

Supplementary Figures

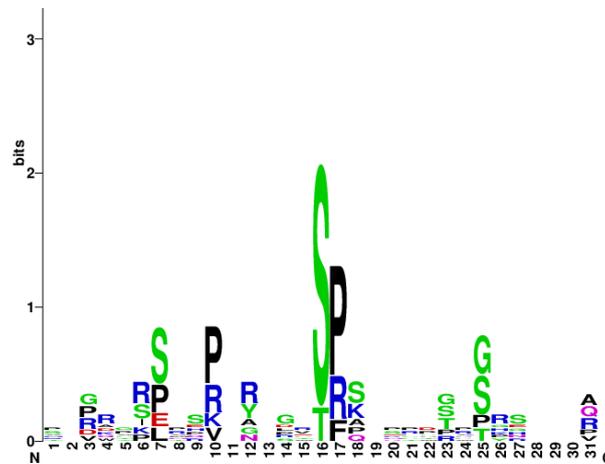


Figure S1. Sequence logo analysis of the 31 amino acid sequence windows surrounding the phosphorylation sites (located on position 16 on the x-axis) of the splicing factor network of Reactome pathway I showed in Figure 3c of the main text

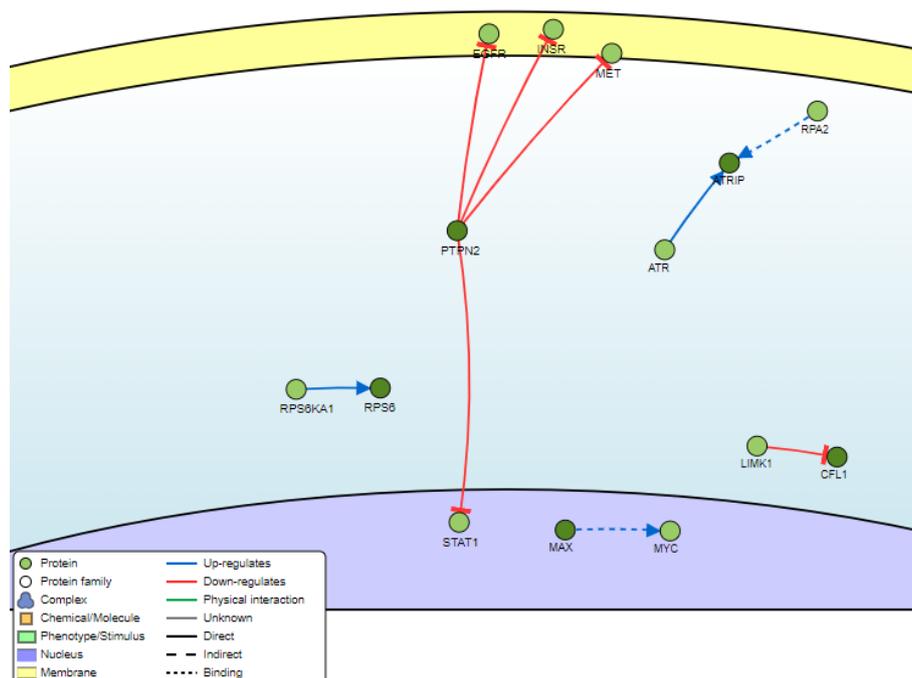


Figure S2. The analysis of the interactions of five differentially phosphorylated proteins from the PRE-R *vs* PRE-NR phosphoproteomic dataset (dark green circles) with signaling molecules from the SIGNOR database

Nodes and types of relationships are displayed as indicated at the bottom part of the design created by SIGNOR [53].

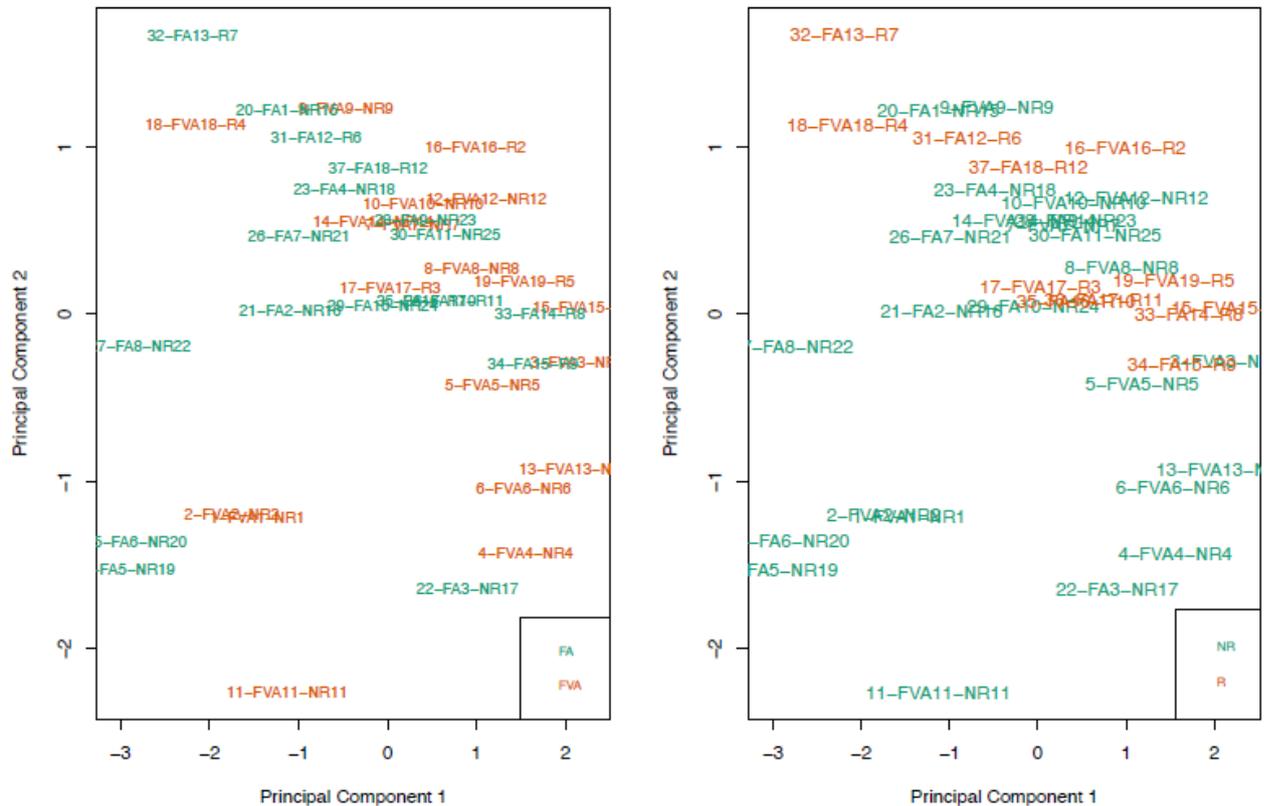


Figure S4. DNA methylation study of 12 PRE-R vs 25 PRE-NR patient samples before treatment

Principal component analysis plots of M values ($M = \log(\text{Meth}/\text{Unmeth})$ calculated with the getM function from the minfi package). The top 1000 probes were used to calculate the pairwise distances to create the plots. The dataset was normalized with functional normalization and SNPs; cross-hybridizing probes and XY chromosome associated probes were filtered.

The left plot is colored by treatment (ATRA-VP-AraC, FVA in the plot annotations, in orange; ATRA-VP-TP, FA in the plot annotations, in green) while the right plot is colored by response (responders, R in the plot annotations, in orange; non-responders, NR in the plot annotations, in green). Fifteen out of the 25 PRE-NR and nine out of the 12 PRE-R patients were part of the MS-based proteomics and phosphoproteomics analyses presented in this study. The rest of the patients belonged to an external patient cohort.

