Imunoterapia em pacientes com mutacoes ativadoras: quando indicar?

VII Simposio Internacional de Cancer de Pulmao
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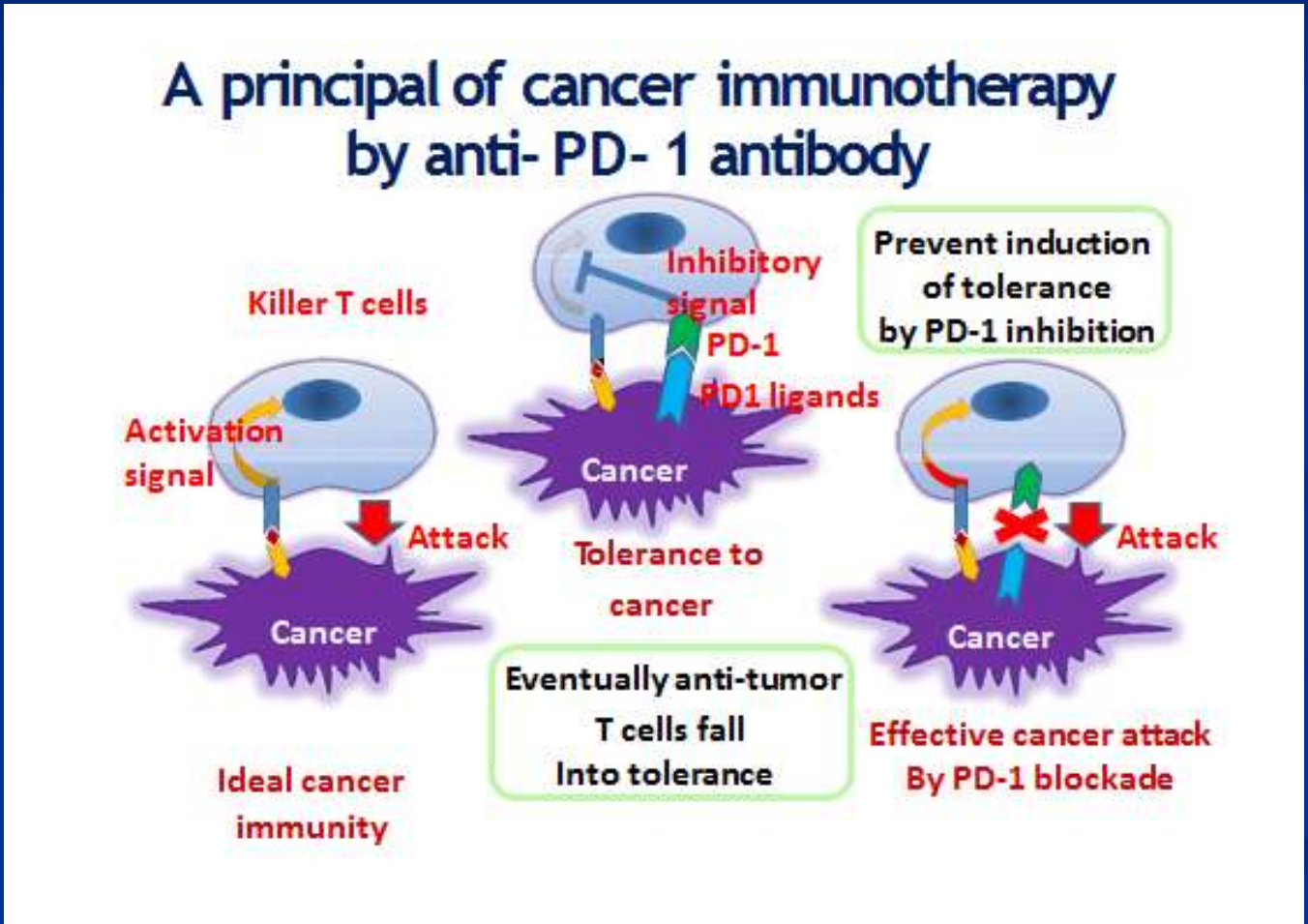
Immunity in Cancer



