Supplementary Tables

Table S1. PolyPhen-2 and SIFT analyses: possible functional effects of COSMIC missense mutations.
Table S2. ConSurf results and MolMol solvent accessibility assessment for Odin-Sam1 residues affected by the COSMIC missense mutations.
Table S3. Odin-Sam1 predicted physico-chemical features (i.e., GRAVY, Theoretical pI, and Instability index values for wild-type and cancer-related variants).
Table S4. Predicted flexibility by MEDUSA.
Table S5. AF2 and AF3 confidence scores for diverse Odin-Sam1 variants.
Table S6. RMSD evaluation (comparison between experimental structure and AF2 models): Odin-Sam1 NMR structure (wild-type) *versus* Odin-Sam1 AF2 models (WT and diverse variants).
Table S7. RMSD evaluation (i.e., comparison of AF2 models): Odin-Sam1 (WT) *versus* Odin-Sam1 variants.
Table S8. RMSD evaluation (i.e., comparison of AF models of diverse Odin-Sam1 variants): AF2 *versus* AF3 predictions.
Table S9. Predicted ΔTm by HoTMuSiC.
Table S10. Average RMSD values along the 4 MD simulations for diverse Odin-Sam1 variants.
Table S11. Validation of the computational protocol: results from the Haddock Refinement Interface and Prodigy based on the EphA2-Sam/Odin-Sam1 Mus Musculus and human complexes carrying or not the R958C/R957C EphA2-Sam mutation.
Table S12. Haddock scores for the EphA2-Sam/Odin-Sam1 wild-type and cancer-related mutated complexes refined starting from the native EphA2-Sam/Odin-Sam1 SWISS-MODEL structure.
Table S13. AF2 and AF3 confidence scores related to the native Odin-Sam1/EphA2-Sam AF predictions.
Table S14. AF2 and AF3 PDB templates.
Table S15. Haddock scores for the EphA2-Sam/Odin-Sam1 wild-type and cancer-related mutated complexes refined starting from the native EphA2-Sam/Odin-Sam1 AF2 Model.

Table S1. Predictions of the functional effects and pathogenicity that COSMIC [1] missense mutations of Odin-Sam1 might be related to (https://cancer.sanger.ac.uk/cosmic/gene/analysis?ln=ANKS1A, access date 14 October 2025). These analyses were conducted through PolyPhen-2 (Polymorphism Phenotyping v2) (http://genetics.bwh.harvard.edu/pph2/index.shtml; access date 16/10/2025) [2], and SIFT (Sorting Intolerant from Tolerant) (https://sift.bii.a-star.edu.sg/www/SIFT_help.html#CHOOSING_DATABASE, access date 16/10/2025) [3, 4]. Underlined residues are those included in the ML (Mid Loop) interaction interface (residues L719-G742) for EphA2-Sam.

OdinSam1	PolyPhen-2 Prediction / score HumDiv#	PolyPhen-2 Prediction / score HumVar$	SIFT Prediction / score
T696M	benign / 0.005	benign / 0.003	TOLERATED / 0.53
E698K	benign / 0.228	benign / 0.098	TOLERATED / 0.67
Q699R	benign / 0.25	benign / 0.22	TOLERATED / 0.06
S707L	possibly damaging / 0.736	Benign / 0.415	AFFECT PROTEIN FUNCTION / 0.04
L710V	probably damaging / 0.999	probably damaging / 0.996	AFFECT PROTEIN FUNCTION / 0.00
E714K	probably damaging / 0.999	probably damaging / 0.997	AFFECT PROTEIN FUNCTION / 0.01
K716R	benign / 0.002	benign / 0.009	TOLERATED / 0.52
D724N	probably damaging / 1.000	probably damaging / 0.987	TOLERATED / 0.54
V725L	possibly damaging / 0.891	possibly damaging / 0.695	TOLERATED / 0.72
G729R	probably damaging / 1.000	probably damaging / 1.000	AFFECT PROTEIN FUNCTION / 0.00
G729W	probably damaging / 1.000	probably damaging / 1.000	AFFECT PROTEIN FUNCTION / 0.00
N731Y	probably damaging / 1.000	probably damaging / 0.999	AFFECT PROTEIN FUNCTION / 0.01
D737N	probably damaging / 0.995	probably damaging / 0.995	AFFECT PROTEIN FUNCTION / 0.00
D745N	probably damaging / 0.999	probably damaging / 0.995	TOLERATED / 0.71
R750W	possibly damaging / 0.887	benign / 0.219	AFFECT PROTEIN FUNCTION / 0.00
L753P	probably damaging / 1.000	probably damaging / 1.000	AFFECT PROTEIN FUNCTION / 0.00
R757H	probably damaging / 0.995	possibly damaging / 0.854	TOLERATED / 0.10

model prediction trained on HumDiv (Human Diversity) dataset $ model prediction trained on HumVar (Human Variation) dataset.

