predictor of response to immune checkpoint blockade across tumour types [6, 7]. A subset of patients with gastroesophageal adenocarcinoma, who are microsatellite stable, but have high TMB, have been identified using whole exome sequencing [8]. This high mutation load population, which would fall into the large predominantly immunologically 'cold' TCGA chromosomally unstable (CIN) subgroup, also had high levels of infiltrating lymphocytes which is suggestive of an active immune response [8, 9]. These results imply that TMB could also be associated with sensitivity to immune checkpoint blockade in GC: therefore, this hypothesis warrants prospective evaluation.

In summary, the negative results of JAVELIN 300 are disappointing for patients with advanced GC. To optimise the benefits of single-agent immunotherapy, work on predictive biomarkers is necessary to identify the minority of GC patients who are likely to experience prolonged disease control before treatment. For most GC patients, who have immunologically evasive tumours, development of combination therapies to overcome resistance to immune checkpoint blockade is likely to be the most successful way forward.

E. C. Smyth[1] & A. Cervantes[2*]
[1]Department of Oncology, Addenbrooke's Hospital, Cambridge, UK; [2]Department of Medical Oncology, CIBERONC, Biomedical Research Institute INCLIVA, University of Valencia, Valencia, Spain
(*E-mail: andres.cervantes@uv.es)

Funding

This work was supported in part by grants from the Spanish Government, Ministerio de Economía y Competitividad (FIS PI12/02767 and PI15/02180 to AC) and Generalitat Valenciana (PROMETEO 2013-005 to AC) and CIBERONC (no grant number is applicable).

Disclosure

AC has previously received honoraria from Servier not conflicting with the current work. ECS has previously received honoraria from Five Prime Therapeutics, Gritstone Oncology, Servier, Celgene and Bristol-Meier-Squibb not conflicting with the current work.

References

1. Kang YK, Boku N, Satoh T et al. Nivolumab in patients with advanced gastric or gastro-oesophageal junction cancer refractory to, or intolerant of, at least two previous chemotherapy regimens (ONO-4538-12, ATTRACTION-2): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 2017; 390(10111): 2461–2471.
2. Tabernero J, Shitara K, Dvorkin M et al. LBA-002 Overall survival results from a phase III trial of trifluridine/tipiracil versus placebo in patients with metastatic gastric cancer refractory to standard therapies (TAGS). Ann Oncol 2018; 29(Suppl 5): LBA nr.2.
3. Fuchs CS, Doi T, Jang RW et al. Safety and efficacy of pembrolizumab monotherapy in patients with previously treated advanced gastric and gastroesophageal junction cancer: phase 2 clinical KEYNOTE-059 trial. JAMA Oncol 2018; 4(5): e180013.
4. Bang Y-J, Ruiz EY, Van Cutsem E et al. Phase III, randomised trial of avelumab versus physician's choice of chemotherapy as third-line treatment for patients with advanced gastric or gastro-oesophageal junction cancer: primary analysis of JAVELIN Gastric 300. Ann Oncol 2018; 29(10): 2052–2060.
5. Shitara K, Özgüroğlu M, Bang YJ et al. Pembrolizumab versus paclitaxel for previously treated, advanced gastric or gastro-oesophageal junction cancer (KEYNOTE-061): a randomised, open-label, controlled, phase 3 trial. Lancet 2018; 392(10142): 123–133.
6. Hellmann MD, Ciuleanu TE, Pluzanski A et al. Nivolumab plus ipilimumab in lung cancer with a high tumor mutational burden. N Engl J Med 2018; 378(22): 2093–2104.
7. Yarchoan M, Hopkins A, Jaffee EM. Tumor mutational burden and response rate to PD-1 inhibition. N Engl J Med 2017; 377(25): 2500–2501.
8. Secrier M, Li X, De Silva N et al. Mutational signatures in esophageal adenocarcinoma define etiologically distinct subgroups with therapeutic relevance. Nat Genet 2016; 48(10): 1131–1141.
9. Sohn BH, Hwang JE, Jang HJ et al. Clinical significance of four molecular subtypes of gastric cancer identified by the Cancer Genome Atlas Project. Clin Cancer Res 2017; 23(15): 4441–4449.

