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Review Article

Critical Role of PET-Scan in Unravelling the Dual Pathology- Review of Literature and a Case Presentation

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1. Abstract

Simultaneous presentation of two lymphatic haematological malignancies is extremely rare. Adequate and optimal diagnostic steps including various imaging techniques and histopathological biopsies are required unpin the exact diagnoses to be able to deliver the best management strategies. Positron Emission Tomography/Computerised Tomography scan (PET/CT) can be used to determine the sites of disease with the highest Standardized Uptake Value (SUV) and hence, the preferred site of biopsy.

3. Introduction

The simultaneous occurrence of two lymphatic malignancies in one patient is extremely rare with an incidence rate of 1.4–6.5 cases/1,000,000 individuals [8]. Co-existence of MM and other lymphoid malignancies like Chronic Lymphocytic Leukemia (CLL) [9], MM and Hodgkin's Disease (HD) [10], MM and Lympho Plasmacytic Lymphoma (LPL) [11] has been reported. However, there are less than 5 reported cases in PubMed of simultaneous presentation of DLBCL and MM [12].

Diffuse Large B-cell Lymphoma (DLBCL) is the most common type of Non-Hodgkin Lymphoma (NHL), comprising about 24% of new cases of NHL [1, 2]. DLBCL is an aggressive NHL which usually present with rapidly enlarging lymph nodes. Positron Emission Tomography/Computerised Tomography scan (PET/CT) can be used to determine the sites of disease with the highest Standardized Uptake Value (SUV) and hence, the preferred site of biopsy.

Multiple Myeloma (MM), a plasma cell neoplasm involving clonal proliferation of terminally differentiated plasma cells and MM is the second most common hematologic cancer [3]. Unlike other metastatic bone malignancies, multiple myeloma related osteolyticbone lesions exhibit no new bone formation [4]. Myeloma relatedbone disease is one of the main causes of morbidity and this can be detected on skeletal radiographs, low-dose Whole Body Computed Tomography (WB-CT), Magnetic Resonance Imaging (MRI) or PET/CT [5,6]. About 1% to 2% of MM patients presents with Extrame Dullary Disease (EMD) and an accurate differentiation of this finding from nodal lymphoma is very crucial as treatments are very different for these two haematological cancers [7].

Positron Emission Tomography (PET) scan is a functional imaging developed in the late 1950s. Radio-labelled glucose analogue Fluorine-18 Fluorodeoxy-Glucose (F-18 FDG) is the most frequently used PET tracer and it allows visualization of the cellular uptake of glucose, which is often up regulated in malignant neoplasms. FDG-PET has replaced Gallium-67 scintigraphy, which was previously used to assess the extent and viability of lymphoma [13, 14]. A major advantage of FDG-PET is the ability to quantify the level of FDG uptake from PET images and resulting in a Standardized Uptake Value (SUV). The combined PET and CT isan important evolution of imaging technique and the CT component of PET/CT provides anatomical information and PET component provides tissue metabolic activity. Combined PET/CT results in a reduced incidence of false-positive and false-negative PET findings.

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4. Case Presentation

70 years old gentleman referred to hematology department with four months history of lethargy. He was initially referred to the gastroenterologist for investigations for his weight loss but he has no clear bowel symptoms and any change of his bowel habits. A colonoscopy and upper gastrointestinal endoscopy did not show any significant pathological findings to cause the patient's symptoms. As part of his investigation, he had a CT scan that showed mediastinal lymphadenopathy as well as bone lesions at thoracic ten vertebra level (T10). There were borderline enlarged left supraclavicular nodes, with some para-vertebral tissue around T10 and the bone lesions. Previous blood test showed an increase of serum kappa light chains to 2148 mg/L, serum lambda light chains were 11mg/L and the kappa lambda ratio was elevated to 189. Serum protein electrophoresis did not show any para protein. Subsequently, he had a Magnetic Resonance Imaging (MRI) of the whole spine which showed multiple marrow deposits through out the spine, with a compression fracture of the T10 vertebra body, with no signs of cord compression. Patient had a biopsy of the T10 para spinal mass, which was compatible with a diagnosis of plasma cell neoplasm (Table 1 and Figure 1). He also had a bone marrow biopsy findings are summarised in (Table 1). He subsequently had a PET (Positron Emission Tomography) /CT scan finding are illustrated in (Table 2).