Table S2. Conservation scores derived from ConSurf [5, 6] and assessment of solvent accessibility by MolMol [7] for Odin-Sam1 residues affected by COSMIC [1] missense mutations. The input consists of the Odin-Sam1 NMR structure [8] edited as indicated in the footnotes. To evaluate the solvent accessible surface, a probe radius equal to 1.4 Å and a precision equal to 5 were employed. Residues included in the ML interface (residues L719-G742) are underlined.

Odin-Sam1@	**ConSurf score**	**MolMol solvent accessibility (%)**
S707L	4	41.0
L710V	8	1.8
E714K	4	16.7
K716R	4	30.9
D724N	6	25.0
V725L	6	18.8
G729R	5	36.9
G729W	5	36.9
N731Y	4	22.7
D737N	8	15.7
D745N	5	20.5
R750W	4	48.6
L753P	6	6.6
R757H	4	48.8

@the first conformer of the Odin-Sam1 NMR ensemble (residues S700-L759), pdb entry 2LMR [8] after removal of the flexible N- and C-tails, 3 cycles of the FoldX RepairPDB macro [9] and the addition of protons by UCSF Chimera [10] was employed as input for the analysis.

Table S3. Results from the "Protparam" tool of "ExPASy": prediction of GRAVY, Theoretical pI, and Instability index values [11, 12] (https://web.expasy.org/protparam/, access date 01/10/2025) employing the human Odin-Sam1 wild-type (WT) and mutated primary sequences as input queries. Underlined residues belong to the ML interface.

Odin-Sam1[1]	GRAVY	Theoretical pI	Instability index
WT@	-0.482	4.92	59.92
T696M	-0.443	4.92	59.92
E698K	-0.488	5.52	59.31
Q699R	-0.497	5.18	57.05
S707L	-0.413	4.92	57.05
L710V	-0.476	4.92	55.06
E714K	-0.488	5.52	58.17
K716R	-0.491	4.92	64.06
D724N	-0.482	5.16	59.92
V725L	-0.488	4.92	59.92
G729R	-0.543	5.18	69.36
G729W	-0.490	4.92	63.46
N731Y	-0.449	4.92	59.92
D737N	-0.482	5.16	57.05
D745N	-0.482	5.16	59.49
R750W	-0.428	4.71	59.92
L753P	-0.563	4.92	60.81
R757H	-0.463	4.90	52.10

[1] Sequence numbers correspond to those of UniprotKB [13] entry Q92625.

[@] The Wild-Type (WT) sequence includes the following protein region: T696-V762.

Table S4. Flexibility class distribution evaluated by the MEDUSA (Multiclass flExibility preDiction from seqUenceS of Amino acids) [14] webserver for WT and mutant sequences. The values indicate the number of residues belonging to the three different flexibility classes.

Odin-Sam1	Class 0 Rigid	Class 1	Class 2 Flexible
WT	7	33	20
S707L	7	34	19
L710V	7	33	20
E714K	7	34	19
K716R	7	33	20
D724N	7	33	20
V725L	7	33	20
G729R	7	33	20
G729W	11	32	17
N731Y	9	37	14
D737N	7	34	19
D745N	7	34	19
R750W	11	31	18
L753P	6	32	22
R757H	7	33	20

Table S5. AF2 (AlphaFold2) [15, 16] and AF3 (AlphaFold3) [17] confidence scores related to the structure predictions of different Odin-Sam1 variants.

