Plasma Cell Neoplasms
Integrated Pathology Reporting Guide

Family/Last name

Given name(s)

Date of birth DD – MM – YYYY

Patient identifiers

Date of request DD – MM – YYYY

Accession/Laboratory number

Elements in **black text** are CORE. Elements in **grey text** are NON-CORE.

☐ indicates multi-select values ◯ indicates single select values

SCOPE OF THIS DATASET

CLINICAL INFORMATION (Note 1)

◯ Information not provided
◯ Information provided

Paraprotein (select all that apply)

◯ Information not provided
◯ Not detected
☐ Serum (e.g., immunoglobulin (Ig) levels, serum protein electrophoresis (SPEP), immunofixation electrophoresis (IFE), free light chains, MassFix), *specify*

☐ Urine (e.g., urine protein electrophoresis (UPEP), urine immunofixation electrophoresis (UIFE), UIFE, 24-hour total protein), *specify*

☐ Other, *specify*

CRAB findings

HYPERCALCAEMIA

◯ Information not provided
◯ No
◯ Yes (serum calcium >0.25 mmol/L (>1 mg/dL) higher than the upper limit of normal or >2.75 mmol/L (>11 mg/dL))

RENAL INSUFFICIENCY

◯ Information not provided
◯ No
◯ Yes (creatinine clearance <40 mL per minute or >177 µmol/L (>2 mg/dL))

ANAEMIA

◯ Information not provided
◯ No
◯ Yes (haemoglobin >2 g/dL below the lower limit of normal or <10 g/dL)

BONE LESIONS

◯ Information not provided
◯ No
◯ Yes (one or more osteolytic lesions on skeletal radiography, CT or PET-CT)

Comments

Previous therapy

◯ Information not provided
◯ No
◯ Yes (select all that apply)
- ☐ Post induction
- ☐ Pre-transplant
- ☐ Post transplant
- ☐ Maintenance

Other clinical information, *specify*

SAMPLING PROCEDURE (select all that apply) (Note 2)

◯ Not specified
☐ Bone marrow core (trephine) biopsy
☐ Bone marrow aspiration
☐ Needle core biopsy
☐ Fine needle aspiration
☐ Other, *specify*

SPECIMEN(S) SUBMITTED (select all that apply) (Note 3)

◯ Not specified
☐ Bone marrow
☐ Bone
☐ Blood
☐ Soft tissue, *specify*

☐ Other, *specify*

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SAMPLE ADEQUACY (select all that apply) (Note 4)
(Applicable to bone marrow only)

- ☐ Aspirate
  - ◯ Adequate
  - ◯ Unsatisfactory, *specify*
- ☐ Core (trephine) biopsy
  - ◯ Adequate
  - ◯ Unsatisfactory, *specify*

TUMOUR SITE (select all that apply) (Note 5)

- ◯ Not specified
- ☐ Peripheral blood
  - Circulating plasma cells ____ %
- ☐ Bone marrow
- ☐ Extramedullary site(s), *specify*
- ☐ Other, *specify*

OVERALL BONE MARROW CELLULARITY (Note 6)
(Applicable to core biopsy and/or clot only)

____ %

EXTENT OF PLASMA CELL INFILTRATE IN THE BONE MARROW (select all that apply) (Note 7)

- ☐ Aspirate/touch smears imprints ____ %
- ☐ Core biopsy and/or clot ____ %

GROWTH PATTERN (Note 8)
(Applicable to bone marrow only)

- ◯ Information not provided
- ◯ Information provided, *specify*

CONGO RED STAIN (Note 9)

- ◯ Amyloid like deposition
- ◯ Positive for amyloid
- ◯ No amyloid detected

BLOCK IDENTIFICATION KEY (Note 10)
(List overleaf or separately with an indication of the nature and origin of all tissue blocks)

FINAL INTEGRATED DIAGNOSIS (Note 11)
(Value list based on the World Health Organization Classification of Haematolymphoid Tumours, 5th Edition (2024))