Table 1: Bone marrow trephine and T10 mass biopsy finding

Trephine: Interstitial infiltrate of kappa light chain restricted neoplastic plasma cell (30-40% disease bulk). Neoplastic cells expessed-IRF4/MUM1, CD20, CD79a, Cyclin D1, CD117 and EMA. Negative for heavy chain expression and Negative for amyloid.
Cytogenetic: By interphase FISH analysis on bone marrow aspirate sample showed-presence of IGH-CCND1[t(11;14)] and additional copy of ATM(11q22.3).
T10 mass: Biopsy showed infiltration of cells withplasmacytic differentiation and the cells are CD138 positive. MNF116 immunostaining is negative for cytokeratin.Further immunostaining shows most cells are positive for MUM1, cyclin D1, CD117 and EMA along with kappa restriction. There is no convincing positivity with IgG, IgA or IgM. There is extensive deposition of amorphous eosinophilic material, both within and outside vessel walls, almost certainly representing amyloid deposition. Congo Red staining confirmed that. Conclusion: Plasma cell neoplasm and amyloid deposition.

This case was discussed multi-disciplinary haematological malignancy meeting and the plan was to treat the patient with VTD regimen for myeloma as he renal function was deteriorating. However, as PET/CT showed discrepancies in FDG uptake in myelomatous bone lesion and in inguinal lymph node, a core biopsy of that lymph gland was taken which confirmed a diagnosis of DLBCL (Table 3 and Figure 2).

Table 2: PET/CT scans findings

A PET/CT scans showed innumerable lucencies throughout the imaged skeleton with mild FDG uptake, comparable with adjacent marrow uptake. There was slightly high FDG uptake (SUVmax 4.3), above background marrow uptake, associated with the moderate to severe pathological collapse of the T10 vertebral body. There were also enlarged left inguinal lymph nodes of (39 x 28) mm diameter which showed much higher FDG uptake of SUVmax 12.4.

Table 3: Left inguinal lymph node biopsy finding

The tumour cells express CD20, CD79a, BCL-6 (weak), CD10, MUM-1, BCL-2, IgM and kappa but are negative for CD3, CD5, CD23, CD117, EMA, CD30 and EBER. The MIB-1 labelling index averages 90%. The tumour cells are negative for CD138.FISH: No evidence of high risk cytogenetic abnormalities. Cyclin D1 is negative, MYC not re-arranged.

Patient was subsequently started treatment with a combination ofrituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone (R-CHOP) plusbortezomiband is he is currently responding very well to treatment with interim PET/CT showed completed resolution of inguinal lymph nodesand improvement in myeloma markers-latestserum Kappa Light Chains 47.94 mg/L, Serum Lambda Light Chains 7.30 mg/L and Kappa Lambda Ratio 6.57, and resolution of T10 vertebra mass. This patient is now undergoing assessment for an Autologous Stem Cell Transplant (ASCT).

5. Discussion

MM is well recognised to be associated with an increased risk of secondary malignancies [15, 16]. However coexistence of DLBCL and MM very rare, and the pathogenesis of this dual diagnosis of DLBCL with MM are not yet well understood. The two malignancies may have been different manifestations of a unique clonal disorder and it has been suggested that NHL clone continues to mature and may eventually rise to MM [17]. A retrospective study showed 6 out of 4165 patients with B-NHL developed MM and only 1 out of 804 MM patients developed B-NHL [18]. Although it has been postulated a common clonal cell of origin

for the coexisting malignancies but studiesusing immunoglobulin light and heavy chain isotype analysis or genotypic studies have demonstrated disparate clonal evolutions in concomitant malignancies. The separate clonal origins indicate DLBCL and MM evolve independently and not from transformation of a B-cell clone [19].