		AF2				AF3			
		pLDDT	$\overline{\text{pLDDT}}$	pTM	$\overline{\text{pTM}}$	pLDDT	$\overline{\text{pLDDT}}$	pTM	$\overline{\text{pTM}}$
WT	Model 1	87.3	85 ± 2	0.66	0.63 ± 0.02	91.91	90.2 ± 0.9	0.81	0.79 ± 0.01
S707L	Model 1	86.9	84 ± 2	0.65	0.62 ± 0.02	92.13	91.2 ± 0.9	0.83	0.81 ± 0.02
L710V	Model 1	87.4	85 ± 2	0.655	0.62 ± 0.02	91.15	90 ± 1	0.8	0.78 ± 0.01
E714K	Model 1	87.4	84 ± 2	0.666	0.62 ± 0.02	90.4	89.4 ± 0.9	0.79	0.78 ± 0.01
K716R	Model 1	87.1	85 ± 2	0.664	0.63 ± 0.02	90.87	90.1 ± 0.6	0.8	0.79 ± 0.01
D724N	Model 1	87.6	84 ± 2	0.66	0.62 ± 0.02	91.81	91 ± 1	0.81	0.79 ± 0.01
V725L	Model 1	87.5	84 ± 3	0.654	0.61 ± 0.03	91.03	90.5 ± 0.4	0.8	0.79 ± 0.01
G729R	Model 1	87.2	84 ± 2	0.658	0.62 ± 0.02	91.12	89 ± 1	0.8	0.78 ± 0.01
G729W	Model 1	84.5	82 ± 2	0.633	0.60 ± 0.02	86.54	86.2 ± 0.4	0.76	0.756 ± 0.005
N731Y	Model 1	86.2	83 ± 2	0.643	0.62 ± 0.03	91.32	90.7 ± 0.9	0.81	0.80 ± 0.01
D737N	Model 1	86.9	84 ± 2	0.656	0.62 ± 0.02	92.41	90 ± 1	0.82	0.79 ± 0.01
D745N	Model 1	88.2	85 ± 2	0.669	0.63 ± 0.02	92.25	91.7 ± 0.6	0.82	0.81 ± 0.01
R750W	Model 1	87.6	85 ± 2	0.66	0.62 ± 0.02	91.6	90.8 ± 0.7	0.81	0.80 ± 0.01
L753P	Model 1	86.3	83 ± 2	0.64	0.59 ± 0.03	89.7	89.2 ± 0.5	0.79	0.78 ± 0.01
R757H	Model 1	87.2	84 ± 2	0.657	0.62 ± 0.02	91.18	90.5 ± 0.6	0.8	0.794 ± 0.005

$\overline{\text{pLDDT}}$ indicates the average pLDDT value over the five AF models. $\overline{\text{pTM}}$ indicates the average pTM value over the five AF models.

Table S6 Comparison of 3D coordinates of wild-type Odin-Sam1 experimental structure with AF2 (AlphaFold2) [15, 16] models for WT and its cancer-related point mutants. The software MolMol [7] was employed for RMSD evaluation and diverse atom sets (as reported in the various columns) were considered for the superposition. "2LMR" represents the reference molecule and corresponds to the first conformer of the Odin-Sam1 NMR ensemble [8] (see footnotes of Table S2 for structure editing details); WT is the AlphaFold2 (AF2) [15, 18] model of wild-type Odin-Sam1 (line 2); AF2 models for several Odin-Sam1 variants are indicated as S707L, L710V, E714K, K716R, D724N, V725L, G729R, G729W, N731Y, D737N, D745N, R750W, L753P and R757H (lines 3-16). "Heavy all" refers to all heavy atoms (C, N, O, S) in all residues from S700 to L759 except those in mutated side chains that were excluded; "bb" stands for backbone atoms (N, Cα and C'). ML designates the Mid Loop interaction surface (i.e., Odin-Sam1 region from L719 to G742).

	Odin-Sam1@	**RMSD (Å)**		
		bb all	**Heavy all**	**bb ML**
1	2LMR	----------	----------	----------
2	WT	1.006	1.931	1.116
3	S707L	0.998	1.976	1.124
4	L710V	0.993	1.972	1.096
5	E714K	1.000	1.881	1.084
6	K716R	0.986	1.925	1.092
7	D724N	0.997	1.904	1.099
8	V725L	0.942	1.908	1.110
9	G729R	1.023	2.057	1.099
10	G729W	1.241	2.049	1.418
11	N731Y	1.142	1.744	1.243
12	D737N	0.976	1.897	1.070
13	D745N	0.998	1.888	1.105
14	R750W	0.993	1.873	1.098
15	L753P	1.474	2.203	1.449
16	R757H	0.974	1.843	1.089

[@] AF2 best models.