Immune checkpoint inhibitor FDA approved in NSCLC

- Atezolizumab
  - 1st line in combination with bev-carbo-pac(nonsqua)
- Pembrolizumab
  - 1st line in combination with platinum-pem(nonsqua)
  - 1st line in combination with plastinum-taxane(SCC)
- Nivolumab; Atezolizumab; Pembrolizumab
  - 2nd line NSCLC stage IV
- Pembrolizumab
  - 1st line NSCLC stage IV with PDL1>50%
- Durvalumab
  - Stage III NSCLC post chemo-RT

Challenges with Immunotherapy for mutated tumors

- Patients harboring EGFR/ALK mutation do not respond in these trials
- Immunotherapy less effective in patients with EGFR/ALK mutation.

CheckMate 057

- Proved Nivolumab in second line is superior to Docetaxel.
- 82 patients with EGFR mutation
  - No PFS benefit
  - No OS benefit

KEYNOTE 010

- Proved pembrolizumab prolongs OS in previously treated patients with NSCLC.
- 86 patients with EGFR mutation
  - No OS survival

OAK trial

- Proved efficacy of Atezolizumab in pretreated NSCLC patients.
- EGFR mutation, no OS benefit (HR 1.24)
- Retrospective data revealed:
  - RR 3.6% EGFR mutant
  - RR 23.3% non EGFR mutant (p=0.053)

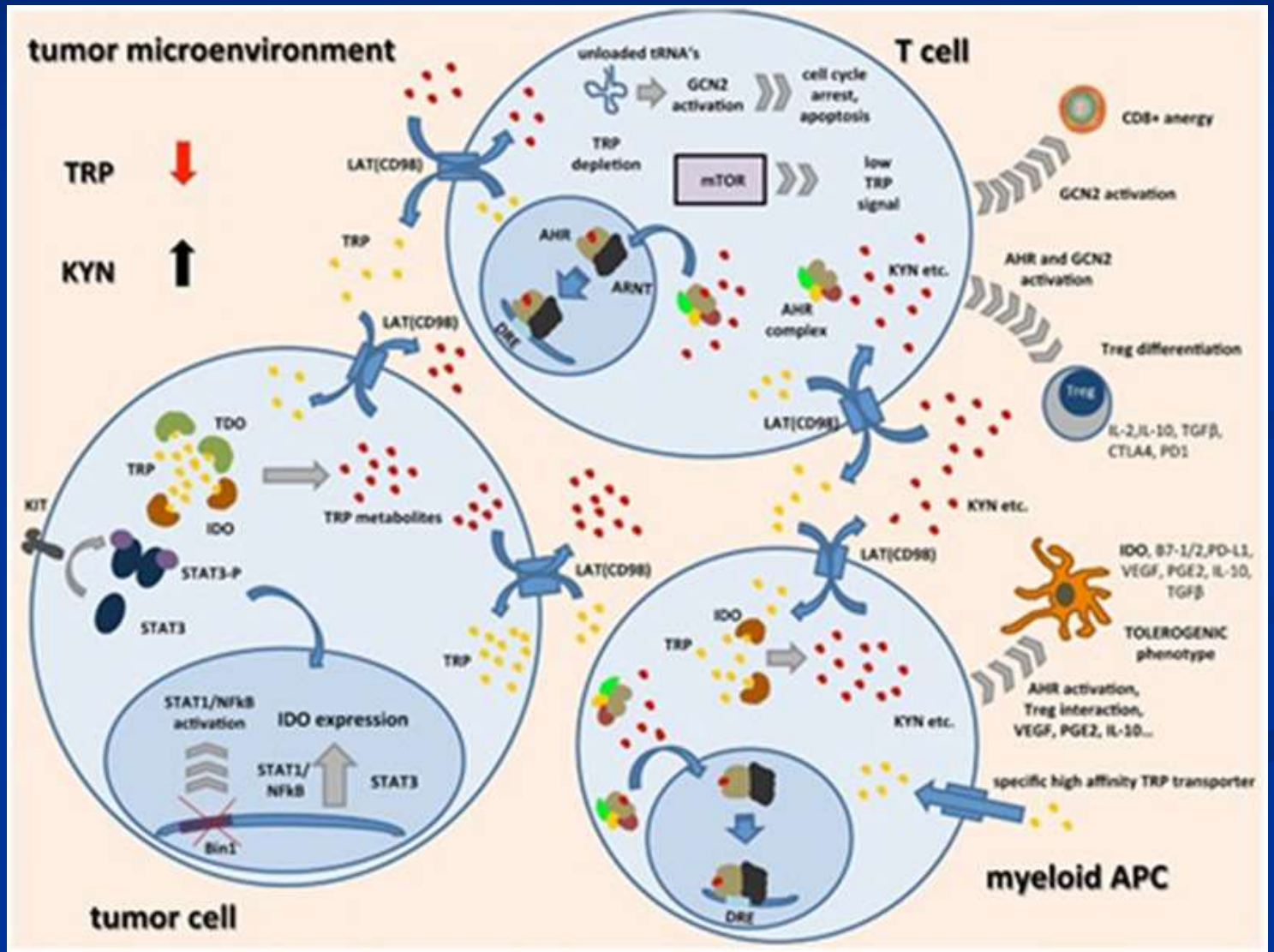
Pooled Analysis (checkmate 057, keynote 010 and POPLAR)