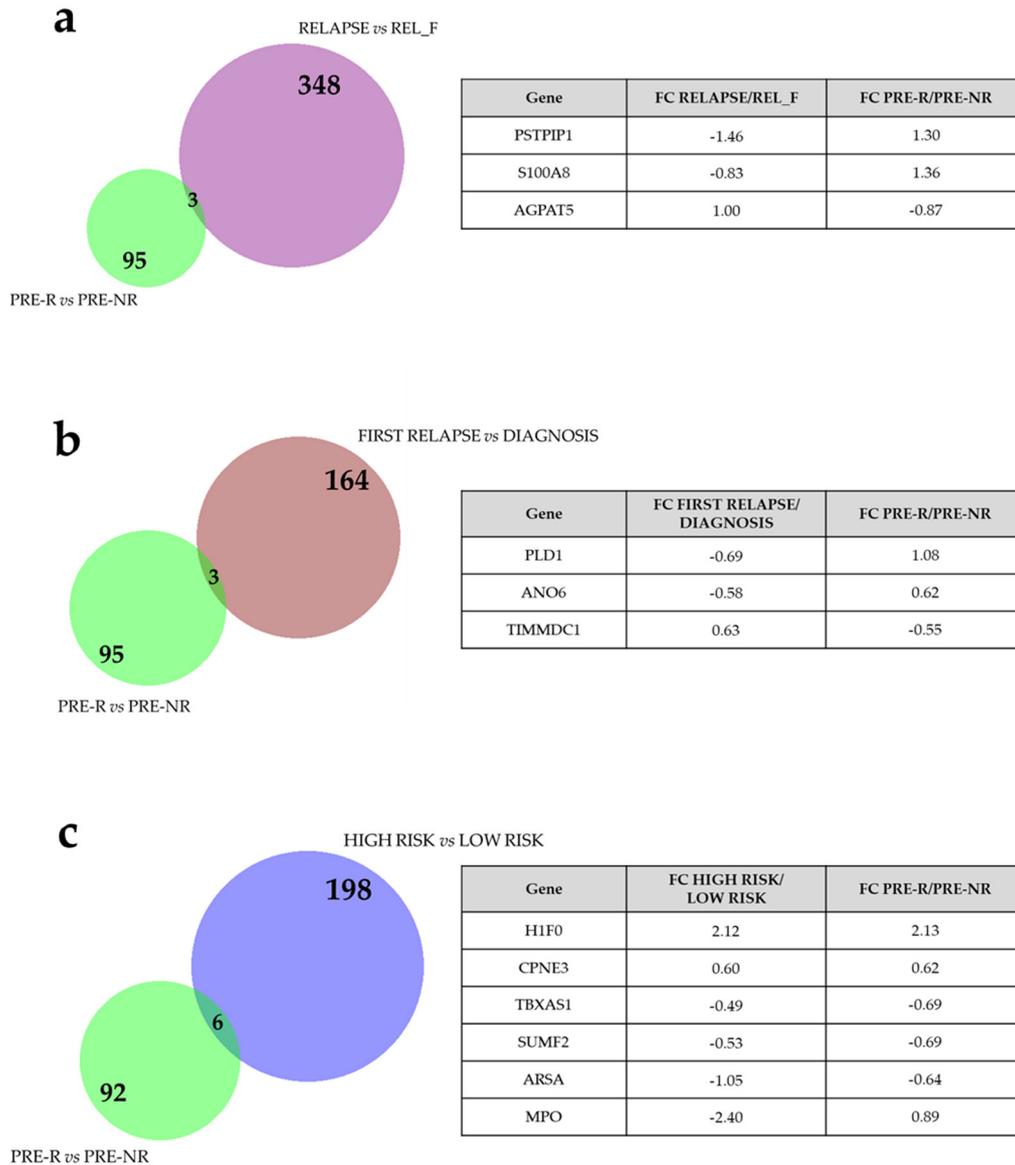
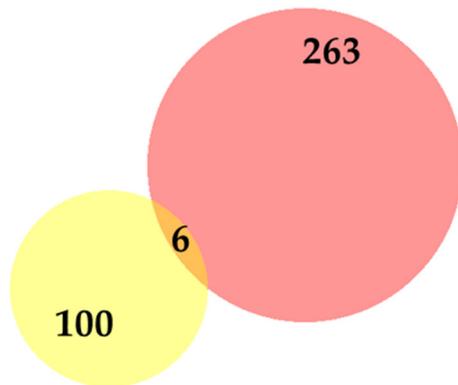
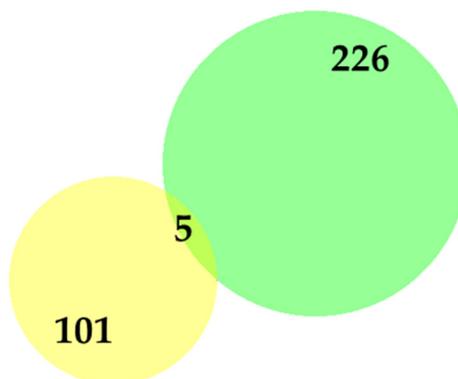


Figure S5. Overlap of regulated proteins from the current PRE-R *vs* PRE-NR study with those identified in previously published MS-based proteomics studies

- (a) Venn diagram of significantly regulated proteins identified in the current PRE-R *vs* PRE-NR and the published relapse *vs* relapse-free study [26]
 - (b) Venn diagram of significantly regulated proteins identified in the current PRE-R *vs* PRE-NR and the published first relapse *vs* first diagnosis study [71]
 - (c) Venn diagram of significantly regulated proteins identified in the current PRE-R *vs* PRE-NR and the published high-risk *vs* low-risk study [90]
- (FC stands for expression fold change)

aRELAPSE *vs* REL_F

| Phosphosite | FC RELAPSE/ REL_F | FC PRE-R/ PRE-NR |
|--------------|----------------------|---------------------|
| NPM1_S125 | 1.21 | 0.91 |
| ZNF22_S42 | 0.85 | -0.63 |
| GFPT1_S243 | -0.81 | 1.15 |
| FAM134C_S320 | 0.62 | -0.71 |
| MAP7D3_S185 | 0.69 | -0.76 |
| DNAJC5_S10 | -1.17 | 0.95 |

PRE-R *vs* PRE-NR**b**HIGH RISK *vs* LOW RISK

| Phosphosite | FC HIGH RISK/ LOW RISK | FC PRE-R/ PRE-NR |
|-------------|---------------------------|---------------------|
| STMN1_S16 | 0.74 | 1.61 |
| ACIN1_S478 | 0.64 | 1.17 |
| TMPO_T160 | -0.86 | 1.25 |
| TMPO_S156 | -1.15 | 1.03 |
| TMPO_S159 | -1.17 | 1.25 |

PRE-R *vs* PRE-NR

Figure S6. Overlap of differentially regulated phosphorylation sites from the current PRE-R *vs* PRE-NR study with those identified in previously published MS-based phosphoproteomics studies

(a) Venn diagram of significantly regulated phosphorylation sites identified in the current PRE-R *vs* PRE-NR and the published relapse *vs* relapse-free study [26]

(b) Venn diagram of significantly regulated phosphorylation sites identified in the current PRE-R *vs* PRE-NR and the published high-risk *vs* low-risk study [90]

