IRE ISTITUTO NAZIONALE TUMORI REGINA ELENA

ISG ISTITUTO DERMATOLOGICO SAN GALLICANO

ISTITUTI DI RICOVERO E CURA A CARATTERE SCIENTIFICO

Clinical trial strategy: focus on lung cancer

Federico Cappuzzo

Istituto Nazionale Tumori Regina Elena

Roma

Outline

- Current algorithm for lung cancer therapy
- Main unmet needs
- Lung cancer clinical trial strategy at IFO
  - Sponsored trials
  - Investigator initiated trials
  - Phase 1

Therapy algorithm and unmet needs in stage III NSCLC

Non-resectable stage III

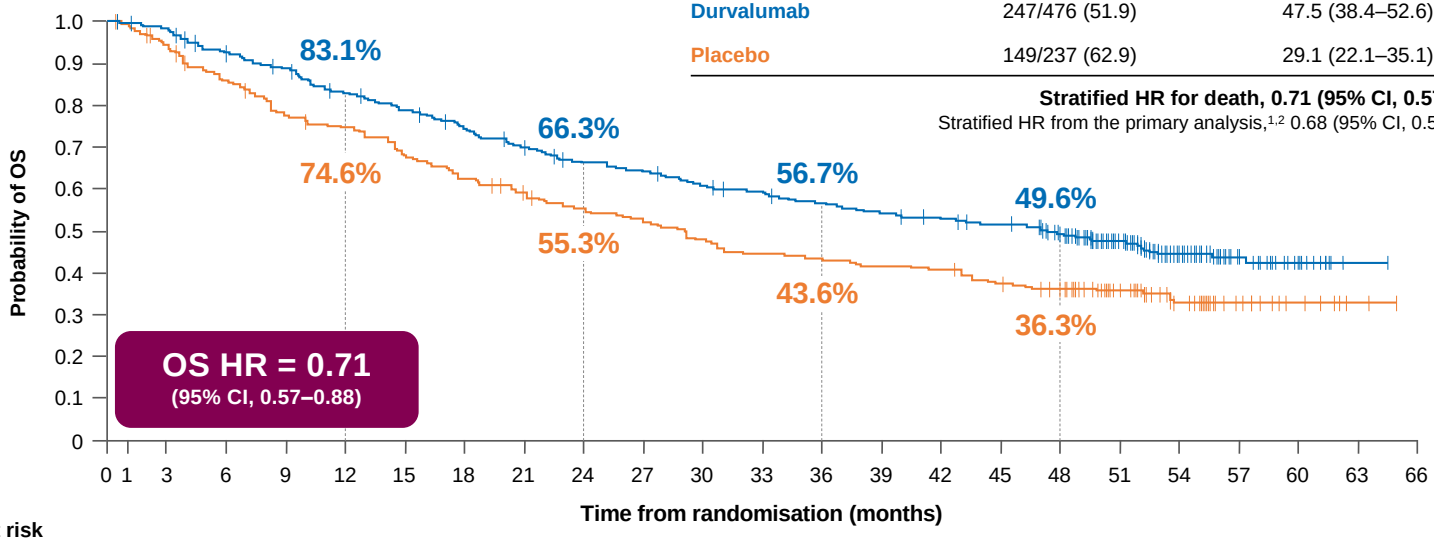
Concurrent CT+RT

Comfort Zone

Durvalumab for 1 year

Discomfort Zone

Best first-line undefined



	No. of events/ total no. of patients (%)	Median OS (95% CI), months
Durvalumab	247/476 (51.9)	47.5 (38.4–52.6)
Placebo	149/237 (62.9)	29.1 (22.1–35.1)

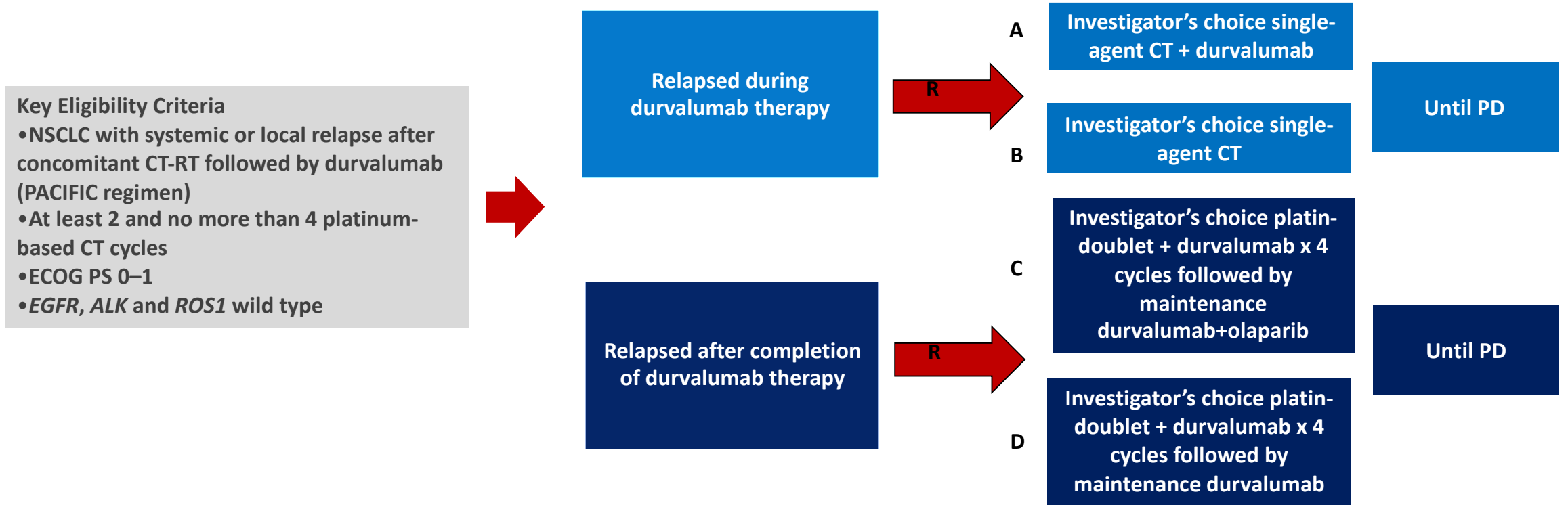
Stratified HR for death, 0.71 (95% CI, 0.57–0.88)
Stratified HR from the primary analysis,[1,2] 0.68 (95% CI, 0.53–0.87)

