Table 1. OS and PFS With Gemcitabine vs BSC

	Gemcitabine	BSC	HR	*P* Value
OS, mo (95% CI)	10 (9.2 to 10.7)	8 (6.7 to 9.2)	0.64 (0.51 to 0.77)	.002
PFS, mo (95% CI)	9 (8.1 to 9.9)	7 (6.3 to 7.7)	0.67 (0.50 to 0.84)	.009

BSC, best supportive care; OS, overall survival; PFS, progression-free survival.
Source: Jakhar SL et al. *Ann Oncol*. 2015 (abstr 100PD).

and not switch therapy; the findings of this trial support results from a larger trial of gemcitabine maintenance therapy [Brodowicz T et al. *Lung Cancer*. 2006] yet stand in contrast to a trial [Belani CP et al. *J Clin Oncol*. 2010] that found no advantage for gemcitabine maintenance plus BSC vs BSC alone.

Patients in the gemcitabine group experienced a higher incidence of grade 3 and 4 adverse events: anemia (12% G; 8.1% BSC), neutropenia (18% G; 4.1% BSC), thrombocytopenia (14% G; 2% BSC), and fatigue (8% G; 2% BSC). Otherwise, the researchers reported that maintenance therapy was well tolerated.

This study has a number of limitations that affect its interpretation. These include the open-label design, which could have influenced the results because the patients and the investigators knew who was receiving active treatment. The histologic subgroups (ie, squamous, nonsquamous) were not reported. Importantly, there is no information about the frequency of follow-up visits or restaging of cancer by imaging for each group and the percentage of patients who eventually had second-line therapy, particularly in the BSC group. The results of this small study may provide a signal that switch maintenance therapy with gemcitabine may extend OS and PFS for patients with advanced NSCLC, a finding that must be interpreted carefully and balanced against the increase in high-grade toxicity.

ASSESS: *EGFR* Mutations Can Be Analyzed With ctDNA

Written by Kathy Boltz, PhD

Circulating tumor DNA (ctDNA) was found to have utility for *EGFR* mutation testing in advanced non–small cell lung cancer (NSCLC) in a real-world setting in the diagnostic ASSESS study [NCT01785888], according to Martin Reck, MD, PhD, Lung Clinic Grosshansdorf, Grosshansdorf, Germany.

The study enrolled 1288 eligible patients, with 997 from Europe and 291 from Japan. Overall, 75.8% of the patients were white and 23.0% were Asian; 19.6% were never-smokers; smokers had 40.0 median pack-years; and the majority of patients (84.6%) had stage IV disease.

The majority of the tissue/cytology samples were obtained during the current diagnosis, derived from the primary tumor, and collected via bronchoscopy. Most samples were prepared as paraffin-embedded tissue blocks and fixed with 4% neutral-buffered formalin. The median turnaround time for *EGFR* mutation testing was 11 days in Europe (95% CI, 14.0 to 17.3) and 8 days in Japan (95% CI, 8.2 to 14.1). The average test success rate was 98.3% in Europe and 99.6% in Japan.

In Japan, the tests used to evaluate tissue/cytology samples and plasma samples for *EGFR* mutations were Cycleave PCR and PNA LNA clamp PCR. In Europe, for tissue/cytology testing, PNA LNA clamp PCR and the older methods of DNA sequencing and pyrosequencing were used, along with newer, more sensitive methods, including the Roche cobas *EGFR* Mutation Test and Sequenom; for plasma testing, the QIAGEN Therascreen RGQ PCR kit and Roche cobas *EGFR* Mutation Test were used.

The overall concordance was 89.1% (1035 of 1162 patients; 95% CI, 87.1 to 90.8) and overall positive predictive value (PPV) was 77.7% (87 of 112; 95% CI, 68.8 to 85.0). In patients in whom the same testing method was used for tissue/cytology and plasma evaluations, the PPV was 92.6% (95% CI, 75.7 to 99.1) compared with 72.9% (95% CI, 62.2 to 82.0) when different testing methods were used for the evaluations. The sensitivity was 46.0% (95% CI, 38.8 to 53.4), specificity was 97.4% (95% CI, 96.2 to 98.3), and the negative predictive value was 90.3% (95% CI, 88.3 to 92.0) in the overall cohort.

The QIAGEN Therascreen RGQ PCR kit had a sensitivity of 72.7%, specificity of 99.1%, and PPV of 94.1% in this trial. A previous trial of white patients, IFUM [Douillard JY et al. *Br J Cancer*. 2014], used the same kit and reported a sensitivity of 65.7%, specificity of 99.8%, and PPV of 98.6%.