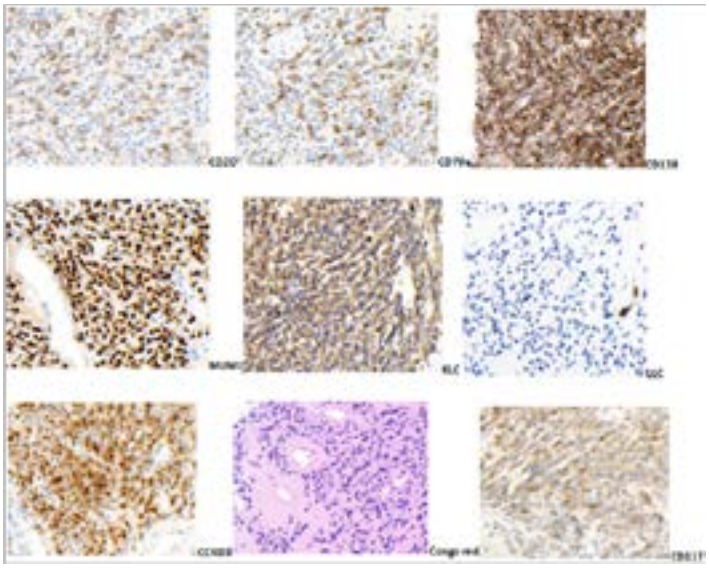

Figure 1:

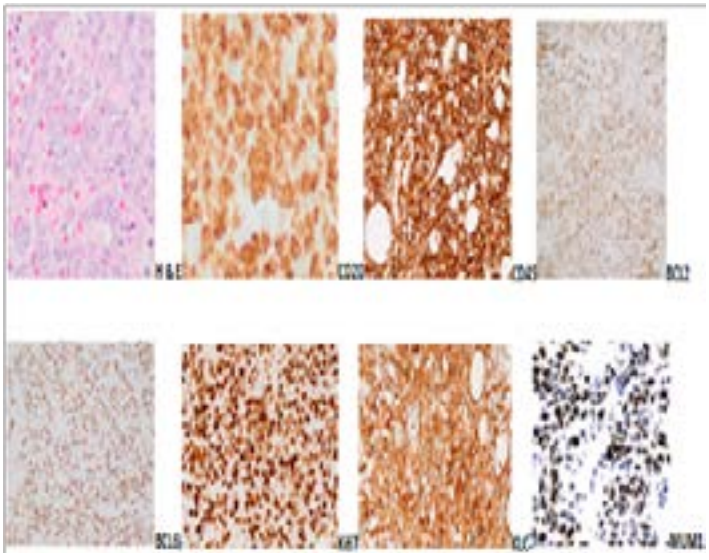

Figure: 2

Until the early 2000s, lymphoma staging was based mainly on CT scan as the main imaging modality along with results from clinical examination and bone marrow biopsy [20]. Since then studies have shown that combined FDG-PET/CT is superior to FDG-PET or contrast-enhanced CT as separate imaging procedures in the staging of lymphoma [21-26]. The 2014 International Myeloma Working Group (IMWG) criteria for the diagnosis of MM highlighted the importance of new imaging techniques for the management of MM in order to early detection of bone disease as a symptomatic MM criterion requiring treatment even when asymptomatic [27]. Studies conducted over recent years have shown better performance using low-dose whole-body CT and MRI scans than standard skeletal radiographs [28, 29]. However PET/CT scan may be better imaging technique as it can simultaneously show the functionality of neoplastic cells as well as show their anatomical position.

A more recent study suggests that PET/CT scan is a reliable imaging for initial staging, therapeutic monitoring and relapse workup in MM, especially because of its prognostic potential [30]. PET/CT scan is very useful in evaluating metabolic activity in malignant tumor. For MM staging PET-FDG allows whole-body exploration and has 90% sensitivity for the detection of medullary disease and 70-100% specificity [31-33]. PET scans are shown to have prognostic importance in myeloma patients as the presence of at least 3 Focal Lesions (FL) and EMD predicted inferior Overall Survival (OS) as well as Progression Free Survival (PFS) [34, 35].

The PET scan identifies the location of lymphoma uptake and distinguishes it from physiologic uptake or other causes of increased FDG uptake i.e. infection, inflammation or any second malignancy as in our case according to distribution and characteristics of FDG uptake. PET/CT appears to be very sensitive and highly specific for detecting NHL in nodal and extra-nodal siteshowever, the reliability of detection lymphoma in bone marrow involvement is no consistent [36-39].