Table S7. Comparison of 3D coordinates between AF2 [15] models of Odin-Sam1 wild-type ("WT" in line 1) and diverse cancer-related mutants (S707L, L710V, E714K, K716R, D724N, V725L, G729R, G729W, N731Y, D737N, D745N, R750W, L753P and R757H, lines 2-15). Mutations affecting the ML interaction interface have been underlined. RMSD values were evaluated with MolMol [7] by employing "WT" as reference model and superimposing on it all other Odin-Sam1 variants on diverse atom sets (as reported in the various Table columns). "bb all" stands for backbone atoms (N, Cα and C') in all residues from S700 to L759. "Heavy all" stands for all heavy atoms (C, N, O, S) in all residues from S700 to L759 except those in mutated side chains that were excluded; "bb ML" stands for backbone (N, Cα and C') atoms in residues positioned within the ML interaction interface (i.e., region from L719 to G742).

	Odin-Sam1@	**RMSD (Å)**		
		bb all	**Heavy all**	**bb ML**
1	WT	----------	----------	----------
2	S707L	0.090	0.745	0.083
3	L710V	0.256	0.797	0.163
4	E714K	0.176	0.860	0.214
5	K716R	0.097	0.705	0.106
6	D724N	0.116	0.757	0.136
7	V725L	0.247	0.831	0.289
8	G729R	0.273	0.787	0.268
9	G729W	0.946	1.493	1.215
10	N731Y	0.344	1.056	0.347
11	D737N	0.145	0.749	0.180
12	D745N	0.163	0.651	0.232
13	R750W	0.171	0.687	0.210
14	L753P	0.936	1.381	0.691
15	R757H	0.149	0.759	0.194

[@] AF2 best models.

Table S8. Comparison of 3D coordinates of AF2 [15, 16] and AF3 [17] models referring to the wild-type Odin-Sam1 and other cancer-related variants. RMSD evaluation was achieved with the software MolMol [7] by considering diverse atom sets (as reported in the various columns) for the superposition. "WT" indicates AF2 [15] and AF3 [17] models of the wild-type Odin-Sam1 (lines 1, 2); in lines 3 to 30 AF3 models of each Odin-Sam1 variant are compared to the corresponding structure predicted by AF2. "Heavy all" refers to all heavy atoms (C, N, O, S) in all residues from S700 to L759; "bb" stands for backbone atoms (N, Cα and C'). ML stands for the Mid Loop interaction surface encompassing Odin-Sam1 a.a. residues from L719 to G742. Mutations affecting the ML interaction interface have been underlined.

	Odin-Sam1@	**RMSD (Å)**		
		bb all	**Heavy all**	**bb ML**
1	AF2 WT	----------	----------	----------
2	AF3 WT	0.945	1.549	1.321
3	AF2 S707L	----------	----------	----------
4	AF3 S707L	0.966	1.593	1.384
5	AF2 L710V	----------	----------	----------
6	AF3 L710V	0.818	1.499	1.138
7	AF2 E714K	----------	----------	----------
8	AF3 E714K	0.513	1.259	0.555
9	AF2 K716R	----------	----------	----------
10	AF3 K716R	0.590	1.382	0.627
11	AF2 D724N	----------	----------	----------
12	AF3 D724N	0.905	1.424	1.244
13	AF2 V725L	----------	----------	----------
14	AF3 V725L	0.537	1.160	0.522
15	AF2 G729R	----------	----------	----------
16	AF3 G729R	0.960	1.675	1.276
17	AF2 G729W	----------	----------	----------
18	AF3 G729W	1.192	2.213	1.587
19	AF2 N731Y	----------	----------	----------
20	AF3 N731Y	0.981	1.462	1.314
21	AF2 D737N	----------	----------	----------
22	AF3 D737N	0.971	1.596	1.340
23	AF2 D745N	----------	----------	----------
24	AF3 D745N	0.843	1.544	1.168
25	AF2 R750W	----------	----------	----------
26	AF3 R750W	0.793	1.449	1.110
27	AF2 L753P	----------	----------	----------
28	AF3 L753P	1.331	1.796	1.524
29	AF2 R757H	----------	----------	----------
30	AF3 R757H	0.815	1.446	1.067

[@] AF best models.

Table S9. ΔTm HoTMuSiC [19, 20] predictions for Odin-Sam1 mutations linked to cancer. Underlined residues are those located within the ML surface. The most destabilizing mutations (i.e., HoTMuSiC values <-1) are highlighted in red.