(None phosphosite was found overlapped between the current PRE-R *vs* PRE-NR and the published first relapse *vs* first diagnosis study [71])

(FC stands for phosphorylation fold change)

Supplementary Tables

Table S1. Proteomic differences between AML patients when comparing AML cells derived from responders *vs* non-responders to antileukemic treatment based on ATRA and VP

A description of differentially expressed proteins included in the neutrophil degranulation Reactome pathway of Figure 2c in the main text. The table presents the protein identity (gene name), a brief description of the protein functionality and keywords with regard to structure/function of the protein. The table is based on information from the Gene database and selected publications included in the PubMed database. Blue-colored cell indicates that the protein level was increased in non-responders; the other proteins showed increased levels in responders.

| Protein (Gene ID) | Comment | Keywords |
|------------------------------|---|---|
| <i>ANO6</i> | Anoctamin 6. This encoded multi-pass transmembrane protein belongs to the anoctamin family. This protein is a part of a calcium-activated anion channel and is important for the calcium-dependent exposure of phosphatidylserine on the cell surface. The scrambling of phospholipid occurs in various biological systems, such as when blood platelets are activated, they expose phosphatidylserine. The protein is a regulator of sheddase activity, and its activity is regulated by the actin cytoskeleton. It also seems to be involved in regulation of apoptosis and cell growth, and these functions seem to be important in carcinogenesis. It can induce apoptosis through various mechanisms, and it is also involved in the regulation of exosomal release. The gene is expressed in many organs, including normal bone marrow and lymphoid organs [115–120] | Anion channel Sheddase Actin Proapoptotic Cancer |
| <i>ARSA</i> | Arylsulfatase A. Arylsulfatases are lysosomal enzymes that are important in cell metabolism. The encoded protein hydrolyzes cerebroside sulfate to cerebroside and sulfate. The gene is expressed in many organs, including normal bone marrow and lymphoid organs. Its expression is reduced in many malignancies, but the possible role of this decreased expression in carcinogenesis is not known [121] | Lysosome metabolism Carcinogenesis? |
| <i>CHI3L1</i> | Chitinase 3 like 1. Chitinases catalyze the hydrolysis of the glycopolymer. The glycoside hydrolase 18 family of chitinases includes eight human family members. This gene encodes a glycoprotein member of the glycosyl hydrolase 18 family. The protein lacks chitinase activity and is secreted by activated macrophages, chondrocytes, neutrophils and synovial cells. It is thought to play a role in the process of inflammation and tissue remodeling, possibly through the stimulation of cytokine release and thereby modulation of the cancer cell microenvironment. The expression is high in normal bone marrow but is lower in lymph nodes [122] | Secreted protein Myeloid cells Cytokine induction Carcinogenesis |
| <i>CPNE3</i> | Copine 3. Calcium-dependent membrane-binding proteins may regulate molecular events at the interface of the cell membrane and cytoplasm. This protein contains two type II C2 domains in the amino-terminus and an A domain-like sequence in the carboxy-terminus. The A domain mediates interactions between integrins and extracellular ligands. The gene is expressed in a wide range of organs including normal bone marrow, lymph nodes and spleen. High expression is associated with an adverse prognosis in human AML [123] | Adverse prognosis in AML Cell membrane Integrins |

| | | |
|--------------|--|--|
| <i>CSTB</i> | Cystatin B. This protein functions as an intracellular thiol protease inhibitor. The protein is able to form a dimer stabilized by noncovalent forces, inhibiting papain and cathepsins l, h and b. The protein is thought to play a role in protecting against the proteases leaking from lysosomes. The expression is low in most organs, including normal bone marrow and lymphoid organs. Observations in an animal model of AML suggest that this molecule is increased during IL6-induced AML cell differentiation that finally leads to growth inhibition and apoptosis [124] | Lysosome Myeloid differentiation AML differentiation? |
| <i>CTSG</i> | Cathepsin G. This protein is a member of the peptidase S1 protein family and is found in azurophil granules (i.e., specialized lysosomes) of neutrophils. The protein participates in connective tissue remodeling. The gene shows high expression in normal bone marrow; the expression is very low or undetectable in other organs. The molecule is regarded as a member of the local bone marrow renin-angiotensin system that has been regarded as an important part of the bone marrow microenvironment, a regulatory system of normal bone marrow stem cells and possibly also a contributor in leukemogenesis [125] | Neutrophil Myeloid differentiation Stem cell niche Peptidase Leukemogenesis? |
| <i>ELANE</i> | Elastase, neutrophil expressed. Elastases form a subfamily of serine proteases that hydrolyze many proteins, including elastase and collagen-IV. The encoded preproprotein is proteolytically processed to generate the active protease. Following activation, this protease hydrolyzes proteins within neutrophil azurophil granules (specialized lysosomes), as well as proteins of the extracellular matrix. Mutations in this gene are associated with cyclic neutropenia and severe congenital neutropenia; some of these mutations also seem to be associated with an increased risk of AML/MDS [126]. The gene shows high expression in normal bone marrow, the expression is very low or undetectable in other organs | Neutrophil Myeloid differentiation Lysosome Leukemogenesis Protease Elastin Collagen |
| <i>FGR</i> | FGR proto-oncogene, Src family tyrosine kinase. This encoded protein is a member of the Src family of protein tyrosine kinases (PTKs). It is involved in mediating protein-protein interactions with phosphotyrosine-containing and proline-rich motifs. The protein localizes to plasma membrane ruffles, and functions as a negative regulator of cell migration and adhesion triggered by the beta-2 integrin signal transduction pathway. Normal bone marrow shows higher expression than other organs. This kinase supports AML proliferation and is associated with chemoresistance and it enhances growth factor dependent AML cell proliferation. High expression of the wild type protein seems to contribute to oncogenic transformation in human AML, and selective inhibition of this kinase suppresses <i>in vitro</i> and <i>in vivo</i> AML cell proliferation [127–129] | Tyrosine kinase Integrin Leukemogenesis |
| <i>GCA</i> | Grancalcin. This calcium-binding protein is abundant in neutrophils and macrophages. In the absence of divalent cation, this protein localizes to the cytosolic fraction; with magnesium alone, it partitions with the granule fraction; and in the presence of magnesium and calcium, it associates with both the granule and membrane fractions. The gene is expressed in many different organs/tissues, but high expression is seen especially in normal bone marrow. The protein can modulate intracellular signaling through interactions with Toll-like receptors, it can mediate chemoresistance in chronic myeloid leukemia cells through activation of autophagy, and it may influence autophagy as well as exocytosis through its interactions with annexin 7 [130–132] | Myeloid differentiation Autophagy Lysosome Chemoresistance? |
| <i>HLA-B</i> | Major histocompatibility complex, class I, B. This HLA class I molecule is a heterodimer consisting of a heavy chain and a light chain (beta-2 microglobulin). The heavy chain is anchored in the membrane. Class I molecules play a central role in the immune system by presenting peptides derived from the endoplasmic | Immunoregulation Antileukemic immune regulation? |