- ◯ Plasma cell myeloma (multiple myeloma)
- ◯ Plasma cell neoplasm/dyscrasia (MGUS)
- ◯ Plasmacytoma (select all that apply)
  - ☐ Extraosseous ☐ Osseous
  - ☐ Plasmacytoma with minimal bone marrow involvement ____ %
- ◯ Plasma cell leukaemia
  - ◯ Primary
  - ◯ Secondary
- ◯ Ig deposition disease (select all that apply)
  - ☐ Light chain
  - ☐ Heavy chain
- ◯ AL amyloidosis
  - ◯ Immunohistochemistry ◯ Electron microscopy
  - ◯ Mass spectometry
- ◯ Heavy chain disease (HCD)
  - ◯ Alpha HCD ◯ Mu HCD
  - ◯ Gamma HCD
- ◯ Other (e.g., cold agglutinin disease, paraneoplastic syndrome, POEMS, TEMPI or AESOP syndrome), *specify*

Comments

DISEASE STATUS (Note 12)

- ◯ Not known
- ◯ De novo disease
- ◯ Persistent disease
- ◯ Relapsed disease
  - Date of initial diagnosis DD – MM – YYYY
- ◯ Refractory disease
  - Date of initial diagnosis DD – MM – YYYY

Prior lines of therapy (select all that apply)

- ☐ Monoclonal antibody (e.g., daratumumab, isatumixmab)
- ☐ CART/BiTE or TriTE
- ☐ Stem cell transplant
- ☐ Other, *specify*

DISEASE PROGRESSION STATUS (Note 13)
(Applicable to plasmacytoma to myeloma, MGUS to myeloma and myeloma to leukaemia only)

- ◯ Progressed disease confirmed
- ◯ Progressed disease suspected

Progressed from, *specify*

OTHER PATHOLOGY (Note 14)

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IMMUNOPROFILING/PHENOTYPING STUDIES (Note 15)

Immunohistochemistry

- ◯ Not performed
- ◯ Performed (select all that apply)
  - ☐ CD138
  - ☐ Kappa and lambda
    - ☐ In situ hybridisation
    - ☐ Immunohistochemistry
  - ☐ Other markers, *specify*

Flow cytometry

- ◯ Not performed
- ◯ Performed (select all that apply)
  - ☐ CD38
    - ◯ Positive ◯ Negative
  - ☐ CD45
    - ◯ Positive ◯ Negative
  - ☐ CD19
    - ◯ Positive ◯ Negative
  - ☐ CD56
    - ◯ Positive ◯ Negative
  - ☐ CD138
    - ◯ Positive ◯ Negative
  - ☐ Other (e.g., cyto kappa/lambda, CD27, CD81, CD200, CD319, BCMA), *specify test(s) and result(s)*

Performed on peripheral blood sample or other, *specify*

Minimal residual disease (MRD) testing

(Applicable to bone marrow only)

- ◯ Not performed
- ◯ Performed

Method (e.g., next generation sequencing (NGS), next generation flow (NGF)), *specify*

Time point, *specify*

- ◯ Negative
- ◯ Positive

%

Lower limit of detection (LLOD)

◯ 10^{-6} ◯ 10^{-5} ◯ 10^{-4}

Comments

MOLECULAR GENETIC STUDIES (Note 16)

- ◯ Not performed
- ◯ Performed (select all that apply)
  - ☐ FISH analysis (refer to Table 2)

◯ CD138 enriched plasma cells ◯ Not plasma cell enriched

- ☐ 14q32/*IGH* breakapart[a]

%

Number of positive/ total number of nuclei /

- ☐ 17p13/*TP53* deletion

%

Number of positive/ total number of nuclei /

- ☐ 1p/*CDKN2C* deletion

%

Number of positive/ total number of nuclei /

- ☐ 1q/*CKS1B* gain or amplification

%

Number of positive/ total number of nuclei /

- ☐ Other, *specify*

- ☐ Chromosomal analysis (karyotyping according to ISCN), *specify result(s)*
- ☐ NGS (*TP53*, *NRAS*, *BRAF* mutations according to HGVS), *specify result(s)*
- ☐ Other, *specify test(s) and result(s)*

Comments

Representative blocks for ancillary studies, *specify those blocks best representing tumour and/or normal tissue for further study*

[a] If 14q/*IGH* breakapart is positive, the following are to be done: t(4;14)(*NSD2*::*IGH*), t(14;16)(*MAF*::*IGH*), t(14;20)(*IGH*::*MAFB*), t(11;14)(*CCND1*::*IGH*).

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Definitions

CORE elements

CORE elements are those which are essential for the clinical management, staging or prognosis of the cancer. These elements will either have evidentiary support at Level P2 or higher (based on the Hierarchy of Research Evidence for Tumour Pathology[1]). In rare circumstances, where level P2 evidence is not available an element may be made a CORE element where there is unanimous agreement in the Dataset Authoring Committee (DAC).

