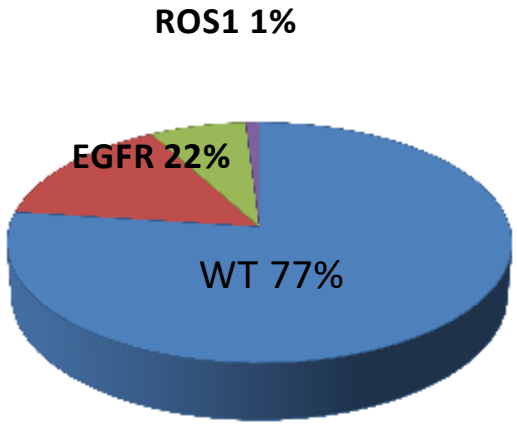
2006/12: suddivisione dei NSCLC



L'Istologia diventa fattore di trattamento

Assetto dei biomarcatori nei NSCLC oggi[4]

I biomarcatori diventano un fattore importante per le terapie mirate

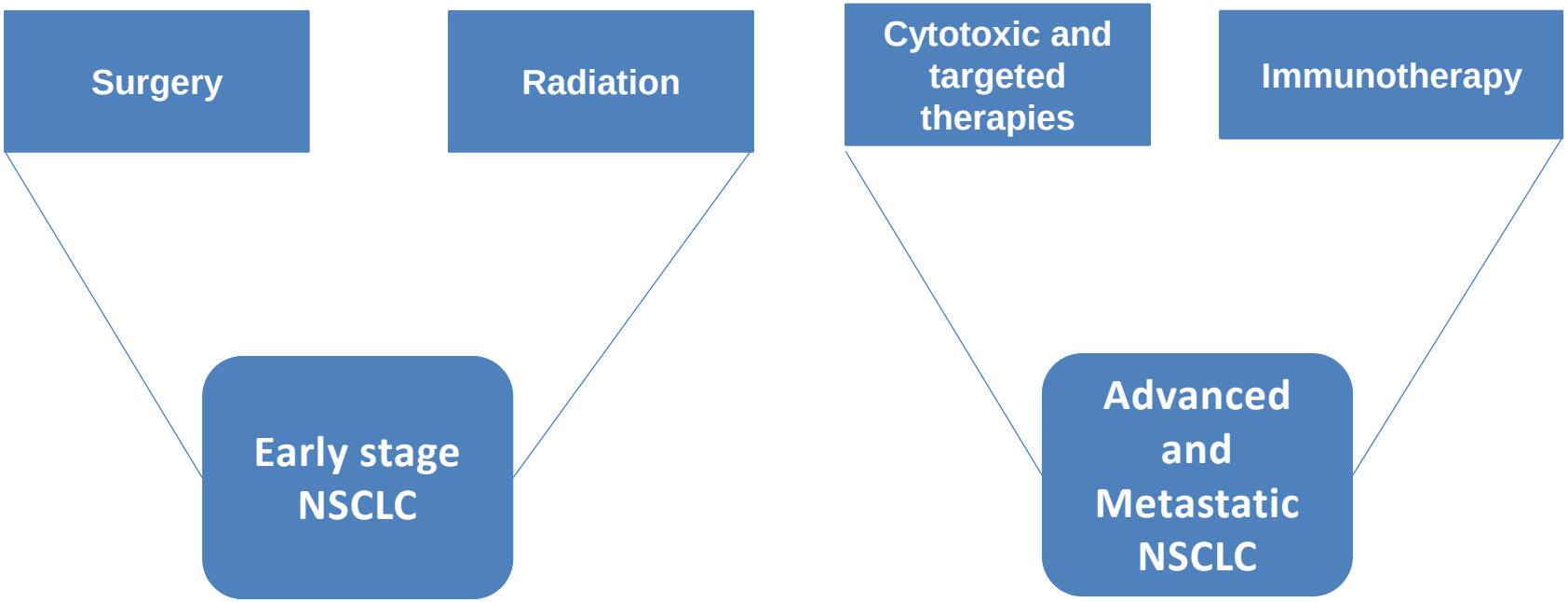


NOS), other specified carcinomas, and unspecified carcinomas.

1. SEER Cancer Statistics Review. 2. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for NSCLC V.4.2016. © National Comprehensive Cancer Network, Inc 2016. All rights reserved. Accessed January 12, 2016. To view the most recent and complete version of the guideline, go online to NCCN.org. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, and all other NCCN Content are trademarks owned by the National Comprehensive Cancer Network, Inc.

8. My Cancer Genome. Molecular Profiling of Lung Cancer. 9.

Le opzioni di trattamento per NSCLC

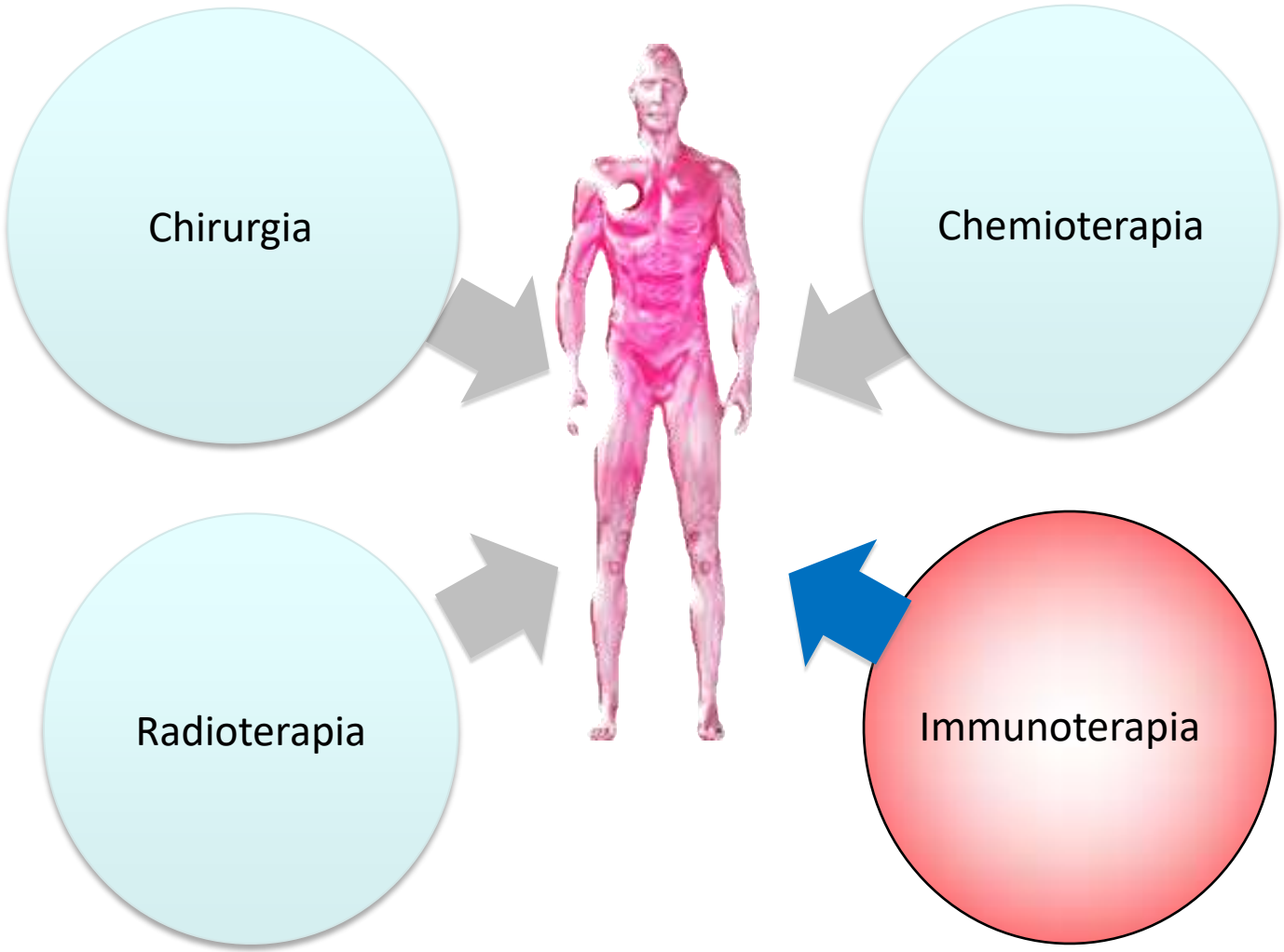


- **Il trattamento dipende dalla fase di malattia[1,2]:**
  - **La chirurgia, la radioterapia e la terapia adiuvante sono opzioni per la fase precoce NSCLC e per alcuni stadi avanzati NSCLC[1]**
  - **Le terapie citotossiche e mirate sono le opzioni di trattamento standard per NSCLC[1,2] avanzato e metastatico**

NSCLC = non-small cell lung cancer.