However, PET scan findings are usually different between MM and high grade lymphoma as the latter group shows more intense FDG uptake than neoplastic cell of MM [40-45]. Moreover, MM does not usually present with lymphadenopathy. Our patient had lymphadenopathy as well as there was a differential FDG uptake between para-spinal mass and the groin lymph nodes which prompted further investigation in our patient. In this case, the patient was found to have a second malignancy in the form of DLBCL which is potentially curable versus myeloma which at present time is an incurable malignancy. Therapeutic decision making was complicated by the fact that for these two different malignancies patients usually receive very different treatment regimens. However, our patient was treated with a regimen based on the ReMODL-B trial with excellent response for both MM and

NHL [46].

6. Conclusion

PET/CT is an invaluable diagnostic tool that should be integrated in evaluating lymphoid malignancies, during initial diagnosis and as subsequent response assessment. The specific mechanisms underlying the simultaneous presentation of two B-cell malignancies have yet to be established. Hence, there are no consistent treatment guidelines. Due to the lack of specific guidelines management of such should be based on available evidence and the doctor's experience, the characteristics of the patient's illness and the performance status.

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References:

1. Gherlinzoni F, Cavo M, Pileri S, Rivano MT, Boriani S, Biagini R et.al. Solitary plasmocytoma of the bone in a case of Hodgkin's disease. ActaHaematol. 1986; 76: 178-80.

2. Ailawadhi S ,Dholaria BR , Khurana S , Sher T, Alegria V, Paulus A et.al. Outcomes of patients with simultaneous diagnosis of chronic lymphocytic leukaemia/small lymphocytic lymphoma and multiple myeloma British Journal of Haematology. 2019; 185: 347-50.

3. Huang C, Zhao G, Wang L, Zhang H, Wu X, Zhang M et.al. Simultaneous occurrence of Hodgkin's lymphoma and multiple myeloma: A case report and review of the literature. OncolLett. 2016; 11: 4139-43.

4. Carulli G, Ciancia EM, AzzaraA, Ottaviano V, Grassi S, Ciabatti E et.al. Simultaneous presentation of Waldenströmmacroglobulinemia and multiple myeloma: multidisciplinary diagnosis, treatment and 30-month follow-up. J ClinExpHematop. 2013; 53: 29-36.

5. Jamani K, Duggan P, Neri P, Bahlis N, Jimenez-Zepeda VH. Co-existent B-cell and plasma cell neoplasms: a case series providing novel clinical insight. Leuk Lymphoma. 2016; 57: 557-62.

6. Siegel R, Miller K, Jemal A. Cancer statistics, 2019. CA Cancer J Clin. 2019; 68: 7-30.

7. SEER. SEER Database: All Lymphoid Neoplasms with Detailed Non-Hodgkin Lymphoma Subtypes; SEERb Incidence Rates and Annual Percent Change by Age at Diagnosis. NCI; 2002-11.

8. Zhou S, Ma Y, Bi L, Shen Z, Yu K. Simultaneous occurrence of two B-cell malignancies: A case report. OncolLett. 2014; 8: 908-10.

9. Roodman GD. Pathogenesis of myeloma bone disease. Leukemia. 2009; 23: 435-41.

10. Regelink JC, Minnem a MC, Terpos E, Kamphuis MH, Raijmakers PG, Pieteras- van den Bos IC et al. Comparison of modern and conventional imaging techniques in establishing multiple myeloma-related bone disease: a systematic review. Br J Haematol. 2013; 162: 50-61.

11. Hillengass J, Moulopoulos LA, Delorme S, Koutoulidis V, Mosebach J, Hielscher T et al. Whole-body computed tomography versus conventional skeletal survey in patients with multiple myeloma: a study of the International Myeloma Working Group. Blood Cancer J. 2017; 7: e599.

12. Short KD, Rajkumar SV, Larson D, Buadi F, Hayman S, Dispenzieri A et al. Incidence of extramedullary disease in patients with multiple myeloma in the era of novel therapy, and the activity of pomalidomide on extramedullary myeloma. Leukemia. 2011; 25: 906-8.

13. Seam P, Juweid ME, Cheson BD. The role of FDG-PET scans in patients with lymphoma. Blood. 2007; 110: 3507-16.

14. Kostakoglu L, Leonard JP, Kuji I, Coleman M, Vallabajosula S, Goldsmith SJ et.al. Comparison of fluorine-18 fluorodeoxy-glucose positron emission tomography and Ga-67 scintigraphy in evaluation of lymphoma. Cancer. 2002; 94: 879-88.

