Optimizing olverembatinib dose in chronic phase chronic myeloid leukemia

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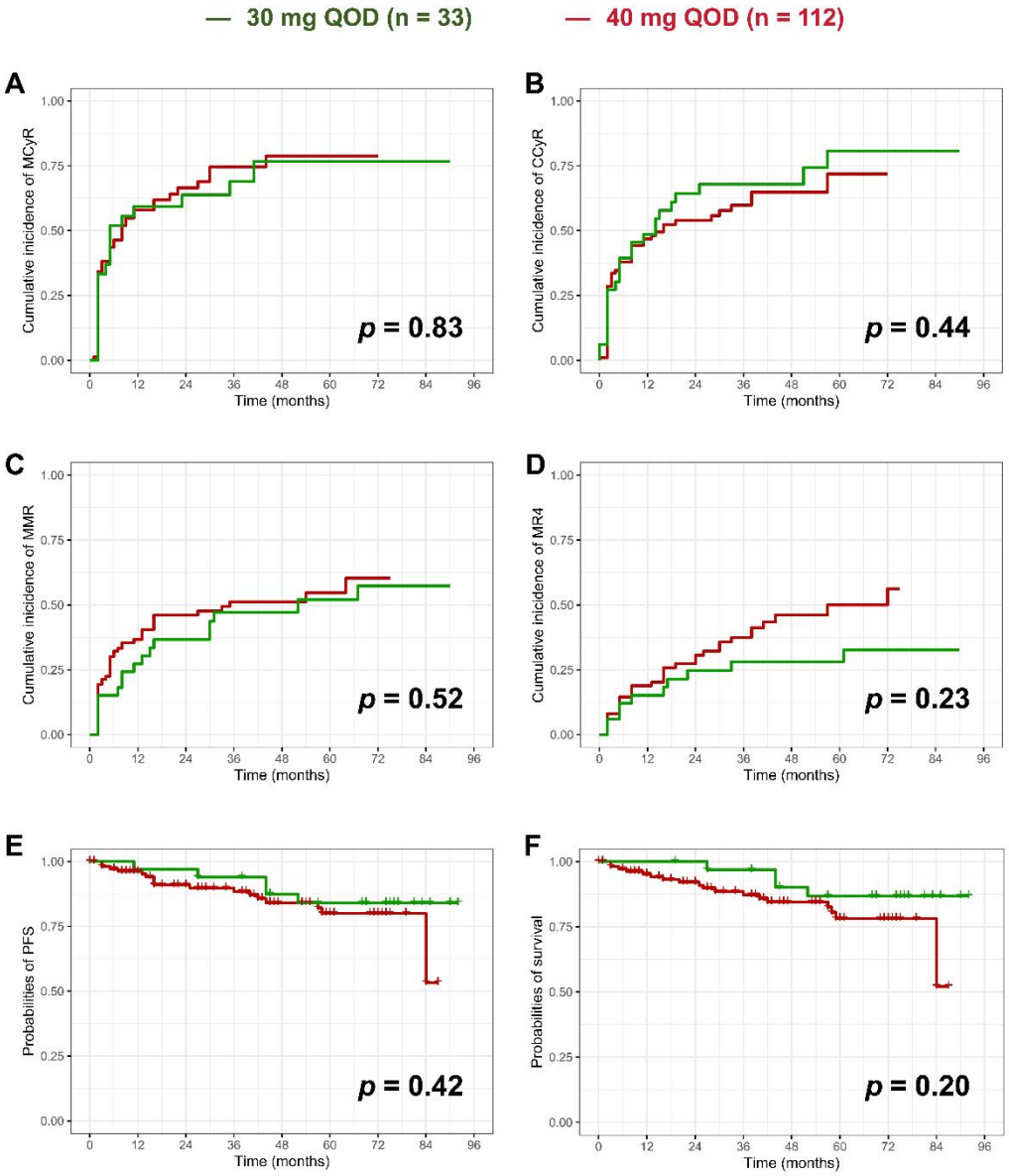
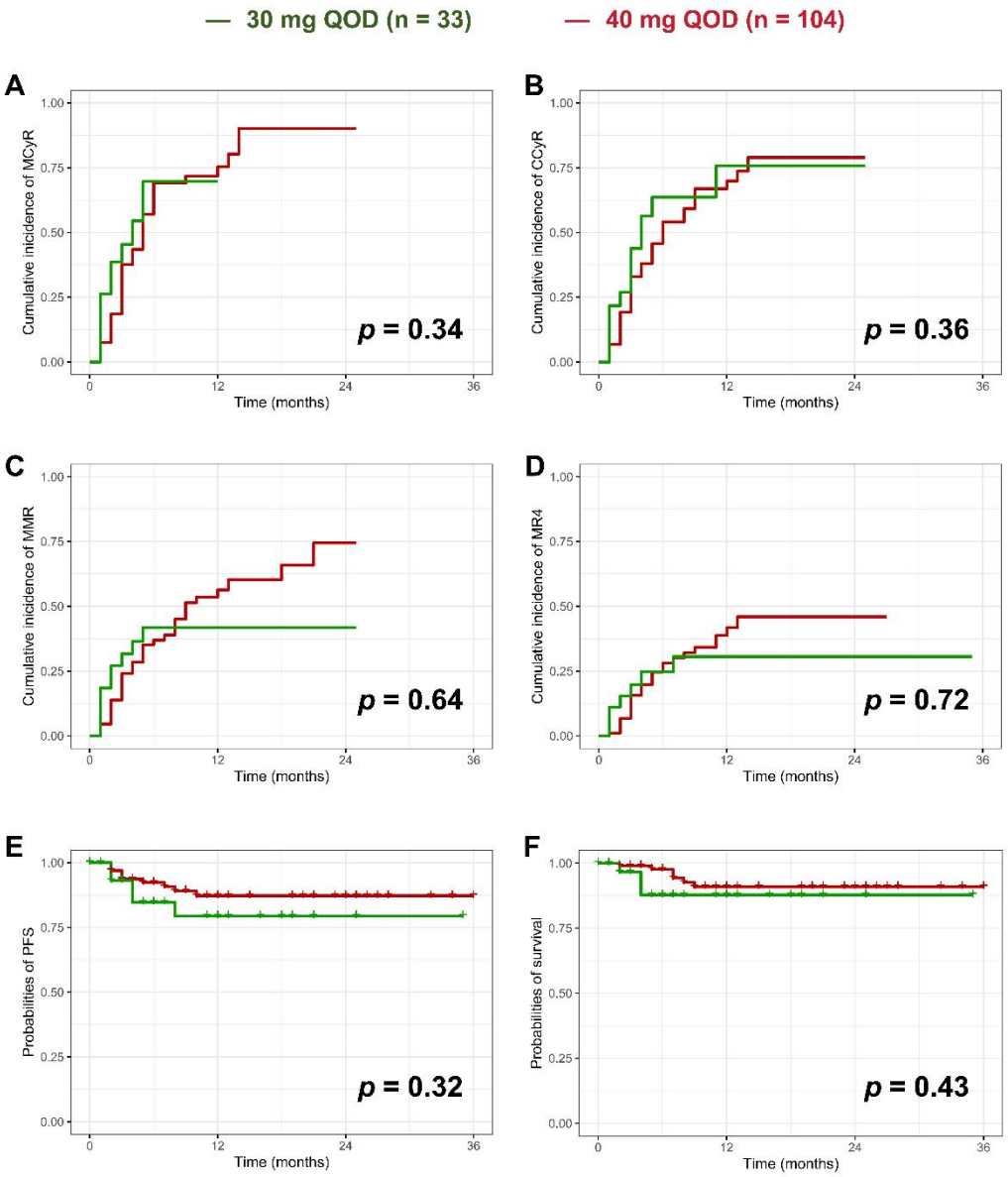