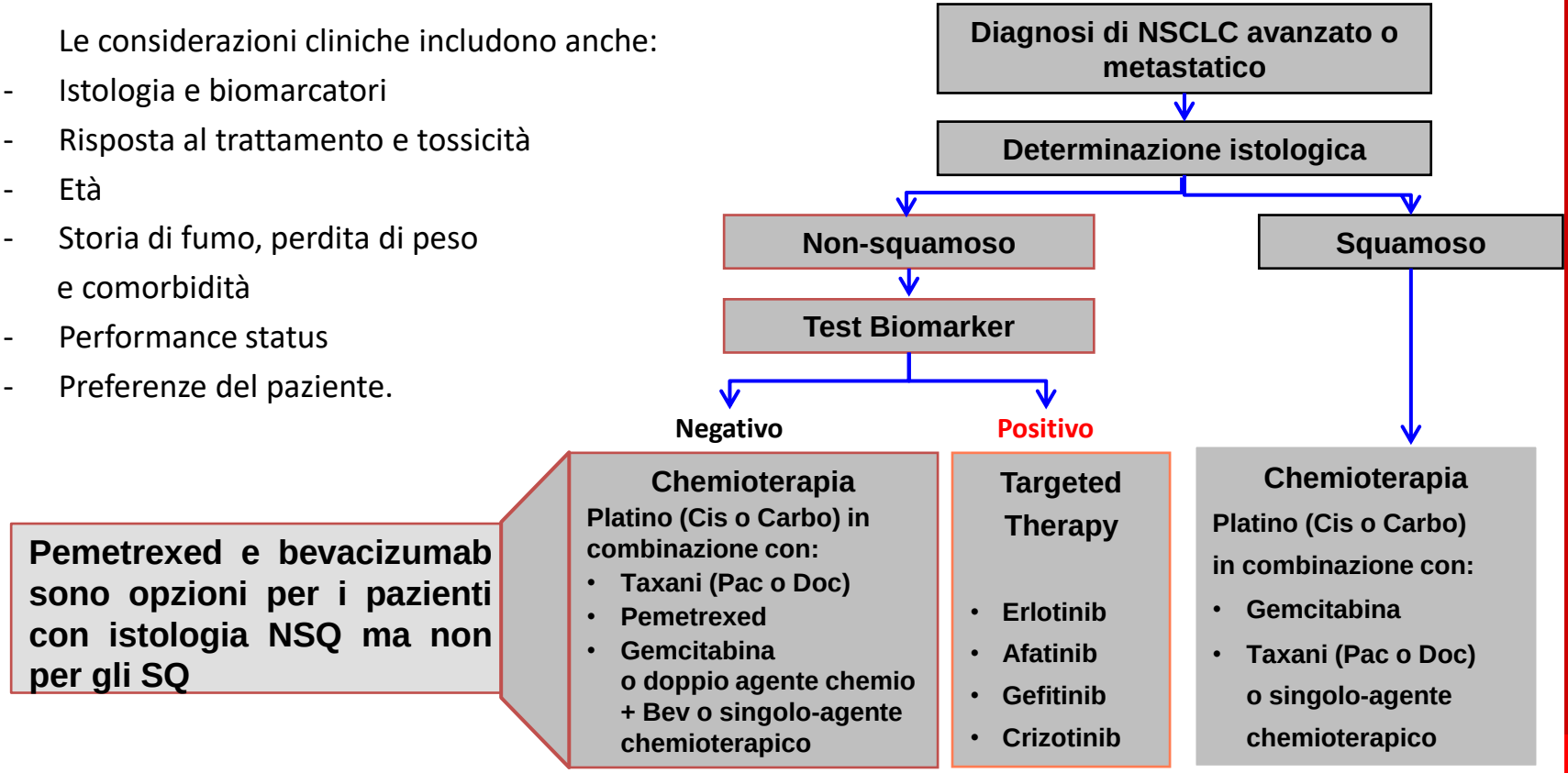
1. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for NSCLC V.4.2016. © National Comprehensive Cancer Network, Inc 2016. All rights reserved. Accessed January 12, 2016. To view the most recent and complete version of the guideline, go online to NCCN.org. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, and all other NCCN Content are trademarks owned by the National Comprehensive Cancer Network, Inc. 2. Reck M, et al. *Ann Oncol*. 2014;25(suppl 3):iii27-iii39.

Evoluzione delle opzioni terapeutiche



La scelta del trattamento del NSCLC 1L è guidata dall'istologia del tumore e dai biomarker

- Le considerazioni cliniche includono anche:
  - Istologia e biomarcatori
  - Risposta al trattamento e tossicità
  - Età
  - Storia di fumo, perdita di peso e comorbidità
  - Performance status
  - Preferenze del paziente.

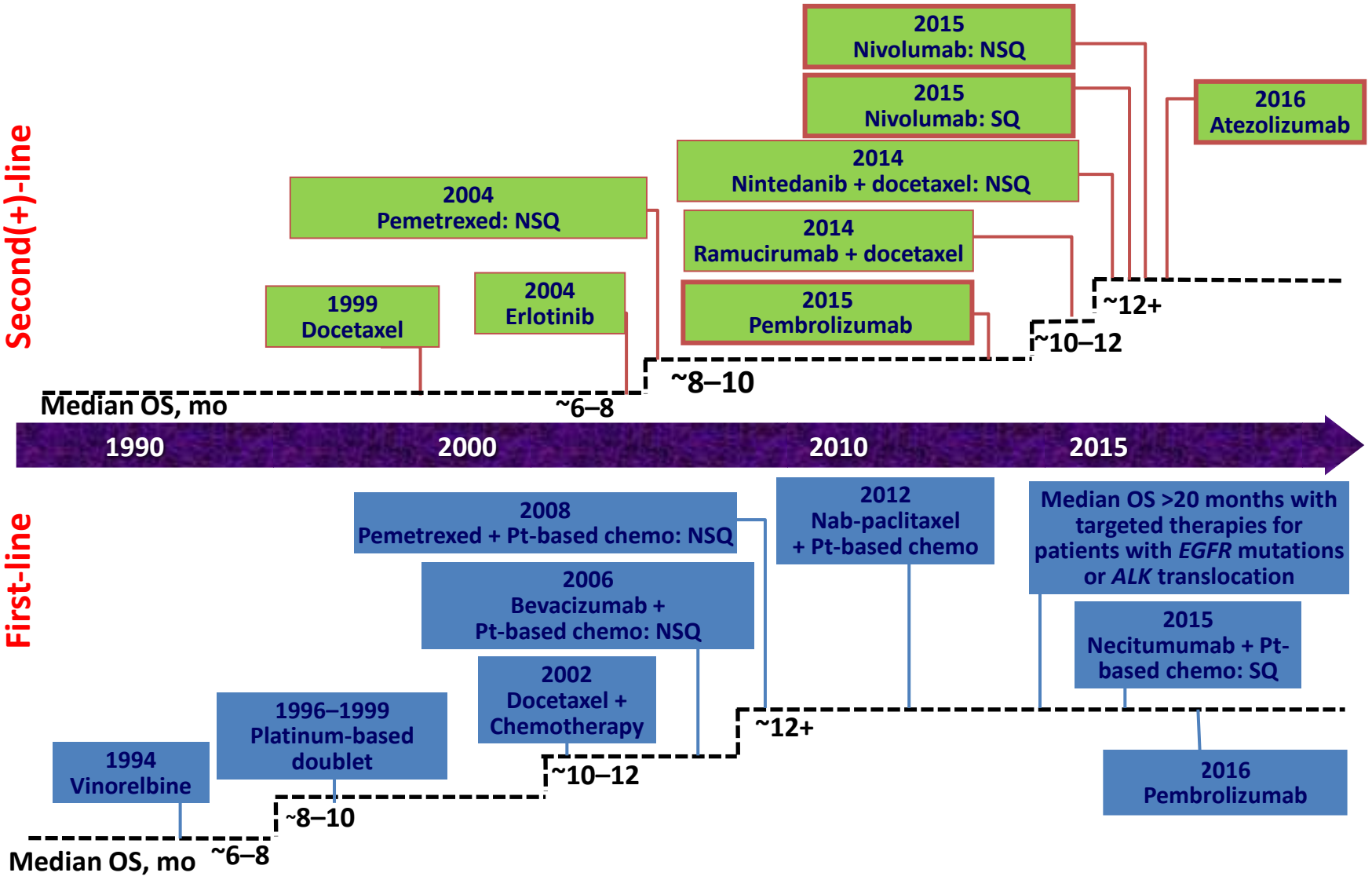


* Non-squamous NSCLC includes adenocarcinoma, large-cell carcinoma, and bronchioalveolar carcinoma. † EGFR and ALK biomarker testing is not routinely performed in squamous NSCLC. NCCN endorses broader molecular profiling to identify rare driver mutations for which effective drugs may be available.

ALK = anaplastic lymphoma kinase; Bev = bevacizumab; BSC = best supportive care; Cis = cisplatin; Carbo = carboplatin; Doc = docetaxel; EGFR = epidermal growth factor receptor; NSCLC = non-small cell lung cancer; NSQ = non-squamous; Pac = paclitaxel; SQ = squamous; TKI = tyrosine kinase inhibitor.

References available in speaker notes.