15. Mailankody S, Pfeiffer RM, Kristinsson SY, Korde N, Bjorkholm M, Goldin LR et al. Risk of acute myeloid leukemia and myelodysplastic syndromes after multiple myeloma and its precursor disease (MGUS). Blood 2011; 118: 4086-92.

16. Razavi P, Rand KA, Cozen W, Chanan-Khan A, Usmani S, Ailawadhi S. Patterns of second primary malignancy risk in multiple myeloma patients before and after the introduction of novel therapeutics. Blood Cancer J. 2013; 3: e121.

17. Nagamura F, Goto S, Iseki T, Saotome T, Takeshita A, Kikuno K et al. Molecular evidence for a single clonal origin in a patient with multiple myeloma and non-Hodgkin's lymphoma. RinshoKetsueki. 1995; 36: 1182-7.

18. Mahindra AK, Sohani AR, Toomey CE, Michaelson JS, Barnes JA, Abramson JS et al. B cell lymphoma in association with multiple myeloma: Analysis of the biologic relationship. Poster presented at: ASH Annual

Meeting; 10, December 2011. San Diego, CA: Blood (ASH Annual Meeting Abstracts); 2011; 118: 1590.

19. Wei Q, Sebastian S, Papavassiliou P, Rehder C, Wang E. Metachronous/concomitant B-cell neoplasms with discordant light-chain or heavy-chain isotype restrictions: Evidence of distinct B-cell neoplasms rather than clonal evolutions. Hum Pathol 2014; 45: 2063-76.

20. Kwee TC, Kwee RM, Nievelstein RA. Imaging in staging of malignant lymphoma: a systematic review. Blood. 2008; 111: 504-16.

21. Seam P, Juweid ME, Cheson BD. The role of FDG-PET scans in patients with lymphoma. Blood. 2007; 110: 3507-16.

22. Schaefer NG, Hany TF, Taverna C, Seifert B, Stumpe KD, von Schulthess GK et al. Non-Hodgkin lymphoma and Hodgkin disease: co-registered FDG PET and CT at staging and restaging--do we need contrast-enhanced CT? Radiology. 2004; 232: 823-9.

23. Lister TA, Crowther D, Sutcliffe SB, Glatstein E, Canellos GP, Young RC et al. Report of a committee convened to discuss the evaluation and staging of patients with Hodgkin's disease: Cotswolds meeting. J ClinOncol. 1989; 7: 1630-6.

24. Freudenberg LS, Antoch G, Schutt P, Beyer T, Jentzen W, Muller P et al. FDG-PET/CT in re-staging of patients with lymphoma. Eur J Nucl Med Mol Imaging. 2004; 31: 325-9.

25. Hutchings M, Loft A, Hansen M, Pedersen LM, Berthelaen AK, Keiding S et al. Position emission tomography with or without computed tomography in the primary staging of Hodgkin's lymphoma. Haematologica. 2006; 91: 482-9.

26. Elstrom RL, Leonard JP, Coleman M, Brown RK. Combined PET and low-dose, non-contrast CT scanning obviates the need for additional diagnostic contrast-enhanced CT scans in patients undergoing staging or restaging for lymphoma. Ann Oncol. 2008; 19: 1770-3.

27. Rajkumar SV, Dimopoulos MA, Palumbo A, Blade J, Merlini G, Mateos MV et al. International myeloma working group updated criteria for the diagnosis of multiple myeloma. Lancet Oncol. 2014; 15: 538-48.

28. Dimopoulos M, Hillengass J, Usmani S, Zamagni E, Lentzsch S, Davies FE et al. Role of magnetic resonance imaging in the management of patients with multiple myeloma: a consensus statement. J ClinOncol. 2015; 33: 657-64.

29. Terpos E, Kleber M, Engelhardt M, Zweegman S, Gay F, Kastritis E et al. European Myeloma Network guidelines for the management of multiple myeloma-related complications. Haematologica. 2015; 100: 1254-66.