Supplement Figure 1. Comparison of therapy responses and outcomes between 30 and 40 mg QOD cohorts in the clinical trial cohort.



Supplement Figure 2. Comparison of therapy responses and outcomes between 30 and 40 mg QOD cohorts in the real-world post-marketing cohort.

Supplement Table 1. Results of uni-variable Cox analyses for therapy responses and outcomes of olverembatinib.

Co-variates	MCyR		CCyR		MMR		MR^4		PFS		Survival	
	HR (95%CI)	*p* value	HR (95%CI)	*p* value	HR (95%CI)	*p* value	HR (95%CI)	*p* value	HR (95%CI)	*p* value	HR (95%CI)	*p* value
Male (Female as Ref.)	0.7 (0.5-1.1)	0.14	0.8 (0.6-1.2)	0.367	0.8 (0.5-1.2)	0.343	0.8 (0.5-1.3)	0.437	0.8 (0.4-1.7)	0.526	0.7 (0.3-1.7)	0.467
Age	0.9 (0.9-1.1)	0.35	0.9 (0.9-1.0)	0.223	0.9 (0.9-1.0)	0.217	0.9 (0.9-1.0)	0.819	1.0 (1.0-1.0)	0.516	1.0 (1.0-1.0)	0.232
Comorbidity(ies)	0.7 (0.5-1.1)	0.10	0.8 (0.5-1.2)	0.217	0.8 (0.5-1.2)	0.204	0.7 (0.4-1.1)	0.100	1.3 (0.7-2.6)	0.401	1.5 (0.7-3.1)	0.267
Prior TKI-therapy lines	0.6 (0.5-0.7)	<0.001	0.6 (0.5-0.7)	<0.001	0.5 (0.4-0.7)	<0.001	0.5 (0.4-0.7)	<0.001	1.3 (0.9-1.9)	0.219	1.3 (0.8-1.9)	0.313
Best prior TKI-therapy response < CCyR (≥ CCyR as Ref.)	0.4 (0.2-0.5)	<0.001	0.3 (0.2-0.4)	<0.001	0.3 (0.2-0.4)	<0.001	0.2 (0.1-0.4)	<0.001	1.9 (0.7-5.2)	0.199	2.1 (0.7-6.2)	0.195
Duration of prior TKI therapy	0.9 (0.9-1.0)	0.147	0.9 (0.9-1.0)	0.062	0.9 (0.9-1.0)	0.085	0.9 (0.9-1.0)	0.325	1.0 (1.0-1.0)	0.366	1.0 (1.0-1.0)	0.194
Experienced ≥ Grade 3 hematologic toxicity on prior TKI therapy (Not experienced as Ref.)	0.5 (0.4-0.8)	0.001	0.6 (0.4-0.9)	0.013	0.5 (0.3-0.7)	<0.001	0.4 (0.2-0.6)	<0.001	1.9 (1.0-3.6)	0.054	1.8 (0.9-3.7)	0.101
Initial 2G-TKI therapy (imatinib as Ref.)	1.3 (0.8-2.1)	0.292	1.1 (0.7-1.8)	0.657	1.3 (0.8-2.1)	0.306	1.5 (0.8-2.7)	0.188	2.2 (1.0-4.8)	0.063	1.7 (0.6-4.6)	0.279
Blood blasts	0.6 (0.4-1.1)	0.123	0.6 (0.3-1.2)	0.130	0.7 (0.4-1.3)	0.223	0.8 (0.5-1.3)	0.361	1.2 (1.0-1.3)	0.007	1.1 (1.0-1.3)	0.050
Blood basophils	0.9 (0.9-1.1)	0.909	0.9 (0.9-1.0)	0.742	1.0 (1.0-1.0)	0.434	1.0 (1.0-1.0)	0.191	1.1 (1.0-1.2)	0.009	1.1 (1.0-1.2)	0.012
Ph^+ ACAs (no ACAs as Ref.)	0.7 (0.4-1.3)	0.256	0.8 (0.5-1.3)	0.417	0.9 (0.5-1.6)	0.724	0.9 (0.5-1.7)	0.828	2.2 (1.0-4.7)	0.045	2.6 (1.2-5.8)	0.016
100% Ph^+ cells (<100% Ph^+ cells as Ref.)	0.4 (0.3-0.6)	<0.001	0.4 (0.3-0.6)	<0.001	0.4 (0.2-0.5)	<0.001	0.4 (0.2-0.6)	<0.001	2.2 (1.0-4.9)	0.062	1.9 (0.8-4.2)	0.144
***BCR::ABL1* mutation status**		0.008		<0.001		<0.001		0.001		0.523		0.627
Single *T315I* mutation (Ref.)	1		1		1		1		1		1	
T315I + additional mutations	0.5 (0.3-0.9)	0.032	0.5 (0.3-0.9)	0.032	0.5 (0.3-0.9)	0.041	0.7 (0.4-1.3)	0.260	1.0 (0.4-2.6)	0.964	0.9 (0.3-2.7)	0.832
Other mutations	0.9 (0.6-1.7)	0.983	0.9 (0.6-1.6)	0.997	0.8 (0.5-1.3)	0.378	1.0 (0.6-1.7)	0.986	0.5 (0.2-1.8)	0.304	0.6 (0.2-2.0)	0.385