Progressi nella sopravvivenza da NSCLC



INNOVAZIONE

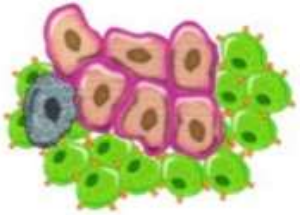
TEMPO

Chemioterapia

Distruzione Cellule Tumorali

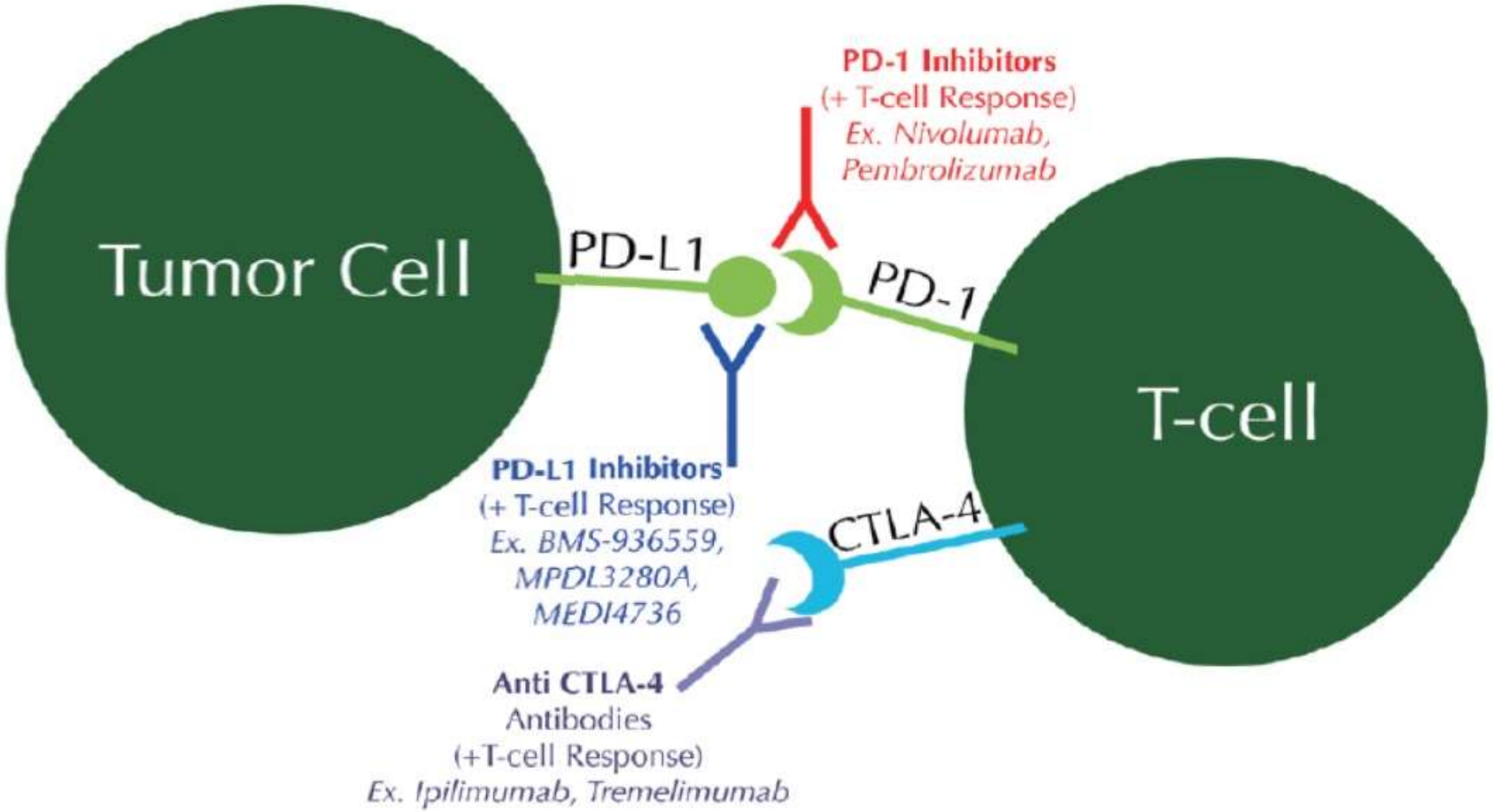
Immunoterapia

Attivazione Sistema Immunitario



Distruzione Cellule Tumorali

Immunoterapia Oncologica: meccanismo d'azione



Background: IO revolution in thoracic oncology

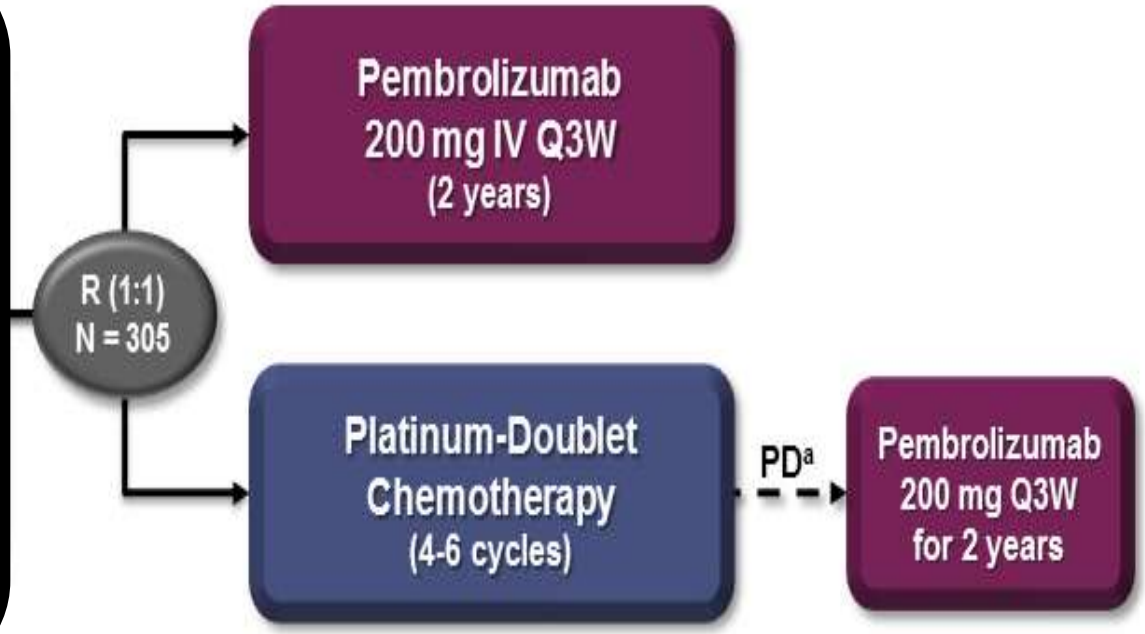
Studi conclusivi di NSCLC dell'inibitore PD-1 / PDL-1 di fase III

	Trial	Line	PDL-1	HR OS	HR PFS	result
Pembrolizumab	Keynote-024	1st v PDCT	≥50%	0.60	0.50	positive
Nivolumab	CheckMate-026	1st v PDCT	≥5%	1.02	1.15	neg
Pembrolizumab	Keynote-010	2nd v Doc	≥1%	0.61	0.71	positive
Nivolumab	CheckMate-017 squamous	2nd v Doc	na	0.62	0.63	positive
Nivolumab	CheckMate-057 non-squamous	2nd v Doc	na	0.73	0.92	positive
Atezolizumab	OAK	2nd v Doc	na	0.73	0.95	positive

Disegno dello Studio KEYNOTE - 024

Criteri di eleggibilità:

- NSCLC stadio IV non trattati
- Espres. PD-L1 ≥ 50%
- EGFR WT, ALK non traslocato
- MTS cerebrali non trattate
- Nessuna malattia autoimmune attiva che richiede una terapia sistemica



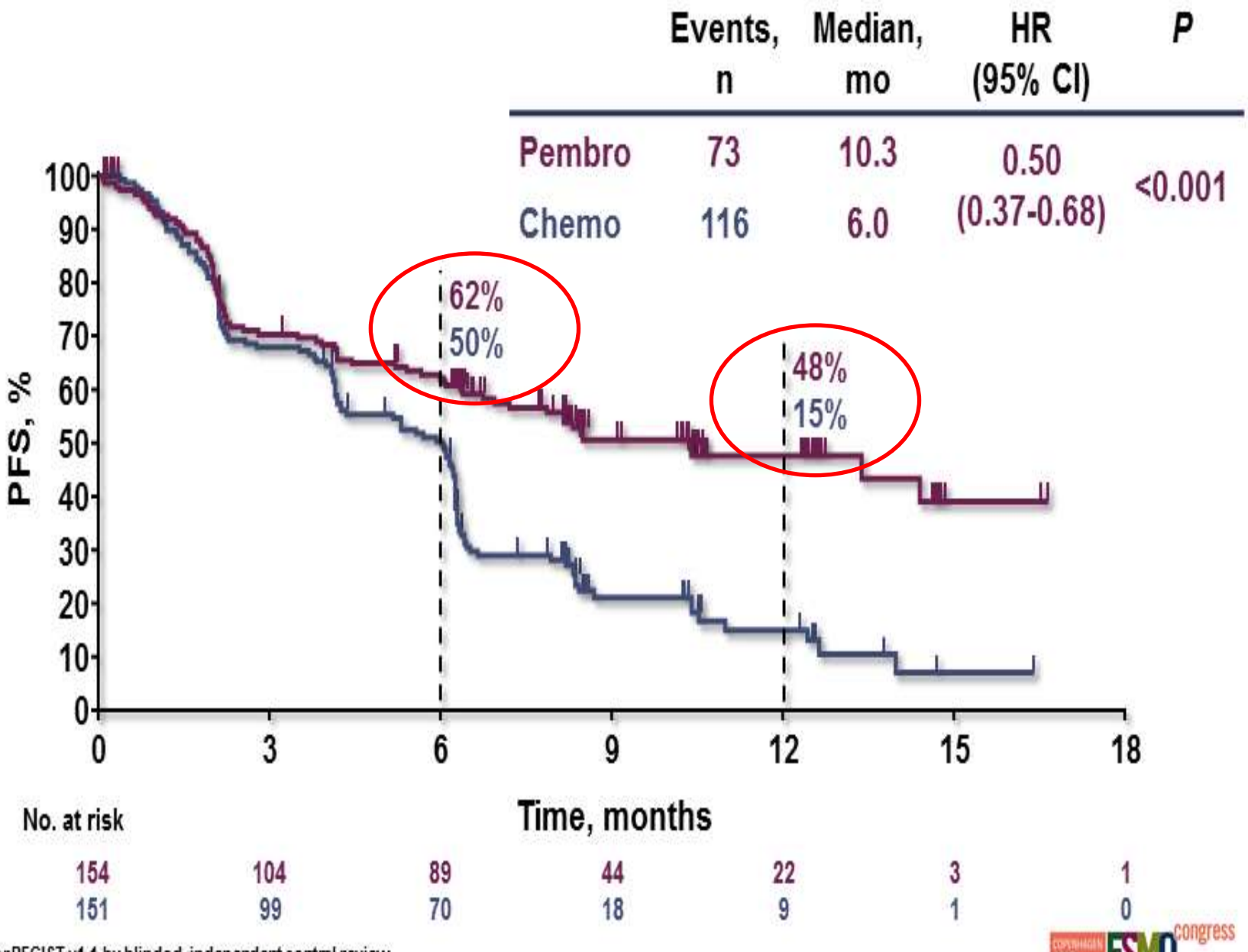
Key End Points

Primary: PFS (RECIST v1.1 per blinded, independent central review)