- Imunotherapy do not enhance OS in EGFR-mutant NSCLC compared to docetaxel
- N=186
- HR=1.05
- P<0.81
- Pooled Analysis (Checkmate 017, Checkmate 057, Keynote 010, OAK, and POPLAR) also did not observe OS benefit for EGFR +

A Phase II trial (NCT-0287994)

- Pembrolizumab in TKI-naïve patients with EGFR mutated EGFR.
- Enrollment ceased because of lack of efficacy in 11/25 pts treated.
- None of the patients responded.

Why?
It is complicated.



Why?

- Do they have TIL?
  - Data shows it is a desert (uniflmamed)tumor with low TIL.
- Do they carry low TMB?
  - Yes.
- Is PDL-1 expressed in EGFR mutant NSCLC.
  - Yes and No. Data is conflicting

Why?

- STAT3 (downstream target EGFR)
  - Prevents DC maturation, induces IDO and suppresses MDSCs (exossomes/hsp72).
- Upregulation of IDO
  - Tolerogenic DCS
- EGFR signaling reduces Treg
  - AREG

What to do?
Third line immunotherapy?

- Osimertinib, third-generation
  - Increase CD8+; create a "clean" EGFR tumor at resistance?
- ATLANTIC trial (3rd line durvalumab)
  - 111 patients EGFR or ALK
  - PDL1>25% - ORR 12.2%
  - PDL1<25% - ORR 4%

How about combine EGFR TKI with Immunotherapy?

- TATTON trial
  - Phase IB
  - Osimertinib/Durvalumab
  - RR 12/21
  - 38% serious PNEUMONITIS
  - Ended development

Gefitinib + Durvalumab

- Well tolerated
- ORR 77.9%
- Further development, ongoing trials.

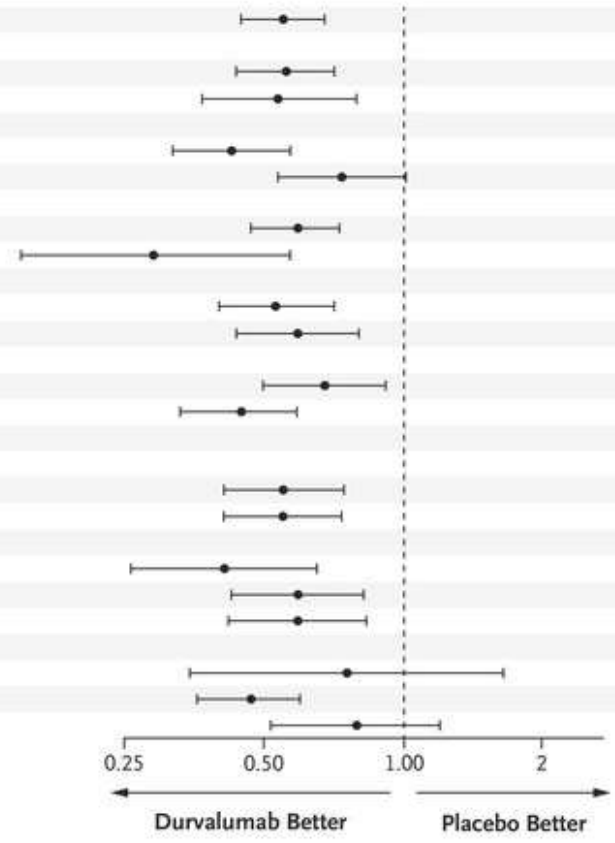
How about chemotherapy plus Immunotherapy?

