Letters to the editor

The hard road to data interpretation: the road is hard too for the patient

As patients and patient advocates, we read with great interest the article by Sobrero et al. [1] investigating whether patients with stage III colon cancer should have 3 or 6 months of adjuvant chemotherapy.

EuropaColon and its members are supportive of all clinical research conducted to improve outcomes for patients, whether in terms of improved survival, side-effects or quality of life. We appreciate that oxaliplatin is associated with peripheral neurotoxicity, which can have a significant impact on quality of life.

We have spoken to many of our members on this topic. Peripheral neurotoxicity is present among the vast majority of this specific patient population, and for many it does affect their everyday activities. However, the majority of patients are also of the opinion that the primary goal of treatment of stage III colorectal cancer is to provide the best possible chance of survival, without recurrence of the disease. Although there is some difference of opinion among patients on whether 3 or 6 months treatment is preferable, all would like the opportunity to make their own informed decision.

We passionately believe that the best treatment option for each colorectal cancer patient can only be determined through an individualized approach. Each oncologist should explain to their patients in plain, non-technical language, the potential benefits,

side-effects and outcomes of treatment. Only when armed with all the relevant information can each patient, in partnership with their oncologist, make an informed decision about their own treatment.

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Reference

1. Sobrero A, Grothey A, Iveson T et al. The hard road to data interpretation: three or six months of adjuvant chemotherapy for patients with stage III colon cancer? *Ann Oncol* 2018; 29(5): 1099–1107.

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Functional immune characterization of HIV-associated non-small-cell lung cancer

Dear Editor,

In the combined anti-retroviral therapy (cART) era, non-small-cell lung cancer (NSCLC) is a highly incident cause of morbidity and mortality in people living with HIV (PLHIV) [1]. The immune-pathogenesis of NSCLC and HIV infection both rely on programmed-death 1 (PD-1) receptor–ligand interaction as a mechanism to induce T-cell exhaustion. To date, PLHIV have been excluded from clinical trials of immune-checkpoint inhibitors (ICPI), on the presumption that antitumour immunity might be compromised by HIV infection. To verify this, we evaluated the clinico-pathological significance of PD-ligands expression in a consecutive series of 221 archival NSCLC samples, 24 of which were HIV-associated (supplementary Table S1, available at *Annals of Oncology* online).

Most patients with HIV-associated NSCLC were active smokers ($n = 18$, 75%; median 40 packs/year, IQR 48), established on cART ($n = 22$, 92%) for a median duration of 9.7 years (IQR 7.1) with

CD4 counts >250 cells/mm³ ($n = 19$, 79%) and suppressed HIV RNA ($n = 20$, 80%). Molecular profiling data ($n = 12/24$) revealed two EGFR mutation carriers. Tissue-microarray sections underwent PD-L1, PD-L2 immunostaining and multiplex immunohistochemistry ($n = 21$) for PD-1, CD4, CD8 and CD68 (Figure 1A–D, supplementary materials, available at *Annals of Oncology* online). Prevalence of PD-L1 positivity was 45% in tumour ($n = 11/24$) and 8% ($n = 2/24$) in tumour-infiltrating cells, whereas tumoural PD-L2 positivity was found in 33% ($n = 8/24$) (supplementary Figures S1, available at *Annals of Oncology* online). Following 2 : 1 case–control matching for age, gender, grade, stage and histotype ($n = 66$), PD-L1 (12/23 versus 14/43, $P = 0.12$) and PD-L2 expression (9/23 versus 25/45, $P = 0.20$) were unrelated to the presence and severity of HIV-related immune dysfunction as indicated by nadir CD4 counts ($P = 1.0$, $P = 0.8$), HIV RNA levels ($P = 0.14$, $P = 0.24$), duration of HIV infection and cART ($P > 0.05$) suggesting independence between antiviral and antitumour immune-tolerogenesis. In keeping with this view, we documented a positive correlation between PD-L1 expression and density of tumour-infiltrating (TIL) (Figure 1A–F) but not peripherally circulating lymphocytes