| | | |
|-----------------|--|---|
| | reticulum lumen. They are expressed in nearly all cells. The HLA class I molecules may also be important for antileukemic immunoregulation and thereby influence the prognosis in AML [133,134] | |
| <i>LYZ</i> | Lysozyme. This gene encodes human lysozyme. Lysozyme is one of the antimicrobial agents found in human milk, and is also present in spleen, lung, kidney, white blood cells, plasma, saliva, and tears. Lysozyme is present in neutrophil and monocyte granules, and it can also be expressed in AML cells [135] | Lysosome AML |
| <i>MCEMP1</i> | Mast cell expressed membrane protein 1. This single-pass transmembrane protein is possibly involved in regulating mast cell differentiation. It shows high expression especially in normal bone marrow; its expression is lower in other organs. The molecule may also be expressed by other myeloid cells in certain biological contexts [136] | Mast cell differentiation? |
| <i>MOSPD2</i> | Motile sperm domain containing 2. The encoded protein is expressed by the endoplasmic reticulum and is important for the contact between endoplasmic reticulum and other organelles (e.g., endosomes, mitochondria, Golgi). It shows high expression in a wide range of tissues and is important for monocyte chemotaxis and activation [137–139] | Endoplasmic reticulum Monocyte differentiation? |
| <i>MPO</i> | Myeloperoxidase. The myeloperoxidase (MPO) protein is synthesized during myeloid differentiation and constitutes the major component of neutrophil azurophilic granules. The mature myeloperoxidase is a tetramer composed of 2 light chains and 2 heavy chains. This enzyme is expressed only in bone marrow/myeloid cells, including most AML cells. The fraction of myeloperoxidase-positive AML cells varies between patients and is associated with distinct gene mutation patterns; favorable cytogenetic abnormalities are associated with high levels and for the intermediate AML risk group high expression seems to be associated with a favorable prognosis [140,141] | Myeloid differentiation Favorable prognosis? |
| <i>PLD1</i> | Phospholipase D1. This gene encodes a phosphatidylcholine-specific phospholipase which catalyzes the hydrolysis of phosphatidylcholine in order to yield phosphatidic acid and choline. The enzyme may play a role in signal transduction and subcellular trafficking. Detectable expression is observed in several organs/tissues, including normal bone marrow. It localizes to secretory granules and lysosomes but can also be a regulator of p38 mediated signaling. The protein shows relatively high expression in human AML cells; this expression seems to be associated with differentiation, but low levels are also associated with an adverse prognosis [142–144] | Lysosome Secretory granules AML differentiation AML prognosis |
| <i>PRTN3</i> | Proteinase 3. The gene shows high expression only in bone marrow with no detectable expression in lymphoid organs. This molecule is a regulator of normal hematopoietic stem cells, it is associated with myeloid differentiation in human AML and has a prognostic impact in several solid tumors (pancreatic, breast and renal cancer) [145–149] | Myeloid differentiation Cancer prognosis Hematopoietic stem cells |
| <i>SERPINB1</i> | Serpin family B member 1. The protein is a member of the serpin family of proteinase inhibitors. It inhibits the neutrophil-derived proteinases neutrophil elastase, cathepsin G, and proteinase-3 and thus protects tissues from damage at inflammatory sites [150]. Detectable expression in several organs, high expression especially in normal bone marrow | Inhibits neutrophil proteases |

Table S2. Regulated proteins that have both phosphorylation and expression fold change (FC) in the PRE-R vs PRE-NR study

| Gene | Protein name | Uniprot accession number | Amino acid | Position | Phosphorylation FC PRE-R/PRE-NR | Expression FC PRE-R/PRE-NR |
|----------------|---|--------------------------|------------|----------|---------------------------------|----------------------------|
| <i>CARHSP1</i> | Calcium regulated heat stable protein 1 | Q9Y2V2 | S | 30 | 1.56 | 0.92 |
| <i>CARHSP1</i> | Calcium regulated heat stable protein 1 | Q9Y2V2 | S | 32 | 1.56 | 0.92 |
| <i>DNAJC5</i> | DnaJ heat shock protein family (Hsp40) member 5 | Q9H3Z4 | S | 10 | 0.95 | 0.46 |
| <i>BCL7C</i> | BAF chromatin remodeling complex subunit BCL7C | Q8WUZ0 | S | 126 | 0.80 | 0.51 |
| <i>MAP4</i> | Microtubule associated protein 4 | P27816 | S | 280 | -0.79 | -0.60 |
| <i>MAP4</i> | Microtubule associated protein 4 | P27816 | S | 825 | -1.33 | -0.60 |
| <i>PDLIM2</i> | PDZ and LIM domain 2 | Q96JY6 | S | 129 | -1.42 | -0.82 |
| <i>PDLIM2</i> | PDZ and LIM domain 2 | Q96JY6 | S | 124 | -1.61 | -0.82 |
| | | | | | $R = 0.992$ | |

Table S3. Pair-wised fold change (FC) of regulated protein expression in responder patients considering quantitative values at pre-treatment (PRE), day 3 (3D) and day 8 (8D) of the ATRA-VP-TP treatment

| PROTEOME OF RESPONDERS | | | | | |
|---------------------------------|-----------------|---|------------------|------------------|-----------------|
| Uniprot accession number | Gene | Protein name | FC 3D/PRE | FC 8D/PRE | FC 8D/3D |
| Q9H019-3 | <i>MTFR1L</i> | Mitochondrial fission regulator 1 like | 0.58 | | -0.66 |
| Q8IX01 | <i>SUGP2</i> | SURP and G-patch domain-containing 2 | 0.53 | | |
| Q9BR77-2 | <i>CCDC77</i> | Coiled-coil domain-containing 77 | 0.50 | | |
| P17026 | <i>ZNF22</i> | Zinc finger protein 22 | 0.42 | | |
| Q00534 | <i>CDK6</i> | Cyclin dependent kinase 6 | 0.39 | | |
| P55010 | <i>EIF5</i> | Eukaryotic translation initiation factor 5 | 0.33 | | |
| P26373 | <i>RPL13</i> | Ribosomal protein L13 | 0.33 | | |
| Q13144 | <i>EIF2B5</i> | Eukaryotic translation initiation factor 2B subunit epsilon | 0.32 | | |
| Q96AQ6 | <i>PBXIP1</i> | PBX homeobox interacting protein 1 | 0.29 | | |
| P11234 | <i>RALB</i> | Ras like proto-oncogene B | 0.29 | | |
| P51608-2 | <i>MECP2</i> | Methyl-CpG binding protein 2 | 0.28 | | |
| Q6UXN9 | <i>WDR82</i> | WD repeat domain 82 | -0.26 | -0.39 | |
| O75676-2 | <i>RPS6KA4</i> | Ribosomal protein S6 kinase A4 | -0.30 | | |
| Q9BYT8 | <i>NLN</i> | Neurolysin | -0.33 | | |
| O00560-2 | <i>SDCBP</i> | Syndecan binding protein | -0.39 | | |
| Q5MIZ7-3 | <i>PPP4R3B</i> | Protein phosphatase 4 regulatory subunit 3B | -0.45 | | |
| Q8N335 | <i>GPD1L</i> | Glycerol-3-phosphate dehydrogenase 1 like | -0.48 | | |
| P00915 | <i>CA1</i> | Carbonic anhydrase 1 | | 0.84 | |
| P49588 | <i>AARS1</i> | Alanyl-tRNA synthetase 1 | | 0.74 | |
| Q06203 | <i>PPAT</i> | Phosphoribosyl pyrophosphatase amidotransferase | | 0.59 | |
| P22732 | <i>SLC2A5</i> | Solute carrier family 2 member 5 | | 0.56 | |
| Q9Y3A5 | <i>SBDS</i> | SBDS ribosome maturation factor | | 0.56 | |
| Q13526 | <i>PIN1</i> | Peptidylprolyl cis/trans isomerase, NIMA-interacting 1 | | 0.55 | |
| O75312 | <i>ZPR1</i> | ZPR1 zinc protein | | 0.51 | 0.80 |
| Q8N0X7 | <i>SPART</i> | Spartin | | 0.50 | |
| P25815 | <i>S100P</i> | S100 calcium binding protein P | | 0.49 | |
| P48643 | <i>CCT5</i> | Chaperonin containing TCP1 subunit 5 | | 0.43 | |
| Q6PGP7 | <i>TTC37</i> | Tetratricopeptide repeat protein 37 | | 0.42 | |
| P22234 | <i>PAICS</i> | ; Phosphoribosylaminoimidazole carboxylase and phosphoribosylaminoimidazole-succinocarboxamide synthase | | 0.42 | |
| P41250 | <i>GARS1</i> | Glycyl-tRNA synthetase 1 | | 0.38 | |
| P46379-2 | <i>BAG6</i> | BAG cochaperone 6 | | 0.38 | |
| Q13442 | <i>PDAP1</i> | PDGFA associated protein 1 | | 0.37 | |
| O95139 | <i>NDUFB6</i> | NADH:ubiquinone oxidoreductase subunit B6 | | -0.34 | |
| Q93050-1 | <i>ATP6V0A1</i> | ATPase H ⁺ transporting V0 subunit a1 | | -0.35 | |
| P61421 | <i>ATP6V0D1</i> | ATPase H ⁺ transporting V0 subunit d1 | | -0.35 | |
| Q9HD20 | <i>ATP13A1</i> | ATPase 13A1 | | -0.35 | |
| Q9BSJ8 | <i>ESYT1</i> | Extended synaptotagmin 1 | | -0.35 | |
| Q96FV9 | <i>THOC1</i> | THO complex 1 | | -0.35 | |
| Q96DV4 | <i>MRPL38</i> | Mitochondrial ribosomal protein L38 | | -0.35 | |