Secondary: OS, ORR, safety

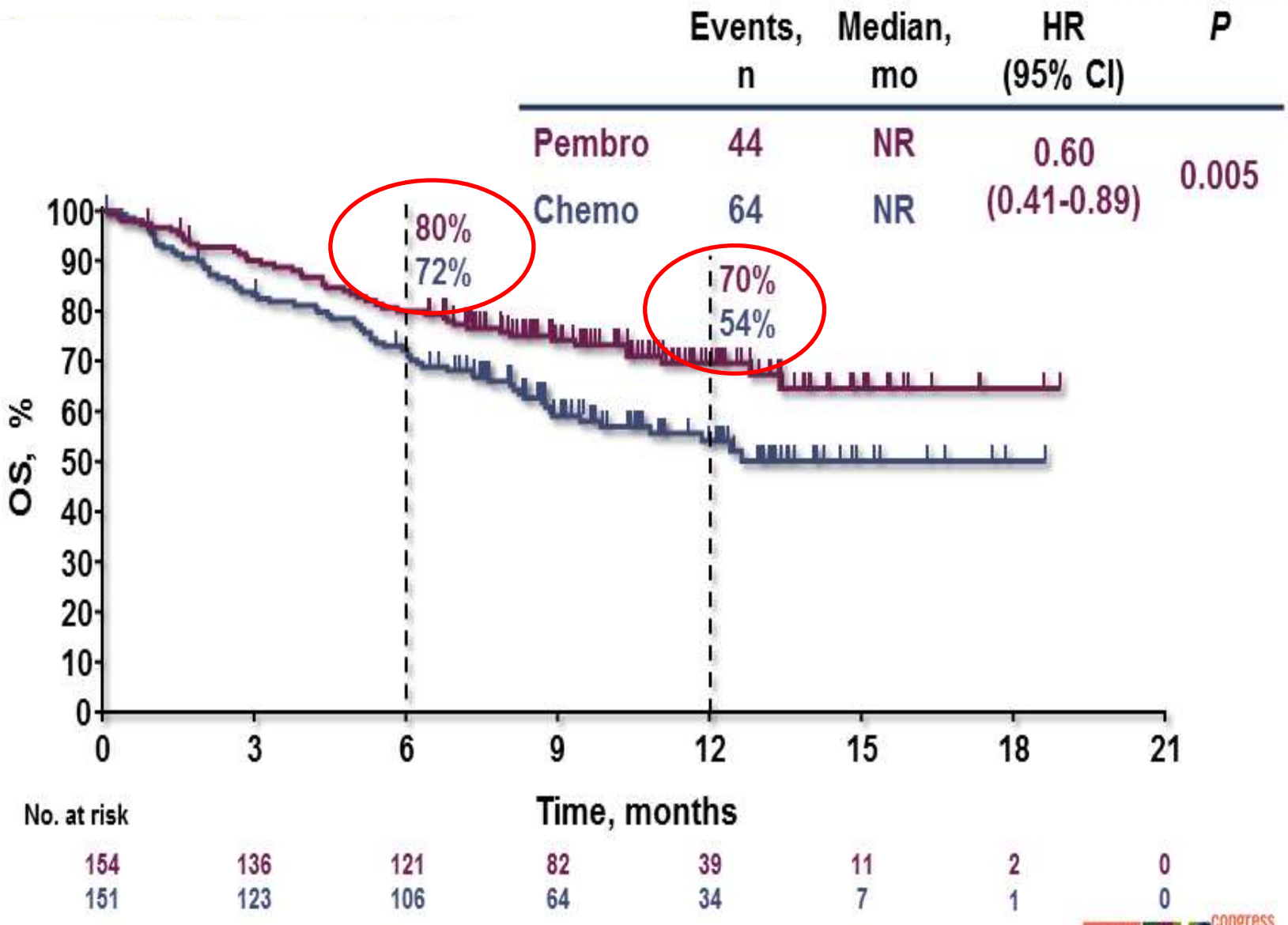
[a]To be eligible for crossover, progressive disease (PD) had to be confirmed by blinded, independent central radiology review and all safety criteria had to be met.

Sopravvivenza libera da progressione (PFS)



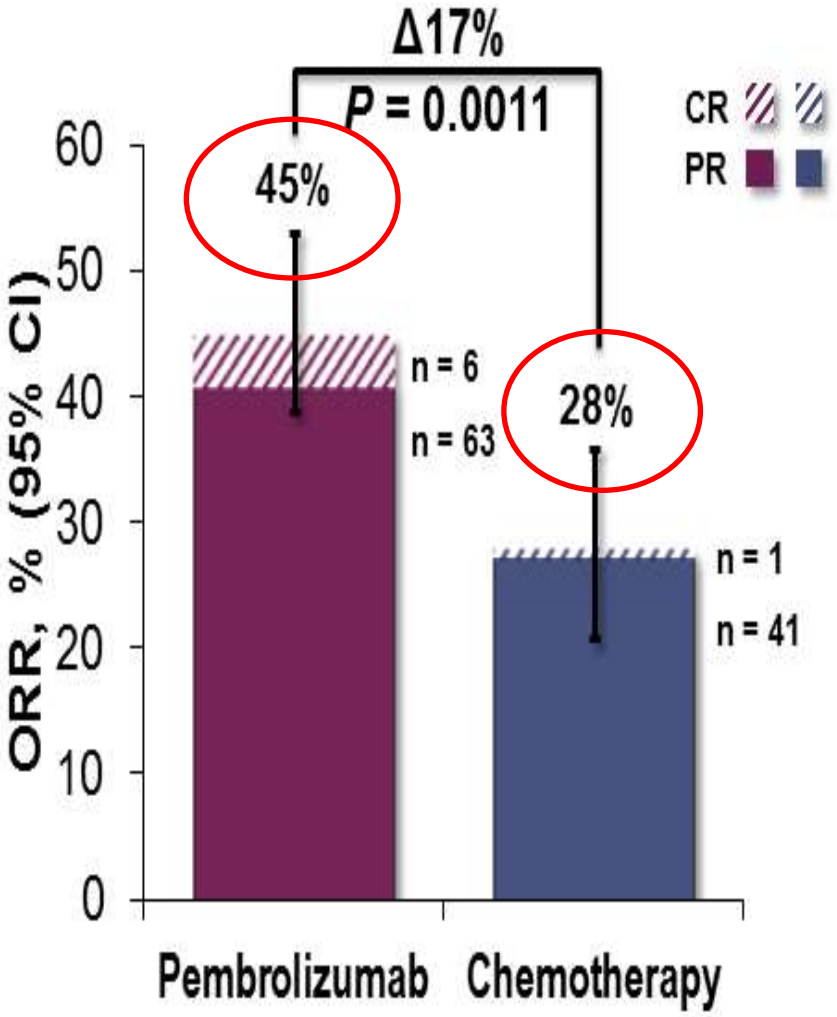
Assessed per RECIST v1.1 by blinded, independent central review.
Data cut-off: May 9, 2016.

SOPRAVVIVENZA GLOBALE (OS)



Data cut-off: May 9, 2016.

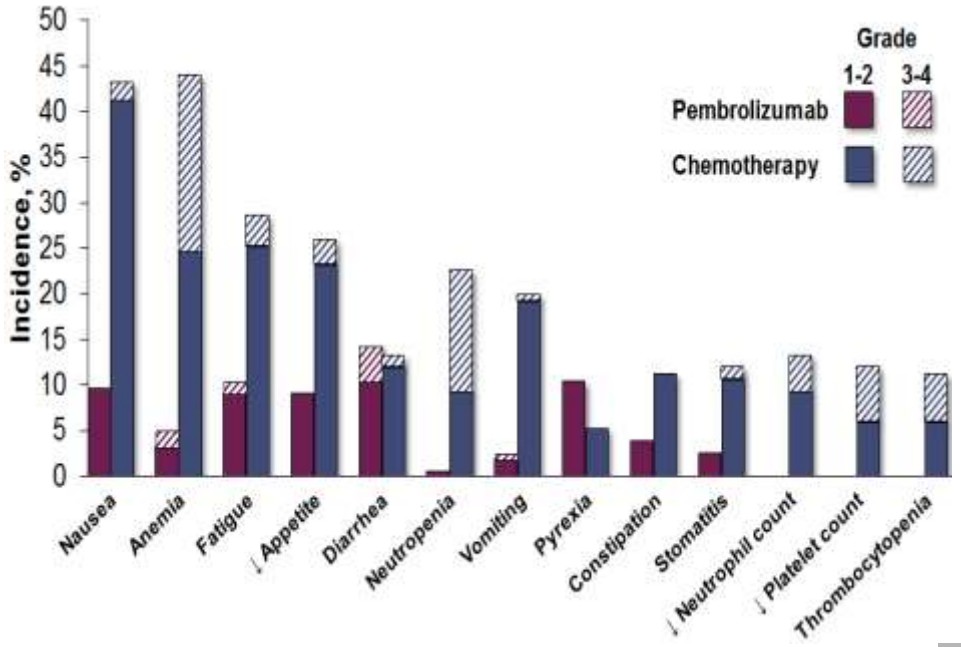
RISPOSTE OBIETTIVE (OSS)

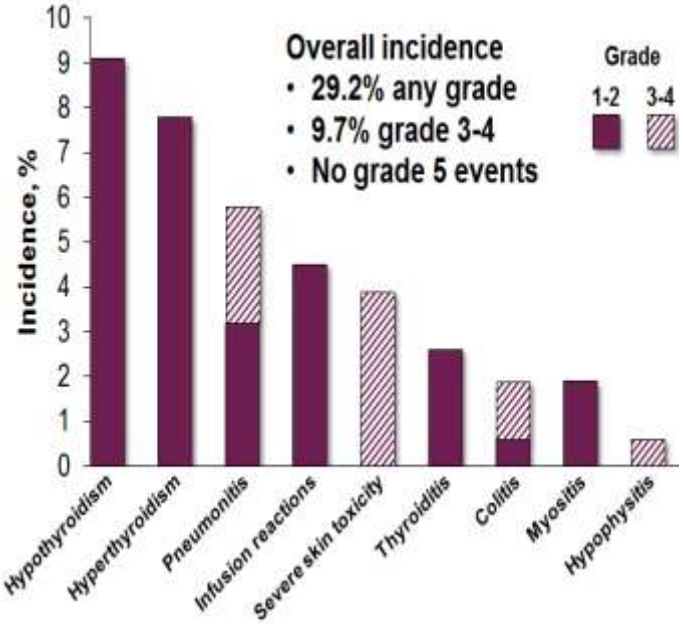


	Pembro Responders n = 69	Chemo Responders n = 42
TTR, mo median (range)	2.2 (1.4-8.2)	2.2 (1.8-12.2)
DOR, mo median (range)	NR (1.9+ to 14.5+)	6.3 (2.1+ to 12.6+)

Assessed per RECIST v1.1 by blinded, independent central review.
Data cut-off: May 9, 2016.