False-positive results, meaning an *EGFR* mutation-positive plasma sample and an *EGFR* mutation-negative tissue/cytology sample, were believed to have come from 25 patients. These patients were from multiple sites and countries, indicating no specific laboratory-based

issues. Among these patients, 56% of the tumors were tested by DNA sequencing or pyrosequencing (vs 25% of the overall population), 76% of the patients were never-, former-, or light-smokers (vs 45% of the overall population), and 32% of the tumor samples were needle biopsies/cytology (vs 21% of the overall population). The false-positive rate may have been contributed to by possible over-representation of cytology samples, meaning inadequate tumor samples, or by use of the less sensitive DNA sequencing or pyrosequencing methodologies that had inadequate mutation analysis to detect mutation.

Among the 191 patients overall who were *EGFR* mutation positive, 30.6% of Japanese patients (86 of 281) and 11.6% of European patients (105 of 903) were positive. The exon 19 deletion was found in 51.3% (n=40) of Japanese patients and in 54.5% (n=54) of European patients. The L858R mutation only was found in 47.4% (n=37) of Japanese patients and 28.3% (n=28) of European patients. *EGFR* mutation-positive status was significantly correlated with female sex, ADC histology, never-smoking status, and Japanese ethnicity (all $P<.001$).

EGFR mutation status was the largest driver of therapy choice. The most common first-line treatment decisions for all *EGFR* mutation-positive patients were gefitinib, erlotinib, and afatinib; *EGFR* mutation-negative patients most commonly received pemetrexed, radiation therapy, carboplatin, and cisplatin.

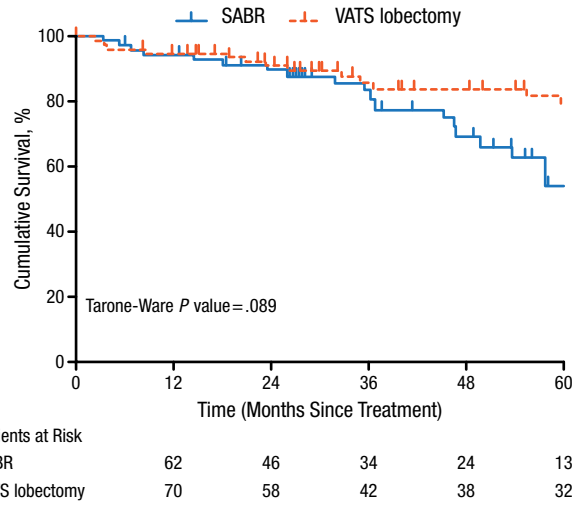
Although practices for both tissue/cytology and plasma samples require improvements, these real-world data from the large, observational ASSESS study suggest that ctDNA may be feasible and suitable for analyzing *EGFR* mutations. The overall concordance of *EGFR* mutation status was 89%.

Hints of Better Survival With Surgery Than Radiation Therapy in Stage I NSCLC

Written by Eleanor Mayfield

Surgical resection is the primary approach to the treatment of stage I non–small cell lung cancer (NSCLC). American College of Chest Physicians evidence-based guidelines [Howington JA et al. *Chest*. 2013] recommend the use of a minimally invasive surgical approach such as video-assisted thoracoscopic surgery (VATS) lobectomy in stage I disease. Nonsurgical approaches such as stereotactic body radiation therapy (SBRT), also known as stereotactic ablative radiation therapy (SABR), may offer an alternative to surgery. No prospective randomized trials comparing surgery with SBRT have been published.

Figure 1. Cumulative Survival in Patients With Stage I NSCLC After Surgery or SABR



NSCLC, non–small cell lung cancer; SABR, stereotactic ablative radiation therapy; VATS, video-assisted thoracoscopic surgery.

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Gaetano Rocco, MD, National Cancer Institute, Pascale Foundation, Naples, Italy, discussed a poster by Sahar Mokhles, MD, Erasmus University Medical Center, Rotterdam, the Netherlands, reporting the results of a retrospective, propensity-score matching cohort study that compared clinical outcomes in patients with stage I NSCLC treated with surgery (VATS lobectomy or thoracotomy) vs SBRT [Mokhles S et al. *Ann Oncol*. 2015], with a primary outcome of overall survival. Propensity-score matching, where a propensity score difference of 0.20 was used as the maximum caliper width, generated a cohort of 73 patients treated with surgery and 73 treated with SBRT.

Median follow-up was 49 months for the surgery group and 28 months for the SBRT group; to correct for differences in follow-up time, the investigators compared survival curves using the Tarone-Ware test. Overall survival in the surgery group was 95% at 1 year and 80% at 5 years, compared with 94% at 1 year and 53% at 5 years in the SBRT group ($P=.089$; Figure 1). Although the survival difference between the 2 groups was not statistically significant, after 3 years there seemed to be better survival in surgically treated patients.

Absolute standardized differences for measure covariates were assessed to evaluate covariate balance across the groups, with results visualized using a Love-plot (Figure 2).

Prof Rocco further discussed the grouping together of patients undergoing VATS lobectomy and SBRT, noting