Future Directions in the Treatment of NSCLC

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Disclosure Slide

- Consultancy fees from

  AstraZeneca, Astex, Covagen, Clovis, GSK, GammaMabs,

  Lilly, MSD, Mission Therapeutics, Merus, Pfizer,

  Pierre Fabre, Roche-Genentech, Sanofi, Servier, Takeda.

- Company scientific co-founder

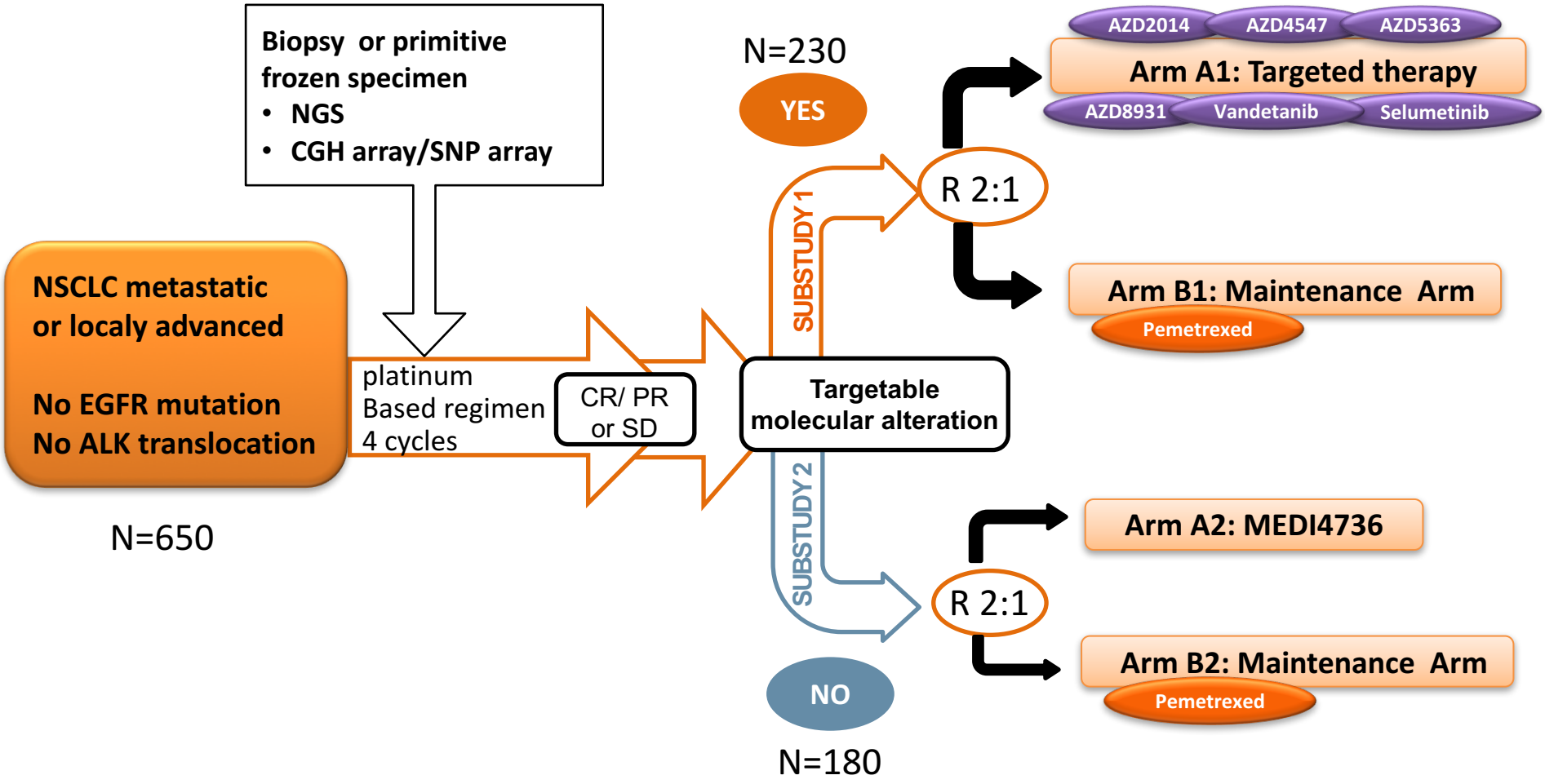
  Gritstone

Outline

- **Non-IO phase 2-3 trials**
- **IO-based phase 3 trials**
  - ✓ IO-IO
  - ✓ IO-chemotherapy
  - ✓ IO-targeted therapies
  - ✓ IO-radiotherapy

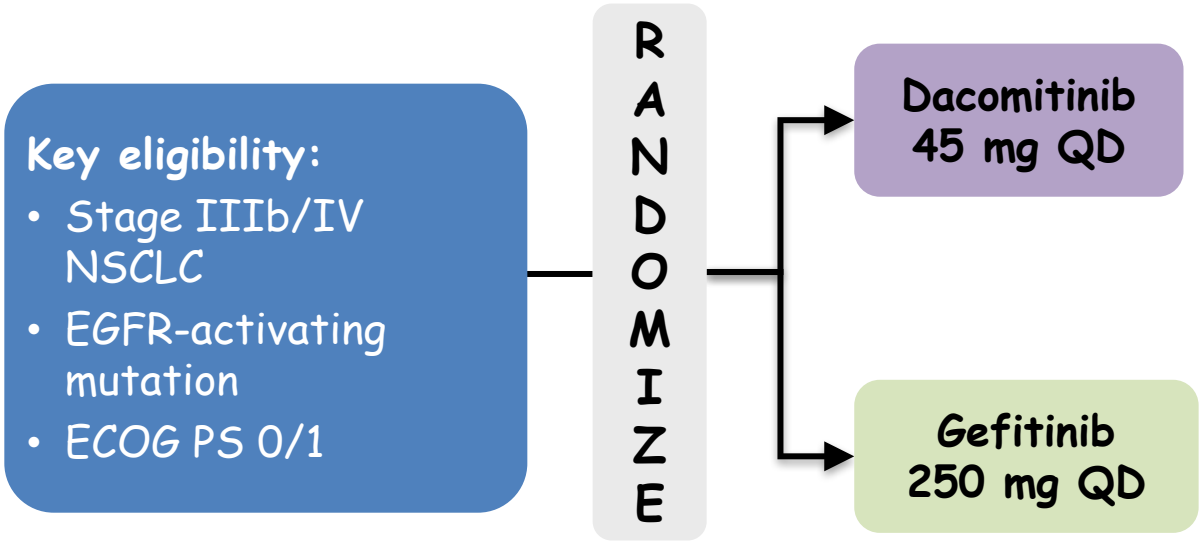
SAFIR02 Lung – IFCT 1301

PI: JC Soria
Co-PI: F Barlesi



Sponsor: UNICANCER-IFCT

ARCHER 1050: First-line Dacomitinib vs. Gefitinib (Phase 3)



