Wang J, Lu S, Yu X, et al. Tislelizumab plus chemotherapy vs chemotherapy alone as first-line treatment for advanced squamous non–small-cell lung cancer: a phase 3 randomized clinical trial. *JAMA Oncol*. Published online April 1, 2021. doi:10.1001/jamaoncol.2021.0366

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This supplemental material has been provided by the authors to give readers additional information about their work.
eMethods.

Additional Inclusion/Exclusion Criteria

Inclusion Criteria:

- Patients had not received prior systemic therapy for advanced or metastatic disease.
- Prior neoadjuvant/adjuvant therapy or chemoradiation therapy with curative intent was allowed if there had been a disease-free interval $\geq 6$ months prior to randomization.

Exclusion Criteria:

- Patients had prior active malignancies $\leq 2$ years from study entry or locally recurring cancers that underwent curative treatment, not including non-small cell lung cancer.
- Patients had prior treatment with inhibitors of EGFR, ALK, and/or PD-1/L1 inhibitors.

Endpoint Definitions

- Progression-free survival: Defined as the time from randomization to the first objectively documented disease progression per RECIST v1.1 or death from any cause, whichever occurs first.
- Overall survival: Time from the date of randomization to the date of death from any cause.
- Objective response rate: Complete response (CR) plus partial response (PR) per RECIST v1.1 criteria.
- Duration of response: Time from the first occurrence of a documented objective response to documented disease progression per RECIST v1.1 criteria or death by any cause, whichever occurs first.
- Disease control rate: CR plus PR plus stable disease ($\geq 6$ weeks).
- Tumor Assessments and Screening for PD-L1 Expression
Tumor assessments and radiographic imaging by MRI or CT were performed every 6 weeks during the first 6 months, every 9 weeks for the remainder of the first year, and every 12 weeks thereafter. Tumor cell PD-L1 membrane staining was assessed during screening with the VENTANA PD-L1 (SP263) assay at a central laboratory.
eFigure 1. Study design

Target accrual was 342 patients, with 114 patients planned per arm.
*A total of 360 patients were randomized; 5 patients (n=1 [B]; n=4 [C]) did not receive study treatment.
Tislelizumab, carboplatin, and paclitaxel were administered on D1.
Nab-paclitaxel was administered on D1, D8, and D15.
Abbreviations: D, day; ECOG, Eastern Cooperative Oncology Group; nab, nanoparticle albumin-bound; NSCLC, non-small cell lung cancer; Q3W, every 3 weeks; R, randomized.
eFigure 2. Progression-free survival by investigator

(A) Arm A versus Arm C (A) and Arm B versus Arm C (B).

*Descriptive P-value.

Abbreviation: CI, confidence interval.
eFigure 3. Progression-free survival by Independent Review Committee in patients with $\geq 50\%$ tumor cell PD-L1 expression

**Arm A** versus **Arm C** (A) and **Arm B** versus **Arm C** (B).

Abbreviations: CI, confidence interval; NE, not evaluable; PD-L1, programmed death-ligand 1.
eFigure 4. Progression-free survival by Independent Review Committee in patients with 1-49% tumor cell PD-L1 expression

Arm A versus Arm C (A) and Arm B versus Arm C (B).

Abbreviations: CI, confidence interval; NE, not evaluable; PD-L1, programmed death-ligand 1.
eFigure 5. Progression-free survival by Independent Review Committee in patients with <1% tumor cell PD-L1 expression

Arm A versus Arm C (A) and Arm B versus Arm C (B).

