Atezolizumab monotherapy vs docetaxel in 2L/3L non-small cell lung cancer: Primary analysis for efficacy, safety and predictive biomarkers from a randomized Phase II study (POPLAR)

Achim Rittmeyer,[1] Louis Fehrenbacher,[2] Alexander I. Spira,[3,4] Julien Mazieres,[5] Keunchil Park,[6] David Smith,[4,7] Angel Artal-Cortes,[8] Conrad Lewanski,[9] Fadi Braiteh,[4,10] Jing Yi,[11] Pei He,[11] Marcin Kowanetz,[11] Daniel Waterkamp,[11] Marcus Ballinger,[11] Daniel S. Chen,[11] Alan Sandler,[11] Johan Vansteenkiste[12]

[1]Lungenfachklinik Immenhausen, Immenhausen, Germany; [2]Kaiser Permanente Medical Center, Vallejo, CA; [3]Virginia Cancer Specialists Research Institute, Fairfax, VA; [4]US Oncology Research, The Woodlands, TX; [5]Toulouse University Hospital, Toulouse, France; [6]Samsung Medical Centre; Division of Hematology/Oncology, Seoul, South Korea; [7]Compass Oncology, Vancouver, WA; [8]Servicio de Oncologia Medica, Hospital Universitario Miguel Servet, Zaragosa, Spain; [9]Department of Oncology, Charing Cross Hospital, London, UK; [10]Comprehensive Cancer Centers of Nevada, Las Vegas, NV; [11]Genentech, Inc., South San Francisco, CA; [12]University Hospitals KU Leuven, Leuven, Belgium

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  - MSD
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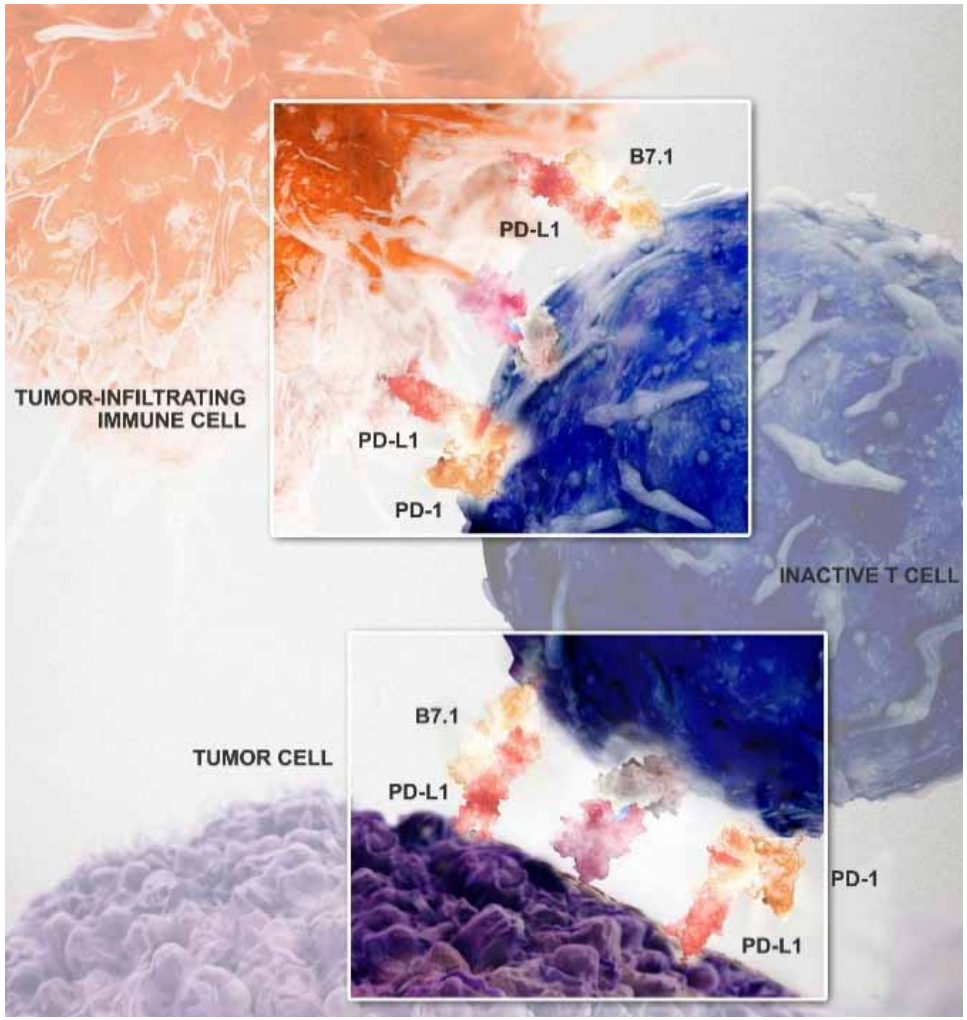
  - Pfizer

Atezolizumab is a Humanized Anti-PDL1 Antibody That Inhibits the Binding of PD-L1 to PD-1 and B7.1



- Inhibiting PD-L1/PD-1 and PD-L1/B7.1 interactions can restore anti-tumor T-cell activity and enhance T-cell priming
- Targeting PD-L1 leaves the PD-L2/PD-1 interaction intact, thereby potentially preserving peripheral immune homeostasis
- Atezolizumab (anti-PDL1) has demonstrated promising response rates in NSCLC that correlated with PD-L1 expression on tumor cells (TC) and/or tumor-infiltrating immune cells (IC); (Horn et al., ASCO 2015; Fehrenbacher et al., *Lancet* 2016)

POPLAR: A Randomized All-comer Phase II Study (NCT01903993)

Metastatic or locally advanced NSCLC (2L/3L)
Disease progression on a prior platinum therapy
N = 287

Stratification Factors
- PD-L1 IC expression (0 vs 1 vs 2 vs 3)[a]
- Histology (squamous vs non-squamous)
- Prior chemotherapy regimens (1 vs 2)

R
1:1

Atezolizumab
1200 mg IV q3w
until loss of clinical benefit

Docetaxel
75 mg/m^2 IV q3w
until disease progression

Primary study objective:
- **Estimate OS in ITT and PD-L1 expression subgroups**

Secondary study objectives:
- Estimate PFS, ORR and DOR in ITT and PD-L1 expression subgroups
- Evaluate safety

- Primary analysis conducted with 173 events, minimum follow-up 13 months
- Interim analysis with 153 events, minimum follow-up 10 months was presented at ASCO 2015 (Spira et al., Abstract 8010)