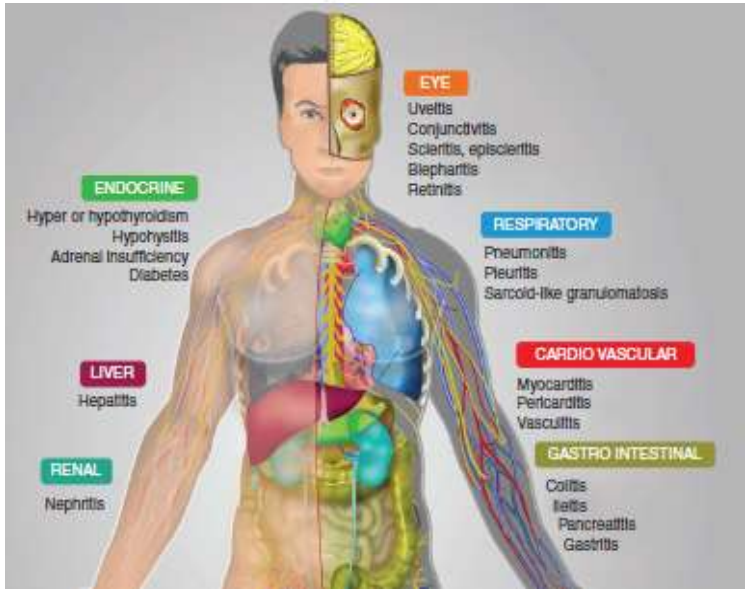
DATI DI TOLLERABILITA’



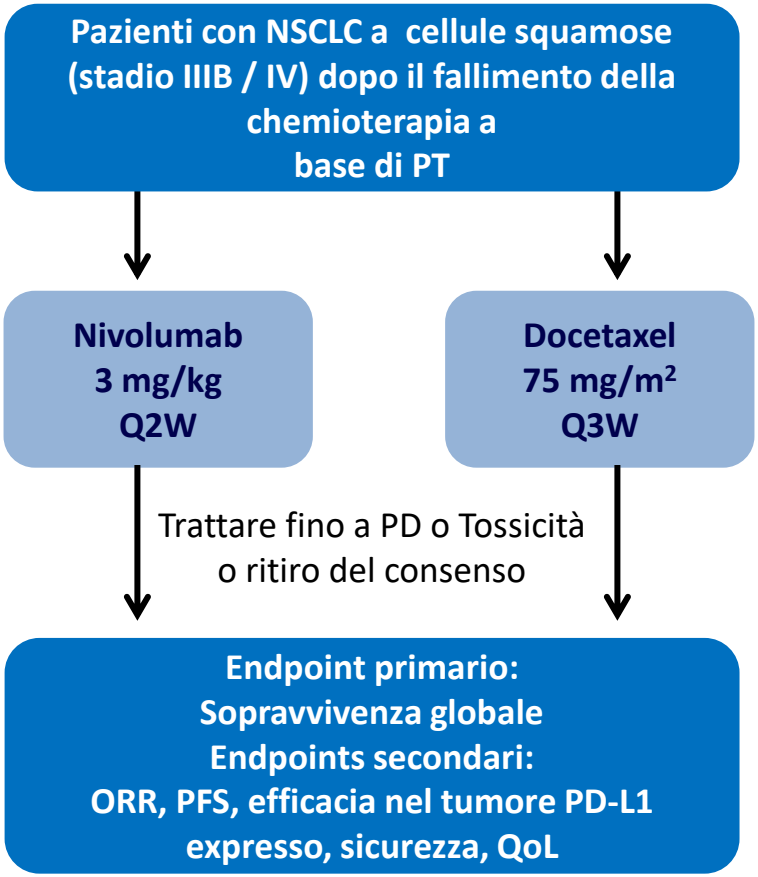


❖ Pembrolizumab

- Meno Eventi Avversi (AE)
- Migliore profilo di tollerabilità globale
- Diverso spettro di tossicità
- AE Immuno-mediati nel 30% dei pazienti, Il 10% di loro gravi (G3-4)



Studio 017: Nivolumab in monoterapia in 2° linea



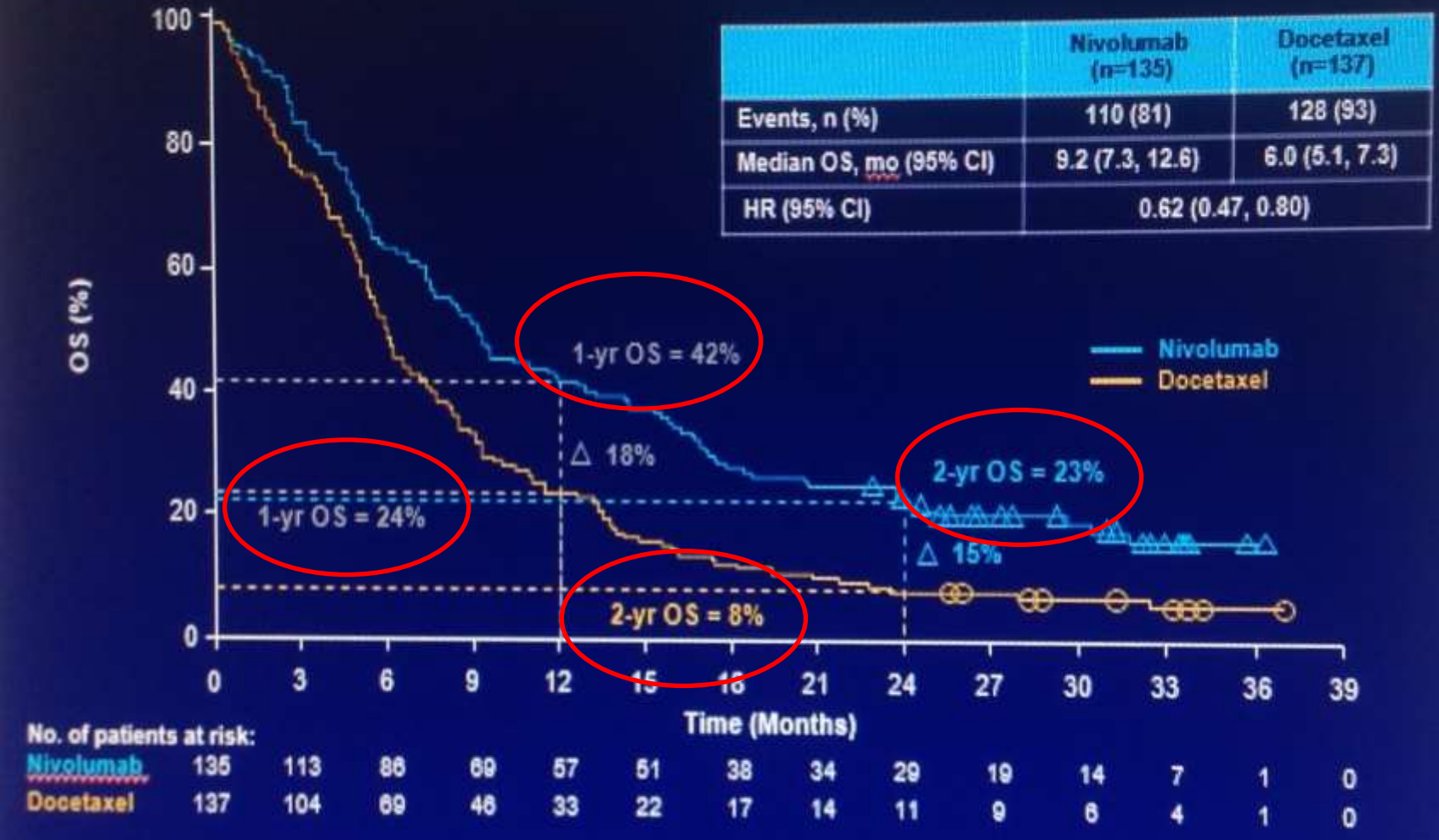
Ulteriori criteri di idoneità:

- **≥18 anni di età**
- **Una precedente chemioterapia a base di platino**
- **ECOG PS 0-1**
- **Campioni tumorali pretrattati (archiviati o freschi) necessari per l'analisi PD-L1**
- **Nessuna metastasi attiva, conosciuta o sospetta malattia autoimmune e nessuna meningite, carcinoma o malattia polmonare interstiziale**
- **Nessun trattamento precedente con docetaxel, anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CTLA-4 o anti-CD137**
- **Nessun trattamento precedente con CA184-104**

Data di inizio: Settembre 2012
Chiusura dello Studio: Gennaio 2017
Data prima stima: Novembre 2014
Stato: Attivo, non reclutare

Adapted from Borghaei H, et al. Presentation at ASCO 2016 (Abstract 9025).
Abbreviations and references can be found in the speaker notes.

SOPRAVVIVENZA GLOBALE (OS)



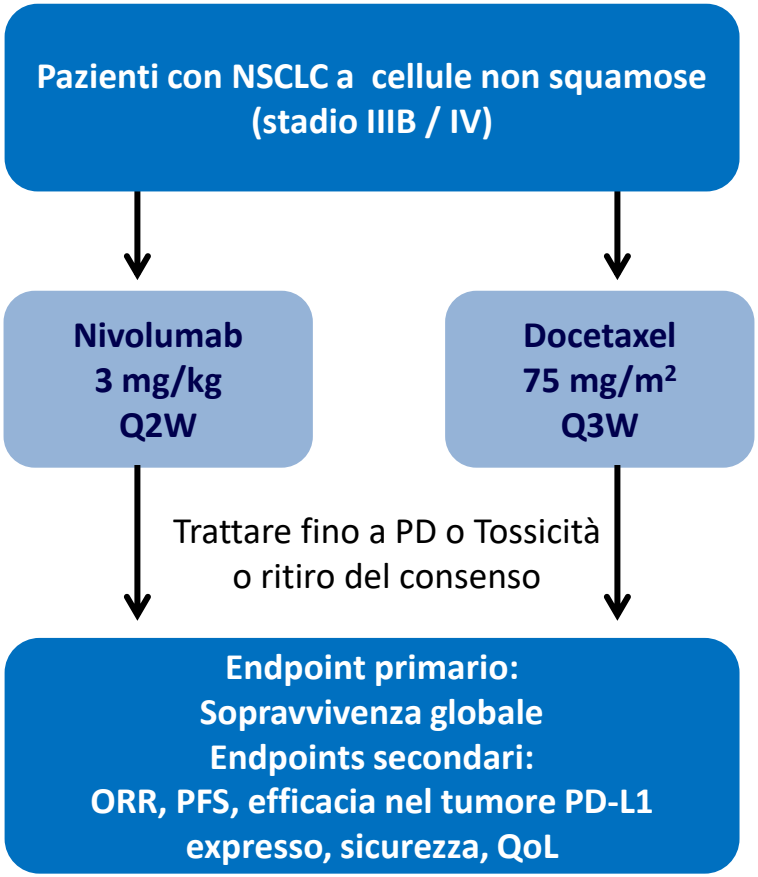
	Nivolumab (n=135)	Docetaxel (n=137)
Events, n (%)	110 (81)	128 (93)
Median OS, mo (95% CI)	9.2 (7.3, 12.6)	6.0 (5.1, 7.3)
HR (95% CI)	0.62 (0.47, 0.80)	

No. of patients at risk:

Nivolumab	135	113	86	69	57	51	38	34	29	19	14	7	1	0
Docetaxel	137	104	69	46	33	22	17	14	11	9	6	4	1	0

Based on February 2016 database lock; Minimum follow-up for survival: 24.2 months; symbols refer to censored observations.
Adapted from Barlesi F, et al. Presented at ESMO. 2016_1215.
Abbreviations and references can be found in the speaker notes.