Primary endpoint:
- PFS*

Secondary endpoints:
- OS
- OS at 30 months
- PFS by investigator assessment
- Response
- Safety
- PROs

Stratification:
- Race
- EGFR-mutation status (19 vs. 21)

N = 440

ASCO 2017
Tuesday, June 6, 2017, 9:45 am – 12:45 pm
Dacomitinib versus gefitinib for the first-line treatment of advanced EGFR mutation positive non-small cell lung cancer (ARCHER 1050): A randomized, open-label phase III trial. Abstract LBA9007

* Per blinded IRC review. Ha: HR≤ 0.667(50%↑)

www.clinicaltrials.gov: NCT01774721

SWOG-S1403 Phase 2/3 Study Design

Estimated enrollment: 605

- Stage IV or recurrent NSCLC
- EGFR exon 19 del or exon 21 L858R
- EGFR T790M or other mutation allowed if accompanied by exon 19 or exon 21 mutation
- No prior systemic treatment for advanced or metastatic disease

R

- **Afatinib + cetuximab**
- **Afatinib**

Primary endpoint
OS (Phase 3)

Secondary endpoints include
PFS, ORR, time to treatment discontinuation, time to treatment failure, toxicity

Clinicaltrials.gov. Accessed June 2017 (NCT02438722)

Phase II Trial of T-DM1 in HER2-Positive Locally Advanced or Metastatic NSCLC

- HER2-overexpressing NSCLC
- Previously treated with platinum-based therapy

→ **T-DM1**
3.6 mg/kg
D1 q3wk
(n = 49)

Response rates (median follow-up 16.3 mo)

IHC2+ (n = 29): 0%

IHC3+ (n = 20): 20% (4 PR)

Median DoR: 7.3 mo

Median PFS

IHC2+ 2.6 mo IHC3+ 2.7 mo

Stinchcombe T et al. ASCO 2017;Abstract 8509.

Phase II Basket Trial of T-DM1 in HER2 Amplified or Mutant Cancers

COHORTS

- **Lung cancers – HER2 mutant (n = 18)**
- Lung cancers – HER2 amplified
- Bladder/urinary tract cancers – HER2 amplified
- Other solid tumors – HER2 amplified

→ **T-DM1 3.6 mg/kg D1 q3wk**

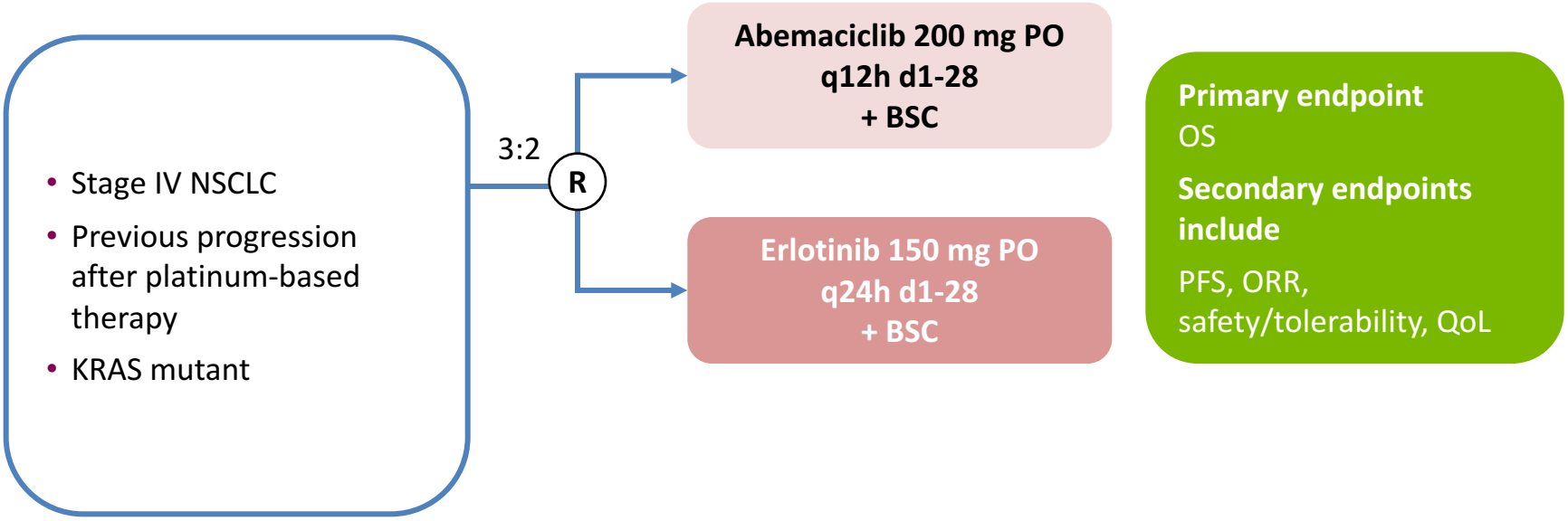
ORR: 33% (5/15)
Median DoR: Not reached
Median PFS: 4 mo

- There were 10 HER2 exon 20 insertions and 8 point mutations
- Responders were observed across mutation subtypes

Li BT et al. ASCO 2017;Abstract 8510.

JUNIPER Phase 3 Study Design

Estimated enrollment: 450 (closed)



NCT02152631
ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/show/NCT02152631
Goldman JW et al. Clin Lung Cancer 2016;17(1):80-4.