Figure 1. (A–D) Representative sections of HIV-associated NSCLC co-immunostained for CD8 (red chromogen), CD4 (brown chromogen), PD-1 (blue chromogen) and CD68 (green chromogen) illustrating CD4/CD8 enrichment in PD-L1-positive HIV-associated NSCLC (A–C) compared with PD-L1-negative counterparts (B–D). Histograms of multiplex immunohistochemistry data illustrating the relationship between the CD4- and CD8-positive immune infiltrate expressed as number of immunopositive cells per high power field (HPF) according to tumour cell PD-L1 (E) and PD-L2 expression status (F) in HIV-associated NSCLC ($n = 21$). Peripheral blood immunophenotyping illustrates the relationship between peripheral CD4, CD8, CD19 and CD56-positive cell counts categorized according to tumoural PD-L1 (G) and PD-L2 expression status (H) in HIV-associated NSCLC ($n = 24$). Medians and interquartile ranges are reported. (I) Volcano plot of differentially regulated genes identified by Nanostring analysis. The Benjamini–Hochberg P -values are correlated to fold-changes in transcripts identified in HIV-positive NSCLC ($n = 5$) versus HIV-negative controls ($n = 3$). Transcripts achieving statistical significance (FDR q -value of 5%) are highlighted by the presence of the corresponding gene name. (J) Heat map profile of the 12 transcripts that are differentially regulated in HIV-associated NSCLC compared with controls. Expression levels are shown as log transformed values of normalized counts ($\ln 2$).

(Figure 1G and H), highlighting polarization of the tumour micro-environment to a type-1 response [2]. In type-1 or PD-L1⁺/TIL⁺ tumours, TILs are chemo-attracted to malignant cells and turned off by PD-L1 engagement. Type-1 tumours are generally sensitive to single-agent PD-1/PD-L1-targeted checkpoint blockade, due to the presence of an immune-reactive microenvironment [3].

In an exploratory targeted transcriptomic analysis of five HIV-positive cases and three stage/histotype-matched controls using the NanoString PanCancer-Immune panel (NanoString Technologies, Seattle), we demonstrated enrichment of transcripts involved in chemotaxis (CCL18), antigen presentation (HLA-A, HLA-DRA), cytotoxic T-cell (LAMP-1) and macrophage activation (SPP1, Figure 1I and J) in HIV-associated NSCLC, consistent with previous studies [4]. Whilst not exhaustive and limited by sample size, our findings challenge the conception that well-controlled HIV infection may negatively influence cancer-specific immune dysfunction by preliminarily demonstrating the presence of an immune-reactive microenvironment in HIV-associated NSCLC (supplementary Figures S2, S3, Tables S2 and S3, available at *Annals of Oncology* online). This concept should be further explored by comparing normal and neoplastic lung tissues in prospective studies.

As accumulating evidence shows PD-1/PD-L1-targeted ICPI to be safe and capable of enhancing HIV-specific immunity [5] without unexpected toxicity, taken together, our data suggest that HIV-associated NSCLC may be equally reactive to ICPI. Whilst preliminary in nature and warranting validation in larger patient cohorts treated with ICPI, our study supports an immunobiological rationale for the development of PD-1/PD-L1-targeted ICPI in HIV-associated NSCLC.

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Complete response to CSF1R inhibitor in a translocation variant of teno-synovial giant cell tumor without genomic alteration of the CSF1 gene

Teno-synovial giant cell tumour (TGCT), also known as pigmented villonodular synovitis (PVNS), is a rare neoplasm affecting the synovium and tendon sheaths in young adults, with recurrent translocations involving *COL6A3* and *CSF1* genes [1]. The fusion protein is cleaved, resulting in the overproduction of CSF1, which attracts CSF1R-expressing non-neoplastic cells (macrophages and monocytes) through a paracrine effect [1]. Complete surgical resection is not always feasible and/or may lead to functional impairment or amputation. Tyrosine kinase inhibitors or antibodies, such as imatinib, pexidartinib or

emactuzumab showed encouraging clinical activity in clinical studies [2–4]. *CSF1* gene alteration is therefore considered as the actionable driver oncogene in PVNS.

We report the case of a 61-year-old female with a rapidly growing TGCT of the dominant hand (Figure 1). Because complete surgery could not be conservative, this patient was proposed for inclusion in a phase III study testing pexidartinib [4]. She achieved complete response still ongoing at 17 months. A PCR analysis failed to identify the classical fusion gene *COL6A3-CSF1*. The tumour was submitted to RNAseq analysis from FFPE tissues using TruSeq RNA Access Library Prep Kit (Illumina®) and NextSeq sequencing system. Two in-frame fusion transcripts, *HMG2-NCOR2* and *NCOR2-SUPT3H*, were identified. High level of *CSF1* gene expression was also detected, similar to 15 other PVNS, and relatively higher *IL-34* gene expression was