doi:10.1093/annonc/mdy331
Published online 21 August 2018

TP53 mutations are predictive and prognostic when co-occurring with *ALK* rearrangements in lung cancer

The entity now known as anaplastic lymphoma kinase (ALK) gene rearrangement positive non-small-cell lung cancer (NSCLC) was first identified in 2007 [1] and the enrollment of patients with these NSCLCs into the original clinical trial of the multitargeted tyrosine kinase inhibitor (TKI) crizotinib dates back to 2008 [2–5]. Fast forward a decade and the preclinical to clinical advances seen in *ALK* rearranged NSCLC place it at the forefront of the precision oncology revolution that has transformed the palliation of advanced NSCLCs [6]. Four different ALK TKIs—crizotinib (since 2011), ceritinib (since 2014), alectinib (since 2015) and brigatinib (since 2017)—are available worldwide with additional inhibitors, such as lorlatinib, in the last stages of regulatory approval [7–10]. The pace of clinical trial development has been so brisk that evidence-based standards have shifted multiple times and the 'oldest' ALK TKI crizotinib has been displaced in the initial line of treatment by the 'next-generation' ALK TKI alectinib, which is associated with exceedingly high initial overall response rate and median progression-free survival (PFS) times that can almost reach 3 years [11]. Although biological resistance, mainly through the development of *ALK* kinase resistant mutations (one example *ALK*-G1202R), is invariable with ALK TKI monotherapy and the central nervous system a common site of progression; significantly active ALK inhibitors such as lorlatinib can transiently control these resistant clones or brain sanctuary sites, respectively [12, 13]. The majority of patients with advanced *ALK* rearranged NSCLC can expect to receive sequential oral TKI monotherapy for prolonged periods of time with reported median overall survival (OS) that exceeds

4 years and nearly half of initially treated patients will be 5-year survivors following diagnosis [14, 15], a true shit in the natural history of this subtype of lung cancer.

However, there is significant heterogeneity in how an individual patient with *ALK* rearranged tumor will benefit from ALK TKIs and other therapies. A minority of patients can have exceedingly high (>5 years) PFS times with crizotinib [14] while others can rapidly progress in the central nervous system or systemically with below 1 year in OS times [16]. This heterogeneity remains unexplained but prevailing hypotheses harken to differences in patient characteristics (smoking status, age, co-morbidities, metabolism of ALK TKIs, immune system status) and more importantly in co-occurring genomic aberrations that can modulate the benefit of ALK TKIs (i.e. can be putative predictive biomarkers) or survival (i.e. can be putative prognostic biomarkers). The latter are of extreme importance not only for *ALK* rearranged NSCLC—where initial efforts have indicated that even the *ALK* fusion partner may alter clinical outcomes [17]—but also for other oncogene-driven NSCLCs. As an example, epidermal growth factor receptor (*EGFR*) mutated NSCLCs are known to harbor a multitude of co-occurring genomic events when analyzed by comprehensive genomic profiling, including mutations in: tumor protein P53 (*TP53*), phosphatidylinositol-4, 5-bisphosphate 3-kinase catalytic subunit alpha (*PIK3CA*), phosphatase and tensin homolog (*PTEN*), Erb-B2 receptor tyrosine kinase 2 (*ERBB2*), MET proto-oncogene receptor tyrosine kinase (*MET*) among others [18, 19]. Some of these co-occurring genomic events can completely abrogate the ability to induce a response to EGFR TKI monotherapy, as in the case of high-level *ERBB2* or *MET* amplification [20], while others have less impact on initial EGFR TKI response, as is the case of *PIK3CA* mutations and heterozygous *PTEN* mutations [18, 19]. *TP53* mutations in these *EGFR* mutated cohorts are both predictive of shorter duration of tumor responses to EGFR TKIs and also prognostic of shorter lifespans in these patients [18, 19]. *TP53* mutations are the most common mutations found in NSCLCs and co-occur frequently with driver oncogenes. Indeed, the Lung Cancer Mutation Consortium (LCMC) confirms that *TP53* mutations are the most common co-occurring event with *EGFR* mutations or *ALK* rearrangements or ROS proto-oncogene 1 receptor tyrosine kinase (*ROS1*) or other driver alterations; and the presence of *TP53* mutations is one of the strongest prognostic markers for shorter survival times in advanced lung cancers [21]. The underlying biological basis for the prognostic impact of *TP53* mutations—a surrogate for P53 protein loss—is still an active area of investigation but it is already known that this tumor suppressor has critical anti-proliferative/antiapoptotic functions [22], its loss can accelerate the transforming potential of oncogenes in lung cancers [23] and its loss can hamper tumor response to TKIs [24].