Abbreviations: CI, confidence interval; NE, not evaluable; PD-L1, programmed death-ligand 1.
eFigure 6. Objective response rate by PD-L1 expression as assessed by Independent Review Committee

| Response/Patients (n) | Objective Response Rate (95% CI) | ETD (95% CI) |
|-----------------------|-----------------------------------|--------------|
| **PD-L1 Expression in TC ≥50%** | | |
| Arm A 33/42 | 75.6 (63.2, 89.7) | 24.90 (5.2, 44.6) |
| Arm B 37/42 | 88.1 (74.4, 96.0) | 34.4 (16.3, 52.8) |
| Arm C 22/41 | 53.7 (37.4, 69.3) | |
| **PD-L1 Expression in TC 1-49%** | | |
| Arm A 21/30 | 70.0 (50.6, 85.3) | 28.1 (4.2, 52.0) |
| Arm B 20/30 | 66.7 (47.2, 82.7) | 24.7 (0.5, 48.9) |
| Arm C 13/31 | 41.9 (24.5, 60.9) | |
| **PD-L1 Expression in TC <1%** | | |
| Arm A 33/48 | 68.8 (53.7, 81.3) | 17.7 (-1.4, 36.9) |
| Arm B 32/47 | 68.1 (52.9, 80.9) | 17.1 (-2.3, 36.4) |
| Arm C 25/49 | 51.0 (36.3, 65.6) | |

Abbreviations: CI, confidence interval; ETD, estimated treatment difference; PD-L1, programmed death-ligand 1; TC, tumor cell.
Potential immune-mediated AEs were selected from a group of preferred terms, regardless of whether the investigator attributed the event to a trial regimen or considered the event to be immune related.

**Arm A:** Tislelizumab + PC.

**Arm B:** Tislelizumab + nab-PC.

**Arm C:** PC alone.

Abbreviations: AEs, adverse events; GGT, γ-glutamyltransferase; nab, nanoparticle albumin-bound; PC, paclitaxel and carboplatin.
### Table 1. Tislelizumab Treatment Exposure

|                  | Arm A: Tislelizumab + Paclitaxel + Carboplatin (n=120) | Arm B: Tislelizumab + nab-Paclitaxel + Carboplatin (n=118) | Arm C: Paclitaxel + Carboplatin (n=117) |
|------------------|--------------------------------------------------------|------------------------------------------------------------|----------------------------------------|
| **Relative dose intensity**<sup>a</sup> | Median (range)                                         | 97.7 (64-108)                                              | 91.3 (55-100)                          | NA                                      |
| **Number of cycles received with tislelizumab** | Median (range)                                         | 10 (1-20)                                                  | 10 (1-19)                              | NA                                      |
|                  | 1-4 cycle, n (%)                                      | 23 (19.2)                                                  | 20 (16.9)                              | NA                                      |
|                  | 5-8 cycles, n (%)                                     | 16 (13.3)                                                  | 26 (22.0)                              | NA                                      |
|                  | 9-12 cycles, n (%)                                    | 49 (40.8)                                                  | 44 (37.3)                              | NA                                      |
|                  | >12 cycles, n (%)                                     | 32 (26.7)                                                  | 28 (23.7)                              | NA                                      |

<sup>a</sup>Relative dose intensity was defined as the ratio of the actual dose intensity (mg/cycle) and the planned dose intensity (mg/cycle).

**Abbreviations:** NA, not applicable; nab, nanoparticle albumin-bound.

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## eTable 2. Chemotherapy Treatment Exposure

|                   | Arm A | Arm B | Arm C |
|-------------------|-------|-------|-------|
|                   | Paclitaxel | Carboplatin | nab-Paclitaxel | Carboplatin | Paclitaxel | Carboplatin |
| Relative dose intensity (%) per patient* | 94.83 (62.2, 104.2) | 94.81 (63.5, 110.1) | 55.07 (23.3, 80.0) | 82.56 (47.0, 105.9) | 97.67 (62.1, 105.5) | 96.68 (51.7, 123.0) |
| Duration of exposure, weeks | 15.07 (3.0, 24.3) | 15.07 (3.0, 24.3) | 14.00 (3.0, 24.9) | 14.00 (3.0, 24.9) | 13.43 (0.3, 22.4) | 13.43 (0.3, 26.1) |
| Number of cycles received | 4.5 (1, 6) | 4.5 (1, 6) | 4.0 (1, 6) | 4.0 (1, 6) | 4.0 (1, 6) | 4.0 (1, 6) |
| 1 cycle, n (%) | 7 (5.8) | 7 (5.8) | 9 (7.6) | 9 (7.6) | 7 (6.0) | 7 (6.0) |
| 2 cycles, n (%) | 10 (8.3) | 9 (7.5) | 5 (4.2) | 5 (4.2) | 7 (6.0) | 7 (6.0) |
| 3 cycles, n (%) | 4 (3.3) | 4 (3.3) | 18 (15.3) | 18 (15.3) | 8 (6.8) | 8 (6.8) |
| 4 cycles, n (%) | 39 (32.5) | 40 (33.3) | 49 (41.5) | 52 (44.1) | 38 (32.5) | 38 (32.5) |
| >4 cycles, n (%) | 60 (50) | 60 (50) | 37 (31.4) | 34 (28.8) | 57 (48.7) | 57 (48.7) |