Studio 057: Nivolumab in monoterapia ≥2° linea



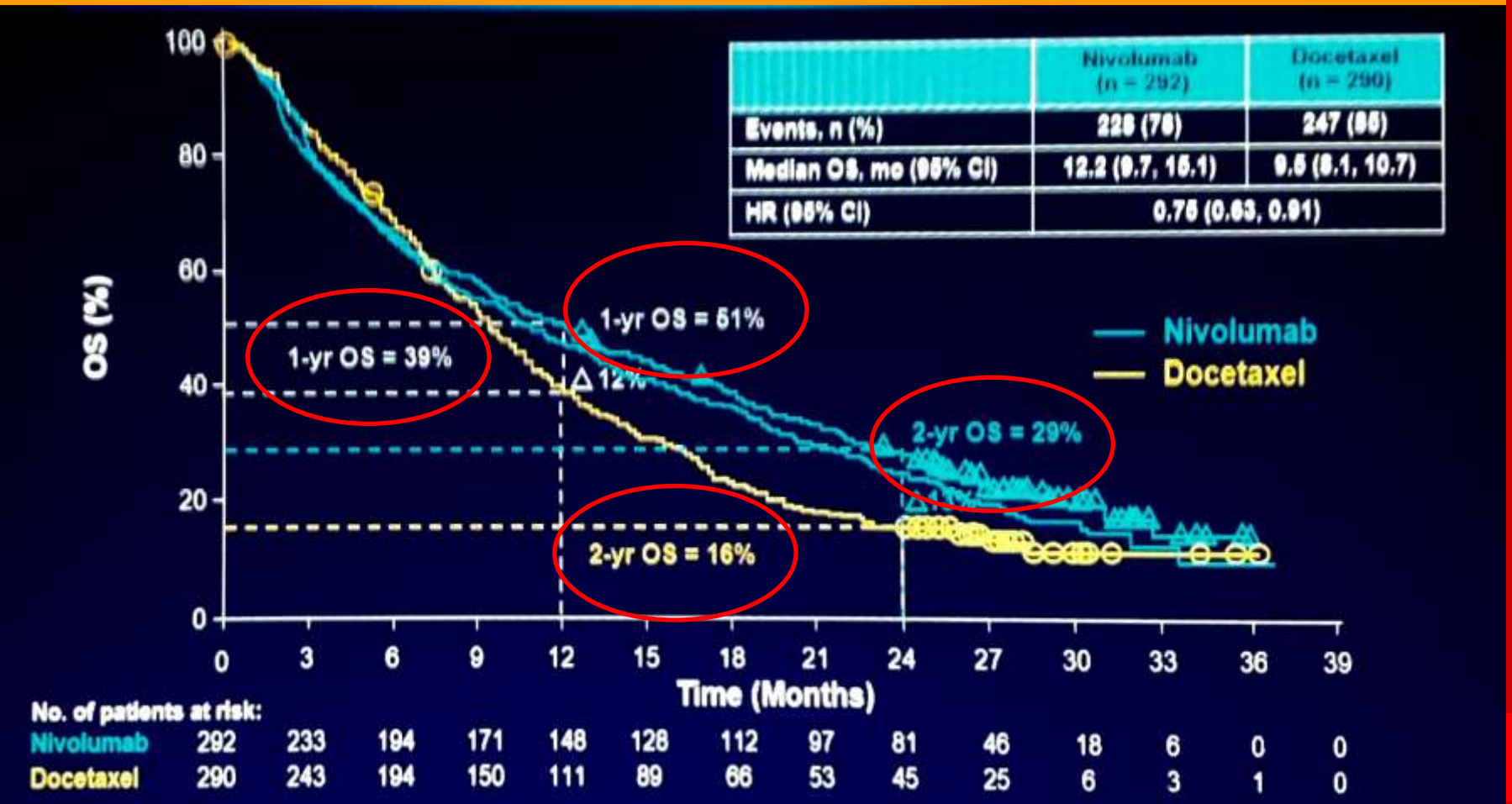
Ulteriori criteri di idoneità:

- **≥18 anni di età**
- **ECOG PS 0-1**
- **Una precedente chemioterapia a base di platino**
- **Campioni tumorali necessari per l'analisi PD-L1**
- **La terapia preventiva di mantenimento è consentita**
- **La terapia con TKI precedente consentiva la nota traslocazione ALK o la mutazione EGFR**
- **Nessun trattamento precedente con docetaxel, anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137 o anti-CTLA-4**
- **Nessuna malattia o metastasi non trattate, meningite carcinomatosa o malattia autoimmune**
- **Nessun trattamento sistemico con immunosoppressori entro 14 giorni dalla randomizzazione**

Data di inizio: Ottobre 2012
Chiusura dello Studio: Maggio 2016
Data prima stima: Febbraio 2015
Stato: chiuso

Adapted from Boghaei H, et al. Presented at ASCO. 2016_9025.
Abbreviations and references can be found in the speaker notes.

Sopravvivenza globale con follow-up esteso



	Nivolumab (n = 292)	Docetaxel (n = 290)
Events, n (%)	226 (78)	247 (85)
Median OS, mo (95% CI)	12.2 (9.7, 15.1)	9.5 (8.1, 10.7)
HR (95% CI)	0.76 (0.63, 0.91)	

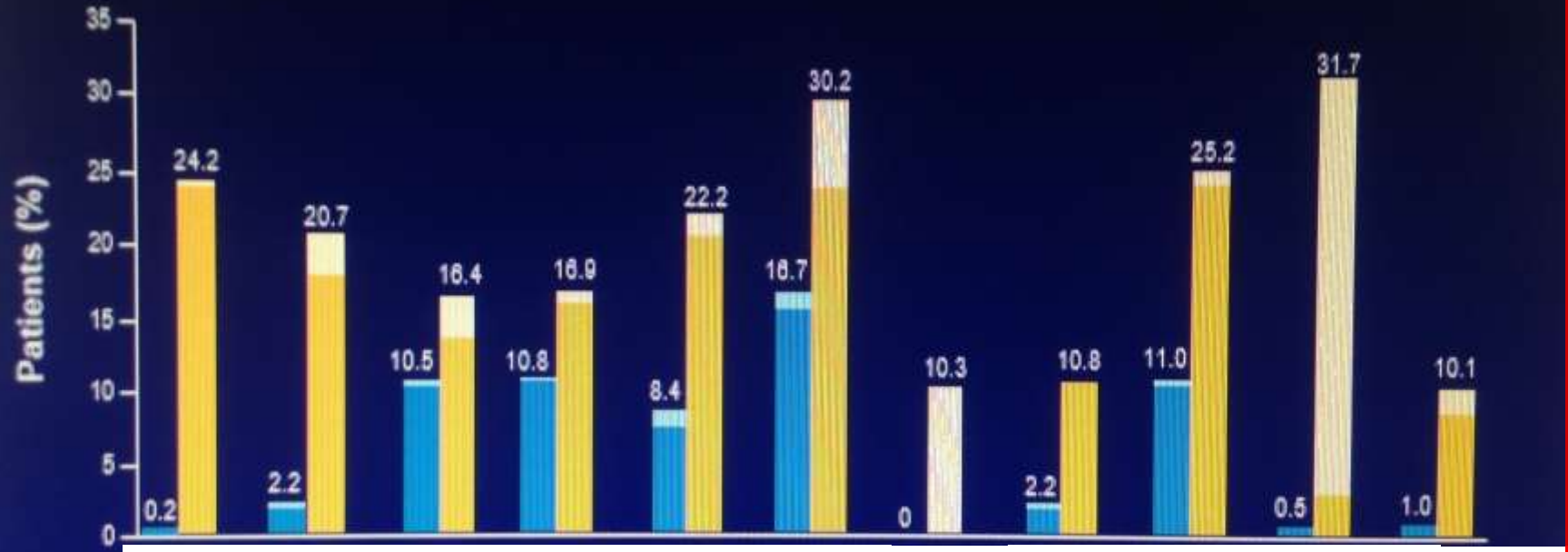
No. of patients at risk:													
Nivolumab	292	233	194	171	148	128	112	97	81	46	18	6	0	0
Docetaxel	290	243	194	150	111	89	66	53	45	25	6	3	1	0

Based on a February 2016 database lock.

Adapted from Barlesi F, et al. Presented at ESMO. 2016_1215.

Abbreviations and references can be found in the speaker notes.

EA più frequenti correlati al trattamento



Data are based on a February 18, 2016 database lock.

*Reported in ≥10% of patients in either treatment group. †Mean treatment duration was 7.5 months with nivolumab and 2.5 months with docetaxel in CheckMate 017, and 7.0 months with nivolumab and 3.3 months with docetaxel in CheckMate 057.