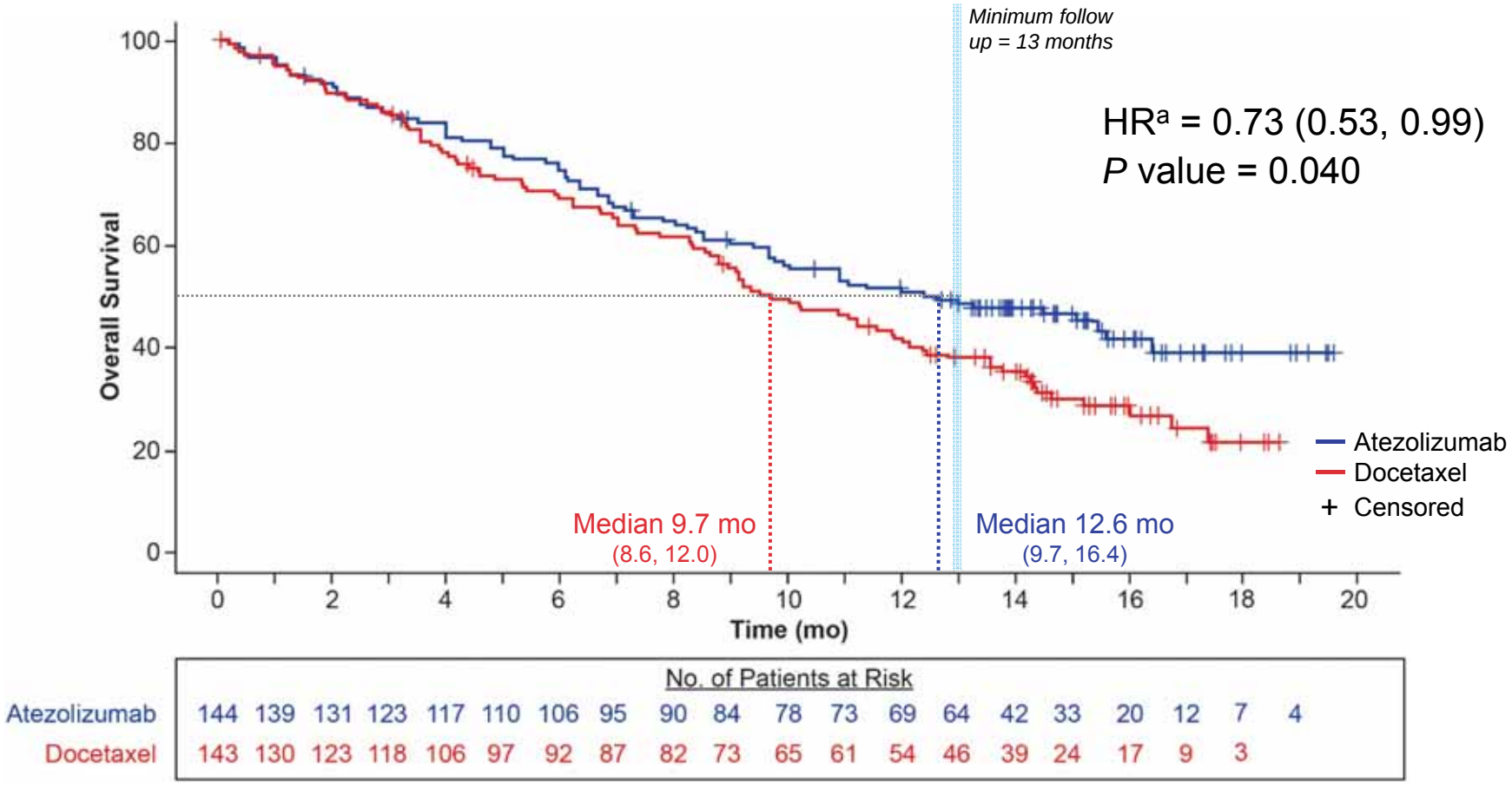
[a]Archival or new tissue required for pre-dose testing.

POPLAR: Baseline Characteristics (ITT)

Characteristics of Patients with NSCLC	Atezolizumab (n = 144)	Docetaxel (n = 143)
Median age, y	62	62
≥ 65 y	40%	39%
Male	65%	53%
Histology		
Non-squamous	66%	66%
Squamous	34%	34%
ECOG score, 0 / 1	32% / 68%	32% / 68%
No. of prior therapies, 1 / 2	65% / 35%	67% / 33%
History of tobacco use		
Never	19%	20%
Current	17%	15%
Previous	64%	65%

Data cut-off May 8, 2015.

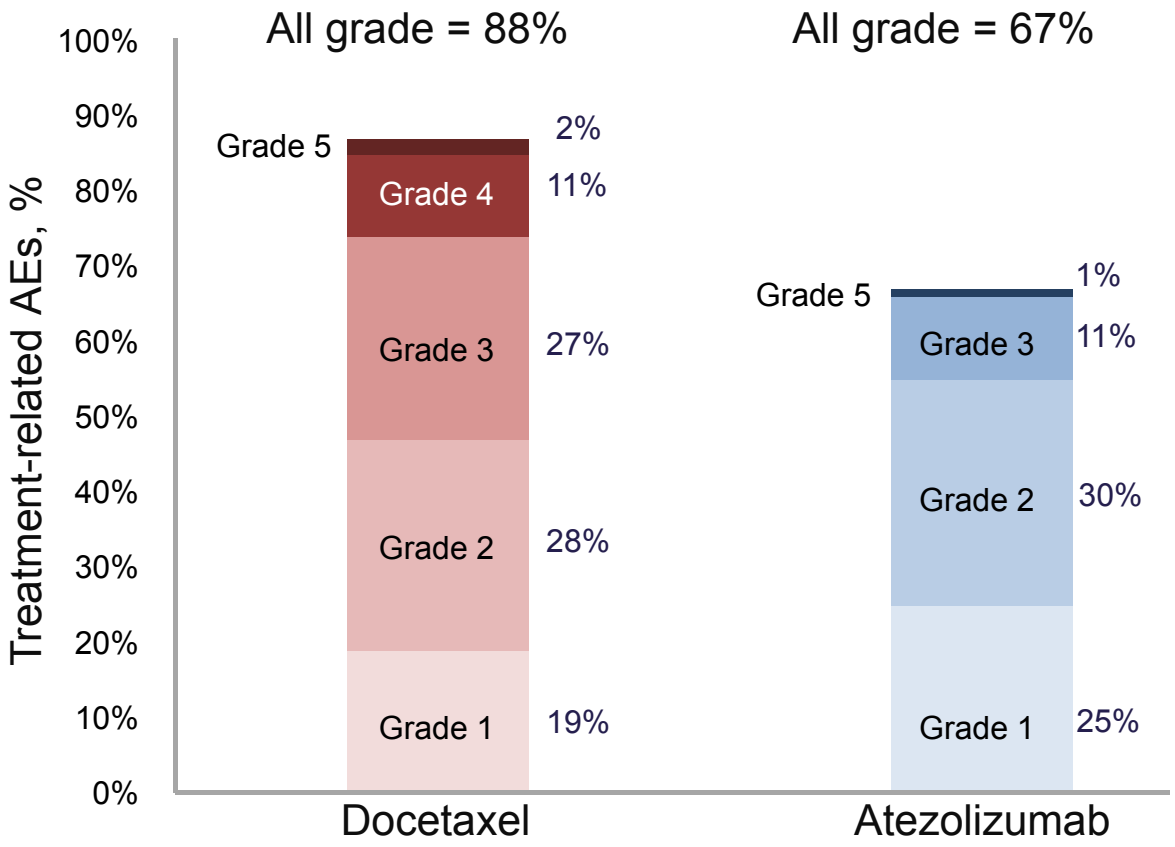
POPLAR: All Patient Efficacy
ITT OS (N = 287)