| | | | | | |
|----------|----------------|---|--|-------|-------|
| Q9NQ50 | <i>MRPL40</i> | Mitochondrial ribosomal protein L4 | | -0.36 | |
| O15269 | <i>SPTLC1</i> | Serine palmitoyltransferase long chain base subunit 1 | | -0.36 | |
| P07099 | <i>EPHX1</i> | Epoxide hydrolase 1 | | -0.37 | |
| Q86Y39 | <i>NDUFA11</i> | NADH:ubiquinone oxidoreductase subunit A11 | | -0.38 | |
| P11279 | <i>LAMP1</i> | Lysosomal associated membrane protein 1 | | -0.38 | -0.55 |
| P30536 | <i>TSPO</i> | Translocator protein | | -0.39 | |
| Q4KMQ2-3 | <i>ANO6</i> | Anoctamin 6 | | -0.40 | |
| Q9HD45 | <i>TM9SF3</i> | Transmembrane 9 superfamily member 3 | | -0.40 | |
| P83111 | <i>LACTB</i> | Lactamase beta | | -0.41 | |
| P62873 | <i>GNB1</i> | G protein subunit beta 1 | | -0.42 | |
| Q7Z7H8 | <i>MRPL10</i> | Mitochondrial ribosomal protein L10 | | -0.42 | |
| P63218 | <i>GNG5</i> | G protein subunit gamma 5 | | -0.42 | |
| Q9BTD8-4 | <i>RBM42</i> | RNA binding motif protein 42 | | -0.43 | |
| Q9BWJ5 | <i>SF3B5</i> | Splicing factor 3b subunit 5 | | -0.44 | |
| Q9NVR2 | <i>INTS10</i> | Integrator complex subunit 10 | | -0.46 | |
| P0DOX5 | <i>IGHG1</i> | Immunoglobulin heavy constant gamma 1 | | -0.46 | |
| Q6IAN0 | <i>DHRS7B</i> | Dehydrogenase/reductase 7B | | -0.47 | |
| P60468 | <i>SEC61B</i> | SEC61 translocon subunit beta | | -0.55 | |
| Q96CU9-3 | <i>FOXRED1</i> | FAD dependent oxidoreductase domain-containing 1 | | -0.57 | |
| Q9H257 | <i>CARD9</i> | Caspase recruitment domain family member 9 | | -0.57 | |
| Q8NHQ9 | <i>DDX55</i> | DEAD-box helicase 55 | | -0.61 | |
| Q9NZK5 | <i>ADA2</i> | Adenosine deaminase 2 | | -0.77 | -0.57 |
| P80723 | <i>BASP1</i> | Brain abundant membrane attached signal protein 1 | | | 0.83 |
| P06493 | <i>CDK1</i> | Cyclin dependent kinase 1 | | | 0.81 |
| Q06210-2 | <i>GFPT1</i> | Glutamine--fructose-6-phosphate transaminase 1 | | | 0.81 |
| Q9BTE3-2 | <i>MCMBP</i> | Minichromosome maintenance complex-binding protein | | | 0.69 |
| P03915 | <i>MT-ND5</i> | Mitochondrially encoded NADH:ubiquinone oxidoreductase core subunit 5 | | | -0.57 |
| Q9UDW1 | <i>UQCR10</i> | Ubiquinol-cytochrome c reductase, complex III subunit X | | | -0.57 |
| Q86WV6 | <i>TMEM173</i> | Stimulator of interferon response cGAMP interactor 1 | | | -0.57 |
| P12694 | <i>BCKDHA</i> | Branched chain keto acid dehydrogenase E1 subunit alpha | | | -0.58 |
| P04439 | <i>HLA-A</i> | Major histocompatibility complex, class I, A | | | -0.59 |
| Q8IYJ3 | <i>SYTL1</i> | Synaptotagmin like 1 | | | -0.71 |
| P13284 | <i>IFI30</i> | IFI30 lysosomal thiol reductase | | | -1.36 |

Table S4. Pair-wised fold change (FC) of regulated protein expression in non-responder patients considering quantitative values at pre-treatment (PRE), day 3 (3D) and day 8 (8D) of the ATRA-VP-TP treatment