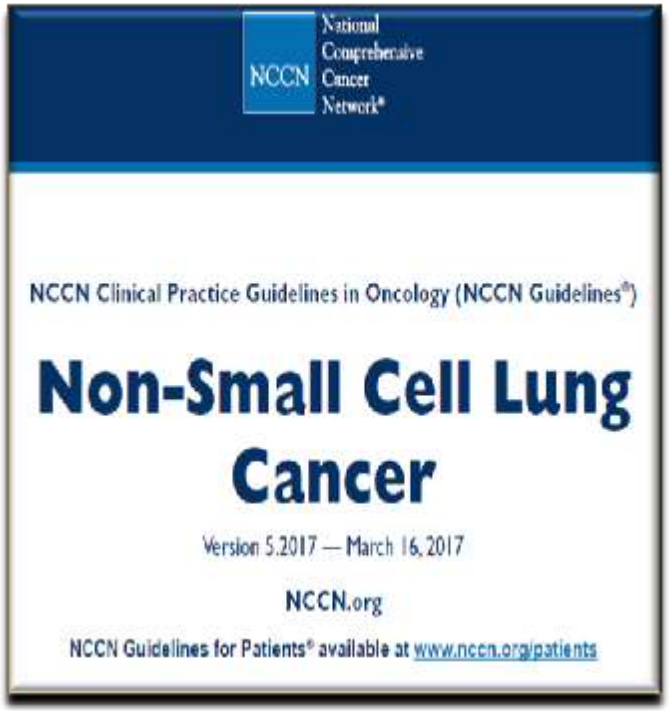
Adapted from Barlesi F, et al. Poster presented at ESMO 2016_1215.

Abbreviations and references can be found in the speaker notes.

Regole generali:
Gestione di AEs connessi con Nivolumab

Grado	Gestione	Continuare il farmaco?
Basso	Ritardare la dose	Riprendi il Nivolumab quando gli AE si risolvono
Moderato ~ alto	Somministrare i corticosteroidi Immunosoppressori (Anti-TNF, micofenolato, ecc)	Interrompere definitivamente il Nivolumab (Ritardo in alcune situazioni)

Linee Guida
AIOM-ESMO-NCCN



NCCN National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Non-Small Cell Lung Cancer

Version 5.2017 — March 16, 2017

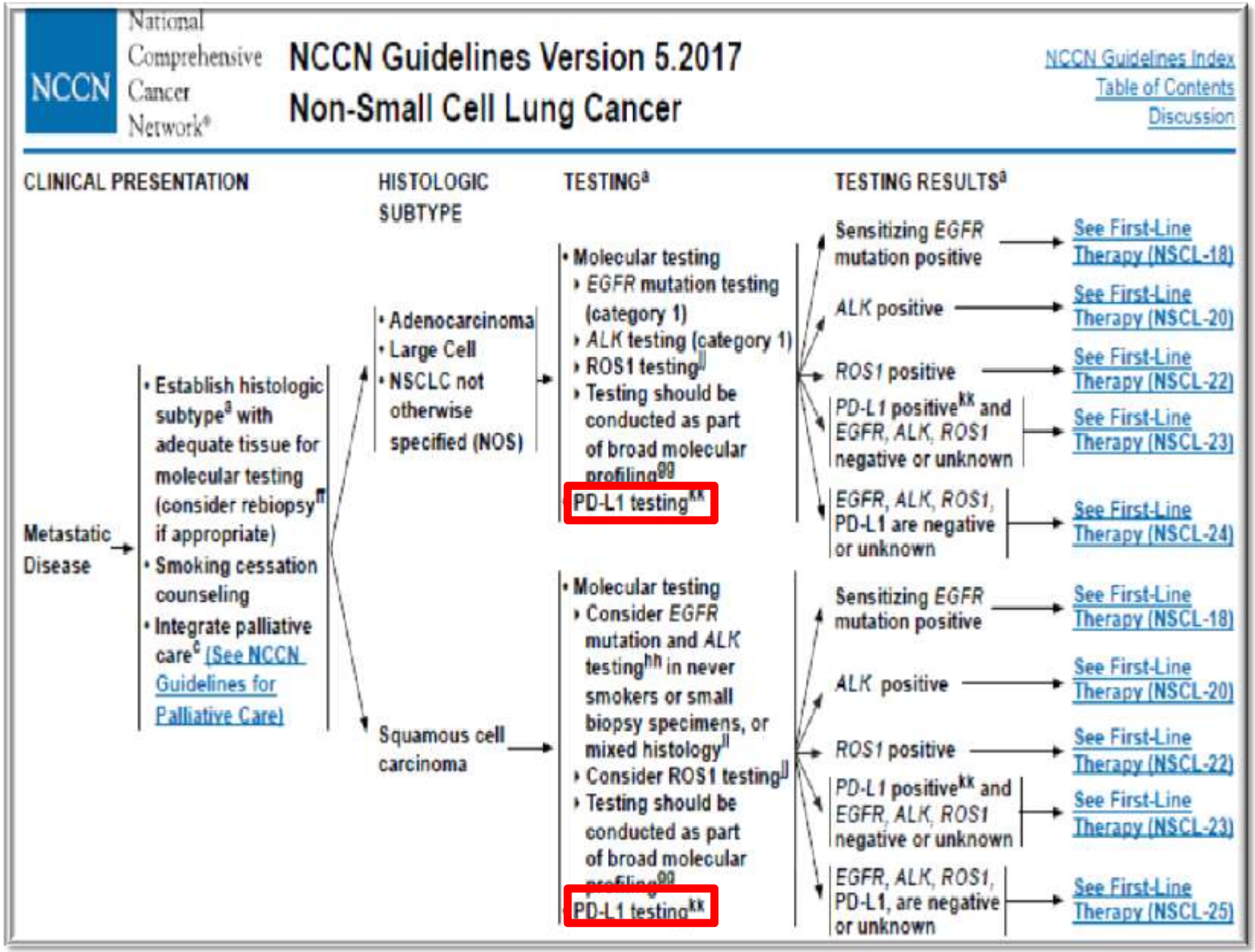
NCCN.org

NCCN Guidelines for Patients® available at www.nccn.org/patients

Per l'aggiornamento del 2017, il pannello NCCN raccomanda gli inibitori del controllo immunitario come agenti preferiti per la seconda linea e oltre di terapia in pazienti con NSCLC metastatico.

Le Linee Guida NCCN raccomandano la valutazione dell'espressione di PD-L1 alla diagnosi di NSCLC localmente avanzato o metastatico

- Il test di PD-L1 dovrebbe essere eseguito alla diagnosi.[12]
- La caratterizzazione molecolare del carcinoma polmonare è raccomandata alla diagnosi per l'identificazione del trattamento al quale il paziente ha maggior probabilità di rispondere.
- Il paziente che non è stato testato alla diagnosi, dovrebbe comunque esser testato per PD-L1.