- **Event/patient ratio:** 60% (54% for atezolizumab, 66% for docetaxel)

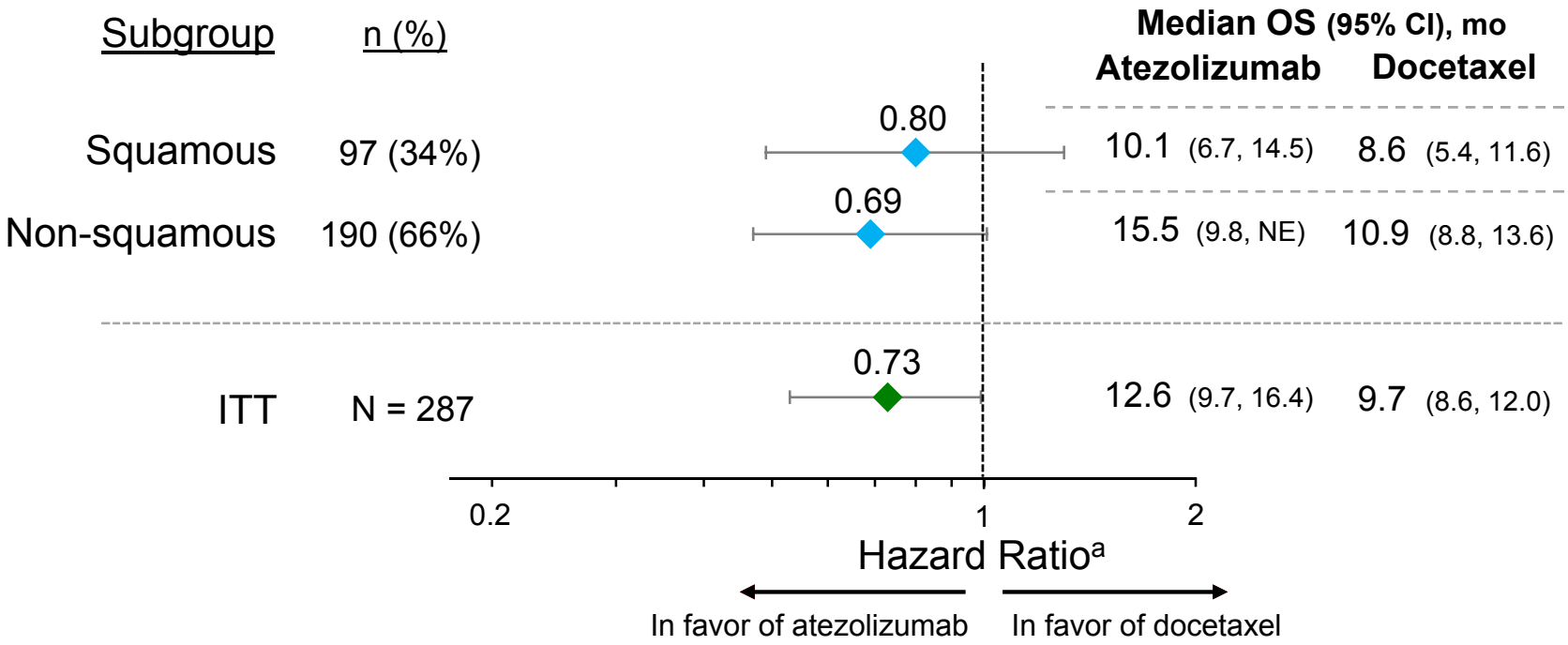
[a]Stratified HR.
Data cut-off May 8, 2015.

POPLAR: Treatment-related AEs



Safety population includes patients who received any amount of either study treatment.
Data cut-off May 8, 2015.

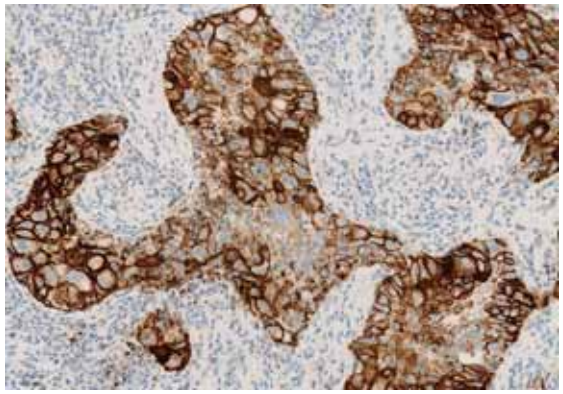
POPLAR: Overall Survival by Histology



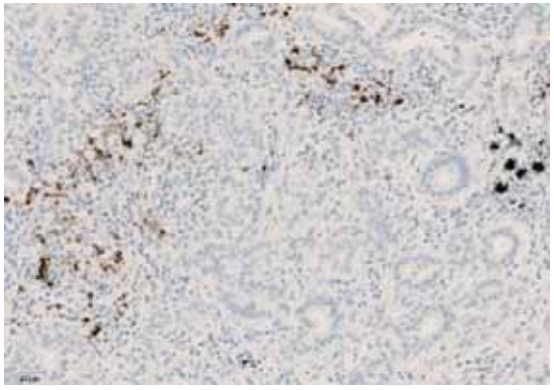
- **Event/patient ratio: Squamous 69%** (63% for atezolizumab, 75% for docetaxel)
  Non-squamous 56% (49% for atezolizumab, 62% for docetaxel)

[a]Unstratified HR for subgroups and stratified HR for ITT.
Data cut-off May 8, 2015.