No. at risk

Durvalumab	476	464	431	414	385	364	343	319	299	290	274	265	252	241	235	225	195	138	75	36	15	2	0
Placebo	237	220	199	179	171	156	143	133	123	116	107	99	97	93	91	83	75	53	29	15	7	2	0

Data cut-off: 20 March 2020 (median follow-up, 34.2 months [range, 0.2–64.9])
CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; OS, overall survival
1. Antonia SJ, et al. *New Engl J Med* 2017;377:1919–1929; 2. European Medicines Agency. Durvalumab (Imfinzi). Summary of product characteristics 2020. https://www.ema.europa.eu/en/documents/product-information/imfizi-epar-product-information_en.pdf. Accessed August 2020

Lung cancer research strategy at IFO: CONDOR trial



Primary endpoints:

- OS

Select secondary endpoints:

- PFS
- ORR
- Safety
- Association with study biomarkers

Supported by FoRT - Fondazion Ricerca Traslazionale

Therapy algorithm and unmet needs in oncogene-addicted

Oncogene addicted

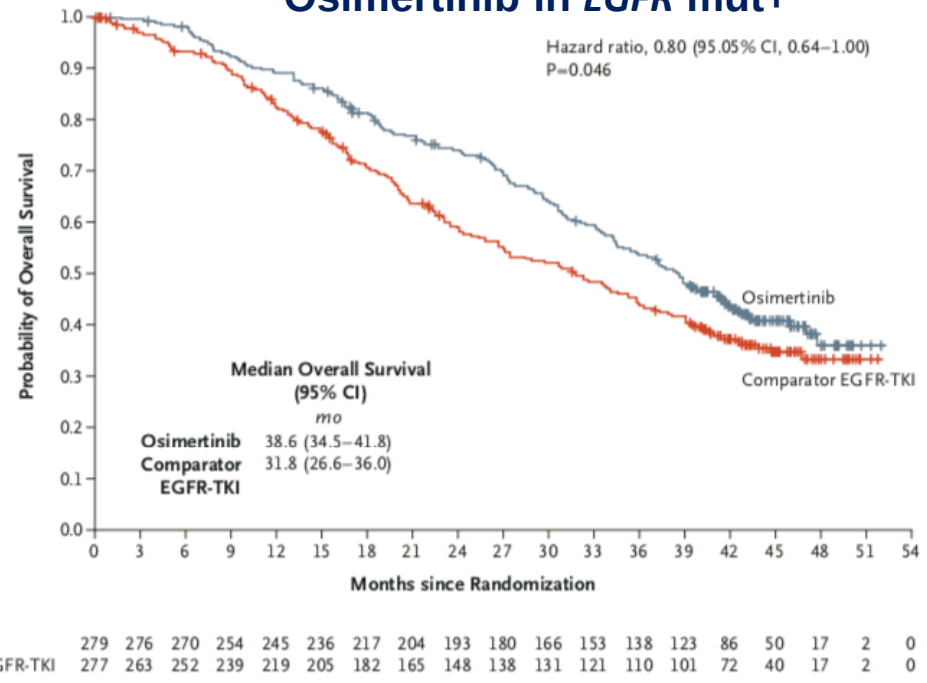
Comfort Zone

Target therapy

Discomfort Zone

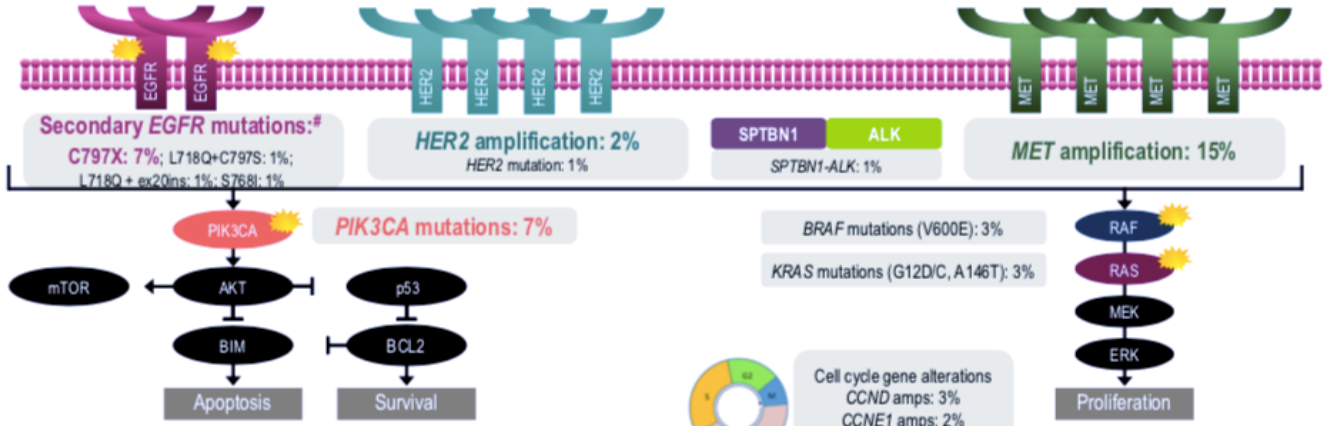
Best sequencing and acquired resistance

Osimertinib in *EGFR* mut+

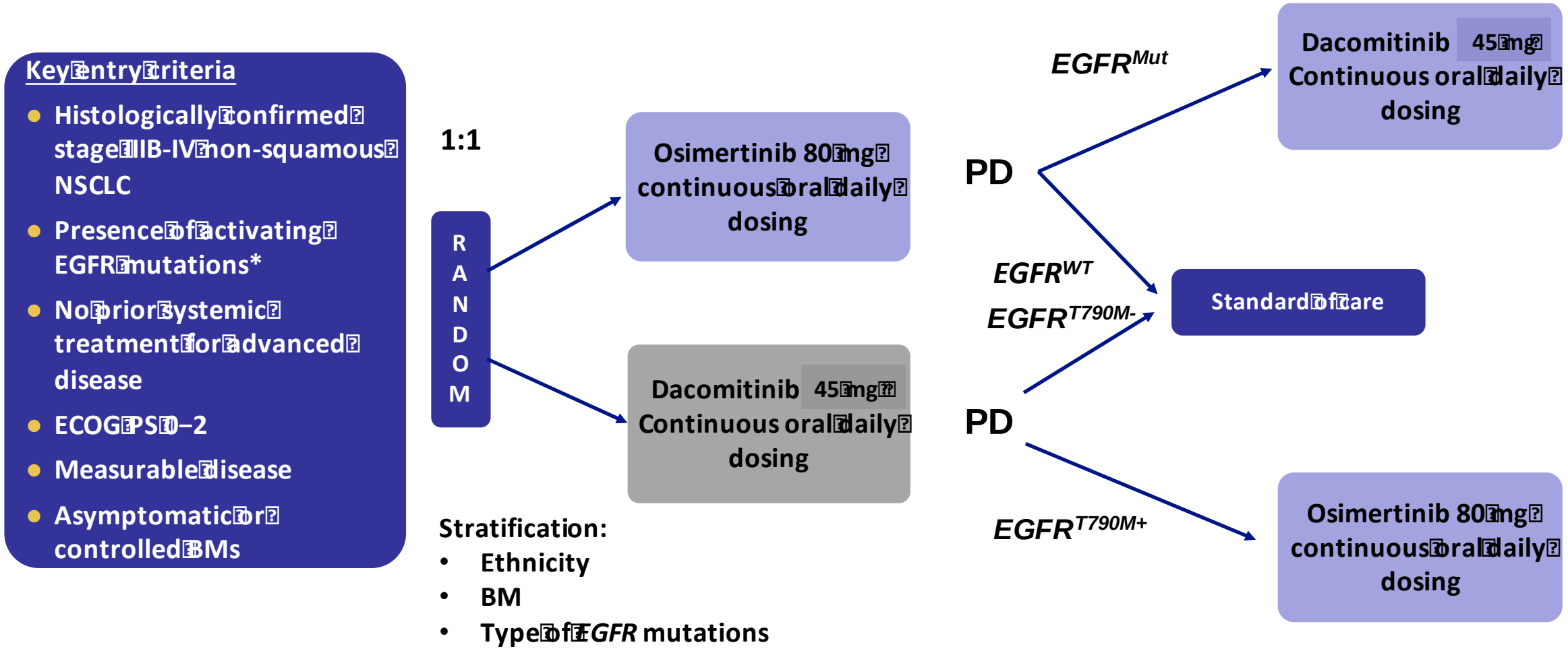


Acquired resistance

- No evidence of acquired EGFR T790M
- The most common resistance mechanisms were *MET* amplification and EGFR C797S mutation
  - Other mechanisms included *HER2* amplification, *PIK3CA* and *RAS* mutations



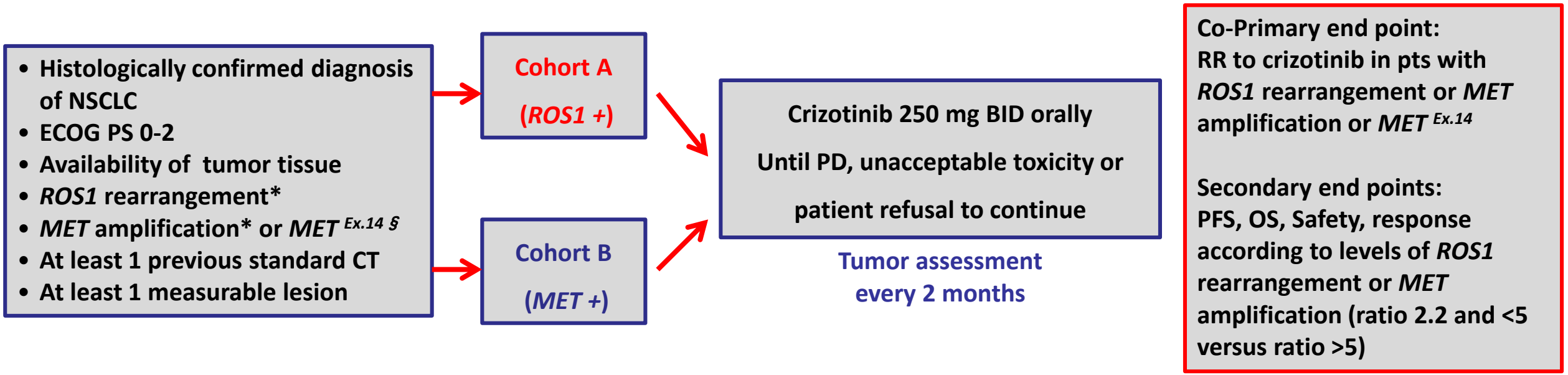
Lung cancer research strategy at IFO: CAPLAND trial



*Activating EGFR mutations include: exon 19 deletion or exon 21 L858R mutation or other activating/sensitizing mutations, such as exon 21 L861Q, exon 18 G719S, G719A and G719C, exon 20 S768I and V769L.