| PROTEOME OF NON-RESPONDERS | | | | | |
|----------------------------|----------------|--|-----------|-----------|----------|
| Uniprot accession number | Gene | Protein name | FC 3D/PRE | FC 8D/PRE | FC 8D/3D |
| O14519 | <i>CDK2AP1</i> | Cyclin dependent kinase 2-associated protein 1 | 0.48 | | |
| Q96C01 | <i>FAM136A</i> | Family sequence similarity 136 member A | 0.41 | | |
| Q9NVC6 | <i>MED17</i> | Mediator complex subunit 17 | 0.31 | 0.33 | |
| P28799 | <i>GRN</i> | Granulin precursor | 0.31 | 0.31 | |
| P40937 | <i>RFC5</i> | Replication factor C subunit 5 | 0.31 | 0.27 | |
| Q8ND56-2 | <i>LSM14A</i> | LSM14 mRNA processing body assembly factor | 0.25 | | |
| Q9NZK5 | <i>CECR1</i> | Adenosine deaminase 2 | -0.41 | | |
| P05109 | <i>S100A8</i> | S100 calcium binding protein A8 | -0.89 | | |
| P36222 | <i>CHI3L1</i> | Chitinase 3 like 1 | | 1.24 | |
| P22732 | <i>SLC2A5</i> | Solute carrier family 2 member 5 | | 0.84 | |
| P28907 | <i>CD38</i> | CD38 molecule | | 0.74 | |
| Q8IWZ8 | <i>SUGP1</i> | SURP and G-patch domain-containing 1 | | 0.66 | |
| Q6P6C2 | <i>ALKBH5</i> | Alkb homolog 5, RNA demethylase | | 0.63 | |
| Q99543 | <i>DNAJC2</i> | DnaJ heat shock protein family (Hsp40) member C2 | | 0.49 | |
| P21266 | <i>GSTM3</i> | Glutathione S-transferase mu 3 | | 0.47 | |
| Q9BRJ6 | <i>C7orf50</i> | Chromosome 7 open reading frame 50 | | 0.44 | |
| O14975 | <i>SLC27A2</i> | Solute carrier family 27 member 2 | | 0.44 | |
| Q9UI36-2 | <i>DACH1</i> | Dachshund family transcription factor 1 | | 0.44 | |
| Q9NX62 | <i>IMPAD1</i> | 3'(2'), 5'-biphosphate nucleotidase 2 | | 0.43 | |
| Q9UJX3 | <i>ANAPC7</i> | Anaphase promoting complex subunit 7 | | 0.42 | |
| Q13085 | <i>ACACA</i> | Acetyl-CoA carboxylase 1 alpha | | 0.41 | |
| P33992 | <i>MCM5</i> | Minichromosome maintenance complex component 5 | | 0.39 | |
| Q9Y5Q8-2 | <i>GTF3C5</i> | General transcription factor IIIC subunit 5 | | 0.39 | |
| O43148 | <i>RNMT</i> | RNA guanine-7 methyltransferase | | 0.37 | |
| P33991 | <i>MCM4</i> | Minichromosome maintenance complex component 4 | | 0.37 | |
| P49736 | <i>MCM2</i> | Minichromosome maintenance complex component 2 | | 0.37 | |
| Q01826 | <i>SATB1</i> | SATB homeobox 1 | | 0.36 | |
| P33993 | <i>MCM7</i> | Minichromosome maintenance complex component 7 | | 0.35 | |
| Q7Z5L9-2 | <i>IRF2BP2</i> | Interferon regulatory factor 2 binding protein 2 | | 0.34 | |
| P25205 | <i>MCM3</i> | Minichromosome maintenance complex component 3 | | 0.34 | |
| Q9Y3Q3 | <i>TMED3</i> | Transmembrane p24 trafficking protein 3 | | 0.33 | |
| Q14566 | <i>MCM6</i> | Minichromosome maintenance complex component 6 | | 0.32 | |
| Q96P11-2 | <i>NSUN5</i> | NOP2/Sun RNA methyltransferase 5 | | 0.31 | |
| Q15154 | <i>PCM1</i> | Pericentriolar material 1 | | 0.31 | |
| Q9NRX2 | <i>MRPL17</i> | Mitochondrial ribosomal protein L17 | | 0.31 | |
| P28340 | <i>POLD1</i> | DNA polymerase delta 1, catalytic subunit | | 0.28 | |
| P39748 | <i>FEN1</i> | Flap structure-specific endonuclease 1 | | 0.27 | |
| Q15005 | <i>SPCS2</i> | Signal peptidase complex subunit 2 | | 0.27 | |
| Q9UBU8-2 | <i>MORF4L1</i> | Mortality factor 4 like 1 | | 0.27 | |

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|-----------|-----------------|--|--|-------|-------|
| Q6ZMZ3-2 | <i>SYNE3</i> | Spectrin repeat containing nuclear envelope family member 3 | | -0.38 | |
| Q9UNH7 | <i>SNX6</i> | Sorting nexin 6 | | -0.39 | |
| P13489 | <i>RNH1</i> | Ribonuclease/angiogenin inhibitor 1 | | -0.40 | |
| O43586 | <i>PSTPIP1</i> | Proline-serine-threonine phosphatase-interacting protein 1 | | -0.40 | |
| P84243 | <i>H3F3A</i> | H3.3 histone A | | -0.40 | -0.39 |
| Q13045 | <i>FLII</i> | FLII actin remodeling protein | | -0.41 | |
| P49407-2 | <i>ARRB1</i> | Arrestin beta 1 | | -0.42 | |
| P0DMV9 | <i>HSPA1B</i> | Heat shock protein family A (Hsp70) member 1B | | -0.42 | |
| P11215 | <i>ITGAM</i> | Integrin subunit alpha M | | -0.46 | -0.44 |
| P16070-18 | <i>CD44</i> | CD44 molecule | | -0.51 | |
| Q13510 | <i>ASAH1</i> | N-acylsphingosine amidohydrolase 1 | | -0.55 | -0.34 |
| O15145 | <i>ARPC3</i> | Actin related protein 2/3 complex subunit 3 | | -0.55 | |
| P42331-4 | <i>ARHGAP25</i> | Rho GTPase activating protein 25 | | -0.55 | |
| P61626 | <i>LYZ</i> | Lysozyme | | -0.56 | |
| Q16644 | <i>MAPKAPK3</i> | MAP kinase activated protein kinase 3 | | -0.58 | |
| P12429 | <i>ANXA3</i> | Annexin A3 | | -0.63 | |
| P27707 | <i>DCK</i> | Deoxycytidine kinase | | -0.67 | |
| O75351 | <i>VPS4B</i> | Vacuolar protein sorting4 homolog B | | -0.67 | |
| Q7Z5R6 | <i>APBB1IP</i> | Amyloid beta precursor protein binding family B member 1 interacting protein | | -0.70 | |
| O95466-2 | <i>FMNL1</i> | Formin like 1 | | -0.73 | |
| Q9BRF8 | <i>CPPED1</i> | Calcineurin like phosphoesterase domain containing 1 | | -0.76 | |
| Q12882 | <i>DPYD</i> | Dihydropyrimidine dehydrogenase | | -0.81 | |
| P33241 | <i>LSP1</i> | Lymphocyte specific protein 1 | | -1.11 | |
| Q8N0X4 | <i>CLYBL</i> | Cytramalyl-CoA lyase | | | 0.40 |
| Q9NYV4-2 | <i>CDK12</i> | Cyclin dependent kinase 12 | | | 0.27 |
| Q9BQ61 | <i>TRIR</i> | Telomerase RNA component interacting RNase | | | -0.21 |
| Q9C005 | <i>DPY30</i> | Dpy-30 histone methyltransferase complex regulatory subunit | | | -0.22 |
| Q9Y6M1 | <i>IGF2BP2</i> | Insulin like growth factor 2 mRNA binding protein 2 | | | -0.23 |
| P63218 | <i>GNG5</i> | G protein subunit gamma 5 | | | -0.24 |
| Q14254 | <i>FLOT2</i> | Flotillin 2 | | | -0.25 |
| Q86Y39 | <i>NDUFA11</i> | NADH:ubiquinone oxidoreductase subunit A11 | | | -0.26 |
| Q9UH99 | <i>SUN2</i> | Sad1 and UNC84 domain containing 2 | | | -0.28 |
| Q14004 | <i>CDK13</i> | Cyclin dependent kinase 13 | | | -0.30 |
| P05107 | <i>ITGB2</i> | Integrin subunit beta 2 | | | -0.31 |
| Q15554 | <i>TERF2</i> | Telomeric repeat binding factor 2 | | | -0.31 |
| P32942 | <i>ICAM3</i> | Intercellular adhesion molecule 3 | | | -0.31 |
| Q8TBP6 | <i>SLC25A40</i> | Solute carrier family 25 member 40 | | | -0.46 |