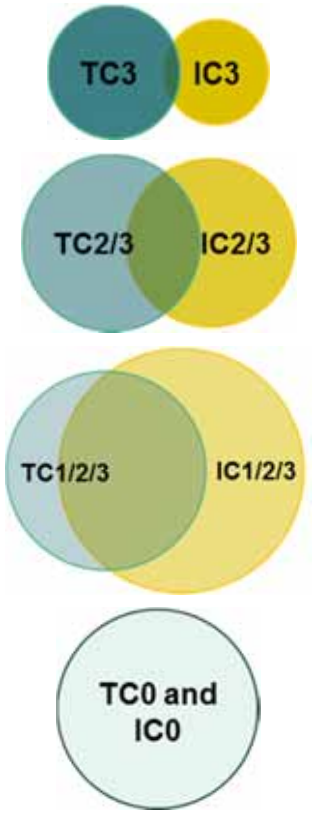
PD-L1 Expression on TC and IC is a Potential Predictive Biomarker for Atezolizumab in NSCLC



Intrinsic PD-L1 expression on tumor cells (TC)



Adaptive PD-L1 expression on tumor-infiltrating immune cells (IC)

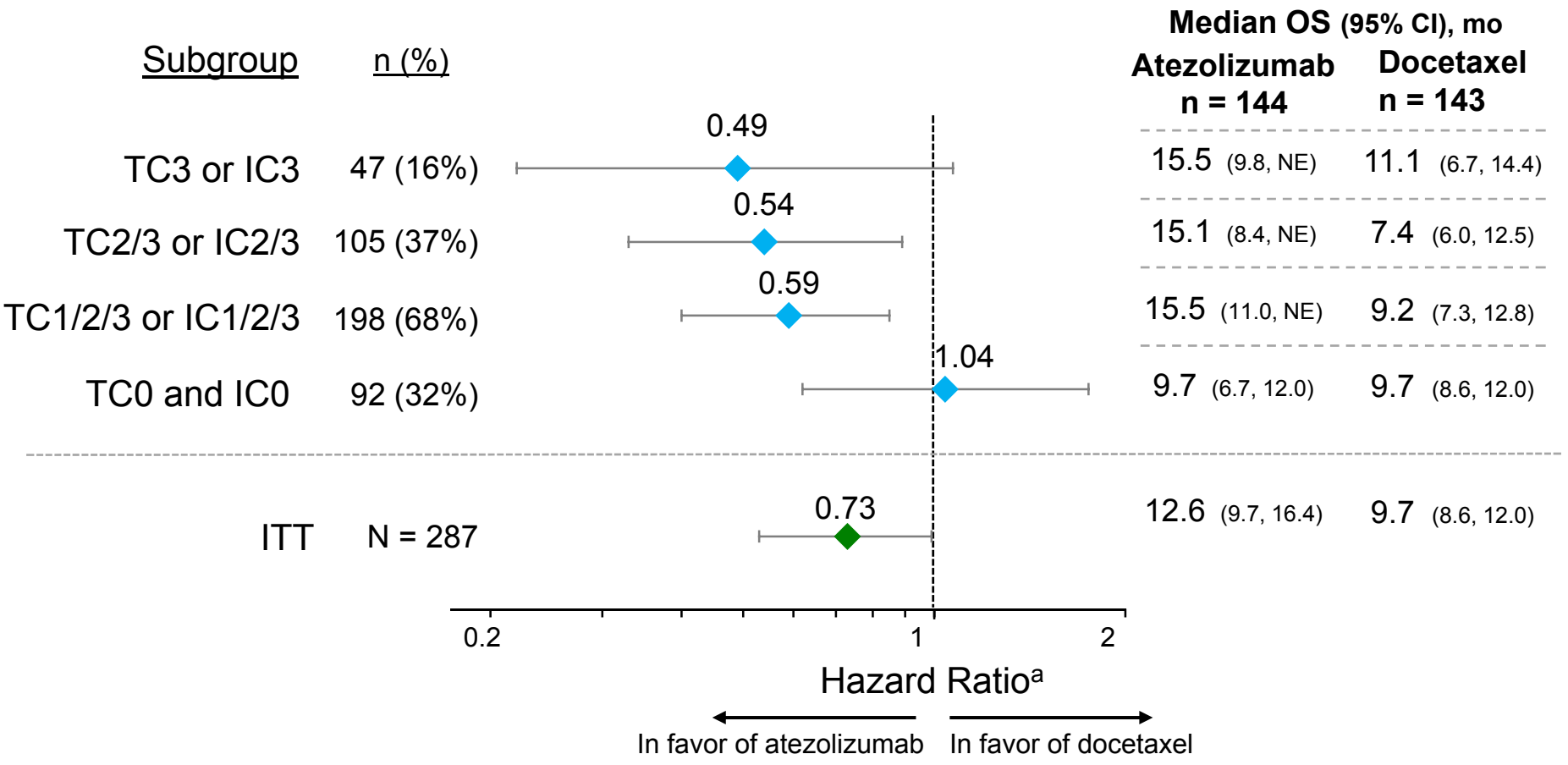


PD-L1 expression levels and TC/IC overlap in POPLAR

- SP142 IHC assay is sensitive and specific for PD-L1 expression on both TC and IC
- Distinct TC and IC sub-populations exist at each of four cutoff levels[a] (Gettinger et al., ASCO 2015; Schmid et al., ECC 2015)
- PD-L1 expression on TC and IC was independently predictive of response (Horn et al., ASCO 2015)