With this background, Kron reports in this issue of *Annals of Oncology* a detailed analysis of co-occurring mutations in *ALK* rearranged NSCLC [25]. A total of 216 tumors are analyzed and pathogenic *TP53* mutations are identified in close to a quarter (23.8%) of these cancers. Other genomic aberrations using the author's limited gene panel have frequencies below 1%–5%. As seen in the aforementioned cases from the LCMC of co-occurring driver oncogene mutations (in *EGFR*, *ALK*, *ROS1* and others) with *TP53* mutations, the presence of an *ALK* rearrangement with a *TP53* mutation is both predictive of shorter durations of PFS to ALK TKIs and is prognostic for shorter OS times. The authors carry out a detailed statistical analysis that takes into account patient characteristics (age, sex, smoking history, current smoker status, performance status and number of brain metastases), treatment choices (number of treatment lines before crizotinib and number of treatment lines before ceritinib) and the genomic *TP53* mutation status. Only current smoker status and *TP53* mutations are significant negative prognostic factors for OS in univariate analysis, and merely *TP53* mutations remain a negative prognostic factor in multivariate Cox regression analysis.

The results highlight the powerful prognostic role of *TP53* mutations but it is unclear how they will alter the current treatment paradigms in *ALK* rearranged NSCLC. Unfortunately, therapeutic efforts to re-establish P53 protein function in cancer have been disappointing and no candidate is available clinically [26]. Therefore, the prevailing question remains if a provider will omit the use of an ALK TKI in a tumor with an *ALK* rearrangement co-occurring with a *TP53* mutation? The answer is likely no, as ALK TKIs are significantly superior to other forms of approved NSCLC therapy—be them cytotoxic chemotherapy or immune checkpoint inhibitors—irrespective of *TP53* mutational status [27, 28]. Indeed, worldwide only a fraction of *ALK* rearranged NSCLCs are diagnosed by comprehensive genomic profiling assays that incorporate analysis of *TP53* mutation status [6, 29]. This scenario compiled by the lack of recommendation for *TP53* mutation analysis in diagnostic specimens with NSCLC [30, 31] limit the real-world applicability of considering *TP53* mutations status as a predictive and prognostic marker in the offices of most oncologists that treat patients with these tumors. Kron concludes their work affirming that 'future clinical trials stratification of this patient subgroup should be considered' and that 'new treatment strategies should be investigated to improve the outcome of *ALK*/*TP53* co-mutated patients' [25]. I agree that as ALK TKI monotherapies improve the duration of control for *ALK* rearranged NSCLC and novel combination therapies are tested in clinical trials, it may be important to understand prognostic markers such as *TP53* mutation status in future trial designs. And I wholeheartedly recommend that the improvement and/or development of therapies for tumors driven by an oncogene with P53 function loss should be prioritized by academic plus pharmaceuticals consortiums evaluating advanced NSCLCs.

D. B. Costa
Division of Hematology/Oncology, Department of Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, USA
(E-mail: dbcosta@bidmc.harvard.edu)

Funding

This work was funded in part through an American Cancer Society grant RSG 11-186 (to DBC) and National Institutes of Health (NIH)/National Cancer Institute (NCI) grant CA218707 (to DBC).