Coordinators: Lorenza Landi and Federico Cappuzzo; PI Alessandro Morabito

METROS: A Phase II, two arms, parallel, non comparative trial

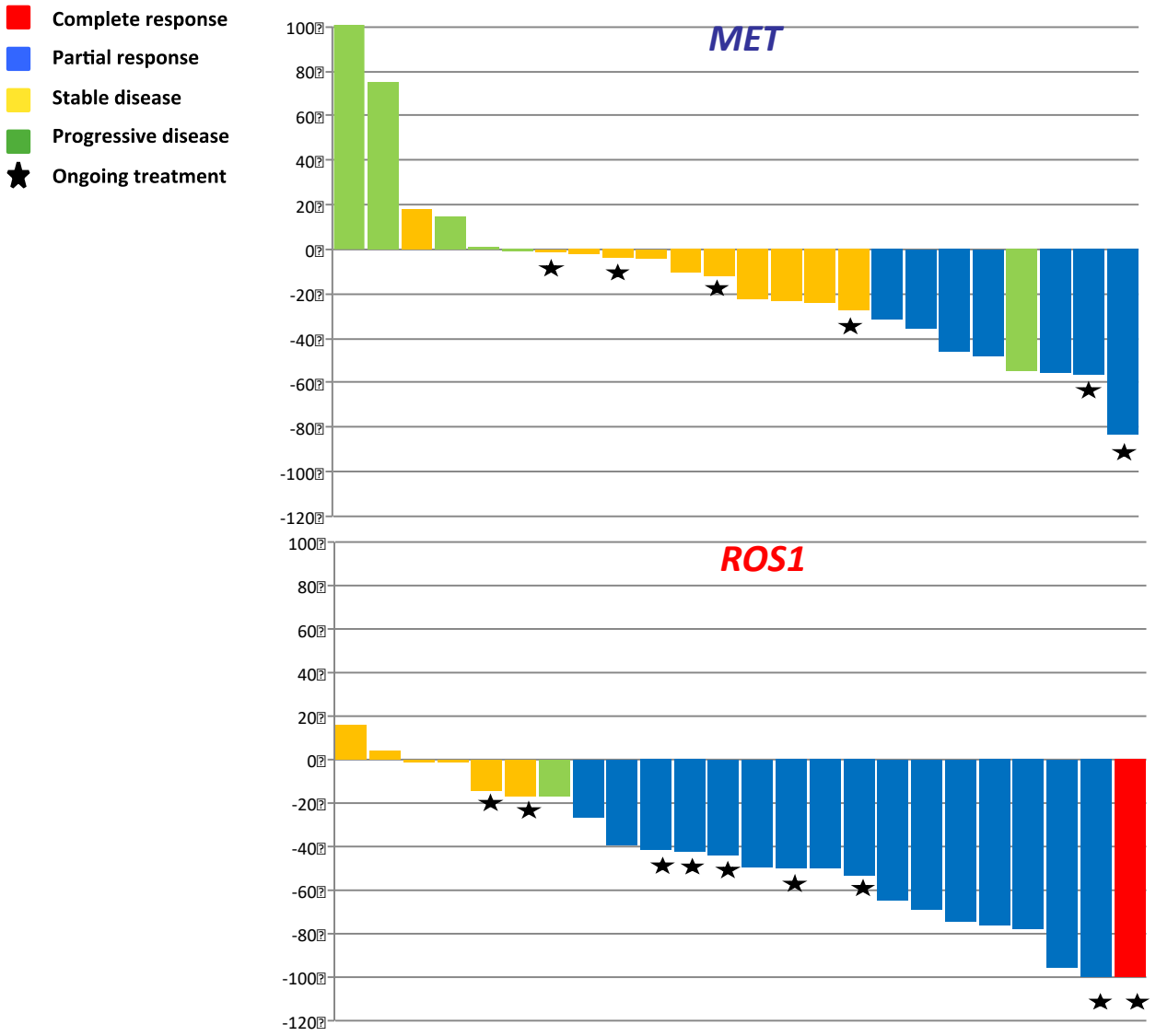


* *MET* amplification and *ROS1* rearrangement were centrally assessed by FISH using the specific probes (Abbott, USA). In case of evidence of evidence of *ROS1* rearrangement or a ratio MET/CEP7 >2.2 patients were considered eligible for the study; § *MET* Ex.14 mutation was assessed at the local lab using the mutation test locally available

Sample size estimation: a total of 40 patients (20 for each arm) were required to obtain a RR for both groups of 50%, assuming a 10% drop-off with a power of 98% in each arm, with a significance level of 0.05 (1-tailed test)

Landi L et al, Clin Cancer Res 2019

Response in ITT population



	MET		ROS1	
	N	%	N	%
Overall response (complete response + partial response)	7	27	17	65
Complete response	0	0	1	4
Partial response	7	27	16	61
Stable disease	11	42	6	23
Progressive disease	6	23	1	4
Not evaluable	2	8	2	8
Duration of response, months (95% CI)	3.8 (3.0 - 4.4)		14.7 (6.4 - 23.0)	

Landi L et al, Clin Cancer Res 2019

Lorlatinib for crizotinib pretreated ROS1 positive NSCLC: a phase II Trial

- Histologically confirmed diagnosis of NSCLC
- ECOG PS 0-2
- *ROS1* rearrangement*
- Prior Tx with chemo and crizotinib
- Availability of tumor tissue at crizorinib PD
- At least 1 measurable lesion
- Asymptomatic BMs or leptomeningeal disease allowed

