followed by up-front chemotherapy before surgery, improves 3-year DFS in patients with LARC when compared with conventional chemoradiation.

SURGICAL TREATMENT OF LARC

According to Prof van de Velde, the Beyond TME Collaborative group concluded that achieving an R0 resection with free resection margins is the most important goal in these patients [Beyond TME Collaborative. *Br J Surg*. 2013]. Given the heterogeneity of these cases, he added that a variety of surgical solutions may be considered to accomplish this goal, so the procedure must be personalized to suit the individual patient's clinical situation.

Discussing the evolution of surgical approaches to LARC in recent years, he noted that although the extended resection technique is used, it is hazardous and should be performed only in centers of excellence. Robotic surgery is in a learning curve and aims to reduce technical difficulties associated with performing standard laparoscopic surgery within the narrow pelvic cavity, offering similar operative time and quality of mesorectal excision, with a reduced duration of hospital stay [Baik SH et al. *Surg Endosc*. 2008]. The ongoing prospective randomized controlled ROLARR trial [Collinson FJ et al. *Int J Colorectal Dis*. 2012] aims to provide a comprehensive assessment of robotic-assisted and standard laparoscopic surgery for the curative resection of rectal cancer.

Prof van de Velde noted that near-infrared fluorescence imaging represents another exciting development with the potential to dramatically change current staging methods in the management of patients with LARC. In Europe, audit of the treatment results of rectal cancer has been one of the most important developments, leading to initiation of the European Registration of Cancer Care to improve the quality of care for patients with colon and rectal cancer [van de Velde CJ et al. *Eur J Cancer*. 2014].

Despite advances in the surgical treatment of LARC, however, he emphasized that there is still room for improvement, especially in a multidisciplinary setting and in particular with respect to enhancing the ability to identify nerves and avoid damaging them. Surgical techniques must also be refined to improve organ preservation, concluded Prof van de Velde.

Systemic Treatment for Advanced NSCLC

Written by Phil Vinall

Non–small cell lung cancer (NSCLC) is a heterogeneous disease with numerous driver mutations, stated Ken J. O'Byrne, Princess Alexandra Hospital, Brisbane, Australia. All malignancies are unified by DNA instability and immune privilege, and new insights into the latter may provide new therapeutic strategies. This may enable personalized medicine, with the right target (identified by genes, phenotypes), right drug (selective design and delivery, specific combination of drugs for complex diseases), and right patient (by genotyping and phenotyping). Genotype-directed therapy (afatinib, eg) can improve overall survival (OS) for patients who have NSCLC with a Del19/L858R endothelial growth factor receptor (EGFR) mutation [Chih-Hsin Yang J et al. *J Clin Oncol*. 2014].

The recent understanding of the relation between the cancer cell and the immune system includes a knowledge of how the cancer cell produces proteins that prevent the immune system from recognizing and killing the cancer cell, as well as the identification of a series of inhibitory receptors, activating receptors, and other pathways. This understanding is advancing the field of systemic immune therapy for oncology.

Improved diagnosis is required to harness the possibility of targeted systemic therapy. According to Ramaswamy Govindan, MD, Washington University School of Medicine, St Louis, Missouri, USA, the field is moving away from histopathology and toward gene expression data (which identify genes that are expressed as proteins) to identify actionable mutations in NSCLC. He cautioned, however, that currently there are no drugs approved by the Food and Drug Administration for actionable mutations in early-stage resected NSCLC. Still, molecular classification will allow understanding of the biology of the cancer and lead to identifying prognostic factors for determining optimal adjuvant therapy and predictive biomarkers to select patients for targeted therapy, especially in advanced disease.

Work is ongoing to improve the classification of lung adenocarcinoma (LUAD) subtypes based on gene expression data. One classification is bronchoid, squamoid, or magnoid, based on microarray studies, which demonstrated that there are distinct differences for the mutations in these subtypes, methylation patterns, genome instability, prognosis, and response to treatment [Wilkerson MD et al. *PLoS One*. 2012]. Another proposed classification is proximal proliferation, proximal inflammation, and terminal respiratory unit, used in a molecular profiling study of LUAD [Cancer Genome Atlas Research Network. *Nature*. 2014].

Actionable oncogenic drivers to identify targeted therapy were seen in 64% of LUADs in one recent study [Kris MG et al. *JAMA*. 2014]. The median survival was 3.5 years for patients with an oncogenic driver and genotype-directed therapy, compared with 2.4 years for patients with an oncogenic driver (or drivers) who did not receive genotype-directed therapy ($P = .006$).

A number of issues must be addressed before molecular profiling can be used to determine treatment—including cost, ability to obtain a sufficient quantity of tissue, turnaround time, and having an Food and Drug Administration–approved drug for actionable mutations. A more comprehensive approach to molecular analyses (beyond limited gene panel testing) may be required in the future, as multiple mechanisms contribute to loss of function (homozygous deletion, methylation, mutation) and a test for one will miss the others.

