other malignancies, and look forward to what future research will bring.

S. Pusceddu1*, R. Buzzoni2 & F. De Braud1
1Medical Oncology Unit; 2Day Hospital/Outpatient Unit, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan ENETS Center of Excellence, Milan, Italy (*E-mail: sara.pusceddu@istitutotumori.mi.it)

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Pancreatic well-differentiated neuroendocrine neoplasms (pWDNENs): what place for everolimus and sunitinib derived from ESMO clinical practice guidelines in the therapeutic algorithm?

We read with interest the paper by Oberg et al. and we appreciated the effort to identify a therapeutic algorithm in pNENs [1].

Everolimus and sunitinib have been recently assessed in phase III placebo-controlled trials, producing significant benefit, with improvement in PFS (sunitinib—HR: 0.42; 95% CI 0.26–0.66; P < 0.001, everolimus—HR: 0.35; 95% CI 0.27–0.45; P < 0.001) [2, 3].

These biological therapies were compared with placebo in a larger series: everolimus (n = 410) and sunitinib (n = 171) of progressive pWDNENs with homogeneous characteristics (functioning tumor or not), pretreated with or without chemotherapy (CT) and/or somatostatin analogues (SSAs).

The objective response rate and stable disease were 9.3% and 63% in the sunitinib group versus 5.0% and 73% in the everolimus group. Both the treatments turned out to be feasible, with a low rate of severe adverse events (AEs) consisted of neutropenia (12%) and hypertension (10%) for sunitinib, and stomatitis (7%) and anemia (6%) for everolimus.

The ESMO Guidelines 2012 recommended their use in advanced pNEN G1/G2 [1].

Although these agents have improved the availability of treatment options in pWDNENs, some weaknesses in their place in therapy still remain. The specific place of targeted drugs in the treatment algorithm of pWDNENs needs to be clarified. Particularly their use in naive patients, instead of SSAs or CT as first-line treatment.

According to the published data, in the phase III trials, no difference in benefit of PFS with everolimus and sunitinib versus placebo was found in patients with and without prior CT or SSAs, and their use did not impact the beneficial effect of following biological agents [2–5].

PNENs are usually more aggressive than carcinoids but the clinical course in pWD is generally indolent, and targeted agents may not always be justifiable as first-line treatment.

The potential long-term AEs have to be evaluated if Sunitinib and Everolimus are proposed upfront, especially in pNET G1, also considered the availability of other effective therapeutic options potentially well tolerated as SSAs.

For this reason, we support that the ESMO treatment algorithm should also consider SSAs options as first line of therapy in the management of pNENs G1/G2.

Furthermore, the two above-mentioned studies fail to clarify whether one therapeutic option would be more effective than the other. The choice of one treatment over the other should reasonably be strictly related to the expected toxicity and tolerability of these drugs.

A good tailored approach could be based on the appropriate distinction between the incidence of AEs and comorbidities on one hand, and the therapeutic strategy and life expectancy on the other hand. Since we are dealing with long-term therapies, it is crucial to avoid those mild-moderate AEs which, when persisting, could lead to worsening of the patient’s quality of life.

Clearly, further clinical trials are required to explain the precise strategy and the optimal specific sequence of these therapeutic options. As well as phase IV studies to gain additional knowledge on safety and potential side-effects, which may occur with long-term use of these target agents.

So far it’s very difficult to standardize a good clinical practice in a strict therapeutic algorithm, and the treatment approach for pWDNENs is only a very individualized one.

S. Pusceddu1*, R. Buzzoni2 & F. De Braud1
1Medical Oncology Unit; 2Day Hospital/Outpatient Unit, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan ENETS Center of Excellence, Milan, Italy (*E-mail: sara.pusceddu@istitutotumori.mi.it)

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Poly (ADP-ribose) polymerase (PARP) inhibitors for the treatment of advanced germline BRCA2 mutant prostate cancer

Therapeutic exploitation of the synthetic lethality between poly (ADP-ribose) polymerase (PARP) and BRCA1/2 is highly promising [1]. Trials have focused on ovarian and breast cancers with limited data available for BRCA1/2 mutant prostate cancer (PCa). Emerging data suggest that homologous recombination (HR) defects are common in PCa, potentially conferring a BRCA1/2 phenotype [2]. PARP is also implicated in ERG transcription and androgen receptor (AR) signaling, key drivers in PCa. PARP inhibition results in antitumor activity in ERG rearranged cancer models and suppresses AR target gene expression and tumor proliferation [3, 4].