*Relative dose intensity was defined as the ratio of the actual dose intensity (mg/cycle) and the planned dose intensity (mg/cycle).

Abbreviation: nab, nanoparticle albumin-bound.
Table 3. Progression-Free Survival by Disease Stage per RECIST version 1.1 by Independent Review Committee in ITT Analysis Set

|                      | Stage IIIB | Stage IV   |
|----------------------|------------|------------|
| **Tislelizumab plus PC versus PC alone** |            |            |
| Median Tislelizumab plus PC (95% CI) | 9.8 (5.95, NE) | 7.6 (5.59, 7.82) |
| Median PFS PC alone (95% CI)           | 5.6 (4.17, 7.43) | 5.2 (4.17, 5.59) |
| PFS HR (95% CI)                        | 0.402 (0.215, 0.750) | 0.570 (0.376, 0.862) |
| **Tislelizumab plus nab-PC versus PC alone** |            |            |
| Median PFS Tislelizumab plus nab-PC (95% CI) | 11.0 (7.56, NE) | 7.4 (5.59, 9.86) |
| Median PFS PC alone (95% CI)           | 5.6 (4.17, 7.43) | 5.2 (4.17, 5.59) |
| PFS HR (95% CI)                        | 0.372 (0.202, 0.686) | 0.537 (0.350, 0.824) |

Abbreviations: CI, confidence interval; ITT, intent-to-treat; nab, nanoparticle albumin-bound; nab-PC, nab-paclitaxel plus carboplatin; PC, paclitaxel plus carboplatin; RECIST, Response Evaluation Criteria in Solid Tumors.
## Table 4. Progression-Free Survival by PD-L1 Expression per RECIST version 1.1 by Independent Review Committee in ITT Analysis Set

|                                   | PD-L1 <1% | PD-L1 ≥1% |
|-----------------------------------|-----------|-----------|
| **Tislelizumab plus PC versus PC alone** |           |           |
| Median PFS Tislelizumab plus PC (95% CI) | 7.6 (5.45, NE) | 7.6 (5.95, 10.41) |
| Median PFS in PC alone (95% CI)    | 5.5 (4.21, 6.97) | 5.0 (4.14, 5.59) |
| PFS HR (95% CI)                    | 0.636 (0.368, 1.101) | 0.453 (0.293, 0.703) |

| **Tislelizumab plus nab-PC versus PC alone** |           |           |
| Median PFS in Tislelizumab plus nab-PC (95% CI) | 7.4 (5.55, 9.69) | 11.0 (5.75, NE) |
| Median PFS in PC alone (95% CI)    | 5.5 (4.21, 6.97) | 5.0 (4.14, 5.59) |
| PFS HR (95% CI)                    | 0.692 (0.406, 1.178) | 0.367 (0.229, 0.588) |

Abbreviations: CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; nab, nanoparticle albumin-bound; nab-PC, nab-paclitaxel plus carboplatin; PC, paclitaxel plus carboplatin; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors.
### eTable 5. Biomarker Interaction Analysis for PD-L1 at Cutoff of 1% TC per RECIST version 1.1 by Independent Review Committee in ITT Analysis Set