PD-L1 expression and response to immunotherapy in patients with *MET* exon 14-altered NSCLC

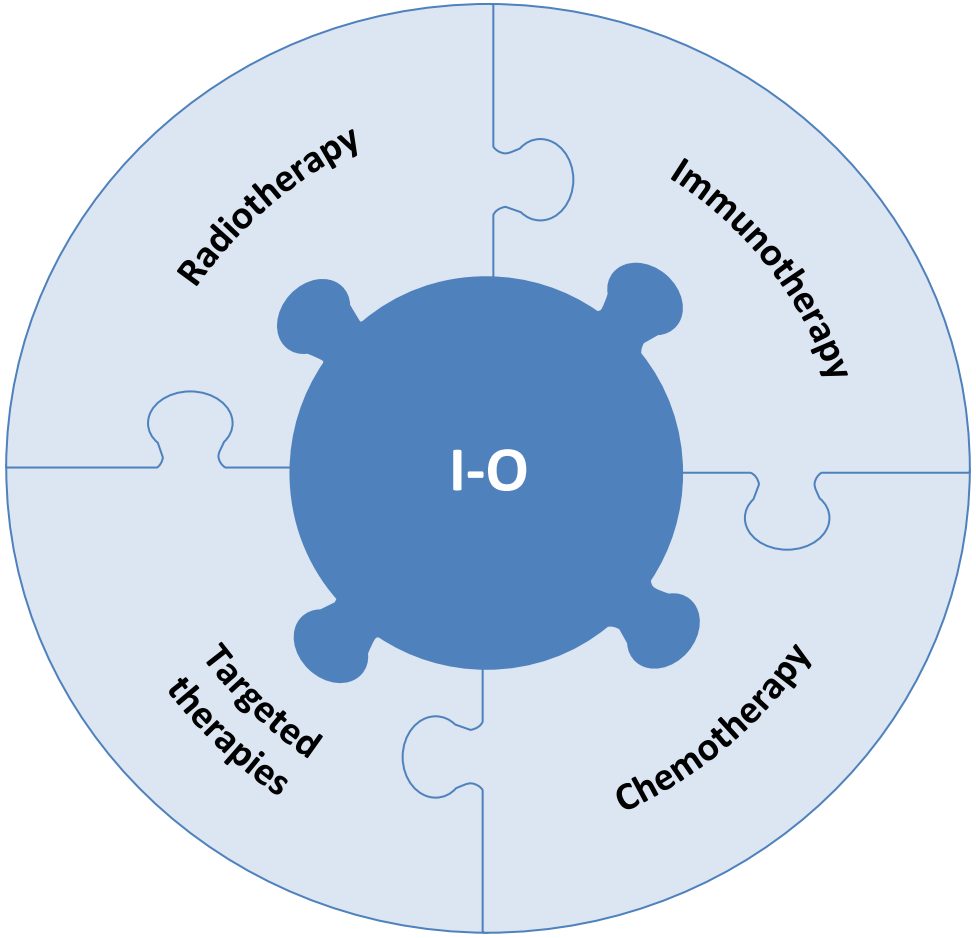
- 41 patients with *MET* exon 14 skipping alterations (*MET*Δ14) and PD-L1 expression analysis
- Substantial portion of patients with *MET*Δ14 NSCLC express PD-L1 (TPS ≥50% = 44%; TPS 1%-49% = 17%)
- Immunotherapy administered to 15 patients:
  - Nivolumab n = 5
  - Ipilimumab + nivolumab n = 4
  - Pembrolizumab n = 3
  - Atezolizumab n = 2
  - Durvalumab n = 1
- **ORR** = 2/15 (13%)
- **ORR for TPS ≥50%** = 1/3 (33%)

Sabari JK et al. ASCO 2017;Abstract 8512.

Outline

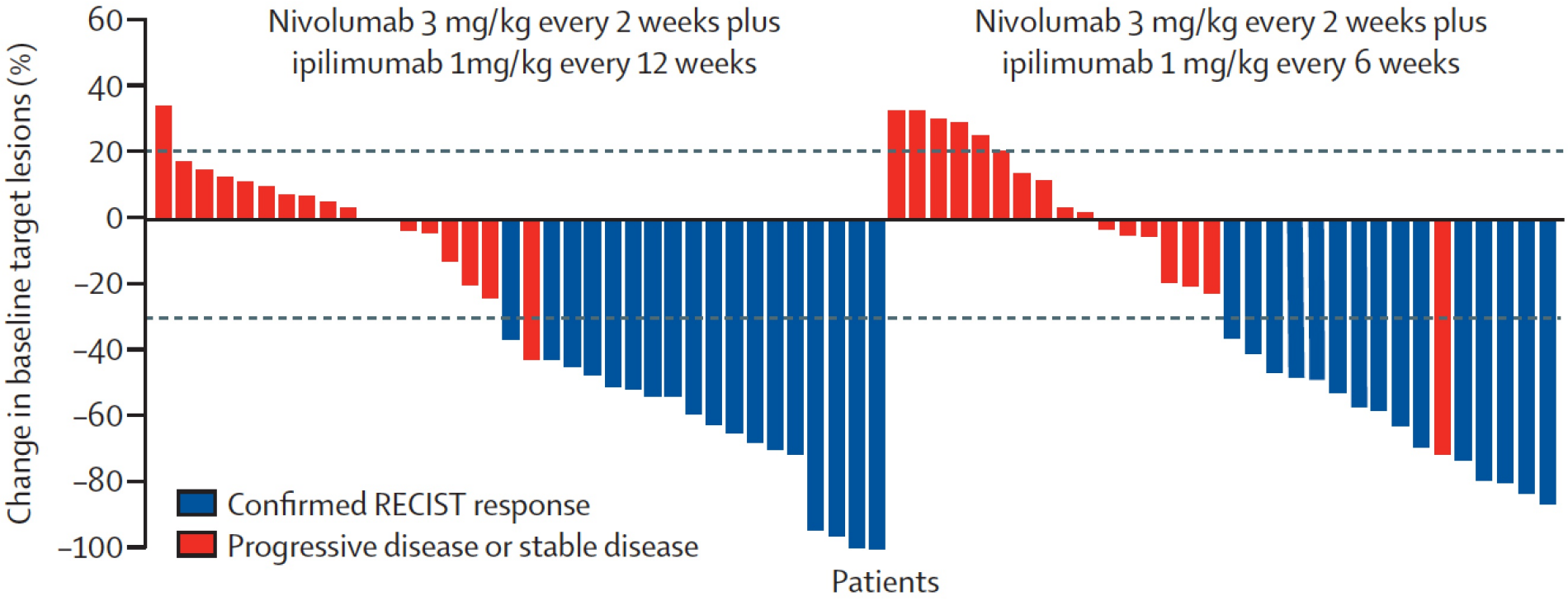
- **Non-IO phase 3 trials**
- **IO-based phase 3 trials**
  - ✓ IO-IO
  - ✓ IO-chemotherapy
  - ✓ IO-targeted therapies
  - ✓ IO-radiotherapy

Combination strategies are necessary to address broad patient populations



I-O = immuno-oncology.