- PACIFIC trial, ph3 comparing Durvalumab vs placebo post chemo-RT in stage III NSCLC
- Trial proved a longer PFS in the durvalumab cohort.
- In the subgroup analysis, patients with EGFR mutation derived a slight benefit with Durva.

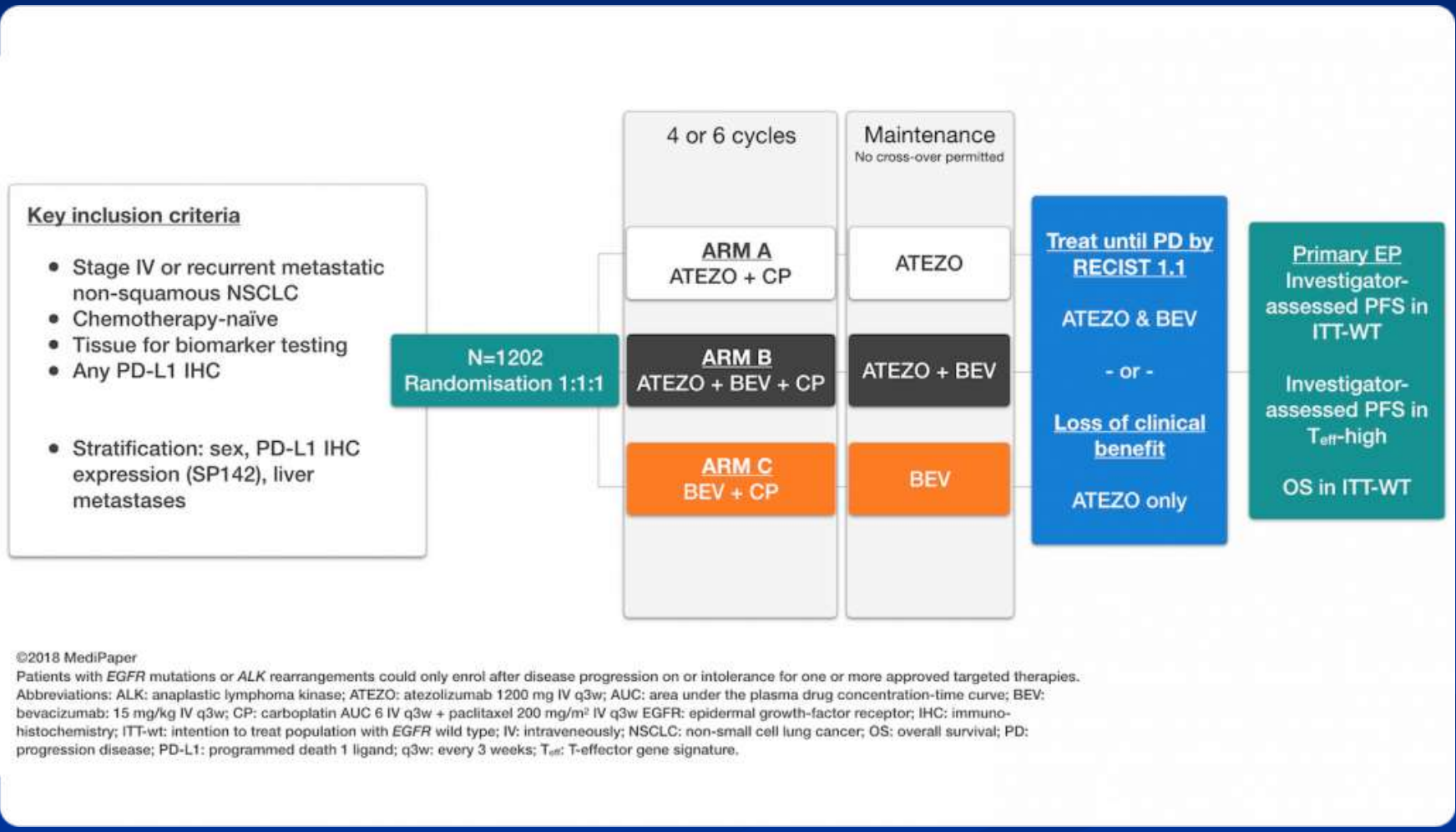
PACIFIC Trial Subgroup analysis

Antonia et al. NEJM Nov 16 2017

Subgroup	Durvalumab	Placebo	Unstratified Hazard Ratio for Disease Progression or Death (95% CI)
	no. of patients		
All patients	476	237	0.55 (0.45–0.68)
Sex			
Male	334	166	0.56 (0.44–0.71)
Female	142	71	0.54 (0.37–0.79)
Age at randomization			
<65 yr	261	130	0.43 (0.32–0.57)
≥65 yr	215	107	0.74 (0.54–1.01)
Smoking status			
Smoker	433	216	0.59 (0.47–0.73)
Nonsmoker	43	21	0.29 (0.15–0.57)
NSCLC disease stage			
IIIA	252	125	0.53 (0.40–0.71)
IIIB	212	107	0.59 (0.44–0.80)
Tumor histologic type			
Squamous	224	102	0.68 (0.50–0.92)
Nonsquamous	252	135	0.45 (0.33–0.59)
Best response			
Complete response	9	7	—
Partial response	232	111	0.55 (0.41–0.75)
Stable disease	222	114	0.55 (0.41–0.74)
PD-L1 status			
≥25%	115	44	0.41 (0.26–0.65)
<25%	187	105	0.59 (0.43–0.82)
Unknown	174	88	0.59 (0.42–0.83)
EGFR mutation			
Positive	29	14	0.76 (0.35–1.64)
Negative	315	165	0.47 (0.36–0.60)
Unknown	132	58	0.79 (0.52–1.20)