|                      | PD-L1 ≥1% | PD-L1 <1% | PD-L1 ≥1%: PD-L1 <1% Ratio | P-Value |
|----------------------|-----------|-----------|-----------------------------|---------|
| **Tislelizumab plus PC versus PC alone** |           |           |                             |         |
| Progression-free survival, HR (95% CI) | 0.449 (0.290, 0.695) | 0.621 (0.358, 1.075) | 0.723 (0.358, 1.458) | 0.3651 |
| Objective response rate, OR (95% CI)  | 3.372 (1.648, 6.901) | 2.196 (0.950, 5.073) | 1.536 (0.512, 4.605) | 0.4438 |
| **Tislelizumab plus nab-PC versus PC alone** |           |           |                             |         |
| Progression-free survival, HR (95% CI) | 0.361 (0.227, 0.576) | 0.689 (0.404, 1.174) | 0.525 (0.258, 1.065) | 0.0743 |
| Objective response rate, OR (95% CI)  | 4.145 (1.980, 8.677) | 2.099 (0.910, 4.843) | 1.975 (0.649, 6.012) | 0.231  |

Abbreviations: CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; nab, nanoparticle albumin-bound; nab-PC, nab-paclitaxel plus carboplatin; OR, odds ratio; PC, paclitaxel plus carboplatin; PD-L1, programmed death-ligand 1; RECIST, Response Evaluation Criteria in Solid Tumors; TC, tumor cell.
**Table 6. Overall Summary of Treatment-Emergent Adverse Events**

|                      | Arm A Tislelizumab + Paclitaxel + Carboplatin (n=120) | Arm B Tislelizumab + nab-Paclitaxel Carboplatin (n=118) | Arm C Paclitaxel + Carboplatin (n=117) |
|----------------------|-----------------------------------------------------|--------------------------------------------------------|---------------------------------------|
| Patients with ≥1 TEAE| 120 (100.0)                                         | 117 (99.2)                                             | 117 (100.0)                           |
| Grade ≥3 TEAE        | 106 (88.3)                                          | 102 (86.4)                                             | 98 (83.8)                             |
| Serious TEAE         | 44 (36.7)                                           | 45 (38.1)                                              | 29 (24.8)                             |
| TEAE leading to death| 4 (3.3)                                              | 5 (4.2)                                                 | 5 (4.3)                               |

**TEAEs leading to discontinuation**

|                      | Arm A Tislelizumab + Paclitaxel + Carboplatin (n=120) | Arm B Tislelizumab + nab-Paclitaxel Carboplatin (n=118) | Arm C Paclitaxel + Carboplatin (n=117) |
|----------------------|-----------------------------------------------------|--------------------------------------------------------|---------------------------------------|
| Any study treatment component | 15 (12.5)                                           | 35 (29.7)                                             | 18 (15.4)                             |
| Tislelizumab          | 12 (10.0)                                           | 12 (10.1)                                             | NA                                    |
| Paclitaxel            | 9 (7.5)                                              | NA                                                    | 17 (14.5)                             |
| nab-paclitaxel        | NA                                                   | 28 (23.7)                                             | NA                                    |
| Carboplatin           | 9 (7.5)                                              | 27 (22.9)                                             | 17 (14.5)                             |

**TEAEs leading to dose modification or treatment delays**

|                      | Arm A Tislelizumab + Paclitaxel + Carboplatin (n=120) | Arm B Tislelizumab + nab-Paclitaxel Carboplatin (n=118) | Arm C Paclitaxel + Carboplatin (n=117) |
|----------------------|-----------------------------------------------------|--------------------------------------------------------|---------------------------------------|
| Tislelizumab          | 53 (44.2)                                           | 93 (78.8)                                             | NA                                    |
| Paclitaxel            | 63 (52.5)                                           | NA                                                    | 47 (40.2)                             |
| nab-paclitaxel        | NA                                                  | 108 (91.5)                                            | NA                                    |
| Carboplatin           | 63 (52.5)                                           | 93 (78.7)                                             | 44 (37.6)                             |

Data presented as n (%).
Abbreviations: NA, not applicable; nab, nanoparticle albumin-bound; TEAE, treatment-emergent adverse event.