Molecular and immunohistochemical testing is a growing feature of cancer reporting. However, in many parts of the world this type of testing is limited by the available resources. To encourage the global adoption of ancillary tests for patient benefit, International Collaboration on Cancer Reporting (ICCR) includes the most relevant ancillary testing in ICCR Datasets as CORE elements, especially when they are necessary for the diagnosis. Where the technical capability does not yet exist, laboratories may consider temporarily using these data elements as NON-CORE items.

The summation of all CORE elements is considered to be the minimum reporting standard for a specific cancer.

NON-CORE elements

NON-CORE elements are those which are unanimously agreed should be included in the dataset but are not supported by level P2 evidence. These elements may be clinically important and recommended as good practice but are not yet validated or regularly used in patient management.

Key information other than that which is essential for clinical management, staging or prognosis of the cancer such as macroscopic observations and interpretation, which are fundamental to the histological diagnosis and conclusion e.g., macroscopic tumour details, may be included as either CORE or NON-CORE elements by consensus of the DAC.

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Scope

This dataset section has been developed for the histologic, immunophenotypic, and genetic assessment and the integrated final diagnosis of plasma cell neoplasms (PCNs) involving bone marrow or extramedullary sites and related neoplasms such as heavy chain diseases or paraneoplastic syndromes as currently defined in the World Health Organization (WHO) Classification of Haematolymphoid Tumours, 5th edition, 2024.[2]

In development of this dataset, the DAC considered evidence up until June 2026.

The authors of this dataset can be accessed here.

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Note 1 – Clinical information (Core and Non-core)

Clinical information provides the context for morphological evaluation and can guide ancillary studies for diagnosis and risk stratification. Symptomatic myeloma patients show signs of organ damage such as hypercalcaemia, renal insufficiency, anaemia and bone lesions (CRAB).[3] They may also suffer from confusion, shortness of breath, bone fractures or recurrent infections. Laboratory values, especially the type and level of serum or urine paraprotein, serum free light chain (sFLC) levels and ratio, levels of serum Immunoglobulin A (IgA), Immunoglobulin G (IgG) and Immunoglobulin M (IgM), creatinine, Beta-2 microglobulin (B2M), and lactate dehydrogenase (LDH) provide additional clues for diagnosis and classification of PCN subtypes. In light chain only myeloma, light chain paraprotein (Bence Jones protein) is present in the urine, but the disorder may manifest in serum only as hypogammaglobulinemia or abnormal sFLC ratio. Immunoglobulin D (IgD) and Immunoglobulin E (IgE) myeloma may show abnormal light chain without associated heavy chain as most labs routinely test only IgA, IgG and IgM. Lytic or sclerotic bone lesions, with or without associated soft tissue mass, detected by imaging studies (bone scan and/or Positron Emission Tomography/Computed Tomography (PET-CT) further support the diagnosis of PCN. In the absence of CRAB, the following three biomarkers are also considered myeloma defining events: ≥60% of clonal plasma cells in bone marrow (from either aspirate or trephine); or sFLC ratio of involved to uninvolved ≥100 (involved sFLC must be ≥100 milligrams/litre); or more than one focal lesion (≥5 millimetres in size) on magnetic resonance imaging (MRI) imaging, the so-called SLiM criteria.[3] A history of immune deficiency may raise differential diagnosis of other plasmablastic neoplasms.[4]

Information regarding previous treatment defines the framework for designation of disease status – de novo (primary, newly diagnosed), persistent, relapsed or refractory. It also informs ancillary studies and provides a context for interpretation of results. For example, anti-CD38 immunotherapy (daratumumab or isatuximab) may affect interpretation of CD38 expression on plasma cells and causes spurious monoclonal κ light chain expression on hematogones. Chimeric Antigen Receptor T cell Therapy (CAR-T), Bispecific T cell Engager (BiTE) or Antibody Drug Conjugate (ADC) targeting surface antigens of myeloma cells or stem cell transplantation also affects the interpretation of immune profile of plasma cells and the background hematopoiesis (such as cytopenia related to CART or cytosis related to corticosteroid).

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Note 2 – Sampling procedure (Core)

The posterior superior iliac crest is the standard site for bone marrow biopsy specimens (not targeted), and specifying laterality (right or left) allows correlation with imaging, and for comparison across different time points. For extramedullary involvement, specific procedures, such as excisional, CT or ultrasound guided needle core biopsy or aspiration of the body cavity fluid (spinal tap or thoracentesis) should be specified.

