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Submitted by:
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NCCN Guidelines Panel: Non-Small Cell Lung Cancer (NSCLC)

On behalf of Genentech, I respectfully request the NCCN NSCLC Guideline Panel to review the enclosed data for:

- Tecentriq™ (atezolizumab): NSCLC

  Barlesi F, Park K, Ciardiello F, et al. Primary analysis from OAK, a randomized phase III study comparing atezolizumab with docetaxel in 2L/3L NSCLC. Presented at: European Society for Medical Oncology (ESMO) 2016 Annual Meeting; October 7-11, 2016; Copenhagen, Denmark, Oral Presentation.

Specific Changes:
Consider the available data on the use of Tecentriq in NSCLC for inclusion in the NCCN Guidelines.

FDA Clearance:
On October 18, 2016, Tecentriq received FDA approval for patients with metastatic NSCLC who have disease progression during or following platinum-containing chemotherapy. Patients with epidermal growth factor receptor (EGFR) or analyplastic lymphoma kinase (ALK) genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving Tecentriq.

Tecentriq is also FDA-approved for the treatment of patients with locally advanced or metastatic urothelial carcinoma who received prior platinum chemotherapy. This indication is approved under accelerated approval based on tumor response rate and duration of response.

Please refer to the Tecentriq prescribing information for the full FDA-approved indication and safety information: https://www.gene.com/download/pdf/tecentriq_prescribing.pdf

Rationale:
The FDA based its approval of Tecentriq on results from the Phase III OAK and Phase II POPLAR studies. Efficacy and safety results from the OAK study were recently presented at the European Society for Medical Oncology 2016 Congress.

OAK is a Phase III, global, multicenter, open-label, randomized, controlled study conducted to evaluate the efficacy and safety of Tecentriq compared with docetaxel in 1225 patients with locally advanced or metastatic NSCLC whose disease has progressed on or after treatment with platinum-containing chemotherapy. The primary analysis population consists of the first 850 enrolled patients, which provided sufficient power to test the co-primary endpoints. Tecentriq 1200 mg was administered intravenously every 3 weeks until progressive disease or loss of clinical benefit, while docetaxel was given at a dose of 75 mg/m^2 every three weeks until disease progression. The study's co-primary endpoints are overall survival (OS) in: 1) all patients randomized to treatment in the study (intention-to-treat or ITT population), and 2) subgroup of patients with ≥1% programmed death-ligand 1 (PD-L1) expression on tumor cells (TC) or tumor infiltrating cells (IC). Secondary endpoints include objective response rate (ORR), progression-free survival (PFS), duration of response (DOR), and safety.

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Efficacy:

- The following table summarizes OS results with a minimum follow-up of 19 months:

OS Efficacy Results from OAK (ITT and ≥1% PD-L1)		
	Tecentriq (n=425)	**Docetaxel (n=425)**
Median OS (ITT), months	13.8	9.6 HR=0.73; 95% CI 0.62-0.87; p=0.0003
Median OS (≥1% PD-L1 TC or IC), months	15.7	10.3 HR=0.74, 95% CI 0.58-0.93; p=0.01
12-month OS (ITT)	55%	41%
18-month OS (ITT)	40%	27%
Abbreviations: CI=Confidence Interval; HR=hazard ratio; IC=tumor-infiltrating immune cell; ITT=intent-to-treat; OS=overall survival; PD-L1= programmed death-ligand 1; TC=tumor cell		

- In a pre-specified exploratory subgroup analysis, non-squamous patients demonstrated 15.6 month median OS in the Tecentriq arm compared with 11.2 months in the docetaxel arm (HR=0.73; 95% CI=0.60-0.89; p=0.0015). Squamous patients achieved a median OS of 8.9 months vs 7.7 months in Tecentriq and docetaxel arms, respectively (HR=0.73; 95% CI=0.54-0.98; p=0.0383).
- In the ITT population, median PFS was 2.8 months and 4.0 months in the Tecentriq- and docetaxel-treated arms (HR=0.95; 95%CI 0.82-1.10; p=0.49), ORR was 14% and 13%, and median DOR was 16.3 months and 6.2 months, respectively.

Safety.

- In the safety-evaluable population (n=1,187), All Grade treatment-related adverse events (AEs) occurred in 64% of Tecentriq-treated patients vs 86% of docetaxel-treated patients. Treatment-related Grade 3-4 adverse events (AEs) were experienced in 15% in the Tecentriq arm compared to 43% in the docetaxel arm.
- In the Tecentriq-treated arm, 8% of patients experienced AE's leading to withdrawal from treatment compared to 19% in the docetaxel arm.
- Selected Grade 3-4 immune-mediated AEs for the Tecentriq patients included: pneumonitis (0.7%), hepatitis (0.3%), colitis (0%).

POPLAR (Study 3 in Tecentriq USPI) is a supporting Phase II, open-label, randomized study that evaluated the efficacy and safety of Tecentriq compared with docetaxel in 287 patients with locally advanced or metastatic NSCLC who had progressed on platinum-containing chemotherapy. Efficacy and safety results have been previously submitted to the NCCN NSCLC Panel.[1,2] The corresponding manuscript and conference proceeding are enclosed. Additional Phase II and III data on the use of Tecentriq in NSCLC are available.[3-5]

Respectfully submitted,

Ellen Yang, Pharm.D.

Supplemental References

1. Fehrenbacher L, Spira A, Ballinger M, et al. Atezolizumab versus docetaxel for patients with previously treated non-small-cell lung cancer (POPLAR): a multicentre, open-label, phase 2 randomised controlled trial. Lancet 2016;387:1837-1846.

2. Smith D, Vansteenkiste J, Fehrenbacher L, et al. Updated survival and biomarker analyses of a randomized Phase II study of atezolizumab vs docetaxel in previously treated NSCLC (POPLAR). Presented at the American Society of Clinical Oncology 2016 Annual Meeting in Chicago, IL; June 3–7, 2016. ASCO Poster #351.

3. Besse B, Johnson ML, Janne PA, et al. Phase II, single-arm trial (BIRCH) of atezolizumab as first-line or subsequent therapy for locally advanced or metastatic PD-L1–selected non-small cell lung cancer (NSCLC). Presented at the European Society for Medical Oncology in Vienna, Austria; September 25–29, 2015. ESMO Oral presentation.

4. Wakelee H, Patel J, Heist R, et al. Phase II trial of atezolizumab for patients with PD-L1–selected advanced NSCLC (BIRCH): updated efficacy and exploratory biomarker results. Presented at the Multidisciplinary Symposium in Thoracic Oncology in Chicago, Illinois; September 22–24, 2016. IASLC Oral presentation.

5. Spigel DR, Chaft JE, Gettinger SN, et al. Clinical activity and safety from a Phase II study (FIR) of atezolizumab (anti-PDL1) in PD-L1–selected patients with non-small cell lung cancer (NSCLC). Presented at the American Society of Clinical Oncology 2015 Annual Meeting in Chicago, Illinois; May 29–June 2, 2015. ASCO Poster #8028.

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