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eTable 7. Incidence of Treatment-Related Adverse Events Occurring in ≥15% of Patients

| Preferred Term       | Arm A Tislelizumab + Paclitaxel + Carboplatin (n=120) | Arm B Tislelizumab + nab-Paclitaxel + Carboplatin (n=118) | Arm C Paclitaxel + Carboplatin (n=117) |
|----------------------|------------------------------------------------------|----------------------------------------------------------|----------------------------------------|
|                      | All Grades, n (%) | Grade ≥3, n (%) | All Grades, n (%) | Grade ≥3, n (%) | All Grades, n (%) | Grade ≥3, n (%) |
| Patients with ≥1 TRAE| 119 (99.2)        | 103 (85.8)     | 117 (99.2)        | 99 (83.9)      | 117 (100.0)      | 94 (80.3)       |
| Anemia               | 99 (82.5)         | 6 (5.0)        | 104 (88.1)        | 24 (20.3)      | 87 (74.4)        | 11 (9.4)        |
| Alopecia             | 77 (64.2)         | 0              | 81 (68.6)         | 0              | 72 (61.5)        | 0              |
| Decreased neutrophil count | 75 (62.5)     | 62 (51.7)     | 72 (61.0)         | 54 (45.8)      | 68 (58.1)        | 53 (45.3)       |
| Decreased white blood cell count | 63 (52.5)    | 26 (21.7)     | 68 (57.6)         | 32 (27.1)      | 62 (53.0)        | 28 (23.9)       |
| Leukopenia           | 57 (47.5)         | 19 (15.8)      | 66 (55.9)         | 30 (25.4)      | 56 (47.9)        | 21 (17.9)       |
| Neutropenia          | 51 (42.5)         | 40 (33.3)      | 50 (42.4)         | 32 (27.1)      | 55 (47.0)        | 47 (40.2)       |
| Decreased appetite   | 50 (41.7)         | 1 (0.8)        | 49 (41.5)         | 1 (0.8)        | 35 (29.9)        | 1 (0.9)         |
| Increased ALT        | 48 (40.0)         | 2 (1.7)        | 40 (33.9)         | 2 (1.7)        | 27 (23.1)        | 0              |
| Decreased platelet count | 40 (33.3)     | 5 (4.2)        | 52 (44.1)         | 16 (13.6)      | 28 (23.9)        | 2 (1.7)         |
| Increased AST        | 39 (32.5)         | 0              | 38 (32.2)         | 1 (0.8)        | 13 (11.1)        | 0              |
| Nausea               | 34 (28.3)         | 0              | 48 (40.7)         | 0              | 29 (24.8)        | 1 (0.9)         |
| Thrombocytopenia     | 33 (27.5)         | 7 (5.8)        | 47 (39.8)         | 15 (12.7)      | 32 (27.4)        | 7 (6.0)         |
| Pain in extremity    | 33 (27.5)         | 3 (2.5)        | 8 (6.8)           | 0              | 23 (19.7)        | 0              |
| Increased blood bilirubin | 27 (22.5)      | 0              | 14 (11.9)         | 0              | 15 (12.8)        | 0              |
| Asthenia             | 26 (21.7)         | 0              | 19 (16.1)         | 0              | 23 (19.7)        | 1 (0.9)         |
| Hypoesthesia         | 25 (20.8)         | 0              | 11 (9.3)          | 0              | 19 (16.2)        | 0              |
| Vomiting             | 24 (20.0)         | 0              | 22 (18.6)         | 0              | 15 (12.8)        | 2 (1.7)         |
| Rash                 | 23 (19.2)         | 4 (3.3)        | 25 (21.2)         | 2 (1.7)        | 4 (3.4)          | 0              |
| Constipation         | 23 (19.2)         | 0              | 13 (11.0)         | 0              | 18 (15.4)        | 0              |
| Arthralgia           | 22 (18.3)         | 0              | 16 (13.6)         | 0              | 16 (13.7)        | 0              |
| Increased blood lactate dehydrogenase | 18 (15.0) | 0 | 15 (12.7) | 0 | 9 (7.7) | 0 |
| Malaise              | 17 (14.2)         | 1 (0.8)        | 19 (16.1)         | 0              | 17 (14.5)        | 0              |

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; nab, nanoparticle albumin-bound; TRAE, treatment-related adverse event.