Table S5. Pair-wised fold change (FC) of differentially regulated phosphorylation sites in responder patients considering quantitative values at pre-treatment (PRE), day 3 (3D) and day 8 (8D) of the ATRA-VP-TP treatment

| PHOSPHOPROTEOME OF RESPONDERS | | | | | |
|-------------------------------|--------------|--|-----------|-----------|----------|
| Uniprot accession number | Phosphosite | Phosphoprotein name | FC 3D/PRE | FC 8D/PRE | FC 8D/3D |
| Q8WWM7 | ATXN2L_S339 | Ataxin 2 like | 0.81 | | |
| Q16643 | DBN1_S142 | Drebrin 1 | 0.64 | | |
| Q8ND56-2 | LSM14A_S192 | LSM14 mRNA processing body assembly factor | -0.37 | | 0.54 |
| Q641Q2-2 | WASHC2A_S284 | WASH complex subunit 2A | -0.42 | | |
| Q9H501 | ESF1_S198 | ESF1 nucleolar pre-rRNA processing protein homolog | -0.43 | | |
| O15164-2 | TRIM24_S777 | Tripartite motif containing 24 | -0.44 | | |
| P62753 | RPS6_S240 | Ribosomal protein S6 | -0.44 | | |
| Q86WB0 | ZC3HC1_S344 | Zinc finger C3HC-type containing 1 | -0.45 | | |
| Q92576-2 | PHF3_S1837 | PHD finger protein 3 | -0.53 | | |
| Q9NQC3-5 | RTN4_S184 | Reticulon 4 | -0.53 | | |
| Q9UH99 | SUN2_S12 | Sad1 and UNC84 domain containing 2 | -0.54 | | |
| Q9Y580 | RBM7_S204 | RNA binding motif protein 7 | -0.57 | -0.44 | |
| Q9UKV3 | ACIN1_S240 | Apoptotic chromatin condensation inducer in the nucleus | -0.77 | | |
| Q9UKV3 | ACIN1_S243 | Apoptotic chromatin condensation inducer 1 | -0.77 | | |
| O43598 | DNPH1_S12 | 2'-deoxynucleoside 5'-phosphate N-hydrolase 1 | | 1.14 | |
| Q13459 | MYO9B_S1267 | Myosin-IXB | | 0.93 | |
| Q13459 | MYO9B_T1271 | Myosin-IXB | | 0.93 | |
| Q13459 | MYO9B_S1290 | Myosin-IXB | | 0.93 | |
| O14683 | TP53I11_S14 | Tumor protein p53 inducible protein 11 | | 0.74 | |
| Q15424-4 | SAFB_S601 | Scaffold attachment factor B | | 0.69 | |
| Q15424-4 | SAFB_S604 | Scaffold attachment factor B | | 0.69 | |
| P14317 | HCLS1_S275 | Hematopoietic cell-specific Lyn substrate 1 | | 0.69 | |
| P23588 | EIF4B_S406 | Eukaryotic translation initiation factor 4B | | 0.68 | |
| P23588 | EIF4B_S409 | Eukaryotic translation initiation factor 4B | | 0.68 | |
| Q6UN15 | FIP1L1_S500 | Factor interacting with PAPOLA and CPSF1 | | 0.64 | |
| Q7Z2W4 | ZC3HAV1_S275 | Zinc finger CCCH-type containing, antiviral 1 | | 0.58 | |
| P48634 | PRRC2A_S1089 | Proline rich coiled-coil 2A | | 0.56 | |
| P23588 | EIF4B_S406 | Eukaryotic translation initiation factor 4B | | 0.56 | |
| Q9UMZ2-5 | SYNRG_S1075 | Synergin gamma | | 0.55 | |
| Q9Y520-4 | PRRC2C_S878 | Proline rich coiled-coil 2A | | 0.54 | |
| Q86TB9-4 | PATL1_S177 | PAT1 homolog 1, processing body mRNA decay factor | | 0.50 | |
| Q66K74-2 | MAP1S_S631 | Microtubule associated protein 1S | | 0.48 | |
| Q6Y7W6 | GIGYF2_S236 | GRB10 interacting GYF protein 2 | | 0.46 | |
| Q04637-8 | EIF4G1_S1210 | Eukaryotic translation initiation factor 4 gamma 1 | | 0.46 | |
| P48634 | PRRC2A_S1085 | Proline rich coiled-coil 2A | | 0.46 | |
| Q92538-3 | GBF1_S1318 | Golgi brefeldin A resistant guanine nucleotide exchange factor 1 | | 0.46 | |

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|----------|--------------|--|--|-------|-------|
| Q92597 | NDRG1_S330 | N-myc downstream regulated 1 | | 0.44 | |
| O75427 | LRCH4_S513 | Leucine rich repeats and calponin homology domain containing 4 | | 0.44 | |
| Q9GZY6 | LAT2_S44 | Linker for activation of Tcells family member 2 | | -0.39 | |
| Q9Y618-3 | NCOR2_S2049 | Nuclear receptor corepressor 2 | | -0.40 | |
| Q9Y618-3 | NCOR2_S2057 | Nuclear receptor corepressor 2 | | -0.40 | |
| O75494-2 | SRSF10_S133 | Serine and arginine rich splicing factor 10 | | -0.43 | |
| Q8NDT2 | RBM15B_S609 | RNA binding motif protein 15B | | -0.47 | |
| Q9PIY6 | PHRF1_S1124 | PHD and ring finger domains 1 | | -0.58 | |
| Q9H1E3 | NUCKS1_S214 | Nuclear casein kinase and cyclin dependent kinase substrate 1 | | -0.61 | |
| Q53EL6-2 | PDCD4_S302 | Programmed cell death 4 | | -0.62 | |
| P05114 | HMG1_S7 | High mobility group nucleosome binding domain 1 | | -0.64 | -0.42 |
| Q8TC07-2 | TBC1D15_S70 | TBC1 domain family member 15 | | -0.72 | |
| O75533 | SF3B1_T257 | Splicing factor 3b subunit 1 | | -0.79 | |
| Q09666 | AHNAK_S2397 | AHNAK protein | | -0.94 | |
| P42166 | TMPO_S159 | Thymopoietin | | -1.63 | |
| P42166 | TMPO_T160 | Thymopoietin | | -1.63 | |
| Q9Y3Z3 | SAMHD1_S33 | SAM and HD domain containing deoxynucleoside triphosphate | | | 0.52 |
| Q8WWQ0 | PHIP_S674 | Pleckstrin homology domain interacting protein | | | -0.46 |
| O75592-2 | MYCBP2_S3467 | MYC binding protein 2 | | | -0.52 |

Table S6. Pair-wised fold change of differentially regulated phosphorylation sites in non-responder patients considering quantitative values at pre-treatment (PRE), day 3 (3D) and day 8 (8D) of the ATRA-VP-TP treatment