Phase I CheckMate 012: Response



ORR (all): 18/38 (47%)
ORR (PD-L1 ≥1%): 12/21 (57%)

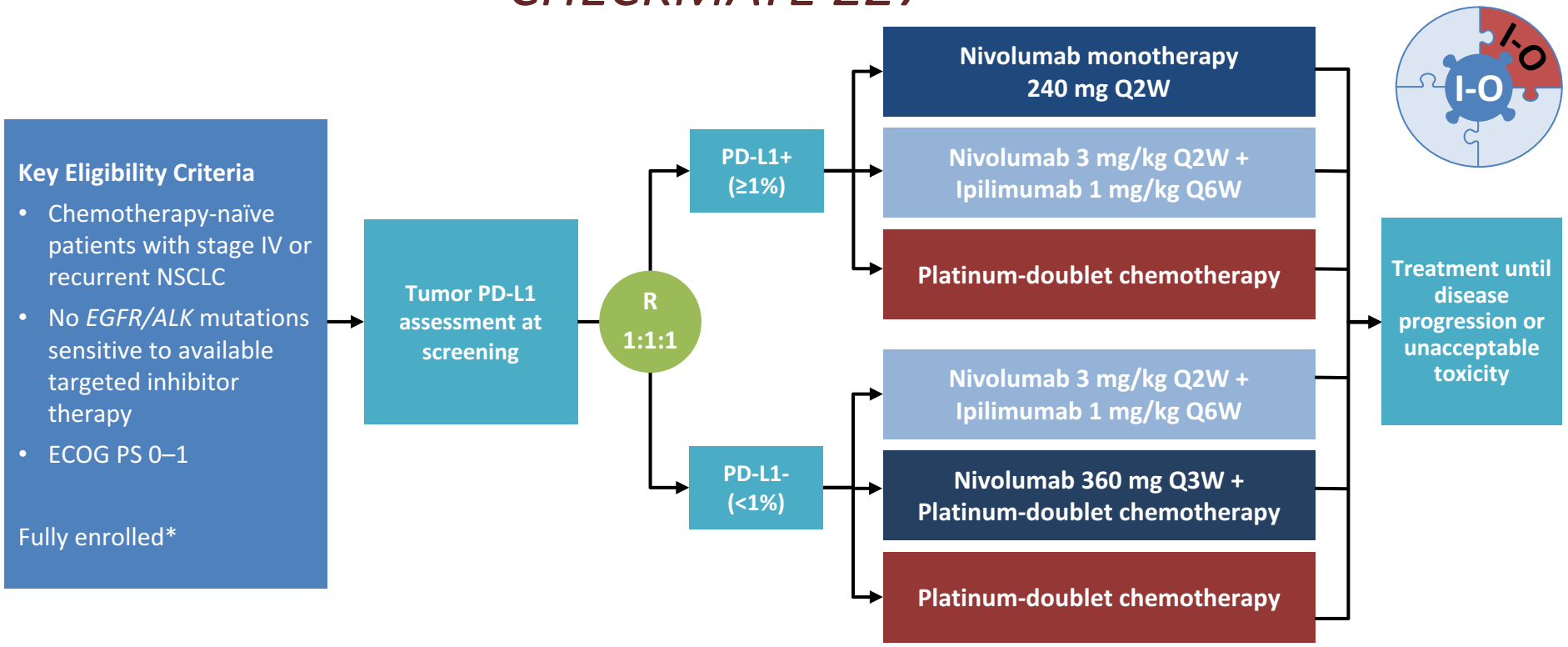
Treatment-related AEs prompting treatment discontinuation: 4/38 (11%)

ORR (all): 15/39 (38%)
ORR (PD-L1 ≥1%): 13/23 (57%)

Treatment-related AEs prompting treatment discontinuation: 5/39 (13%)

Hellmann MD et al. Lancet Oncol 2017;18:31-41.

CHECKMATE 227

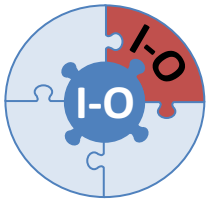


*Stratification factor at randomization: histology (squamous versus non-squamous).
ALK=anaplastic lymphoma kinase; ECOG PS=Eastern Cooperative Oncology Group performance status; *EGFR*=epidermal growth factor receptor; I-O=immuno-oncology; NSCLC=non-small cell lung cancer; PD-L1=programmed death ligand 1; Q2W=every 2 weeks; Q3W=every 3 weeks; Q6W=every 6 weeks; R=randomized.

1. Clinicaltrials.gov. NCT02477826 (CheckMate 227). Accessed April 12, 2017. 2. Data on file. Checkmate 227. 2017.

Neptune and Mystic:

Phase 3, open-label trials of anti–PD-L1 ± anti–CTLA-4 vs Pt-based doublet chemotherapy for first-line treatment of stage IV NSCLC



NEPTUNE[1,2]

N=960

Key Inclusion Criteria
- Treatment naïve, stage IV NSCLC
- No activating *EGFR* or *ALK* rearrangement
- PD-L1 positive* or negative

Primary Endpoint: OS

R 1:1

- **Durvalumab + tremelimumab**
- **Histology-based Pt doublet chemotherapy**

→ **Patients achieving disease control may restart combination treatment upon evidence of PD**

MYSTIC[3-5]

N=1118

Key Inclusion Criteria
- Treatment naïve, stage IV NSCLC
- No activating *EGFR* or *ALK* rearrangement

R 1:1:1

- **Durvalumab**
- **Durvalumab + tremelimumab**
- **Histology-based Pt doublet chemotherapy**

