An mRNA-based predictor of response to Daratumumab in Multiple Myeloma

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Abstract:
The purpose of this study was to develop a predictor of response to treatment with Daratumumab in multiple myeloma. Daratumumab has considerably improved the prognosis of myeloma, however, the treatment is expensive and not all myeloma patients benefit from the treatment. Therefore, a predictor of Daratumumab response would allow to focus on treating patients with high likelihood of responding, and avoid treating those, who are unlikely to respond.

Daratmumab is a monoclonal antibody that binds to CD38, causing apoptosis via antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC). ADCC requires the presence of natural killer cells, and can be measured in vitro with a calcein release assay using multiple myeloma cell lines in the presence of natural killer cells. Measuring the baseline gene expression in the cell lines makes it possible to identify mechanisms of resistance or sensitivity to daratumumab induced ADCC in vitro.

We used published data of lysis of 19 multiple myeloma cell lines and B-cell non-Hodgkin lymphoma cell lines in the presence of daratumumab and natural killer cells from peripheral blood mononuclear cells. Correlating the sensitivity to ADCC to the baseline gene expression of these cell lines, we identified 27 genes correlates to sensitivity and 26 genes correlated to resistance. Among these are genes previously associated with sensitivity to Daratumumab, glucocorticoid response, the proteasome, natural killer cell resistance, nuclear transport, myeloma risk classification, and myeloma cancer drivers.

The 53 genes constitute a drug response predictor (DRP), and a single score of predicted sensitivity to daratumumab can be calculated as the difference between the mean of the positively correlated genes and the mean of the negatively correlated genes.

We used published single-cell RNAseq data from the KYDAR trial of multiple myeloma patients treated with daratumumab, carfilzomib, lenalidomide and dexamethasone, to test the 53 gene DRP on clinical samples. The KYDAR trial enrolled 41 newly diagnosed MM patients, who either failed to respond or experienced early relapse after a bortezomib-containing induction regimen. Baseline single-cell RNA sequencing data and overall response information was availbale for 17 subjects. The overall response to treatment correlated with the DRP score: Pearson correlation coefficient 0.26 (95% CI 0.15 - 0.83). A cutoff can be applied to separate all 10 responding patients from 4 out of 7 nonresponding patients.

These results provide proof-of-concept of an mRNA-based predictor of response in multiple myeloma that warrants further clinical validation in multiple myeloma. When combined with our previously published response signatures for most other treatments used in myeloma, a map of predicted sensitivities can be provided for each patient based on a bone marrow sample.

Table 1. Processes represented in the 53-gene DRP. Resistance genes are shown in italics.

Process	DRP genes
Daratumumab response	TAGLN2 SEL1L3 *CCND1 PDIA4 TMEM2 CAV1*
Glucocorticoid response	NR3C1 TXNIP *CCND1 TMEM2*
Proteasome (bortezomib etc)	PSMB10 ARHGEF2 STAT6 EVI2B *PSMC3IP NUP88*
IMiD response (lenalidomide etc)	EVI2B *CCL20 KPNB1 TMEM2 CAV1*
Selinexor resp	*SF3B1 KPNB1*
Multidrug resistance	MCCC2
NK cell resistance	TRIB2
Nuclear transport	NUP88 *KPNB1*
Myeloma risk profiles	TAGLN2
Cancer drivers	TXNIP SP110 SP140 *CCND1 SF3B1*

Clinical testing in KYDAR cohort: We used published single-cell RNAseq data from the KYDAR[3] trial of multiple myeloma patients treated with daratumumab, carfilzomib, lenalidomide and dexamethasone, to test the 53 gene DRP on clinical samples. The KYDAR trial enrolled 41 newly diagnosed MM patients, who either failed to respond or experienced early relapse after a bortezomib-containing induction regimen. Baseline single-cell RNA sequencing data and overall response information was available for 17 subjects. The overall response to treatment correlated with the DRP score (Figure 1): Pearson correlation coefficient 0.26 (95% CI 0.15 - 0.83). A cutoff can be applied to separate all 10 responding patients from 4 out of 7 nonresponding patients. DRPs for carfilzomib. lenalidomide, and dexamethasone were tested as well but did not predict response to the combination therapy.

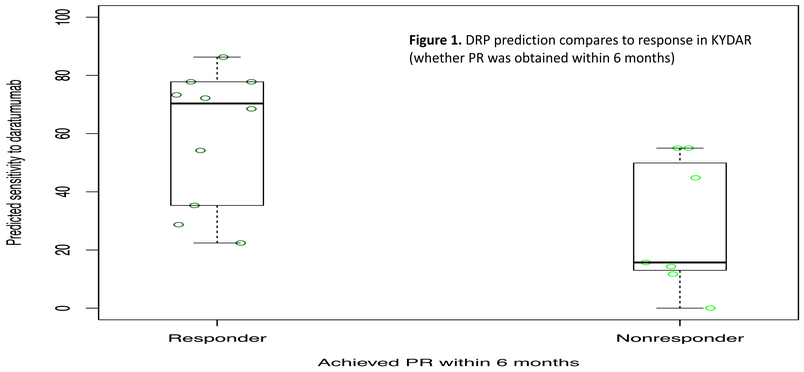

Figure 1. DRP prediction compares to response in KYDAR (whether PR was obtained within 6 months)

Conclusions

These results provide proof-of-concept for an mRNA-based predictor of response to daratumumab in multiple myeloma that warrants further clinical validation in multiple myeloma.