Odin-Sam1[@]	**HoTMuSiC ΔTm (°C)**
S707L	-2.32
L710V	-9.01
E714K	-0.79
K716R	-0.70
D724N	-1.43
V725L	-0.26
G729R	1.50
G729W	1.08
N731Y	-0.42
D737N	-2.13
D745N	-1.36
R750W	-1.91
L753P	-16.98
R757H	-1.26

[@] The first conformer of the Odin-Sam1 NMR ensemble (residues S700-L759), pdb entry 2LMR [8] lacking the flexible N- and C-termini, following 3 cycles of the FoldX RepairPDB macro [9] and the addition of protons by UCSF Chimera [10], was implemented as input structure.

Table S10. Average RMSD values for diverse Odin-Sam1 variants, evaluated along the MD simulations considering the Cα atoms. For WT and the D724N mutant data are reported for the 4 replica simulations, for all the other variants RMSD values refer to the single performed MD run.

		RMSD (nm)	
		Mean values	*Standard Deviations*
Odin-Sam1			
	2LMR	0.13	0.02
	G729R	0.14	0.02
	D737N	0.15	0.03
	L753P	0.12	0.02
	WT run1	0.24	0.02
	WT run2	0.19	0.04
	WT run3	0.17	0.04
	WT run4	0.27	0.09
	D724N run1	0.18	0.04
	D724N run2	0.17	0.03
	D724N run3	0.15	0.03
	D724N run4	0.15	0.04

Table S11. Validation of the in silico strategy: results of the Haddock Refinement Interface [21] and PRODIGY webserver [22] for the Mus Musculus EphA2-Sam/Odin-Sam1 wild-type (Mwt-Mwt), its R958C EphA2-Sam/Odin-Sam1 (R958C-Mwt) mutated complex, for the human EphA2-Sam/Odin-Sam1 wild-type and the R957C EphA2-Sam/Odin-Sam1 (R957C-wt) complexes. For each complex Haddock scores [21] and dissociation constants predicted by PRODIGY [22] are reported. Experimental (Exp.) binding data and associated references are indicated in the last two columns.

EphA2-Sam	**Odin-Sam1**	**Average Haddock Score[@]**	**Average K_D* (μM)**	**Haddock Score[§]**	**K_D[#] (μM)**	**Exp. K_D (μM) ITC [23]**	
Mwt	**Mwt**	-106 ± 1	0.7 ± 0.2	-108.2	0.8	1.05 ± 0.14	[23]
R958C	**Mwt**	-82 ± 1	0.8 ± 0.4	-84.1	0.9	not detectable	[23]
wt	**wt[$]**	-113 ± 1	0.4 ± 0.2	-115	0.6	0.62 ± 0.04	[8]
R957C	**wt**	-87 ± 2	0.6 ± 0.2	-90.9	0.7	----------	

[@] The Haddock scores were averaged over the best 10 output structures; * the K_D values were averaged over the best 10 Haddock structures; [§] the Haddock scores refer to the best structure; [#] the K_D values refer to the best structure; [$] the input model includes Odin-Sam1 residues S700-P760 and EphA2-Sam residue T908-V972.

Table S12. Haddock scores [21] for the EphA2-Sam/Odin-Sam1 wild-type and cancer-related mutated complexes that were refined starting from the native EphA2-Sam/Odin-Sam1 SM [24] prediction. Only Odin-Sam1 mutations included in the ML interface (residues from L719 to G742) have been considered.

EphA2-Sam	Odin-Sam1	Average Haddock Score[@]	Haddock Score[#]
wt	wt[$]	-114 ± 1	-117.9
wt	D724N	-107 ± 1	-109.1
wt	V725L	-117 ± 2	-121.3
wt	G729R	-114 ± 2	-118.5
wt	G729W	-113 ± 1	-114.5
wt	N731Y	-113 ± 1	-115.5
wt	D737N	-99 ± 2	-103.6

[@] The Haddock scores represent average values over the best 10 structures; [#] the Haddock scores refer to the best structure;
[$] the input model includes Odin-Sam1 residues S700-L759 and EphA2-Sam residue T908-V972.

Table S13. AF2 (AlphaFold2) [15, 16] and AF3 (AlphaFold3) [17] confidence scores related to the structure predictions obtained for the wild-type EphA2-Sam/Odin-Sam1 complex.