PF-06463922

100 mg QD orally

Until PD, unacceptable toxicity or patient refusal to continue

Tumor assessment every 2 months

Primary:
RR to PF-06463922 in crizotinib pretreated patients
Secondary:
PFS, OS, Safety
Correlation with biomarkers expression*

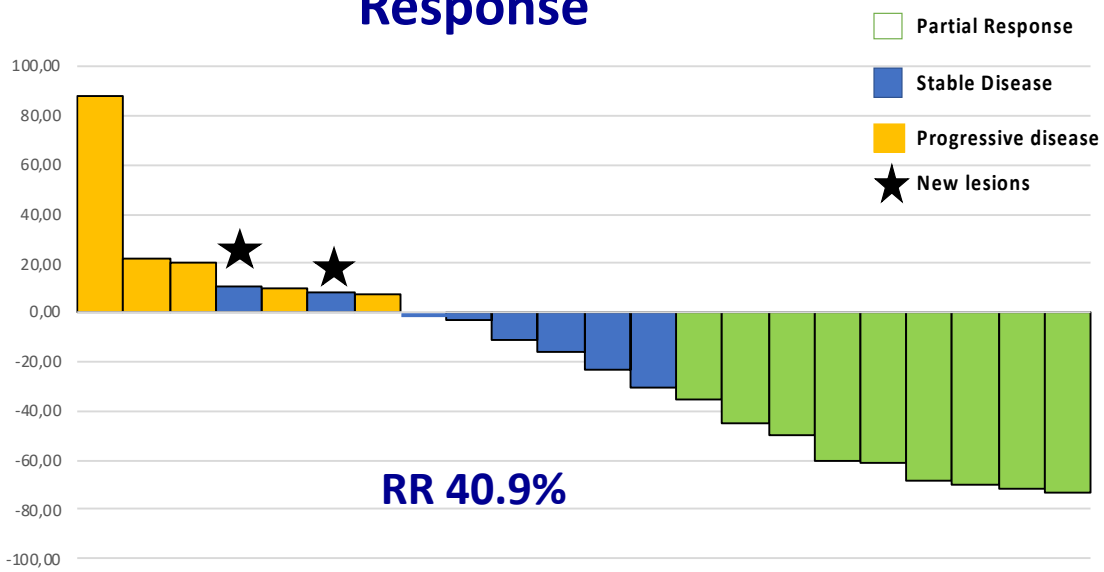
* NGS analyses at NEO Oncology, Cologne, Germany

- **Participating centers: 19**
- **Sample size: 22 patients**
- **Status: Completed**

Landi L et al, ESMO 2019, AIOM 2019

PFROST: Response, PFS and OS

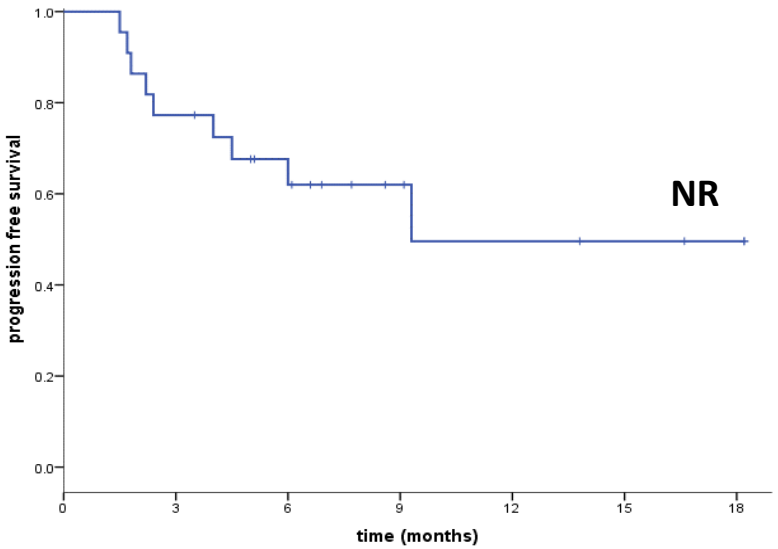
Response



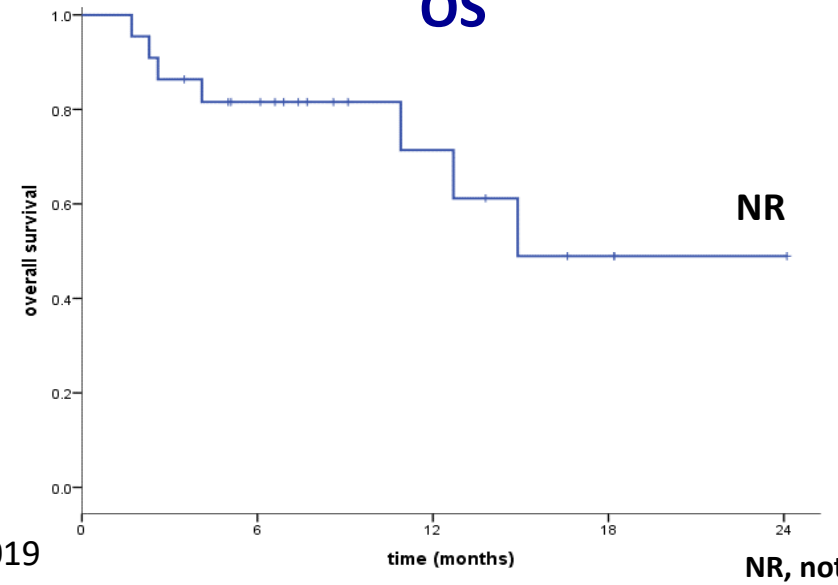
	Overall Population (N=22)
Complete response	0 (0%)
Partial response	9 (40.9%)
Stable disease *	6 (27.2%)
Disease control rate	15 (68.1%)
Progressive disease	7 (31.8%)