Egbert F. Smit, MD, PhD, Vrije University of Medical Center, Amsterdam, Netherlands, discussed the need for drugs to overcome secondary resistance to systemic treatment. Secondary resistance is associated with 3 distinct clinical patterns: oligometastatic progression and slow minimal multifocal progression (in both of which there is decreased tumor burden compared with initial presentation) and rapid multifocal progression (in which tumor burden is increased).

Resistance to the anaplastic lymphoma kinase (ALK) gene inhibitor crizotinib, a first-generation drug, has been overcome in patients with NSCLC using the second-generation ALK inhibitor ceritinib [Shaw AT et al. *N Engl J Med*. 2014]. Ceritinib resistance associated with ALK G1202R has been identified, however [Friboulet L et al. *Cancer Discov.* 2014], and whether the third-generation ALK inhibitors under development will overcome this resistance is unknown. The resistance develops because gatekeeper mutations alter the ability of the drug to bond to the adenosine triphosphate (ATP) site. Restoring the affinity for ATP and downstream signaling may improve treatment success.

Side road resistance, which denotes the ability of a protein to facilitate the same downstream signaling as another protein [Pao W, Chmielecki J. *Nat Rev Cancer.* 2010] is an important mechanism in EGFR and ALK resistance. One treatment strategy for side road resistance is cytotoxic chemotherapy. The optimal chemotherapy is unknown for EGFR-mutation LUAD that becomes resistant to a tyrosine kinase inhibitor (TKI), however. One study suggested that the EGFR-TKI-resistant tumors are more sensitive to taxane-based chemotherapy [Park JH et al. *Lung Cancer.* 2012]. Another strategy suggests retreatment with the initial EGFR-TKI. One series showed an 86% disease control rate after retreatment with the initial drug, after a median 9.5-month drug holiday in patients with LUAD [Becker A et al. *Eur J Cancer*. 2011]. Two ongoing studies will provide evidence on whether this is a reasonable approach.

Dual blockade of EFGR in patients with secondary resistance is another possible strategy. Afatinib plus cetuximab was effective in patients whose tumors progressed while receiving EGFR-TKI treatment (gefitinib and erlotinib), with a 33% control rate in T790M mutations [Janjigian YY et al. *Cancer Discov.* 2014].

It is unclear whether NSCLC is an immune-driven tumor. There is a report of a correlation between infiltrating lymphocytes and prognosis in NSCLC [Hiraoka K et al. *Br J Cancer*. 2006] and immune-related spontaneous tumor regression [Nakamura Y et al. *Lung Cancer*. 2009], but there are insufficient data to be conclusive, according to Martin Reck, MD, Lungen Clinic Grosshansdorf, Grosshansdorf, Germany.

There are 2 possible approaches to immunotherapy. The active approach is designed to act on the immune system, while the passive approach acts on the immune-based mechanism at the tumor level. There are some data of the active approach in LUAD. In antigen-dependent immunotherapy, there are vaccination strategies.

The MAGE-A3 vaccine did not improve disease-free survival or OS in patients with NSCLC after surgical resection in the large-scale randomized MARGRIT study, and it was not possible to identify a predictive gene in these patients [Vansteenkiste JF et al. *Ann Oncol* 2014 (abstr 1173O)]. The TG4010 vaccine in combination with chemotherapy as first-line treatment of MUC1-positive (mucin 1, cell surface associated) advanced NSCLC resulted in a signal of improvement in progression-free survival (PFS) and OS in the TIME trial [Quoix E et al. ESMO 2014 (abstr 5152)]. A phase 3 study will be conducted with this vaccine. The phase 3 START trial [Butts C et al. *Lancet Oncol.* 2014], however, found no significant difference in OS with the MUC1 vaccine called tecemotide in patients with unresectable stage 3 NSCLC, except for a signal of improvement in OS in a subgroup of patients treated with concurrent chemoradiotherapy.

Antigen-independent therapies include checkpoint inhibitors. These drugs target the mechanisms that the tumors use to escape the immune system, which include ineffective presentation of tumor antigens, recruitment of immunosuppressive cells, release of immunosuppressive factors, and T-cell checkpoint dysregulation, which is caused by the tumor disrupting the inhibitory or activating signaling pathways. An evolving approach to cancer treatment is drugs designed to promote an immune response by targeting these pathways.

A phase 2 study in patients with NSCLC who had received chemotherapy demonstrated a signal of benefit with ipilimumab (CA184-041) for immune-related PFS and for PFS [Lynch TJ et al. *J Clin Oncol.* 2012]. Phase 3 trials with ipilimumab in NSCLC and small cell lung cancer will be reported soon. Antibodies are being studied targeting the PD-1 receptor and its ligand, PD-L1, in patients with NSCLC treated with chemotherapy.

Although immunotherapy is a fascinating new approach, Prof Reck concluded, vaccination strategies must be validated; the best surrogates of efficacy must be defined; the diagnostics must be harmonized; and randomized evidence is needed.