Four patients with advanced PCa and germline BRCA2 mutations were treated on three phase I studies- olaparib bioavailability (NCT00777582), olaparib dose-escalation and MK-4827 (NCT00749502) [1]. Methodology, clinical, pathological and molecular data are detailed in Table 1 and Supplementary Data S1 to S3. The median age at diagnosis was 58 years (range: 47–73); The Gleason score ranged between 6 and 9. All patients had bone metastases at diagnosis and subsequently developed visceral and/or soft tissue disease. An increased incidence of visceral metastasis was reported in BRCA1/2 mutant ovarian cancer but not previously described in PCa. The median duration to castration-resistance was 18 months (range 10–28). PSA and radiological responses lasting 34 and 26 months were noted in two patients treated with olaparib with a further patient having disease stabilization for 10 months. One patient exhibited primary resistance to MK-4827.

Molecular analyses focused on key events in prostate carcinogenesis. ERG rearrangements and positive ERG immunostaining were observed in all cases. All patients exhibited either heterozygous or homozygous PTEN allelic loss with the corresponding negative PTEN immunostaining. Massively parallel DNA sequence analysis carried out on tumor tissue obtained from a BRCA2 c.6174delT allele carrier progressing after 34 months of olaparib treatment did not identify secondary BRCA2 mutations (PMID: 18264088) as a putative resistance mechanism (Supplementary Data S1, S3 and Figure 3, available at Annals of Oncology online).

To our knowledge, this report is the largest account of BRCA2 mutant carriers with PCa treated with PARP inhibitors (PARPis) to date. The higher frequency of ERG rearrangements (four out of four cases) compared with the expected rate of 50%–60% in sporadic PCa supports the hypotheses that these gene rearrangements are accelerated in the presence of underlying HR defects [5]. One patient with an ERG rearrangement had a 44-month response to abiraterone and subsequently responded to olaparib. The increased incidence of ERG rearrangements in BRCA2 mutant carriers coupled with our previous data showing ETS rearrangements predict for improved response to abiraterone implies that targeting AR signaling may also be beneficial for these patients [PMID: 19339269].

PARPis are the first molecular stratified treatment for BRCA1/2 mutation carrier PCa patients and has promising antitumor activity. Importantly, the HR/PARP synthetic lethal paradigm may be more broadly relevant in PCa with germline or somatic inactivating mutations in HR DNA repair genes such as CHEK2, BRIP1/FANCI, NBS1 BRCA1 and ATM, collectively reported to occur in 20%–25% of PCas [2].

Future studies of PARPis in sporadic PCa will need to address critical issues, including identifying predictive biomarkers of HR defects, incorporating biomarkers of efficacy beyond PSA and investigating mechanisms of resistance.

S. K. Sandhu1,2, A. Omlin1,2, L. Hylands1, S. Miranda1, L. J. Barber3, R. Riisnaes1, A. H. Reid1,2, G. Attard1,2, L. Chen3, I. Kozarewa3, H. Gevensleben1, J. Campbell3, K. Fenwick3, I. Assiotis4, D. Olmos1,2, T. A. Yap1,2, P. Fong1,2, N. Tunariu2, D. Koh2, L. R. Molife1,2, S. Kaye1,2, C. J. Lord3, A. Ashworth1 & J. de Bono1,2

1Division of Clinical Studies, Institute of Cancer Research, Sutton, 2Drug Development Unit, The Royal Marsden NHS Foundation Trust, Sutton, 3The Breakthrough Breast Cancer Research Centre, The Institute of Cancer Research, Chelsea, UK (*E-mail: johann.de-bono@icr.ac.uk).

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