Disclosure

DBC has received consulting fees and honoraria from Pfizer, Astra-Zeneca and ARIAD/Takeda.

References

1. Soda M, Choi YL, Enomoto M et al. Identification of the transforming EML4-ALK fusion gene in non-small-cell lung cancer. Nature 2007; 448(7153): 561–566.
2. Kwak EL, Bang YJ, Camidge DR et al. Anaplastic lymphoma kinase inhibition in non-small-cell lung cancer. N Engl J Med 2010; 363(18): 1693–1703.
3. Camidge DR, Bang YJ, Kwak EL et al. Activity and safety of crizotinib in patients with ALK-positive non-small-cell lung cancer: updated results from a phase 1 study. Lancet Oncol 2012; 13(10): 1011–1019.
4. Shaw AT, Yeap BY, Mino-Kenudson M et al. Clinical features and outcome of patients with non-small-cell lung cancer who harbor EML4-ALK. J Clin Oncol 2009; 27(26): 4247–4253.
5. Shaw AT, Yeap BY, Solomon BJ et al. Effect of crizotinib on overall survival in patients with advanced non-small-cell lung cancer harbouring ALK gene rearrangement: a retrospective analysis. Lancet Oncol 2011; 12(11): 1004–1012.
6. VanderLaan PA, Rangachari D, Majid A et al. Tumor biomarker testing in non-small-cell lung cancer: a decade of change. Lung Cancer 2018; 116: 90–95.
7. Shaw AT, Kim DW, Mehra R et al. Ceritinib in ALK-rearranged non-small-cell lung cancer. N Engl J Med 2014; 370(13): 1189–1197.
8. Ou SI, Ahn JS, De PL et al. Alectinib in crizotinib-refractory ALK-rearranged non-small-cell lung cancer: a Phase II Global Study. J Clin Oncol 2016; 34(7): 661–668.
9. Kim DW, Tiseo M, Ahn MJ et al. Brigatinib in patients with crizotinib-refractory anaplastic lymphoma kinase-positive non-small-cell lung cancer: a randomized, multicenter phase II trial. J Clin Oncol 2017; 35(22): 2490–2498.
10. Shaw AT, Felip E, Bauer TM et al. Lorlatinib in non-small-cell lung cancer with ALK or ROS1 rearrangement: an international, multicentre, open-label, single-arm first-in-man phase 1 trial. Lancet Oncol 2017; 18(12): 1590–1599.
11. Peters S, Camidge DR, Shaw AT et al. Alectinib versus crizotinib in untreated ALK-positive non-small-cell lung cancer. N Engl J Med 2017; 377(9): 829–838.
12. Yoda S, Lin JJ, Lawrence MS et al. Sequential ALK inhibitors can select for lorlatinib-resistant compound ALK mutations in ALK-positive lung cancer. Cancer Discov 2018; 8(6): 714–729.
13. Rangachari D, Yamaguchi N, VanderLaan PA et al. Brain metastases in patients with EGFR-mutated or ALK-rearranged non-small-cell lung cancers. Lung Cancer 2015; 88(1): 108–111.
14. Rangachari D, Le X, Shea M et al. Cases of ALK-rearranged lung cancer with 5-year progression-free survival with crizotinib as initial precision therapy. J Thorac Oncol 2017; 12(11): e175–e177.
15. Solomon BJ, Kim DW, Wu YL et al. Final overall survival analysis from a study comparing first-line crizotinib versus chemotherapy in ALK-mutation-positive non-small-cell lung cancer. J Clin Oncol 2018; 36(22): 2251–2258.
16. Costa DB, Shaw AT, Ou SH et al. Clinical experience with crizotinib in patients with advanced ALK-rearranged non-small-cell lung cancer and brain metastases. J Clin Oncol 2015; 33(17): 1881–1888.
17. Lin JJ, Zhu VW, Yoda S et al. Impact of EML4-ALK variant on resistance mechanisms and clinical outcomes in ALK-positive lung cancer. J Clin Oncol 2018; 36(12): 1199–1206.
18. VanderLaan PA, Rangachari D, Mockus SM et al. Mutations in TP53, PIK3CA, PTEN and other genes in EGFR mutated lung cancers: correlation with clinical outcomes. Lung Cancer 2017; 106: 17–21.