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Note 3 – Specimen(s) submitted (Core)

Bone marrow aspirate and trephine biopsy (core) are complementary and should be obtained whenever feasible. Plasma cell enumeration is usually higher on the trephine biopsy but not always. Aspirate smears or touch imprints of the biopsy specimen allow better assessment of cytological details, such as the degree of maturation or anaplasia as well as background hematopoiesis. Trephine or clotted aspirate materials (clot section) allow assessment of overall cellularity, topographical distribution and extent of the neoplastic infiltrate, stromal components including fibrosis, bone changes (increased osteoclasts or osteoblasts or osteosclerosis), vasculature and amyloid deposition. Extramedullary specimens are specified in **Note 5 – TUMOUR SITE**.

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Note 4 – Sample adequacy (Core)

Adequate and representative sampling is a prerequisite for accurate diagnosis and classification. Adequacy of sampling is determined by an overall assessment of cellularity and typically depends on the length and integrity of the core biopsy and the number of cellular spicules in the aspirate smears and/or touch imprints. Thick smears or suboptimal staining can affect reading. While subcortical biopsy or those with marked aspiration or distortion artifacts can be misleading. Non-diagnostic samples for morphological or ancillary studies are deemed inadequate, while samples with evaluable elements but that are not entirely satisfactory are considered suboptimal. Examples of suboptimal samples include hemodiluted or pauci-cellular aspirates. For samples to be submitted for minimal residual disease studies, the first draw is recommended.

Heparin is recommended as an anticoagulant for chromosomal analysis and fluorescence in situ hybridization (FISH) whereas EDTA is used for molecular studies. Either EDTA or Heparin can be used for flow cytometry. Decalcification with EDTA protects the integrity of nucleic acid and is preferred over acid decalcification for purpose of potential genetic studies. Non-decalcified clot sections can substitute for an aspirate specimen when the latter is unavailable or unsatisfactory.

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Note 5 – Tumour site (Core)

Bone marrow and peripheral blood are the primary sites of involvement in most PCNs. Extramedullary diseases at presentation or primary plasma cell leukaemia should be distinguished from extramedullary spread of myeloma that is usually associated with relapsed or refractory myeloma. Extension of bone lesion to soft tissue at the site of destructive bone lesion or distal spread to lymph nodes, liver, or skin should also be specified. Solitary plasmacytoma of bone is genetically distinct from extraosseous plasmacytoma and behaves differentially. Percentage of circulating plasma cells in the peripheral blood (≥5%) defines plasma cell leukaemia.

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Note 6 – Overall bone marrow cellularity (Core)

Estimated from the bone marrow trephine biopsy specimen or intact areas of the clot section, the overall cellularity provides a gross estimate of the background hematopoiesis and is the denominator for tumour burden assessment. Marrow cellularity can be designated as hypercellular, normocellular, or hypocellular relative to the expected range for the patient's age. Focal variation in cellularity should be interpreted in the context of biopsy adequacy, sampling site, and concurrent aspirate findings. In aspirate smears, the relative cellular composition is expected to correlate with the trephine biopsy. Discrepancy between aspirate and core biopsy cellularity may reflect hemodilution, patchy involvement, or sampling artifact.

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Note 7 – Extent of plasma cell infiltrate in the bone marrow (Core)

Accurate enumeration of plasma cells is critical for classification, risk stratification and clinical management. For bone marrow aspirate smears or touch imprints, a minimum of 300 cells in the trails from at least four representative bone marrow particles should be assessed.[5] For estimation on biopsy or clot section, immunostaining for CD138 is usually required (see below).

When there is a discordance in the percentage of plasma cells between trephine versus clot or aspirate smears versus touch imprint, report the highest reading from an adequate sample and provide the range.

It is optional to report the total volume of tumour infiltrate (such as tumour collectively replacing certain percentage of marrow space).

Automatic imaging or other artificial intelligence (AI) software facilitated quantification should be noted if employed.