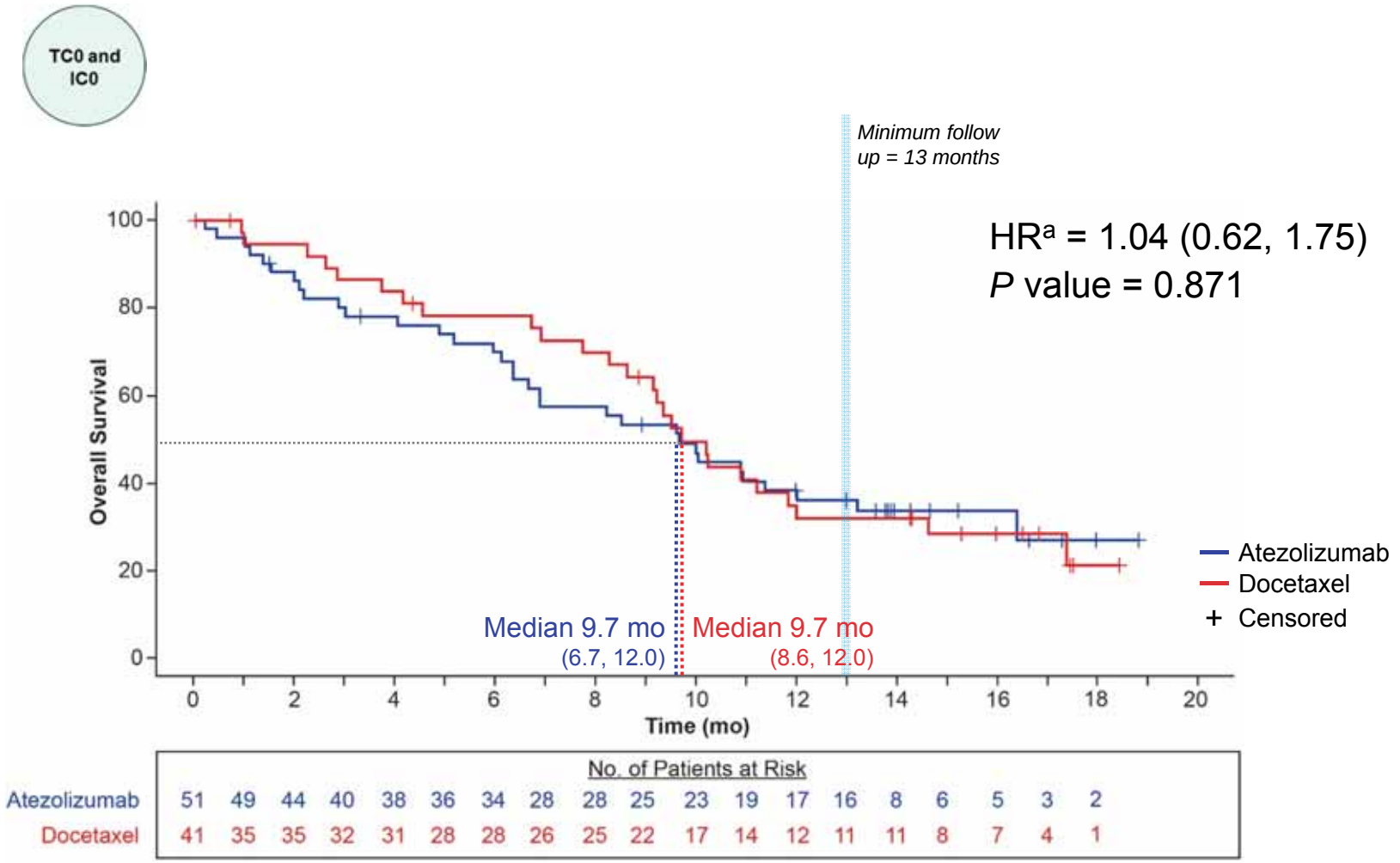
[a]TC3 or IC3 = TC ≥ 50% or IC ≥ 10% PD-L1 expressing cells;
TC2/3 or IC2/3 = TC or IC ≥ 5% PD-L1 expressing cells;
TC1/2/3 or IC1/2/3 = TC or IC ≥ 1% PD-L1 expressing cells;
TC0 and IC0 = TC and IC < 1% PD-L1 expressing cells, respectively.

POPLAR: Overall Survival by PD-L1 Expression



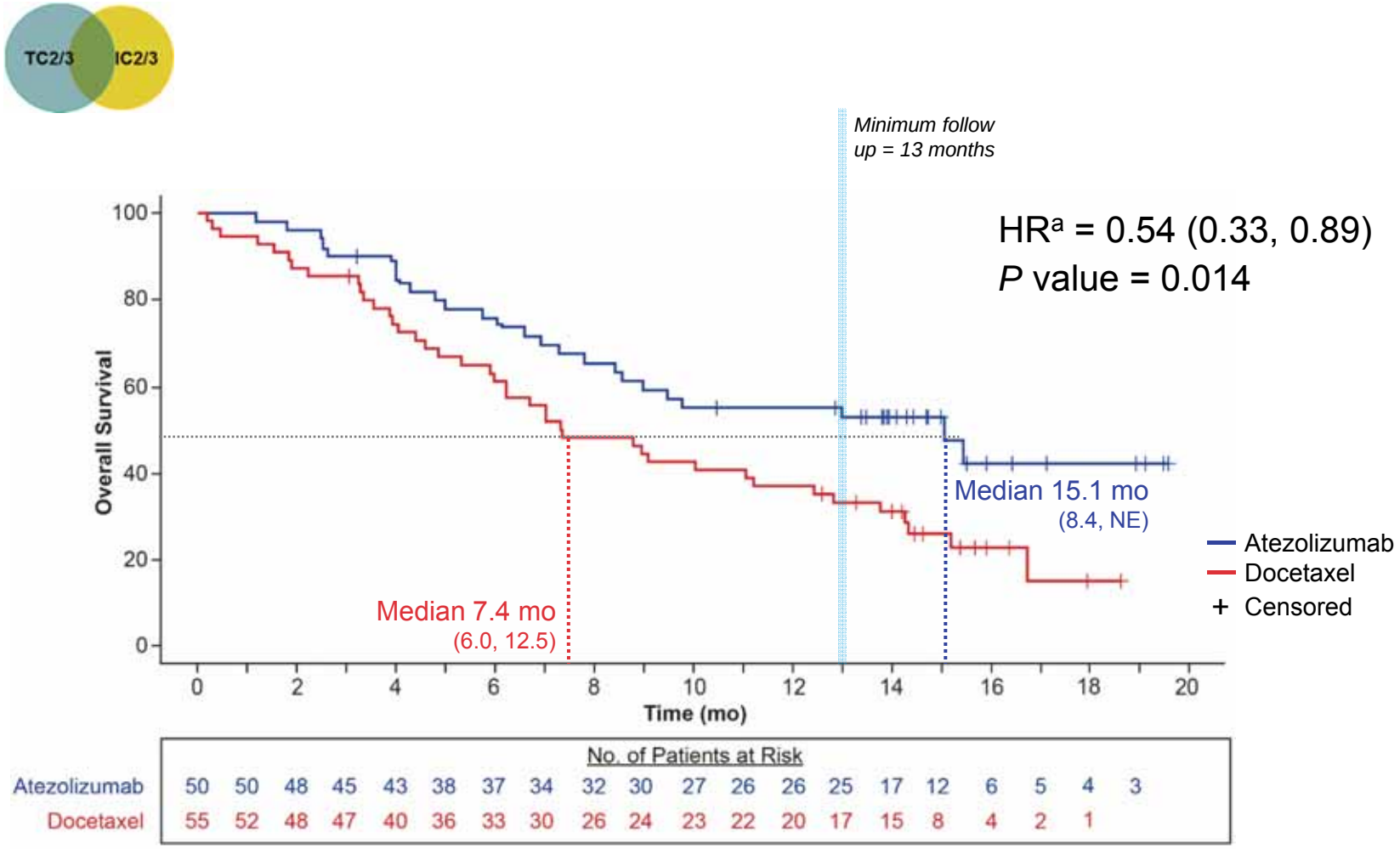
[a]Unstratified HR for subgroups and stratified HR for ITT.
Data cut-off May 8, 2015.