*including 1 unconfirmed SD (PT 014-019 permanently discontinued lorlatinib due to SAE without any other assessment

PFS



OS



Landi L et al, ESMO 2019, AIOM 2019

NR, not reached

Two additional studies following METROS

BioMETROS

METROS patients: N=60

Tumor tissue: Baseline and at progression

Liquid biopsy. Baseline, during therapy and at progression

→ **NGS**

CABinMET

- Citological or histological diagnosis diagnosis of NSCLC
- ECOG PS 0-1
- Availability of tumor tissue for *MET* analyses
- *MET amplification or MET* $^{Ex.14\ skip}$ *
- At least 1 prior line of standard tx
- Asymptomatic or treated BMs allowed

N= 25 →

Cabozantinib

60 mg QD orally

Until PD, unacceptable toxicity or patient refusal to continue

Tumor assessment every 2 months

Primary:
RR to cabozantinib in pts with *MET* amplification or *MET* $^{Ex.14\ skip}$

Secondary:
PFS, OS, DCR, Safety, Exploratory biomarkers on blood and tissue

*** Presence of *MET* mutations (exon 14 skipping mutation) detected at the local lab or in the central lab or *MET* amplification (MET/CEP7 ratio > 2.2) detected in the central lab ONLY**

Exploring new options in patients with acquired resistance: The BRICE trial

Screening for eligibility

Phase I - Dose finding in patients with advanced EGFR+/ALK+/ROS1+ tumors resistant to available inhibitors.
Phase 1 dose levels

Cohort -1 Brigatinib 90 mg PO OD **+** Cetuximab 60 mg/m2 IV weekly from cycle 1 day 15
Cohort 1 Brigatinib 90 mg PO OD for 1 week than 180 mg PO OD + Cetuximab 60 mg/ m2 IV weekly starting on cycle 1 day 15
Cohort 2 Brigatinib 90 mg PO OD for 1 week than 180 mg PO OD + Cetuximab 120 mg/ m2 IV weekly starting on cycle 1 day 15
Cohort 3 Brigatinib 90 mg PO OD for 1 week than 180 mg PO OD + Cetuximab 180 mg/ m2 IV weekly starting on cycle 1 day 15
Cohort 4 Brigatinib 90 mg PO OD for 1 week than 180 mg PO OD + Cetuximab 250 mg/ m2 IV weekly starting on cycle 1 day 15

***Dose escalation will start with the doses of drugs specified for cohort 1. If dose level 1 proves intolerable, dose level -1 will be tested. Further dose levels can be tested according to the available safety data and according to the Safety Committee judgment.**

Open-label, Phase 2 - Simon 2-stage design.

- **Primary endpoint: Overall response rate (ORR)**
- **Population: patients with an on-target mechanism of resistance to EGFR TKIs (i.e. secondary or tertiary resistance mutations of EGFR)**