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Note 8 – Growth pattern (Core)

The pattern of infiltration can be scattered, clustered, macronodular (mass forming) or diffuse/obliterative.[6] Early and indolent diseases are characterised by interstitial or small clusters of tumour cells. As the disease evolves, the neoplastic cells become confluent or obliterate the medullary cavity. The macronodular pattern is characterised by a distinct tumour mass without being accompanied by a significant interstitial infiltrate in the remaining marrow space. It correlates with a mass-like lesion on imaging studies and has prognostic implications.[7] As border between MGUS and smoldering myeloma can be indistinct and the risk of progression for smoldering myeloma spreads over a spectrum, the pattern of infiltrate provides additional clues to the growth potential and disease status. The subcortical areas may harbour tumour cells in post therapy samples.

Cytological grading is optional, two tiers (plasmablastic/anaplastic versus non-plasmablastic) or three tiers (low, moderate or high grade cytology) can be used.[6] Plasmablastic/anaplastic myeloma is clinically aggressive and associated with complex genetic aberrations. The so-called lymphoplasmacytoid (small cell) variant, sometimes

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associated with IgM paraprotein, should be distinguished from lymphoplasmacytic lymphoma/Waldenstrom macroglobulinemia (LPL/WM) and other small B cell lymphomas with plasma cell differentiation.

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Note 9 – Congo red stain (Non-core)

While Congo red stain with appropriate birefringence demonstrates amyloid deposition, mass spectrometry-based proteomics is the reference method for typing the amyloid. It is the gold standard for confirming primary amyloidosis (AL amyloidosis). Immunostaining or electron microscopy can also be performed if mass spectrometry is not available.[8]

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Note 10 – Block identification key (Non-core)

It is recommended to specify those blocks best representing tumour and/or normal tissue. The origin/ designation of all tissue blocks should be recorded. This information should ideally be documented in the final pathology report and is particularly important should the need for internal or external review arise, in which case a subsequent reviewer would need to know the anatomic sites from which samples were taken for proper assessment and staging purposes. If this information is not included in the final pathology report, it should be available on the laboratory computer system and relayed to the reviewing pathologist. It may be useful to have a digital image of the specimen and record of the origin of the tumour blocks.

Recording the origin/designation of tissue blocks also facilitates retrieval of the appropriate blocks for further immunohistochemical, molecular or research studies.

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Note 11 – Final integrated diagnosis (Core and Non-core)

The final integrated diagnosis for PCNs follows the hierarchical diagnostic framework of the WHO Classification of Haematolymphoid Tumours, 5th edition, 2024 (Table 1).[2] Whenever possible, the diagnosis should be assigned to the most specific entity within the category, based on the available evidence, and further defined by subtype when indicated.

Table 1: 5th edition of the World Health Organization Classification of plasma cell neoplasms.[2]

Descriptor	ICD-O codes[a]
Monoclonal gammopathies	
Cold agglutinin disease	9760/1*
IgM monoclonal gammopathy of undetermined significance	9761/1
Non-IgM monoclonal gammopathy of undetermined significance†	9765/1

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Descriptor	ICD-O codes[a]
IgG monoclonal gammopathy of undetermined significance†	9765/1
IgA monoclonal gammopathy of undetermined significance†	9765/1
IgD monoclonal gammopathy of undetermined significance†	9765/1
IgE monoclonal gammopathy of undetermined significance†	9765/1
Light chain monoclonal gammopathy of undetermined significance†	9765/1
Monoclonal gammopathy of renal significance†	9765/1
Diseases with monoclonal immunoglobulin deposition	
Immunoglobulin-related amyloidosis (AL amyloidosis)†	9769/1
Systemic AL amyloidosis†	9769/1
Localised AL amyloidosis†	9769/1
Heavy chain AL amyloidosis†	9769/1
Monoclonal immunoglobulin deposition disease	9769/1
Light chain deposition disease†	9769/1
Light and heavy chain deposition disease†	9769/1
Heavy chain deposition disease	9762/3
Heavy chain diseases	
Mu heavy chain disease	9762/3
Gamma heavy chain disease	9762/3
Alpha heavy chain disease	9762/3
Plasma cell neoplasms	
Plasmacytoma	
Solitary plasmacytoma of bone	9731/3
Extramedullary plasmacytoma	9734/3
Plasma cell myeloma	9732/3
Smouldering (asymptomatic) myeloma†	9732/3
Non-secretory myeloma†	9732/3
Plasma cell leukaemia	9733/3
Plasma cell neoplasms with associated paraneoplastic syndrome (code as tumour type)	

[a] These morphology codes are from the International Classification of Diseases for Oncology, third edition, second revision (ICD-O-3.2).[9] Behaviour is coded /0 for benign tumours; /1 for unspecified, borderline, or uncertain behaviour: /2 for carcinoma in situ and grade lll intraepithelial neoplasia; /3 for malignant tumours, primary site; and /6 for malignant tumours, metastatic site. Behaviour code /6 is not generally used by cancer registries.