POPLAR: Overall Survival by PD-L1 Expression
TC0 and IC0 Subgroup (n = 92)



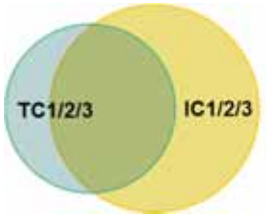
[a]Unstratified HR.
Data cut-off May 8, 2015.

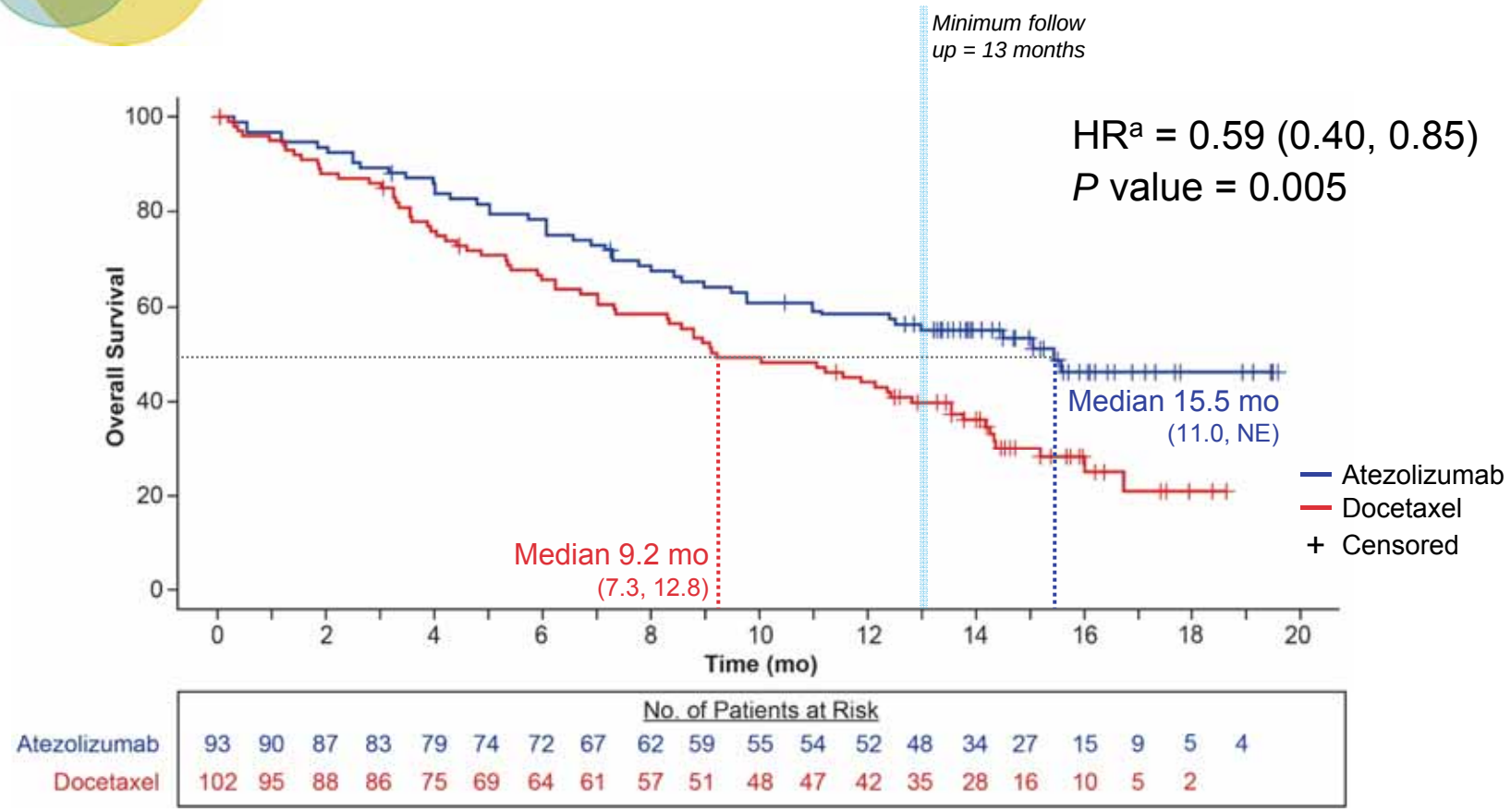
POPLAR: Overall Survival by PD-L1 Expression TC2/3 or IC2/3 Subgroup (n = 105)



[a]Unstratified HR.
Data cut-off May 8, 2015.

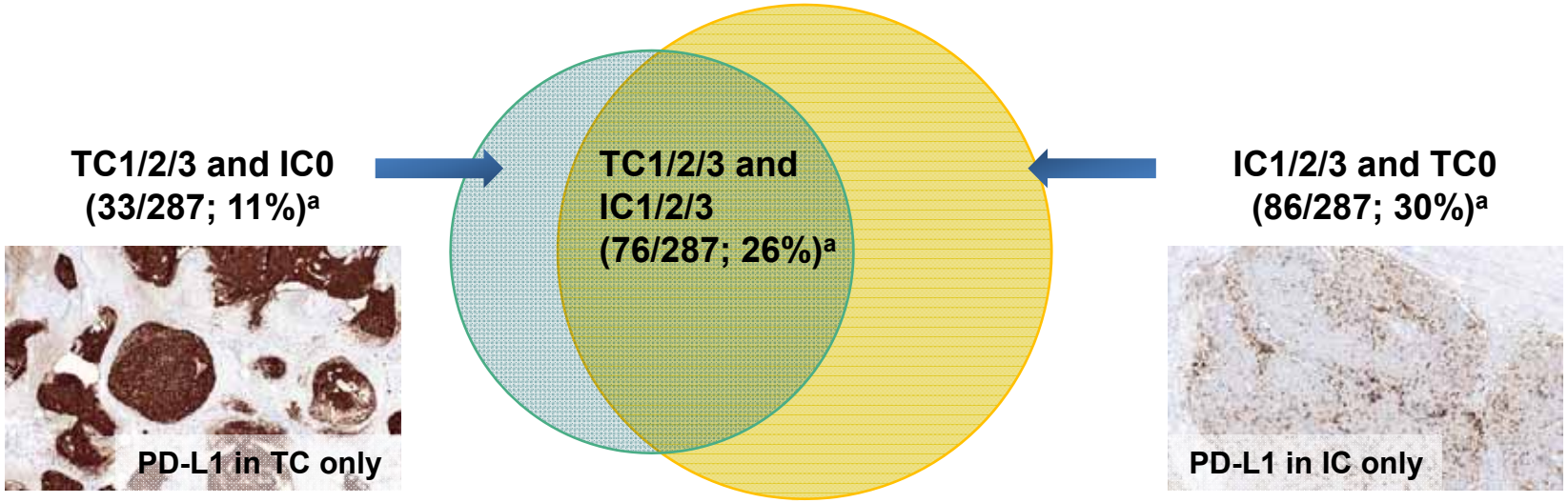
POPLAR: Overall Survival by PD-L1 Expression TC1/2/3 or IC1/2/3 Subgroup (n = 195)





[a]Unstratified HR.
Data cut-off May 8, 2015.