| PHOSPHOPROTEOME OF NON-RESPONDERS | | | | | |
|-----------------------------------|----------------|--|-----------|-----------|----------|
| Uniprot accession number | Phosphosite | Phosphoprotein name | FC 3D/PRE | FC 8D/PRE | FC 8D/3D |
| P20700 | LMNB1_S391 | Lamin B1 | 1.22 | | |
| P10412 | HIST1H1E_T18 | H1.4 linker histone, cluster member | 0.63 | | |
| Q8IY67-2 | RAVER1_S617 | Ribonucleoprotein, PTB binding 1 | 0.48 | | |
| Q8IYB3 | SRRM1_S743 | Serine and arginine repetitive matrix 1 | 0.41 | | |
| Q9ULU4-22 | ZMYND8_S510 | Zinc finger MYND-type containing 8 | 0.40 | | |
| Q9NYF8-2 | BCLAF1_S383 | BCL2 associated transcription factor 1 | 0.38 | | |
| Q9NYF8-2 | BCLAF1_S387 | BCL2 associated transcription factor 1 | 0.38 | | |
| P43243 | MATR3_S604 | Matrin 3 | 0.35 | | |
| Q96KR1 | ZFR_S1054 | Zinc finger RNA binding protein | 0.35 | | |
| Q9NYV4-2 | CDK12_T1244 | Cyclin dependent kinase 12 | 0.35 | | |
| Q9GZY8-2 | MFF_S131 | Mitochondrial fission factor | -0.37 | -0.37 | |
| Q5T1M5 | FKBP15_S1164 | FKBP propyl isomerase family member 15 | -0.38 | | |
| P06702 | S100A9_T113 | S100 calcium binding protein A9 | -0.47 | | |
| Q14204 | DYNC1H1_S4368 | Dynein cytoplasmic 1 heavy chain 1 | -0.51 | | |
| P16070-18 | CD44_S304 | CD44 molecule | -0.51 | | |
| Q05655 | PRKCD_S645 | Protein kinase C delta | -0.54 | | |
| Q09666 | AHNAK_S93 | AHNAK nucleoprotein | -0.63 | | |
| Q12802 | AKAP13_S2563 | A-kinase anchor protein 13 | -0.81 | | |
| B2RUZ4 | SMIM1_S22 | Small integral membrane protein 1 | -0.83 | -0.67 | |
| Q9BVC5 | C2orf49_S189 | Chromosome 2 open reading frame 49 | | 0.96 | |
| Q9BVC5 | C2orf49_S193 | Chromosome 2 open reading frame 49 | | 0.96 | |
| Q9NXE4-2 | SMPD4_S246 | Sphingomyelin phosphodiesterase 4 | | 0.71 | |
| Q9C0C2 | TNKS1BP1_S1666 | Tankyrase 1 binding protein 1 | | 0.71 | 0.52 |
| Q8IYB3 | SRRM1_S748 | Serine and arginine repetitive matrix 1 | | 0.45 | |
| P15336-5 | ATF2_T51 | Activating transcription factor 2 | | 0.43 | |
| P15336-5 | ATF2_T53 | Activating transcription factor 2 | | 0.43 | |
| Q6Y7W6 | GIGYF2_S26 | GRB10 interacting GYF protein 2 | | 0.43 | 0.53 |
| Q96GN5-4 | CDCA7L_S105 | Cell division cycle associated 7 like | | 0.42 | |
| Q04637-8 | EIF4G1_S1188 | Eukaryotic translation initiation factor 4 gamma 1 | | 0.42 | 0.39 |
| Q8WYA6 | CTNNB1_S545 | Catenin beta like 1 | | 0.41 | |
| Q9NWK9 | ZNHIT6_S25 | Zinc finger HIT-type containing 6 | | 0.41 | |
| Q03188 | CENPC_S316 | Centromere protein C | | 0.38 | |
| Q7L4I2 | RSRC2_S32 | Arginine and serine rich coiled-coil 2 | | 0.35 | |
| Q7L4I2 | RSRC2_S30 | Arginine and serine rich coiled-coil 2 | | 0.34 | |
| P49736 | MCM2_S139 | Minichromosome maintenance complex component 2 | | 0.32 | |
| Q14687-3 | GSE1_S753 | Gse1 coiled-coil protein | | 0.31 | |
| Q14687-3 | GSE1_S755 | Activating transcription factor 2 | | 0.31 | |
| Q5T200 | ZC3H13_S325 | Zinc finger CCCH-type containing13 | | 0.31 | |
| Q9Y2W1 | THRAP3_S928 | Thyroid hormone receptor associated protein 3 | | -0.40 | |
| Q9NQ55-2 | PPAN_S359 | Peter pan homolog | | -0.41 | |
| Q13523 | PRPF4B_S87 | Pre-mRNA processing factor 4B | | -0.41 | |

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|----------|--------------|--|--|-------|-------|
| Q13523 | PRPF4B_S93 | Pre-mRNA processing factor 4B | | -0.41 | |
| O95685 | PPP1R3D_S74 | Protein phosphatase 1 regulatory subunit 3D | | -0.44 | |
| O95685 | PPP1R3D_S78 | Protein phosphatase 1 regulatory subunit 3D | | -0.44 | |
| Q8WXI9 | GATAD2B_T120 | GATA zinc finger domain containing 2B | | -0.45 | -0.42 |
| Q14155-1 | ARHGEF7_S340 | Rho guanine nucleotide exchange factor 7 | | -0.50 | |
| Q15052 | ARHGEF6_S488 | Rho guanine nucleotide exchange factor 6 | | -0.50 | |
| Q07866-7 | KLC1_S547 | Kinesin light chain 1 | | -0.52 | |
| Q12802 | AKAP13_S1559 | A-kinase anchor protein 13 | | -0.55 | |
| P57682 | KLF3_S92 | Kruppel-like factor 3 | | -0.57 | |
| P21333-2 | FLNA_S2144 | Filamin A | | -0.58 | |
| P04049 | RAF1_S43 | Raf-1 proto-oncogene serine and threonine kinase | | -0.61 | |
| P13796 | LCP1_S257 | Lymphocyte cytosolic protein 1 | | -0.63 | |
| P33241 | LSP1_S204 | Lymphocyte specific protein 1 | | -0.79 | |
| Q92835-2 | INPP5D_S1038 | Inositol polyphosphatase-5-phosphatase D | | -0.80 | |
| P43405 | SYK_S297 | Spleen associated tyrosine kinase | | -0.80 | |
| Q7Z5R6 | APBB1IP_S526 | Amyloid beta precursor protein-binding family B member 1 interacting protein | | -0.85 | |
| O75995 | SASH3_Y316 | SAM and SH3 domain containing 3 | | -0.86 | |
| B2RUZ4 | SMIM1_S27 | Small integral membrane protein 1 | | -0.91 | |
| I3L115 | SPATA22_S94 | Spermatogenesis associated 22 | | -0.98 | |
| Q13576 | IQGAP2_S16 | IQ motif containing GTPase activating protein 2 | | -1.17 | |
| P26038 | EZR_T558 | Ezrin | | -2.06 | |
| Q9UQ35 | SRRM2_S1329 | Serine and arginine repetitive matrix 2 | | | 0.94 |
| Q9UEY8-2 | ADD3_S649 | Adducin 3 | | | 0.94 |
| Q8IWS0 | PHF6_S145 | PHD finger protein 6 | | | 0.52 |
| Q86WB0 | ZC3HC1_S335 | Zinc finger C3HC-type containing 1 | | | 0.52 |
| Q9BUT9 | MCRIP2_S82 | MAPK regulated corepressor interacting protein 2 | | | 0.45 |
| O75976 | CPD_T1368 | Carboxypeptidase D | | | 0.42 |
| O75976 | CPD_T1370 | Carboxypeptidase D | | | 0.42 |
| Q86WB0 | ZC3HC1_S407 | Zinc finger C3HC-type containing 1 | | | 0.40 |
| Q9UQ35 | SRRM2_S1320 | Serine and arginine repetitive matrix 2 | | | 0.36 |
| P32519 | ELF1_S168 | E74 like ETS transcription factor 1 | | | -0.30 |
| Q96ST2 | IWS1_S398 | Interacts with SUPT6H, CTD assembly factor 1 | | | -0.32 |
| Q96ST2 | IWS1_S400 | Interacts with SUPT6H, CTD assembly factor 1 | | | -0.32 |
| P42166 | TMPO_S159 | Thymopoietin | | | -0.53 |