NCCN
National Comprehensive Cancer Network®
NCCN Guidelines Version 5.2017
Non-Small Cell Lung Cancer
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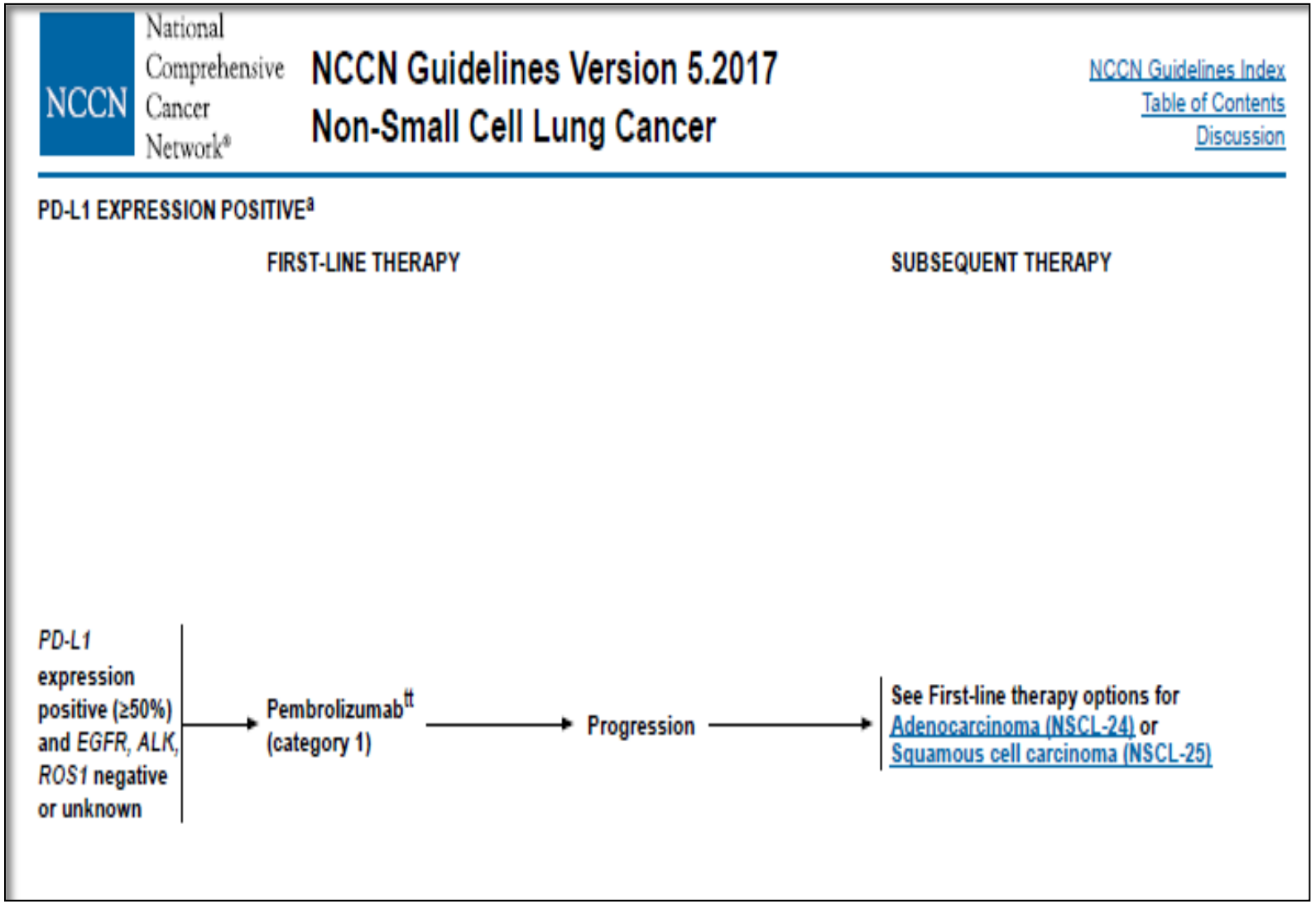
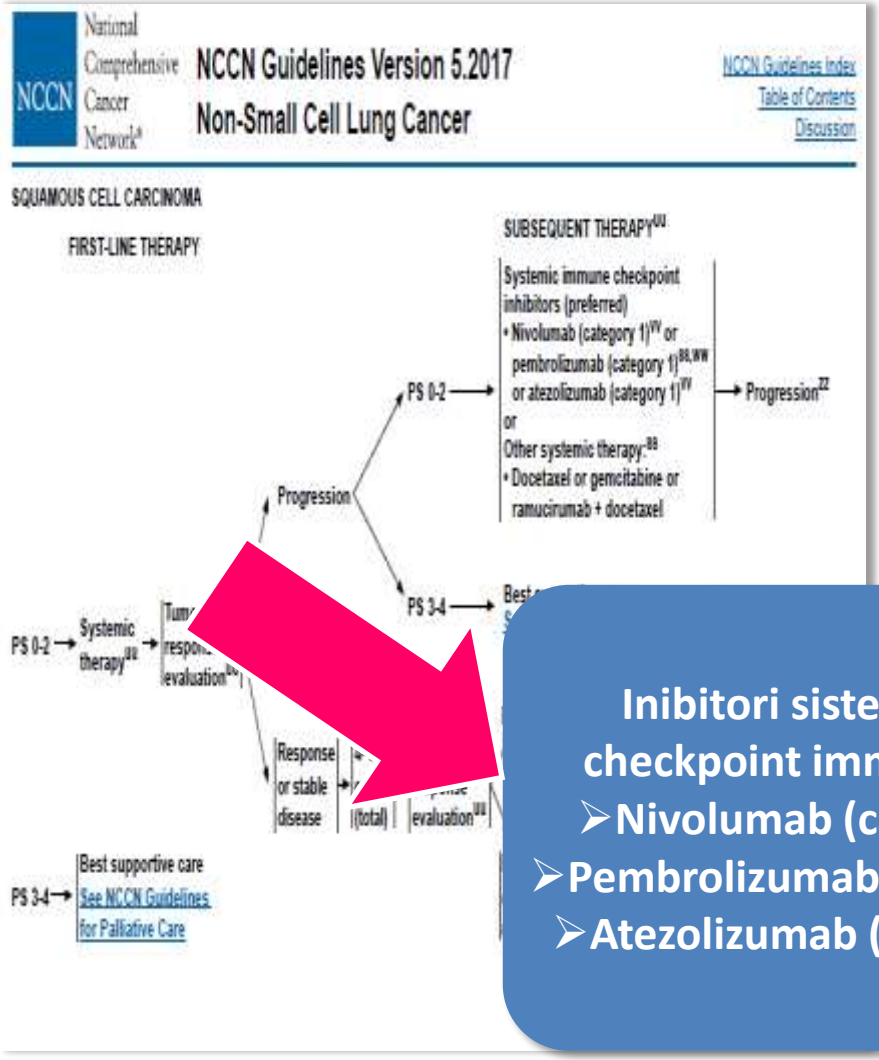
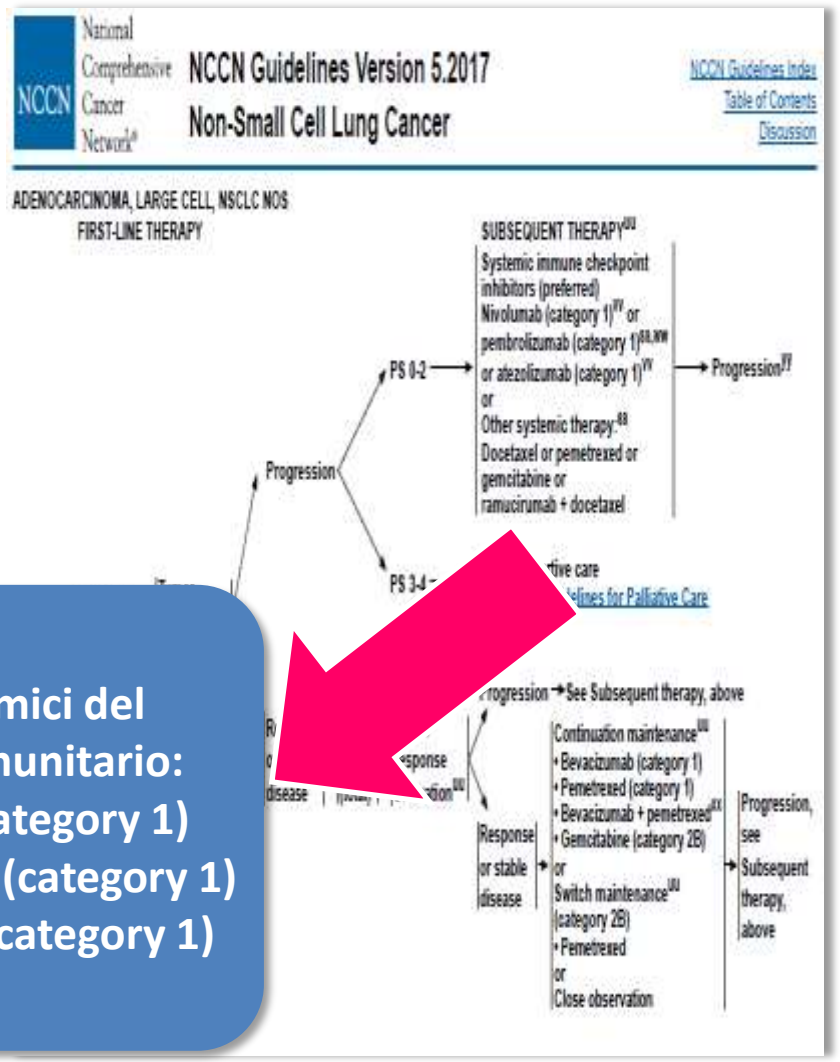
NCCN Guideline:
treatment algorithm for stage IV NSCLC 1°LINE



NCCN Guideline: algoritmo di trattamento per la terapia del IV stadio NSCLC

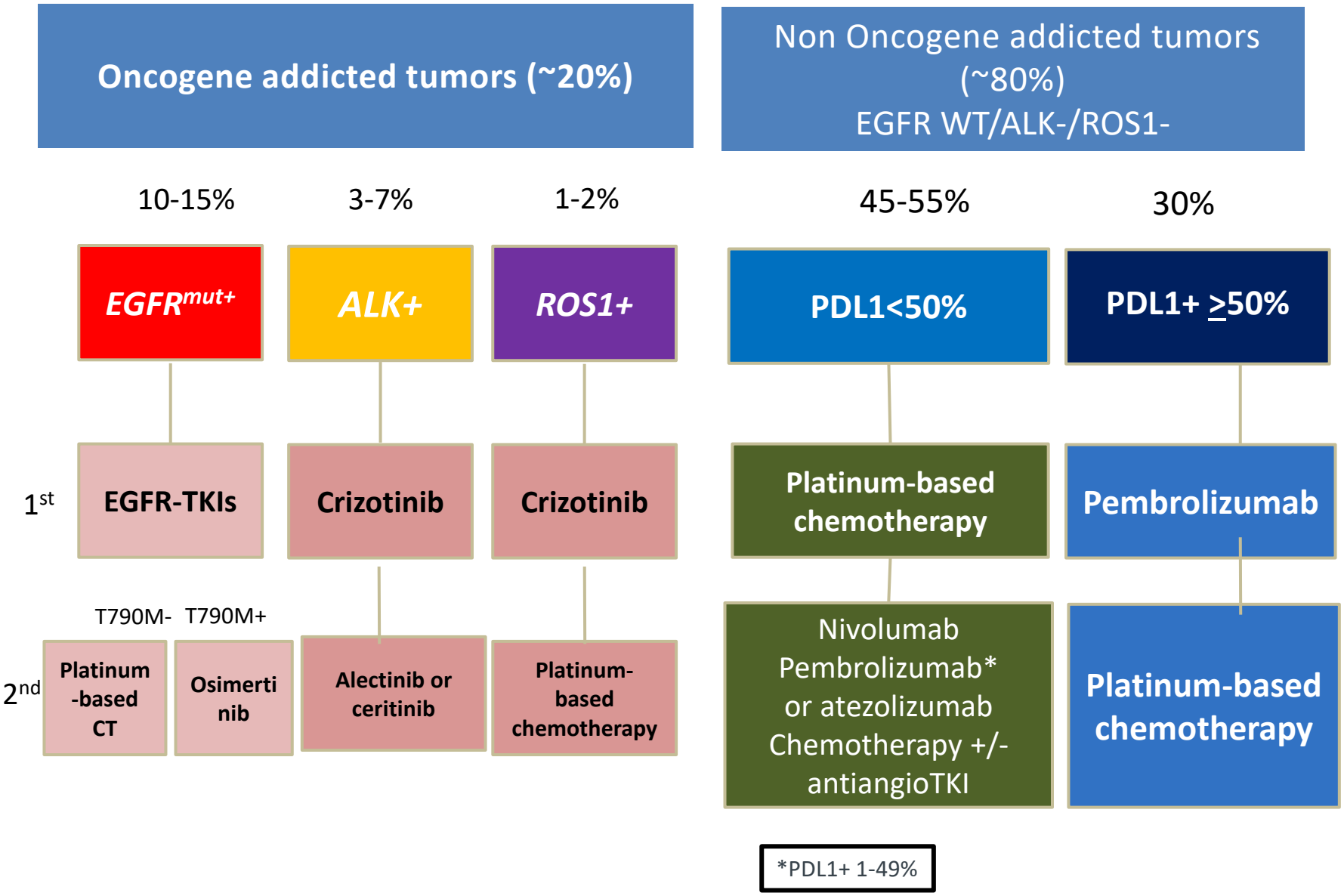




Inibitori sistemici del checkpoint immunitario:

- **Nivolumab (category 1)**
- **Pembrolizumab (category 1)**
- **Atezolizumab (category 1)**

Algoritmo Terapeutico




Grazie