POPLAR: Both TC and IC are Independent Predictors of Survival Improvement

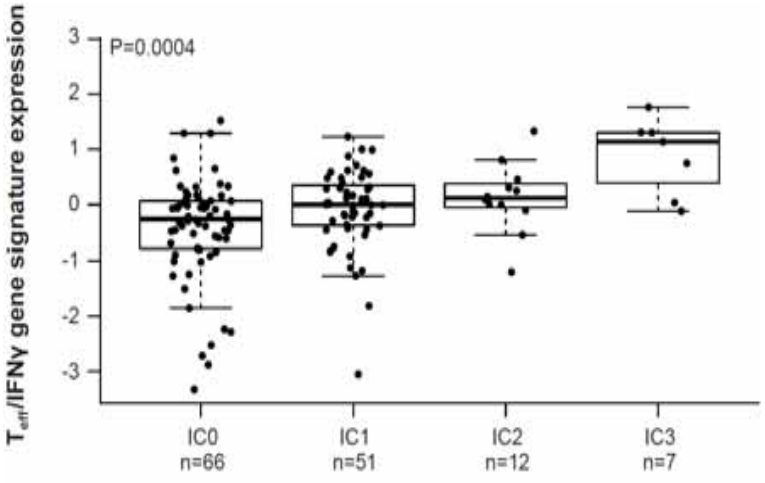


PD-L1 status	OS HR[b] (95% CI)
TC1/2/3 and IC0	0.37 (0.12,1.13)
IC1/2/3 and TC0	0.63 (0.36,1.12)
TC1/2/3 and IC1/2/3	0.60 (0.34, 1.08)
TC1/2/3 or IC1/2/3	0.59 (0.40, 0.85)

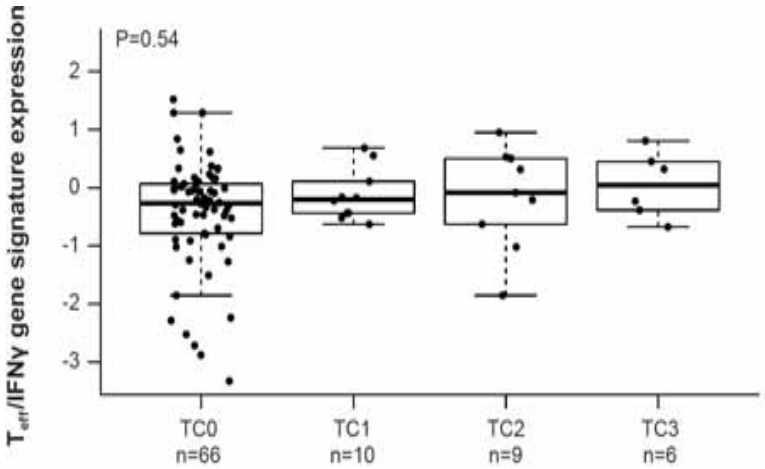
[a]Number of patients within subgroup/total study population; Percentage of total study population.
[b]Unstratified HR.
Data cut-off May 8, 2015.

POPLAR: T_{eff}/IFNγ Gene Signature Is Associated With PD-L1 Expression on IC

T_{eff}/IFNγ vs IC (among TC0)



T_{eff}/IFNγ vs TC (among IC0)

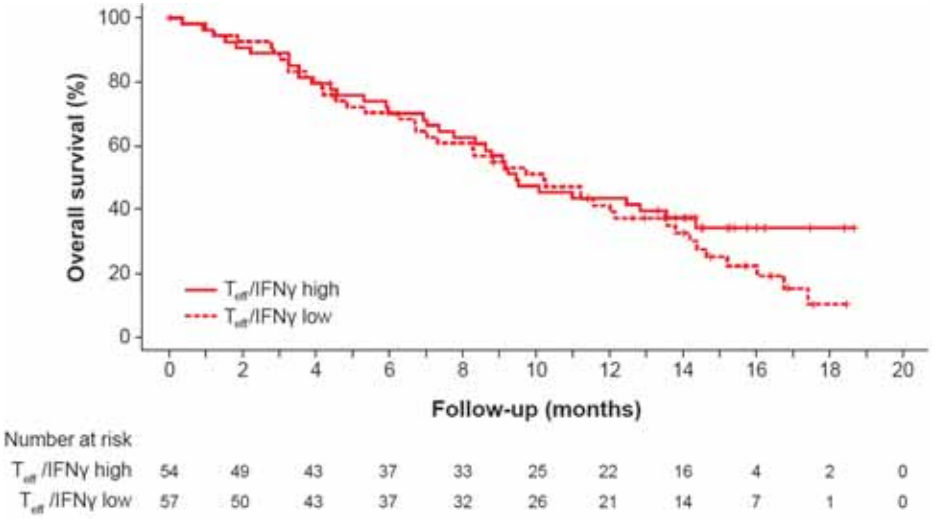


- T_{eff}/IFNγ signature is defined by expression of *CD8A*, *GZMA*, *GZMB*, *IFNγ*, *EOMES*, *CXCL9*, *CXCL10* and *TBX21* genes

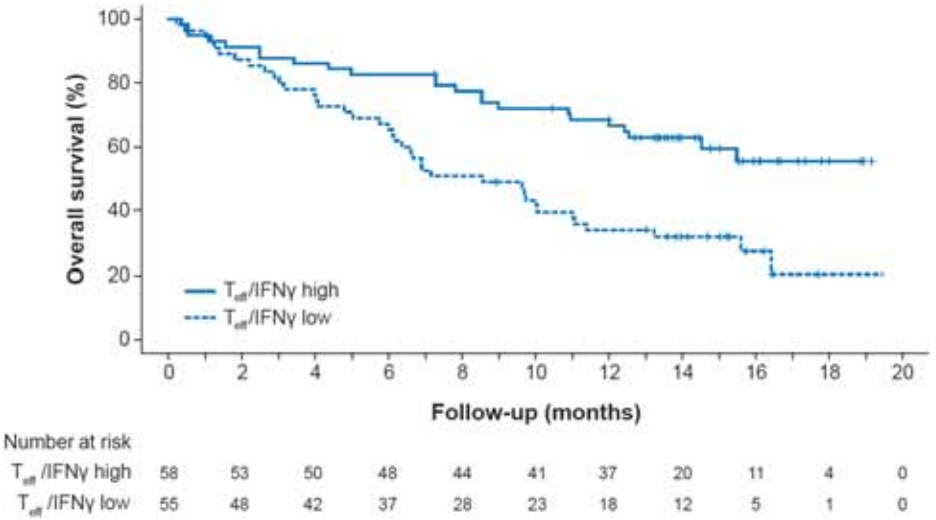
Data cut-off May 8, 2015.