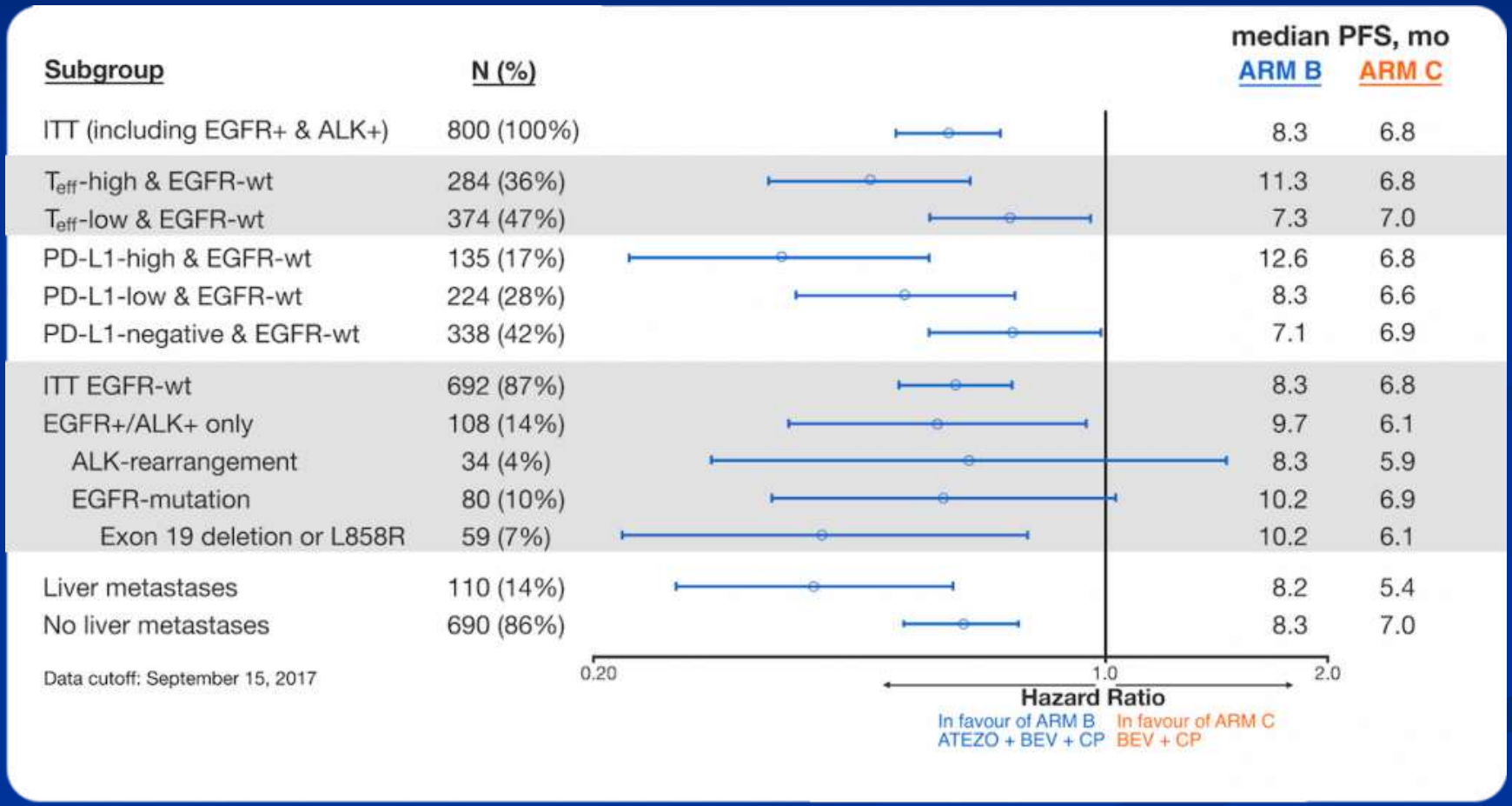
IMpower150



Patients with *EGFR* mutations or *ALK* rearrangements could only enrol after disease progression on or intolerance for one or more approved targeted therapies.
Abbreviations: ALK: anaplastic lymphoma kinase; ATEZO: atezolizumab 1200 mg IV q3w; AUC: area under the plasma drug concentration-time curve; BEV: bevacizumab: 15 mg/kg IV q3w; CP: carboplatin AUC 6 IV q3w + paclitaxel 200 mg/m² IV q3w EGFR: epidermal growth-factor receptor; IHC: immuno-histochemistry; ITT-wt: intention to treat population with *EGFR* wild type; IV: intraveneously; NSCLC: non-small cell lung cancer; OS: overall survival; PD: progression disease; PD-L1: programmed death 1 ligand; q3w: every 3 weeks; T_{eff}: T-effector gene signature.

IMpower150 – Subgroup data

Kowanetz et al. AACR annual meeting April 2018



Future directions for immunotherapy in EGFR mutant

- LYC-55716
  - Retinoic acid receptor-related orphan receptor(ROR)
  - PhIb: LYC-55716 plus Pembro (Preclinical inc TIL)
- Epacadostat (ECHO-306/Keynote-715)
  - Ph 3: IDO1 inhibitor plus pembro plus chemo vs pembro-chemo
  - Ph3: Epacadostat plus pembro vs pembro -1st line
- Pegilodecakin plus anti-PD1
  - Expansion of CD8

Conclusion

- Patients harboring an EGFR mutant NSCLC:
  - Cannot benefit from PD1/PDL1 Rx at first and second line in metastatic setting.
  - PACIFIC trial, mild benefit durvalumab in stage III post chemo-RT.
  - ATLANTIC trial, 3rd line with high PDL1 expression (ORR 12%)
  - IMpower150, 1st line with bev-atezo-carbo-pac
  - Novel therapies: IDO inh, CD8 inducers