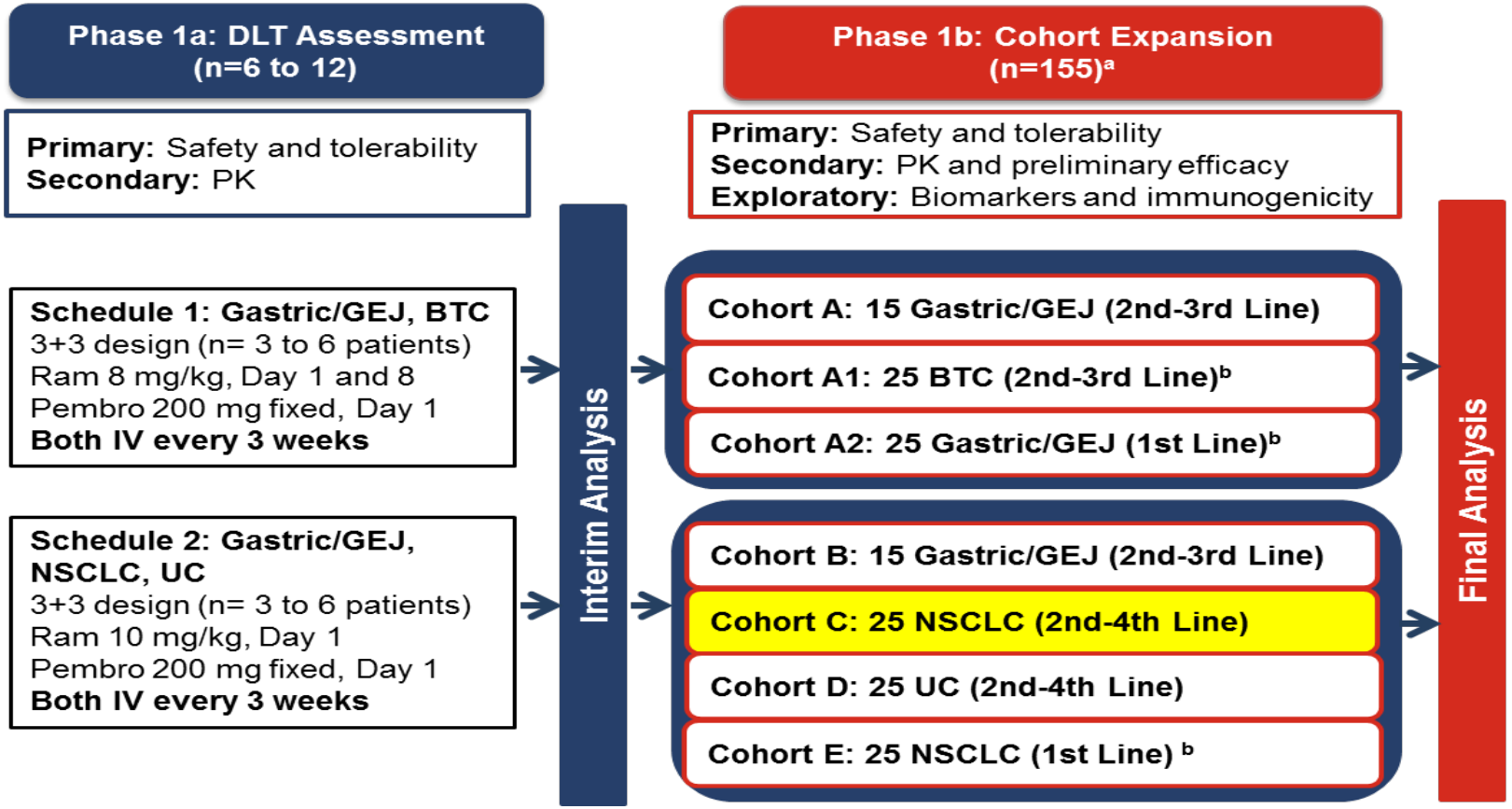
→ **Patients achieving disease control may restart combination treatment upon evidence of PD**

Primary Endpoints: PFS and OS of durva + treme (PD-L1+ and all-comers) and durva monotherapy (PD-L1+ only)

*PD-L1 positivity defined as ≥25% of tumor cells with membrane staining as determined by PD-L1 IHC assay.

1. Clinicaltrials.gov. NCT02542293. Accessed April 28, 2017. 2. Mok T et al. Poster presentation at ESMO Asia 2015. 480TiP.
3. Clinicaltrials.gov. NCT02453282.
Accessed April 28, 2017. 4. Peters S et al. Poster presentation at ELCC 2016. 191TiP. 5. Press release. January 17, 2017.

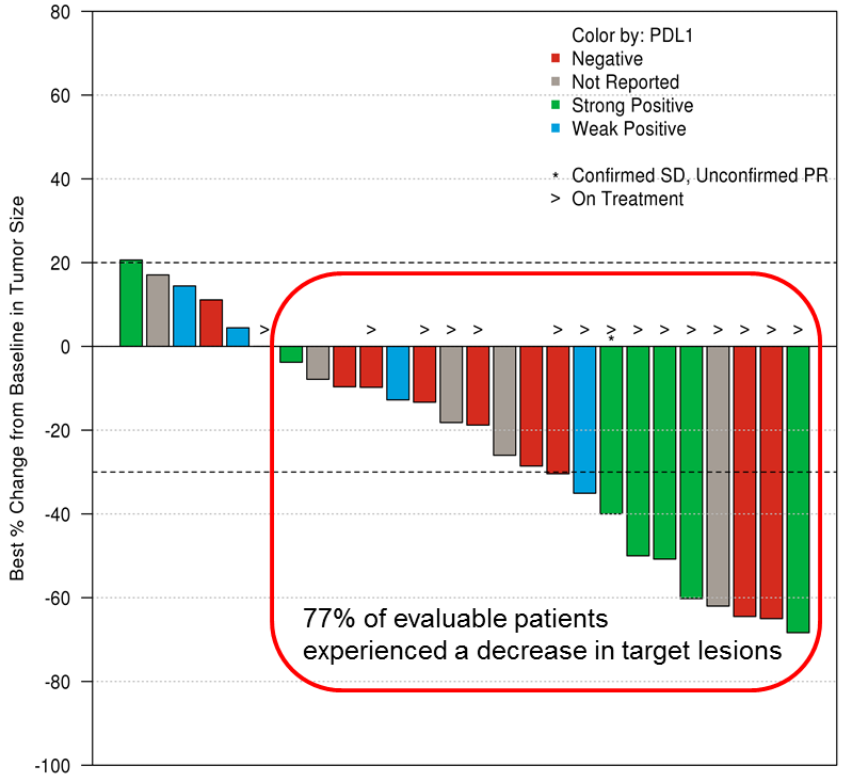
Study JVDF (NCT02443324) Phase 1A/B Study Design