POPLAR: Overall Survival In T_{eff}/IFNγ Gene Signature Subgroups

Docetaxel



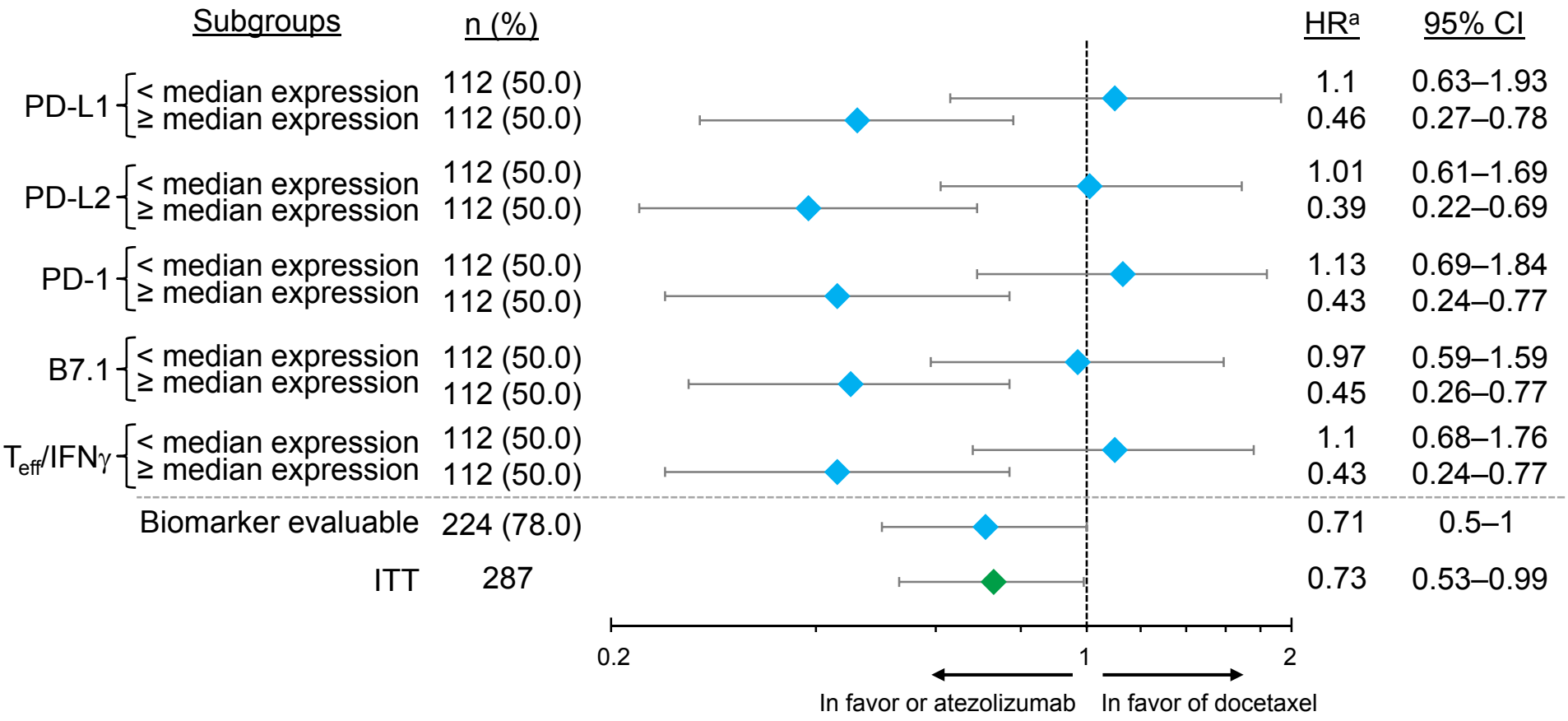
Atezolizumab



T_{eff}/IFNγ signature subgroup[a]	HR[b] (95% CI)
High	0.43 (0.24, 0.77)
Low	1.10 (0.68,1.76)

T_{eff}/IFNγ signature defined by expression of *CD8A*, *GZMA*, *GZMB*, *IFNγ*, *EOMES*, *CXCL9*, *CXCL10* and *TBX21* genes.
[a]High biomarker group defined as gene expression at or above the median level; low biomarker group defined as gene expression below the median level.
[b]Stratified and adjusted HR for survival with atezolizumab vs docetaxel.
Data cut-off May 8, 2015.

POPLAR: Overall Survival In PD-L1/PD-1 Pathway Gene Expression Subgroups



T_{eff}/IFNγ signature defined by expression of *CD8A*, *GZMA*, *GZMB*, *IFNγ*, *EOMES*, *CXCL9*, *CXCL10* and *TBX21* genes.
[a]Stratified and adjusted HR for survival with atezolizumab vs docetaxel.
Data cut-off May 8, 2015.

Rittmeyer et al., Atezolizumab in NSCLC (POPLAR)

Summary

- The POPLAR Phase II randomized study demonstrated significant OS improvements for PD-L1–unselected NSCLC patients receiving atezolizumab vs docetaxel ITT: OS HR = 0.73 (P = 0.040)
- Activity was seen in both squamous and non-squamous patients treated with atezolizumab
- PD-L1 expression on TC and IC was independently predictive of survival improvement with atezolizumab
- Higher PD-L1 expression was associated with improved OS with atezolizumab (HR range, 0.49-0.59)
- TC0 and IC0: no difference in OS (HR = 1.04), but overall safety data shows significantly less toxicity with atezolizumab vs docetaxel
- High gene expression of PD-L2, PD-1, B7.1 and the T_{eff}/IFNγ gene signature was associated with improved OS for atezolizumab treatment (HR range, 0.39-0.45)

Future Atezolizumab Development in NSCLC

- Ongoing randomized trials
  - Phase III study of atezolizumab monotherapy in 2L/3L patients (OAK; NCT01846416)
  - Phase III study of atezolizumab monotherapy in PD-L1-selected 1L patients (IMpower110)
- Phase 1b trial of atezolizumab with chemotherapy showed 67% preliminary ORR and tolerable safety in unselected patients with NSCLC (NCT01633970). (Camidge et al., WCLC 2015; Giaccone et al., ECC 2015)
- Multiple Phase III 1L NSCLC studies are underway
  - IMpower130, IMpower131, IMpower132 and IMpower150 studies of chemotherapy + atezolizumab (NCT02367781; NCT02367794; NCT02657434 and NCT02366143)
- IMpower010 study of atezolizumab vs best supportive care in adjuvant setting (NCT02409342)

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