***Biomarker assessment on baseline tissue and blood samples**

Therapy algorithm and unmet needs in non-oncogene-addicted

Non-oncogene addicted

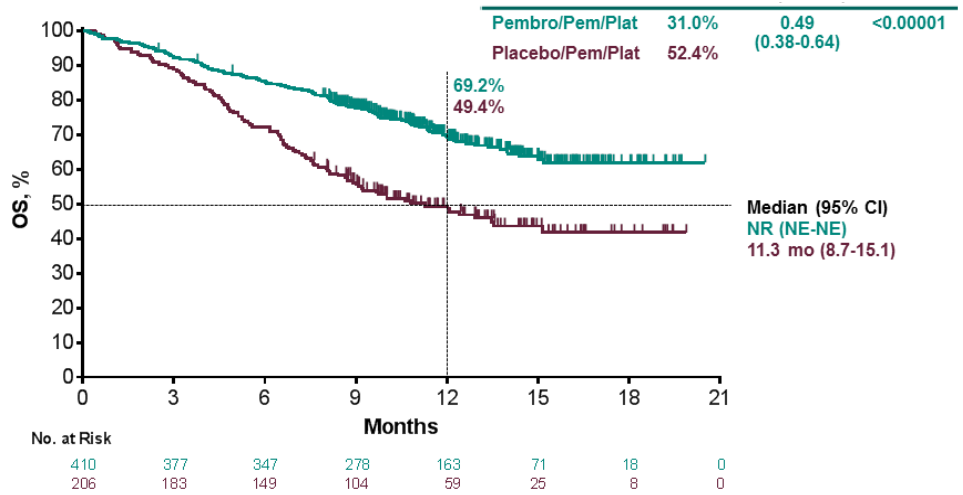
Comfort Zone

Immunotherapy +\- CT

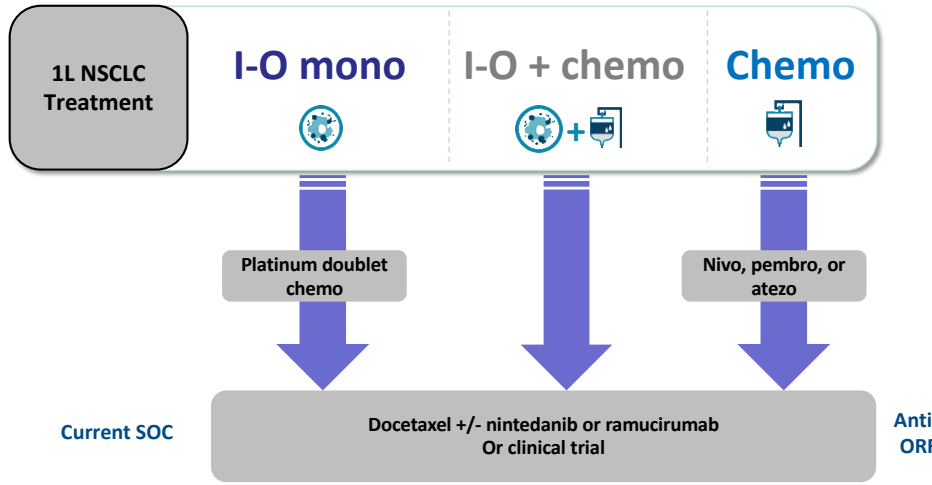
Discomfort Zone

New options and therapy at IO failure

OS: KEYNOTE-189



Few options in second-line

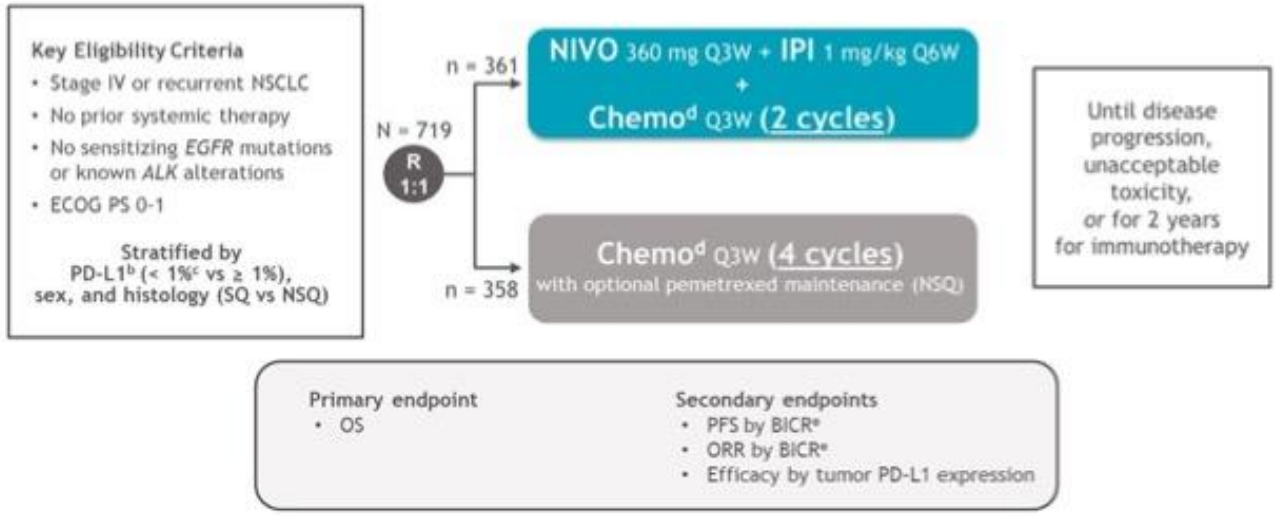


Can we do better?

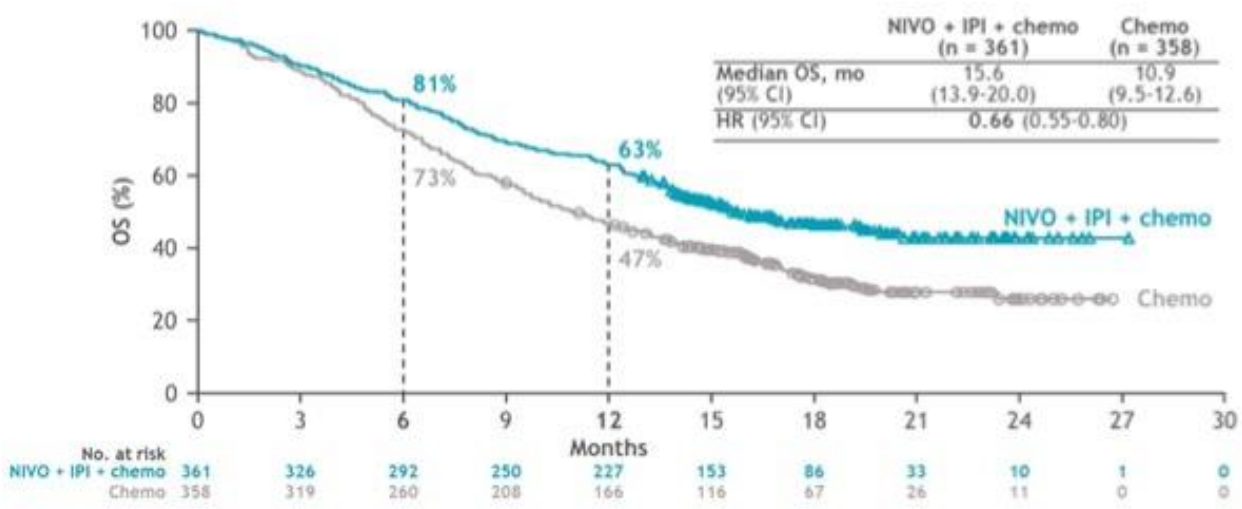
?