19. Yu HA, Suzawa K, Jordan E et al. Concurrent alterations in EGFR-mutant lung cancers associated with resistance to EGFR kinase inhibitors and characterization of MTOR as a mediator of resistance. Clin Cancer Res 2018; 24(13): 3108–3118.
20. Carney BJ, Rangachari D, VanderLaan PA et al. De novo ERBB2 amplification causing intrinsic resistance to erlotinib in EGFR-L858R mutated TKI-naive lung adenocarcinoma. Lung Cancer 2017; 114: 108–110.
21. Aisner DL, Sholl LM, Berry LD et al. The impact of smoking and TP53 mutations in lung adenocarcinoma patients with targetable mutations-The Lung Cancer Mutation Consortium (LCMC2). Clin Cancer Res 2018; 24(5): 1038–1047.
22. Olivier M, Hollstein M, Hainaut P. TP53 mutations in human cancers: origins, consequences, and clinical use. Cold Spring Harb Perspect Biol 2010; 2(1): a001008.
23. Chen Z, Cheng K, Walton Z et al. A murine lung cancer co-clinical trial identifies genetic modifiers of therapeutic response. Nature 2012; 483(7391): 613–617.
24. Huang S, Benavente S, Armstrong EA et al. p53 modulates acquired resistance to EGFR inhibitors and radiation. Cancer Res 2011; 71(22): 7071–7079.
25. Kron A, Alidousty C, Scheffler M et al. Impact of *TP53* mutation status on systemic treatment outcome in *ALK*-rearranged non-small-cell lung cancer. Ann Oncol 2018; 29(10): 2068–2075.
26. Stiewe T, Haran TE. How mutations shape p53 interactions with the genome to promote tumorigenesis and drug resistance. Drug Resist Updat 2018; 38: 27–43.
27. Solomon BJ, Cappuzzo F, Felip E et al. Intracranial efficacy of crizotinib versus chemotherapy in patients with advanced ALK-positive non-small-cell lung cancer: results from PROFILE 1014. J Clin Oncol 2016; 34(24): 2858–2865.
28. Soria JC, Tan DS, Chiari R et al. First-line ceritinib versus platinum-based chemotherapy in advanced ALK-rearranged non-small-cell lung cancer (ASCEND-4): a randomised, open-label, phase 3 study. Lancet 2017; 389(10072): 917–929.
29. DiStasio M, Chen Y, Rangachari D et al. Molecular testing turnaround time for non-small cell lung cancer in routine clinical practice confirms feasibility of CAP/IASLC/AMP guideline recommendations: a single-center analysis. Clin Lung Cancer 2017; 18(5): e349–e356.
30. Ettinger DS, Wood DE, Aisner DL et al. Non-small cell lung cancer, version 5.2017, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw 2017; 15(4): 504–535.
31. Lindeman NI, Cagle PT, Aisner DL et al. Updated molecular testing guideline for the selection of lung cancer patients for treatment with targeted tyrosine kinase inhibitors: guideline From the College of American Pathologists, the International Association for the Study of Lung Cancer, and the Association for Molecular Pathology. J Thorac Oncol 2018; 13(3): 323–358.

doi:10.1093/annonc/mdy339
Published online 23 August 2018

Adjuvant treatment of high-risk renal cell carcinoma: the jury is still out

Renal cell carcinoma (RCC) is a heterogeneous disease [1] with considerable variation in its natural history. Surgery remains the most important curative option for localized disease [2], however, up to 30% of patients will develop metastases after a potentially curative nephrectomy [3]. Several prognostic factors, such as histologic subtype, pathological Fuhrman grade, tumor dimension or extension and lymph node involvement permit to stratify patients according to prognostic models able to predict the risk of recurrence [4].

Adjuvant systemic therapy following nephrectomy has been used to reduce relapse rates and improve survival in high-risk