* Codes marked with an asterisk were approved by the World Health Organization/International Agency for Research on Cancer Committee for ICD-O at its meeting in September 2022, or during subsequent consultation.

† Labels marked with a dagger have undergone a change in terminology of a previous code.

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Of note, the heavy chain diseases, which are currently listed in the PCNs, are essentially lymphoid neoplasms that have paraprotein components. As such, the neoplasms may carry marked plasmacytic components mimicking PCNs. Diagnostic work up of these neoplasms should include both the plasma cell components as well as the lymphoid components. Please refer to the ICCR Lymphoid malignancies dataset for reporting guidelines.[10]

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Note 12 – Disease status (Non-core)

The disease status denotes de novo (primary, newly diagnosed), persistent, relapsed or refractory status.

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Note 13 – Disease progression status (Non-core)

This denotes progression of monoclonal gammopathy of unknown significance to smoldering or symptomatic myeloma or myeloma to plasma cell leukaemia if known.

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Note 14 – Other pathology (Non-core)

Concurrent pathology may include reactive or neoplastic myeloid or lymphoid conditions, such as mastocytosis or VEXAS syndrome, or therapy related changes, such as myelosuppression post therapy or therapy related myeloid neoplasms. Please refer to ICCR Myeloid neoplasms dataset for reporting guidelines.[11]

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Note 15 – Immunoprofiling/Phenotyping studies (Core and Non-core)

Immunoprofiling/phenotyping is essential to characterise the plasma cells. Immunohistochemistry is helpful for assessing tumour burden and growth pattern in the trephine biopsy and clot sections. Neoplastic plasma cells may resemble lymphoma cells or myeloid/erythroid elements on morphology. Essential markers of immunostaining include CD138 and kappa and lambda light chains. Either in situ hybridisation (ISH) or immunostaining (immunohistochemistry (IHC)) can be used for the cytoplasmic light chain assessment. ISH may be more sensitive in low or non-secretory cases. MUM1 can be used as a surrogate marker for plasma cells if CD138 is negative. Other markers such as CD20 and cyclinD1 can be positive in 20-30% of myeloma cases each.[12-18] Cyclin D1+ myeloma is frequently associated with lymphoplasmacytic morphology and increased expression of B cell markers, including CD20. IgM myeloma is often associated with CyclinD1 expression and t(11;14)*(CCND1*::*IGH)* (see below).

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Flow cytometry is useful for distinguishing normal or reactive plasma cells from their neoplastic counterparts which is achieved through light chain restriction pattern and aberrant surface antigen expression pattern.[12-18] It is particularly valuable in morphologically challenging cases, such as non-secretory or bi-clonal diseases or when neoplastic plasma cells represent only a small fraction of the total plasma cells. Additionally, it provides information on expression levels of antigens/proteins that can be used for targeted therapies. It is also a fast and sensitive method for monitoring treatment response and measurable residual disease (MRD). As progression from indolent to more symptomatic disease is characterised by expansion of the neoplastic fraction, the ratio of normal to abnormal plasma cells provides a window for risk assessment. Additionally, it may reveal the dynamics of post-transplant immune reconstitution.

Markers such as CD19, CD45, CD56, CD38 and CD138 are considered essential, while adding cytoplasmic kappa/lambda can further enhance sensitivity and specificity as needed.[19] Other markers such as CD27, CD54, CD81, CD117, CD200, CD229 and CD319 can be used if available to enhance sensitivity and specificity, especially in the post treatment setting.[19,20] In patients treated with anti-CD38 immunotherapy, such as daratumumab, CD38 may be assessed by flow cytometry using alternative anti- CD38 reagents such as CD38ME (multi-epitope) or JK36 (nanobody). Of note, JK36 should not be used in isatuximab treated patients as the binding site is blocked.[21] VS38c (p63) is another alternative marker for identification of plasma cells in the setting of anti-CD38 therapy.[22,23]