NSCLC patients ask for less chemotherapy: CheckMate 9LA as an example

9LA study design



9LA OS



Chemo-free options: IFO clinical trials

- Histologically confirmed diagnosis of Stage IIIB/IV or recurrent lung SqCC (IHC p63/p40+ and TTF1-)
- Availability of tumor tissue for PD-L1 expression analysis
- Availability of PD-L1 status
- Measurable disease
- No prior Tx
- ECOG PS 0-2
- Treated BMs allowed

R 1:1

N= 56

Nivo 240 mgIV Q2W + Ipi 1 mg/kg Q6W

Until PD, unacceptable toxicity or patient refusal to continue

N= 56

Nivolumab+ Investigator choice's platinum-based CT* up to 6 cycles

SQUINT

Primary end point :

- OS rate at 12 months in Arm A and Arm B

Secondary end points:

- RR, DOR, median PFS and median OS in Arm A and Arm B
- RR, DOR, median PFS and median OS in patients with and without bone metastases
- Correlation of PD-L1 expression and/or TMB with outcome in Arm A and Arm B in terms of RR, DOR, median PFS and median OS
- Safety in Arm A and Arm B
- Toxicity in Arm A and Arm B

Inclusion criteria

- Histologically confirmed diagnosis of stage IV non-squamous NSCLC
- No evidence of *EGFR* sensitizing mutations or *ALK* or *ROS1* rearrangements
- Availability of tumor tissue
- PD-L1 expression ≥1%
- No previous chemotherapy
- ECOG Performance status 0-1
- Age ≥ 18 years
- Measurable disease RECIST v1.1

R 1:1

Atezolizumab 1200 mg i.v., every 3 weeks until disease progression, toxicity or patient refusal to continue

N= 103

BEAT

Atezolizumab 1200 mg i.v., every 3 weeks + bevacizumab 15 mg/kg every 3 weeks until disease progression, toxicity or patient refusal to continue

N= 103

Primary:

- Overall Survival (OS) at 18 months in patients treated with atezolizumab alone versus atezolizumab-bevacizumab combination

Secondary:

- Response rate (RR)
- Progression-free survival (PFS)
- Toxicity
- Correlation with tumor biomarkers in tumor tissue

The question on steroid effect in patients treated with immunotherapy: The STARDUST trial

Inclusion criteria

- Histological or cytological confirmed diagnosis of NSCLC with no evidence of *EGFR* mutations or *ALK* rearrangement
- Previous platinum-based chemotherapy (only 1 line allowed)
- ECOG PS 0-1
- Age ≥ 18 years

N= 84

Durvalumab at the fixed dose of 1500 mg i.v., every 28 dd and Prednisone 10 mg/day orally* until progression, unacceptable toxicity or patient's refusal to

Primary:

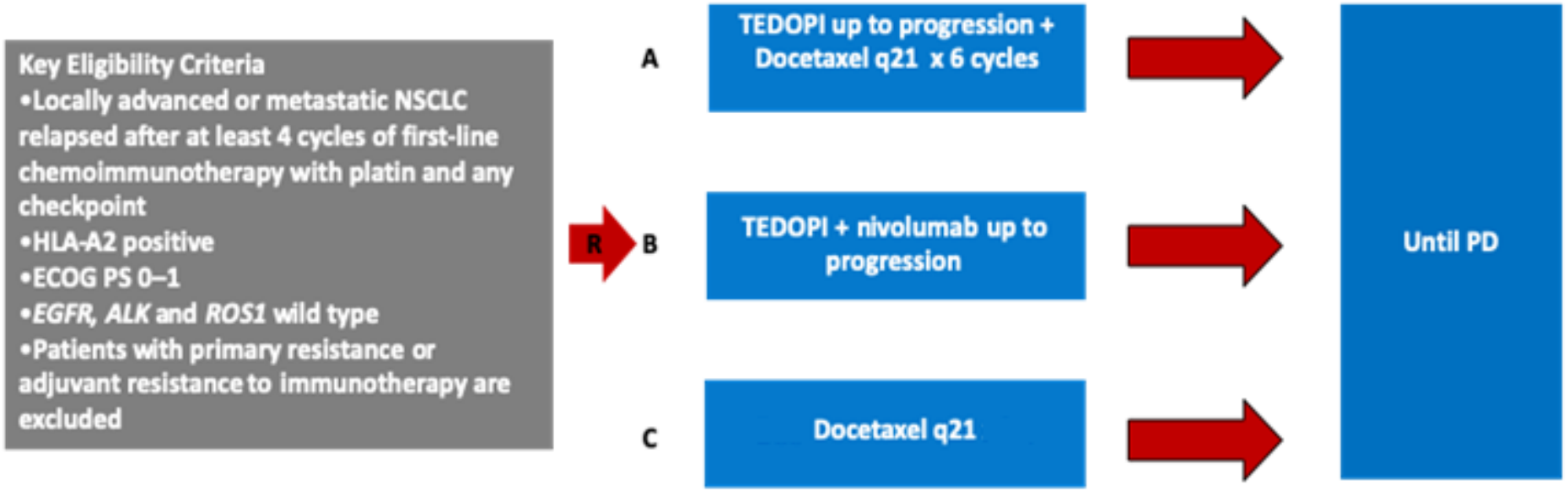
- Incidence of immune-related adverse events
- Response rate

Secondary:

- Overall Survival (OS)
- Progression-free survival (PFS)
- Quality of life, fatigue
- Correlation with tumor biomarkers in tumor tissue or blood, including PD-L1 expression, tumor grading and tumor mutational burden (TMB)

* concomitantly with nutritional support (quercetin 200 mg a day, American Ginseng 200 mg a day and Siberian Ginseng 300 mg a day)

A cancer vaccine for IO pretreated NSCLC: a planned phase II trial



Primary endpoints:

- 1-year OS

Select secondary endpoints:

- PFS
- ORR
- Safety
- Association with study biomarkers

Conclusions

- Treatment of lung cancer is rapidly evolving
- Several questions are arising for optimizing cancer therapy
- An extensive trial program is currently active in our Institution
  - Phase I trials in a dedicated clinical unit
  - Phase II to IV studies
  - Several investigator initiated studies
  - Sponsored trials