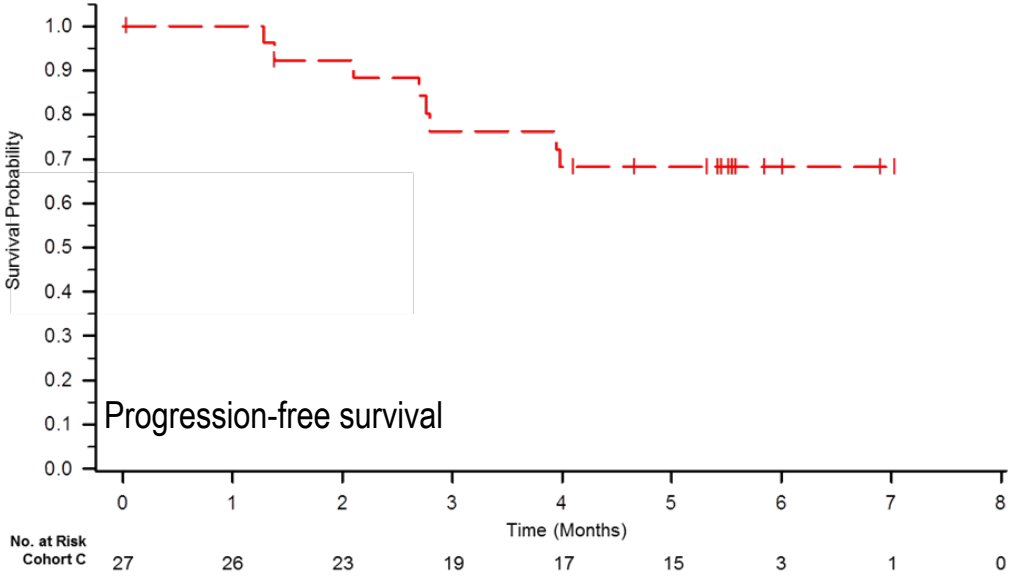


[a] Patients may continue treatment for up to 35 cycles, until confirmed progressive disease or discontinuation for any other reason. [b] Protocol was recently amended to add cohorts A1, A2 and E; cohorts are currently enrolling. DLT dose-limiting toxicity; PK pharmacokinetics; Ram ramucirumab; Pembro pembrolizumab

Herbst RS et al. Proc ESMO 2016;Abstract LBA38.

Study JVDF (NCT02443324)
Cohort C: Interim clinical activity



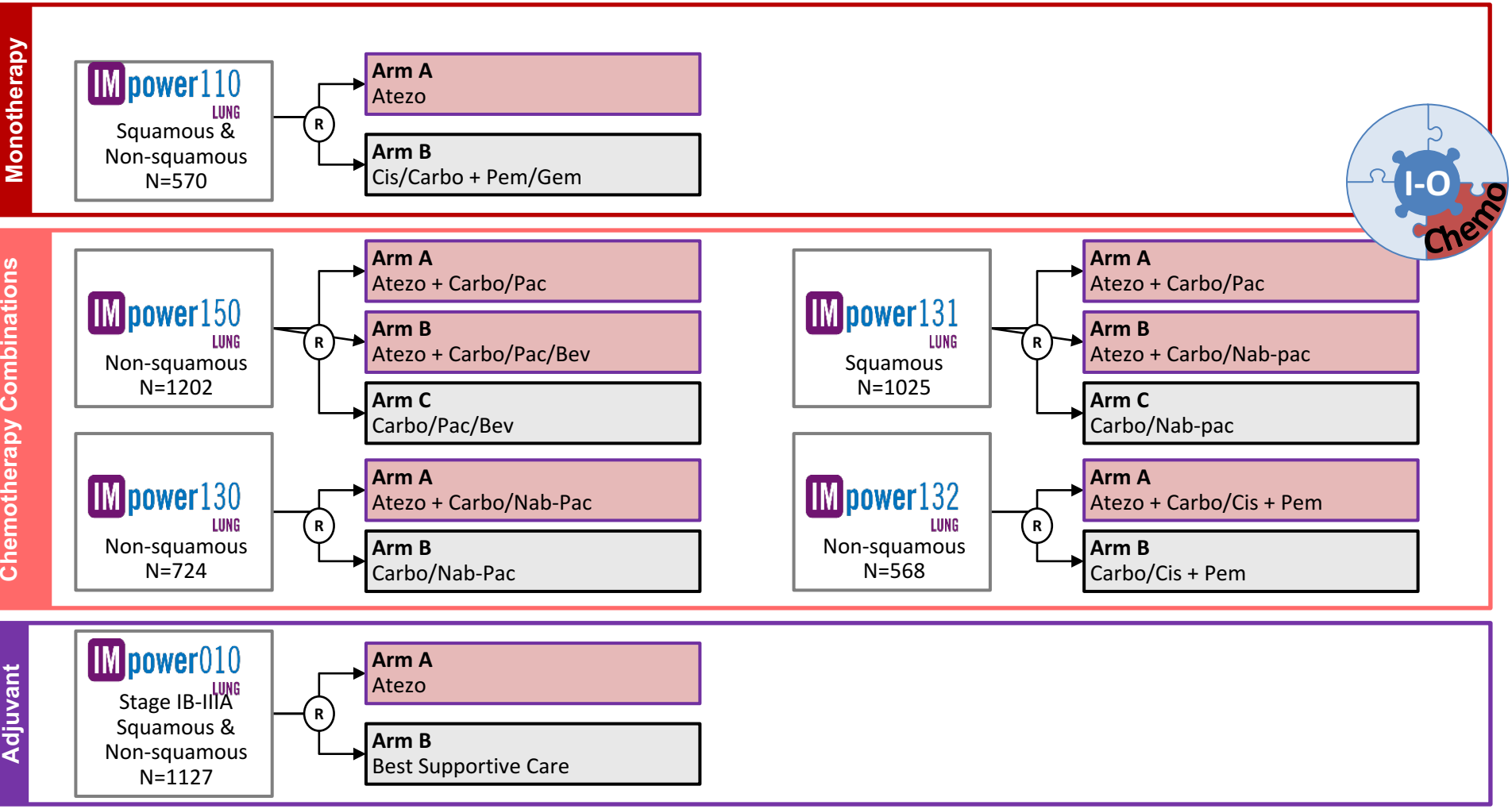


ITT Population	Cohort C NSCLC (n=27)
Objective response rate, n (%)	8 (30%)
Disease control rate, n (%)	23 (85%)

