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NCCN Guidelines Panel: Multiple Myeloma-Relapse Indication

On behalf of Signal Genetics, Inc., I respectfully request the NCCN Multiple Myeloma Panel to review the enclosed data on the use of MyPRS® for patients with previously treated multiple myeloma (MM) at the time of relapse. MyPRS is a registered trademark of Signal Genetics, Inc.

Specific Changes:

The current Guidelines (Ver. 3-2016) provide guidance for "Follow-Up/ Surveillance" including "Bone marrow biopsy and aspirate as clinically indicated" (MYEL-4) as the only recommended cytogenetic or molecular risk assessment tools for relapsed patients. It is suggested that gene expression profiling using GEP-70 (MyPRS) be added to the laboratory evaluation "… if clinically indicated" at the time of relapse at the discretion of the treating physician (MYEL-4).

FDA Clearance:

MyPRS is a CLIA- and CAP-certified assay commercially available in the United States for which FDA Clearance is not required (1). It is also covered by Medicare at both initial diagnosis and relapse as stipulated in Coverage Decision L34796 (Novitas Solutions, Inc.) with an effective date of October 1, 2015.

Rationale: Supportive data can be found in several key citations. The MyPRS genomic assay was initially developed at the University of Arkansas Center for Medical Sciences (UAMS) by Drs. Bart Barlogie, John Shaughnessy and co-workers (2). These clinical scientists are also the authors of the chapter on "Multiple Myeloma" in Williams Textbook of Hematology (8th edition, McGraw Hill Medical, New York, 2011).

While changes in cytogenetics at the time of relapse are unusual, changes in MyPRS risk scores are well documented and can significantly impact survival (3). Patients who were "High Risk" at initial diagnosis and retain this classification at relapse will do poorly with a median survival of < 6 mos. highlighting an aggressive clinical phenotype which "… might be considered for early administration of experimental programs". Further, while only 13% of patients are "High Risk" at initial diagnosis, 76% are "High Risk" at the time of relapse. As the median post-relapse survival of patients with low/low, low/high and high/high MyPRS risk scores at initial diagnosis and relapse differ significantly with values of 6 mos., 14 mos. and NR at 48 mos., respectively, individual patient risk scores should be considered in determining the aggressiveness of their treatment and stratification in clinical trials. "A practical method to identify such patients should notably improve patient care" (4) and likely explains the inclusion of GEP in the relapse evaluation of patients in the Mayo Clinic mSMART Guidelines (5). Further, these same authors have demonstrated that amplification of chromosome "… 1q21 is associated with both disease progression and poor prognosis" and have indicated that a majority of relapsed patients (i.e. 72% vs. 43% at initial diagnosis by FISH, p=0.002) have this phenotype (6).

The clinical utility of knowing the MyPRS risk score and the myeloma disease subtype at the time of relapse accrues from the number of treatment options already given versus those still available and their differing indications and toxicity. As examples, the APEX and SUMMIT trials demonstrated that higher risk patients with del(13) had a "poorer prognosis" which "… may be overcome" by including bortezomib in their chemotherapy regimen (7). The risk score of the GEP-70 profile would be adversely affected by persistence of del(13) at the time of relapse providing a more current determination than one obtained at initial diagnosis (8). Treatment outcomes of patients with high-risk cytogenetics {i.e. del 17p, t(4;14) or t(14;16)} are also "partially overcome … in heavily pre-treated patients" by the addition of carfilzomib to relapse regimens (9), a point well demonstrated by the recently published ASPIRE trial results (10). Given the safety profile of carfilzomib (and other newer agents), titrating its use with prognosis at the time of relapse seems a prudent course of action (11).

References:

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3. Shaughnessy JD et. al., A validated gene expression model of high-risk multiple myeloma is defined by deregulated expression of genes mapping to chromosome 1. Blood 109: 2276-2284, 2007.
4. Zhan F et. al., High-risk myeloma: a gene expression-based risk stratification model for newly diagnosed multiple myeloma treated with high-dose therapy is predictive of outcome in relapsed disease treated with single-agent bortezomib or high-dose dexamethasone. Blood 111: 968-969, 2008.
5. Mikhael JR et. al., Management of newly diagnosed symptomatic multiple myeloma: updated Mayo Stratification of Myeloma and Risk-Adapted Therapy (mSMART) consensus guidelines 2013. Mayo Clin Proc 88: 360-376, 2013.
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7. Jagannath S et. al., Bortezomib appears to overcome the poor prognosis conferred by chromosome 13 deletion in phase 2 and 3 trials. Leukemia 21: 151-157, 2007.
8. Zhou Y et. al., Prediction of cytogenetic abnormalities with gene expression profiles. Blood 119: e148-e150, 2012.
9. Jakubowiak AJ et. al., Treatment outcomes in patients with relapsed and refractory multiple myeloma and high-risk cytogenetics receiving single agent carfilzomib in the PX-171-003-A1 Study. Leukemia 27: 2351-2356, 2013.
10. Stewart AK et. al, Carfilzomib, Lenalidomide and Dexamethasone for Relapsed Multiple Myeloma, N Engl J Med 372: 142-152, 2015.
11. Siegel D et. al., Integrated safety profile of single-agent carfilzomib: experience from 526 patients enrolled in 4 phase II clinical studies. Haematologica 98: 1753-1761, 2013.

The following enclosures are submitted in support of the above proposed changes:

Yours Sincerely,

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