	AF2						AF3					
	pLDDT	$\overline{\text{pLDDT}}$	pTM	$\overline{\text{pTM}}$	ipTM	$\overline{\text{ipTM}}$	pLDDT	$\overline{\text{pLDDT}}$	pTM	$\overline{\text{pTM}}$	ipTM	$\overline{\text{ipTM}}$
Model 1	95.2		0.875		0.863		88.48		0.87		0.85	
Model 2	93.7		0.87		0.858		87.95		0.86		0.84	
Model 3	94.3	94.1 ± 0.7	0.868	0.86 ± 0.01	0.858	0.85 ± 0.01	88.47	88.0 ± 0.5	0.86	0.86 ± 0.01	0.84	0.84 ± 0.01
Model 4	94.1		0.862		0.853		87.79		0.86		0.84	
Model 5	93.1		0.842		0.824		87.25		0.85		0.83	

$\overline{\text{pLDDT}}$ indicates the average pLDDT value over the five AF models. $\overline{\text{pTM}}$ indicates the average pTM value over the five AF models. $\overline{\text{ipTM}}$ indicates the average ipTM value over the five AF models.

Table S14. PDB templates employed by AF2 [15, 16] and AF3 [17] for structure prediction of the WT human EphA2-Sam/Odin-Sam1 complex.

AF2	pdb entry/Title	
	EphA2-Sam	**Odin-Sam1**
Templates	2KSO (chain A) [25] EphA2-Sam/Ship2-Sam complex	2KE7 (chain A) [26] NMR structure of the first Sam domain from AIDA1
	1B0X (chain A) [27] The crystal structure of an Eph receptor Sam domain reveals a mechanism for modular dimerization.	2LMR (chain A) [8] Solution structure of the first Sam domain of Odin
	3KKA (chain D) [28] Co-crystal structure of the Sam domains of EphA1 and EphA2	5ZRZ (chain B) [23] Crystal structure of EphA5/SAMD5 complex
	2E8N (chain A) [29] Solution structure of the C-terminal Sam-domain of EphaA2: Ephrin type-A receptor 2 precursor (EC 2.7.10.1)	2EAM (chain A) [30] Solution structure of the N-terminal Sam-domain of a human putative 47 kDa protein
	3H8M (chains A and B) [31] Sam domain of human ephrin type-A receptor 7 (EPHA7)	2KIV (chain A) [32] AIDA-1 Sam domain tandem
	5ZRZ (chains A and B) [23] Crystal structure of EphA5/SAMD5 Complex	5ZRY (chain B) [23] Crystal structure of EphA6/Odin complex
	1UCV (chain A) [33] Sterile alpha motif (Sam) domain of Ephrin type-A receptor 8	3SEN (chain B) [34] Structure of Caskin1 tandem Sams
	7KJA (chain A) [35] Crystal structure of the EphA2 intracellular KD-Sam domains	
	7KJC (chain A) [35] Crystal structure of the EphA2 S901E mutant intracellular KD-Sam domains	
	1SGG (chain A) [36] The solution structure of Sam domain from the receptor tyrosine kinase EphB2, NMR, 10 structures	
	3HIL (chain B) [37] Sam domain of human Ephrin type-A Receptor 1 (EphA1)	
	1B4F (chain C) [38] Oligomeric structure of the human EphB2 receptor Sam domain	

AF3	pdb entry/Title	
	EphA2-Sam	**Odin-Sam1**
Templates	3SEI (chain A) [34] Crystal structure of Caskin1 tandem Sams	5ZRY (chain A) [23] Crystal structure of EphA6/Odin complex
	3SEN (chain A) [34] Structure of Caskin1 tandem Sams	3SEI (chain A) [34] Crystal structure of Caskin1 tandem Sams
	4IS7 (chain A)[39] Crystal structure of the CASKIN2 Sam domain tandem	

Table S15. Haddock [21] scores for the EphA2-Sam/Odin-Sam1 wild-type complex and for a few of its cancer-related variants. Data refers to the Haddock refinement Interface runs starting from the five AF2 models.

EphA2-Sam	Odin-Sam1	Average Haddock Score[@]	Haddock Score[#]
wt	wt[$]	-107 ± 1	-108.9
wt	D724N	-94 ± 1	-95.5
wt	V725L	-106 ± 1	-109.3
wt	D737N	-97 ± 2	-102.5

[@] These Haddock scores are reported as average values over the best 10 structures; [#] these Haddock scores are related to the best structure; [$] The input model includes Odin-Sam1 residue range S700-L759 and EphA2-Sam residue range T908-V972.

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