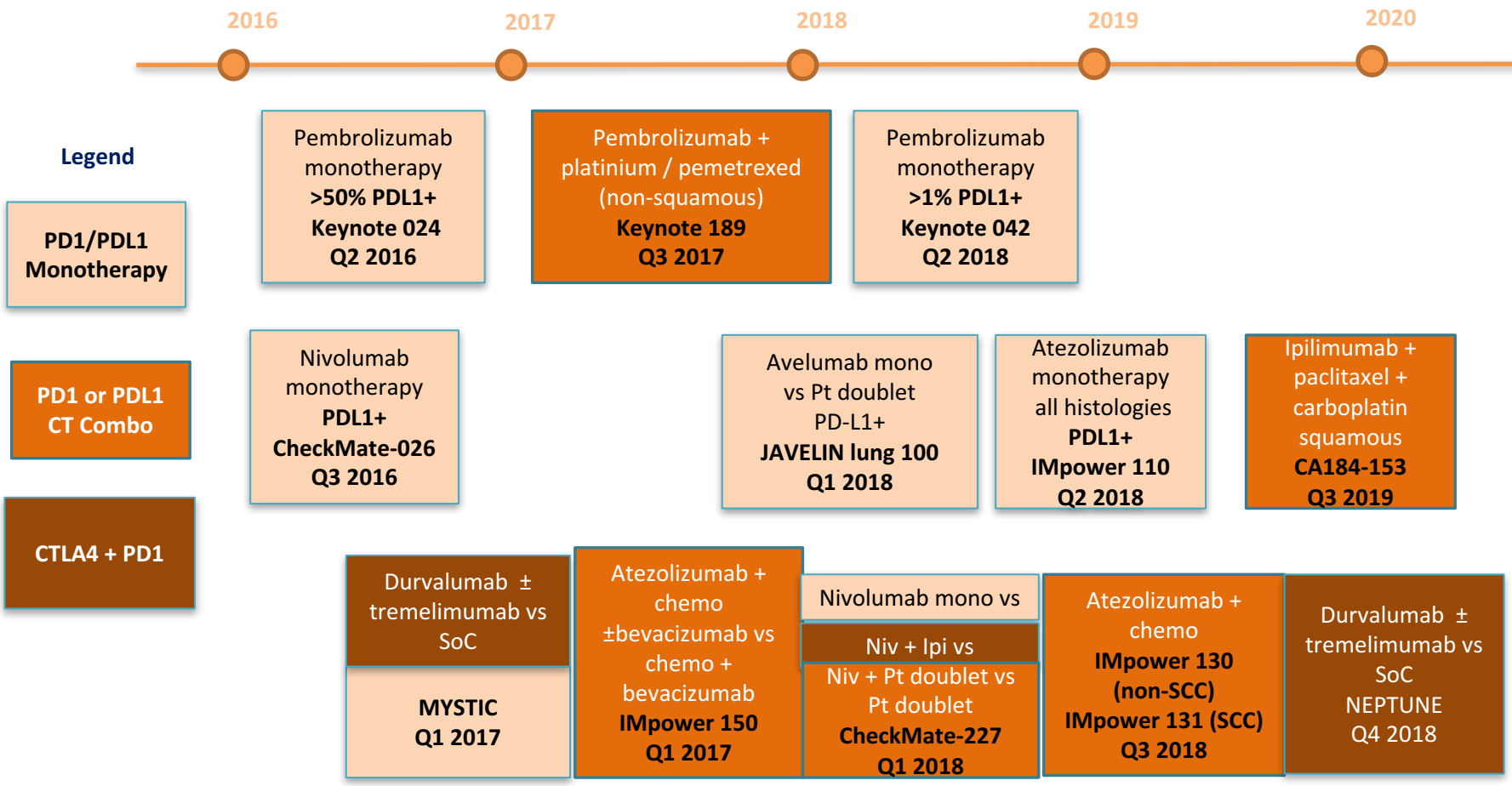
PD-L1 Status	Patients	Events	Median PFS, Mo (95% CI)
All patients	27	8	NR (3.98, —)
Negative	10	2	NR
Weak positive	4	2	3.98 (2.76, —)
Strong positive	7	2	NR
Not reported	6	2	NR

Herbst RS et al. Proc ESMO 2016;Abstract LBA38.