30. Cavo M, Terpos E, Nanni C, Moreau P, Lentzsch S, Zweegmanet S et al. Role of 18F-FDG PET/CT in the diagnosis and management of multiple myeloma and other plasma cell disorders: a consensus statement by the international myeloma working group. Lancet Oncol. 2017; 18: e206-17.

31. Cavo M, Terpos E, Nanni C. Role of 18F-FDG PET/CT in the diagnosis and management of multiple myeloma and other plasma cell disorders: a consensus statement by the international myeloma working group. Lancet Oncol. 2017; 18: e206-17.

32. Dammacco F, Rubini G, Ferrari C. 18F-FDG PET/CT: a review of diagnostic and prognostic features in multiple myeloma and related disorders. ClinExp Med. 2015; 15: 1-18.

33. Weng W-W, Dong M-J, Zhang J. A systematic review of MRI, scintigraphy, FDG-PET and PET/CT for diagnosis of multiple myeloma related bone disease-which is best? Asian Pac J Cancer Prev. 2014; 15: 9879-84.

34. Lu YY, Chen JH, Lin WY. FDG PET or PET/CT for detecting intramedullary and extramedullary lesions in multiple Myeloma: a systematic review and meta-analysis. ClinNucl Med. 2012; 37: 833-7.

35. Aljama MA, Sidiqi MH, Buadi F. Utility and prognostic value of 18 F-FDG positron emission tomography-computed tomography scans in patients with newly diagnosed multiple myeloma. Am J Hematol. 2018; 93: 1518-23.

36. Jung S-H, Kwon SY, Min J-J. 18FFDG PET/CT is useful for determining survival outcomes of patients with multiple myeloma classified as stage II and III with the Revised International Staging System. Eur J NuclMedMol Imaging. 2019; 46: 107-15.

37. Isasi CR, Lu P, Blaufox MD. A meta-analysis of 18F-2-deoxy-2-fluoro-D-glucose positron emission tomography in the staging and restaging of patients with lymphoma. Cancer. 2005; 104: 1066.

38. de Jong PA, van Ufford HM, Baarslag HJ. CT and 18F-FDG PET for non-invasive detection of splenic involvement in patients with malignant lymphoma. AJR Am J Roentgenol. 2009; 192: 745.

39. Carr R, Barrington SF, Madan B. Detection of lymphoma in bone marrow by whole-body positron emission tomography. Blood. 1998; 91:

3340.

40. Elstrom R, Guan L, Baker G. Utility of FDG-PET scanning in lymphoma by WHO classification. Blood. 2003; 101: 3875.

41. Seam P, Juweid ME, Cheson BD. The role of FDG-PET scans in patients with lymphoma. Blood 2007; 110: 3507.

42. Kostakoglu L, Leonard JP, Kuji I. Comparison of fluorine-18 fluorodeoxy-glucose positron emission tomography and Ga-67 scintigraphy in evaluation of lymphoma. Cancer. 2002; 94: 879.

43. Wirth A, Seymour JF, Hicks RJ. Fluorine-18 fluorodeoxy-glucose positron emission tomography, gallium-67 scintigraphy, and conventional staging for Hodgkin's disease and non-Hodgkin's lymphoma. Am J Med. 2002; 112: 262.

44. Zijlstra JM, Hoekstra OS, Raijmakers PG. 18FDG positron emission tomography versus 67Ga scintigraphy as prognostic test during chemotherapy for non-Hodgkin's lymphoma. Br J Haematol. 2003; 123: 454.

45. Tsukamoto N, Kojima M, Hasegawa M. The usefulness of (18) F-fluorodeoxy-glucose positron emission tomography ((18)F-FDG-PET) and a comparison of (18)F-FDG-pet with (67)gallium scintigraphy in the evaluation of lymphoma: relation to histologic subtypes based on the World Health Organization classification. Cancer. 2007; 110: 652.

46. Feeney J, Horwitz S, Gönen M, Schöder H. Characterization of T-cell lymphomas by FDG PET/CT. AJR Am J Roentgenol. 2010; 195: 333.

47. Davies A, Cummin TE, Barrans S. Gene-expression profiling of bortezomib added to standard chemo-immunotherapy for diffuse large B-cell lymphoma (REMoDL-B): an open-label, randomised, phase 3trial. Lancet Oncol. 2019; 20: 649-62.