The immunophenotype of the abnormal populations, including the absence or presence of antigen expression, and the relative level of expression intensity should be noted.[24] A marker is considered positive when its expression is evaluated against an internal control and its intensity is determined by the direct comparison to the internal normal plasma cells. For example, CD38 is very bright in normal plasma cells, but its intensity may be relatively lower in neoplastic plasma cells. The expression level of CD19 and CD45 is weak in the vast majority of cases of PCNs compared to B cell lymphoid neoplasms with marked plasmacytic differentiation. CD56 is positive in neoplastic plasma cells in the majority of cases (60%-75%), and CD117 is expressed in up to one-third (20-32%) of these cases. CD56 can be expressed on a small subset of normal plasma cells, usually in a more heterogeneous pattern, while CD117 is usually negative.[22,23] Hence, assessment of the overall expression profile is essential. CD56 and CD117 are both typically negative on plasma cells associated with lymphoma.[25]

B-cell maturation antigen (BCMA) is currently a commonly used target of immunotherapy and can be assessed by either IHC or flow cytometry. It may also be used as a surrogate marker for plasma cells. GPRC5D is also an emerging target that can be assessed by IHC or flow cytometry. Screening these markers immediately before the initiation of therapy or post therapy to inform therapy if available and indicated.

Assessment of circulating plasma cells by flow cytometry has been shown to have predictive and prognostic values. It may enhance additional risk assessment if available (optional).[19,22,26-29]

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Note 16 – Molecular genetic studies (Core and Non-core)

The most common genetic aberrations in PCNs include chromosomal translocations with a breakpoint in the *IGH* locus and hyperdiploidy. The core FISH panel is listed in Table 2. For initial work up, four probes for chromosome 1q21 (targeting the *CKS1B* gene locus), 1p32 (*CDKN2C*), 17p13 (*TP53*), and 14q32/*IGH* breakapart are required for screening. These probes are designed to capture high risk myelomas in the current myeloma risk

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stratification scheme defined by the International Myeloma Society/International Myeloma Working Group (IMS/IMWG).[30,31] Aberrations such as deletion of 1p32 (*CDKN2C*) or amplifications of 1q21 (*CKS1B*) are considered high risk when biallelic or present in combination with other adverse factor such as t(4;14)(*NSD2*::*IGH*). When *IGH* breakapart probe detects a translocation, further testing with a more expanded panel that includes t(4;14)(*NSD2*::*IGH*), t(14;16) (*IGH*::*MAF*), t(14;20) (*IGH*::*MAFB*) is recommended. The t(11;14)/(*IGH*::*CCND1*) can be performed upfront for identifying potential candidate patients of BCL2 inhibitor (venetoclax) therapy. Testing for translocations involving 8q24*/MYC* locus is optional. For relapsed disease, the FISH panel may include probes for 1q21 (*CKS1B*), 1p32 (*CDKN2C*), 17p13(*TP53*) and any aberrations detected before at initial work up.

Table 2: FISH panel for work up of plasma cell neoplasms

First tier (core):
14q32 (*IGH* breakapart) 17p13 (*TP53*) 1q21 (*CKS1B*) 1p32 (*CDKN2C*)
If *IGH* breakapart positive, reflex testing the following:
t(4;14)(p16;q32) *IGH*::*NSD2* t(11;14)(q13;q32) *IGH*::*CCND1* t(14;16)(q32;q23) *IGH*::*MAF* t(14;20)(q32;q11) *IGH*::*MAFB*

FISH testing should ideally be done on CD138 enriched samples to enhance sensitivity and to better estimate the size of subclones such as *TP53*, as currently cut-off for high-risk myeloma is 20% of interphase nuclei according to IMS/IMWG. While chromosomal analysis is not required as only about one third of myeloma cases show detectable aberrations, it can provide a global genetic landscape when informative and a complex karyotype is correlated with high-risk disease. Other less commonly used techniques such as optical genomic mapping should be specified if applied. Findings should be recorded according to The International System for Human Cytogenomic Nomenclature (ISCN) guidelines.[32]

Mutations of *KRAS, NRAS, BRAF* and *TP53* occur commonly in more advanced diseases.[33] Though molecular testing is not required, the current risk stratification lists *TP53* mutation at any variant allele frequency (VAF) as an adverse risk factor. Record variants according to Human Genome Variation Society (HGVS) guidelines.[34] Assessment of *MYD88* and *CXCR4* mutations contribute to the differential diagnosis of IgM myeloma and lymphoplasmacytic lymphoma. Techniques for molecular testing may include PCR-based assays, targeted gene panel by next-generation sequencing (NGS), targeted RNA sequencing, and other genomic technologies, based on laboratory capability and clinical context.

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