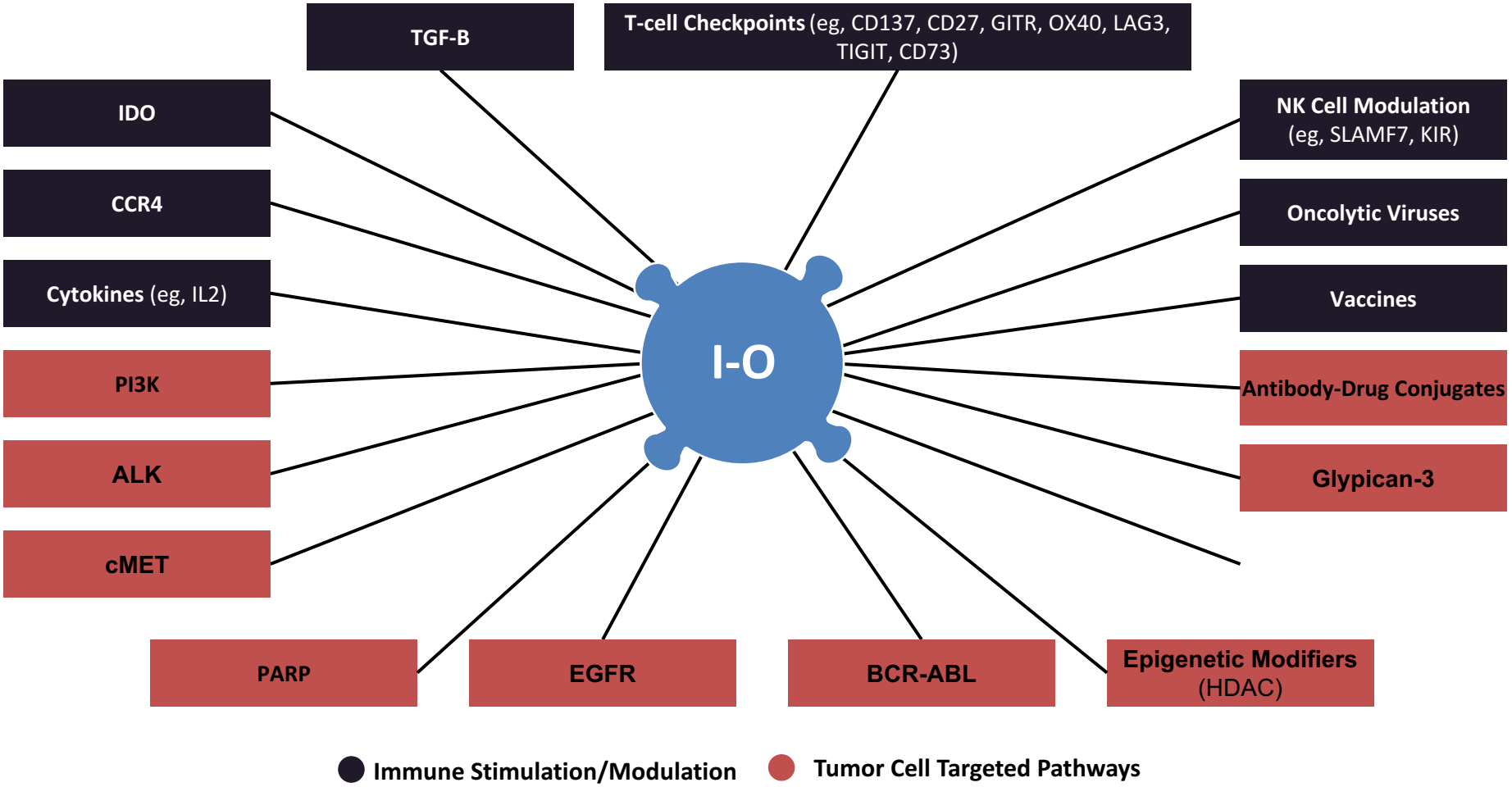
Atezolizumab clinical development programme in first-line and adjuvant NSCLC



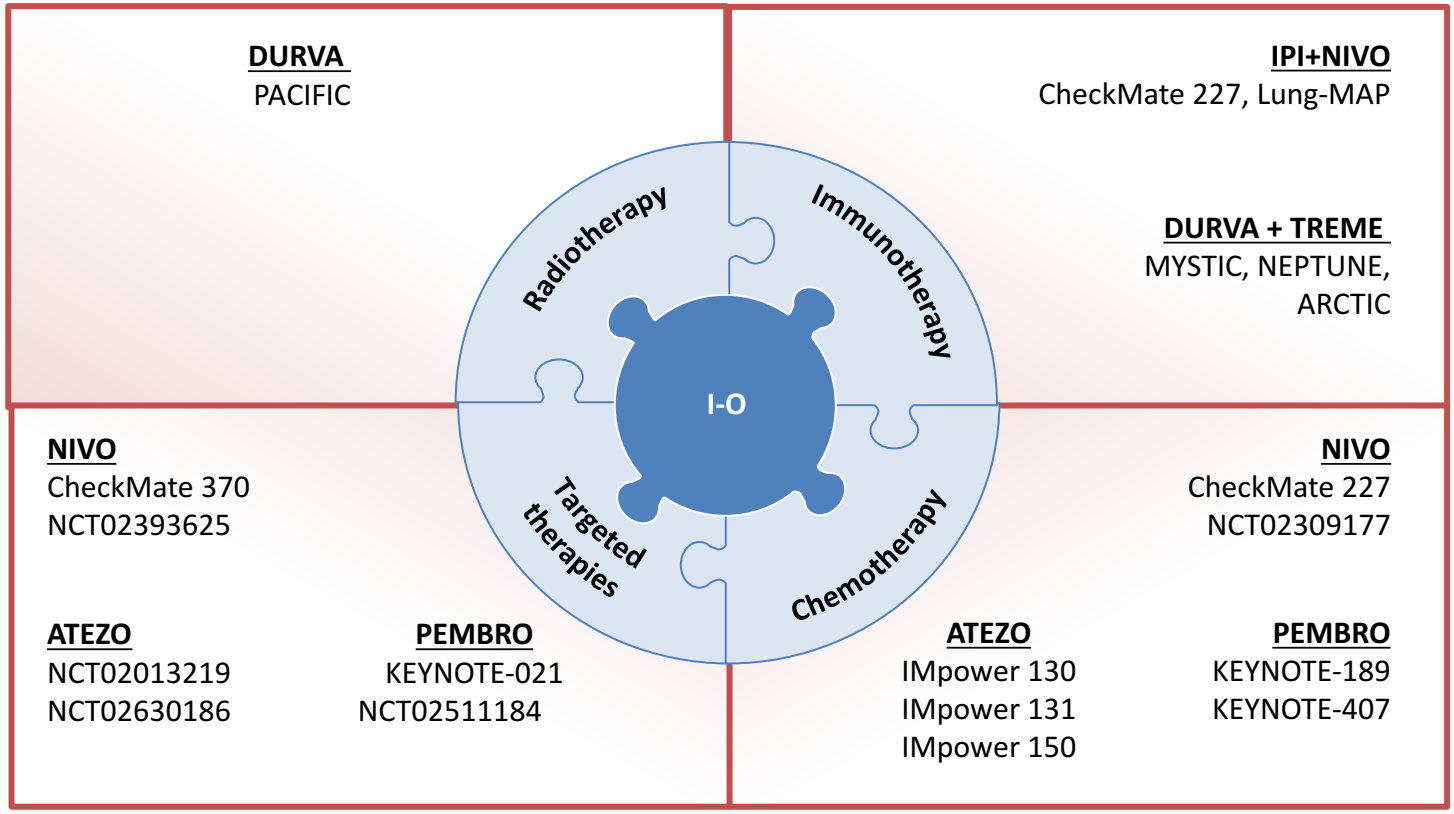
Upcoming randomized immunotherapy trials in 1st line NSCLC and projected read-out timelines



Other candidate combination Targets across Lung cancer



Key trials with I-O therapies: Combinations



Combinations of pembrolizumab, ipilimumab, nivolumab, atezolizumab, and tremelimumab and other therapies are currently not approved for advanced/metastatic NSCLC.

ClinicalTrials.gov. http://www.clinicaltrials.gov.