References

1. Michel de Weers et al (2011) Daratumumab, a Novel Therapeutic Human CD38 Monoclonal Antibody, Induces Killing of Multiple Myeloma and Other Hematological Tumors. J Immunol (2011) 186 (3): 1840–1848.
2. Anna Vidal-Crespo et al (2019) Daratumumab displays in vitro and in vivo anti-tumor activity in models of B-cell non-Hodgkin lymphoma and improves responses to standard chemo-immunotherapy regimens. Haematologica. 2019 Jul 11;105(4):1032–1041
3. Yael C. Cohen et al (2021) Identification of resistance pathways and therapeutic targets in relapsed multiple myeloma patients through single-cell sequencing. Nat Med. 2021 March 01; 27(3): 491–503. doi:10.1038/s41591-021-01232-w
4. Multiple Myeloma Research Foundation (MMRF) CoMMpass longitudinal study. NCT01454297

Clinical testing in MMRF-CoMMpass[4] 28 low risk (ISS I and II) myeloma subjects that received daratumumab were compared to 57 low risk myeloma subjects receiving other treatment than daratumumab. The DRP for Daratumumab applied to RNA-seq data from CD138+ bone marrow samples divided the subjects into those predicted sensitive to daratumumab and those not predicted sensitive. In the daratumumab treated subjects, the hazard ratio between predicted sensitive and not sensitive was <0.1 (P=0.04, see Figure 2), meaning that the DRP identifies a group of low risk subjects not benefitting as much from daratumumab. In the subjects not treated with daratumumab, the hazard ratio between predicted sensitive and not sensitive was 4.1 (95% CI 0.48-35, Figure 3). This confirms that the DRP is specific for Daratumumab and not prognostic.

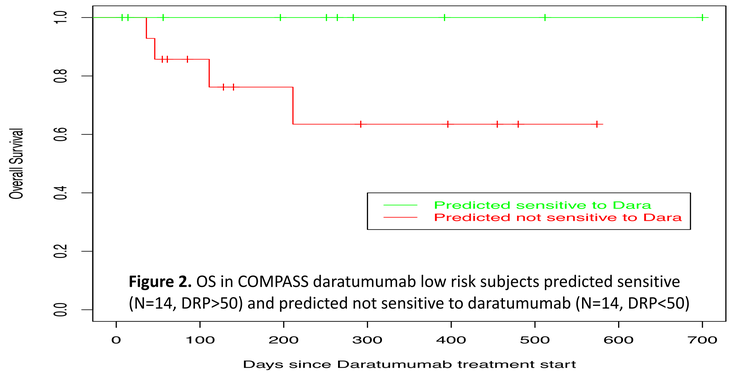

Figure 2. OS in COMPASS daratumumab low risk subjects predicted sensitive (N=14, DRP>50) and predicted not sensitive to daratumumab (N=14, DRP<50)

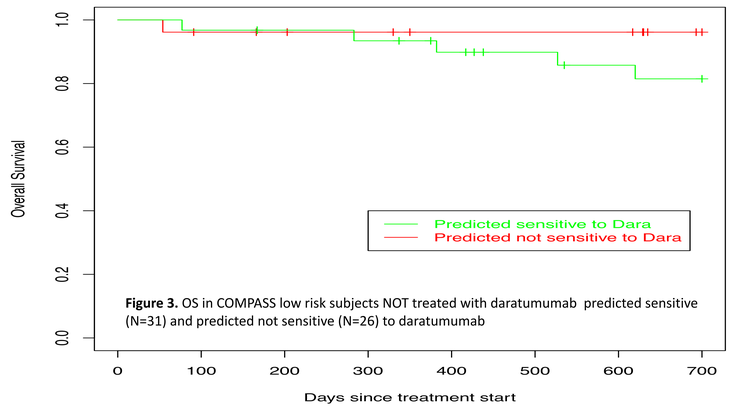

Figure 3. OS in COMPASS low risk subjects NOT treated with daratumumab predicted sensitive (N=31) and predicted not sensitive (N=26) to daratumumab

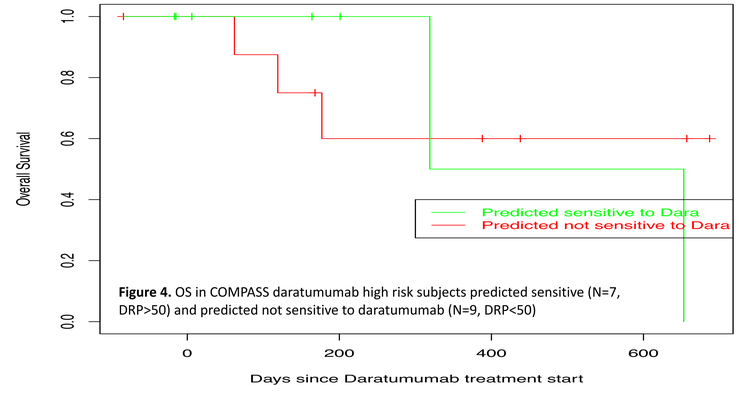

Figure 4. OS in COMPASS daratumumab high risk subjects predicted sensitive (N=7, DRP>50) and predicted not sensitive to daratumumab (N=9, DRP<50)