No mutation	0.5 (0.3-0.8)	0.004	0.3 (0.2-0.6)	<0.001	0.1 (0.1-0.3)	<0.001	0.1 (0.1-0.3)	<0.001	1.0 (0.4-2.3)	0.912	0.8 (0.3-2.1)	0.607
Not detected	0.4 (0.2-1.0)	0.058	0.4 (0.2-0.9)	0.035	0.4 (0.2-1.0)	0.061	0.4 (0.1-1.2)	0.095	2.1 (0.7-6.2)	0.203	2.0 (0.6-7.1)	0.284
Olverembatinib 40 mg QOD as initial dose (30 mg QOD as Ref.)	0.9 (0.6-1.3)	0.482	0.8 (0.6-1.2)	0.362	1.2 (0.8-1.9)	0.389	1.6 (1.0-2.8)	0.144	1.0 (0.5-2.1)	0.953	1.4 (0.6-3.2)	0.466
Clinical trials (Real-world post-marketing as Ref.)	1.6 (1.1-2.3)	0.023	1.6 (1.1-2.3)	0.011	1.6 (1.1-2.4)	0.015	1.7 (1.1-2.8)	0.020	2.4 (1.0-5.3)	0.130	1.7 (0.7-4.3)	0.243

2G-TKI, the second-generation tyrosine kinase inhibitor; ACAs, additional cytogenetic abnormalities; CCyR, complete cytogenetic response; mo, months; MMR, major molecular response; IQR, interquartile range; PFS, progression-free survival; QOD, every other day; Ref, reference.

Supplement Table 2. Treatment-related adverse events (After PSM).

Treatment-related adverse events (Patients with event / total available patients, %)		30mg QOD (n = 66)	40mg QOD (n = 154)
Hematologic (Grade ≥ 3)	Thrombocytopenia	33/66 (50)	71/151 (47)
	Leukopenia	12/66 (18)	22/151(15)
	Neutropenia	9/66 (14)	19/151(13)
Non-hematologic (Any grade)	Skin pigmentation	40/62 (65)	94/148 (64)
	Hypertriglyceridemia	25/63 (40)	52/142 (37)
	Alanine aminotransferase increased	21/63 (33)	41/147 (29)
	Aspartate aminotransferase increased	21/63 (33)	39/147 (27)
	Proteinuria	19/60 (32)	43/144 (30)
	Glutamyl transferase increased	19/63 (30)	36/147 (24)
	Creatine kinase increased	14/62 (23)	35/142 (25)
	Hypokalemia	14/62 (23)	22/142(15)
	Hypocalcemia	14/62 (23)	27/142 (19)
	Sexual dysfunction	14/62 (23)	21/119(18)
	Hyperglycemia	14/63 (22)	35/143 (24)
	Fatigue	10/63 (16)	20/140 (14)
	Hyponatremia	10/62 (16)	14/142 (10)
	Fever	8/59 (14)	13/144 (9)
	Muscle and/or joint pain	9/63 (14)	29/140(21)
	Alkaline phosphatase increased	8/63 (13)	21/147 (14)
	Rash	8/63 (13)	19/142 (13)
	Hypertension	7/62 (11)	22/141 (16)
	Sinus tachycardia	7/66 (11)	9/133 (7)
	Hypoproteinemia	6/63 (10)	24/144 (17)
	Lipase increased	6/60 (10)	13/135 (10)
	Pneumonia	4/60 (7)	6/141 (4)
	Nausea and/or vomiting	4/63 (6)	7/140 (5)
	Hemorrhage	4/66 (6)	4/138 (3)
	Diarrhea	3/63 (5)	5/139 (4)
	Pericardial effusion	2/66 (3)	3/130 (2)
	Arterial and/or venous obstructive events	3/66 (5)	13/152 (9)
	Atrial fibrillation	1/66 (2)	3/133 (2)
	Sinus bradycardia	1/66 (2)	3/133 (2)
	Heart failure	1/66 (2)	2/133 (2)
	Thyroid dysfunction	0/53 (0)	4/108(4)
	Pulmonary arterial hypertension	1/66 (2)	2/133 (2)

PSM, propensity score matching; QOD, every other day.

Supplement Table 3. Treatment-related adverse events (Clinical trial cohort).

Treatment-related adverse events (Patients with event / total available patients, %)		30mg QOD (n = 33)	40mg QOD (n = 112)
Hematologic (Grade ≥ 3)	Thrombocytopenia	20/33 (61)	55/112 (49)
	Leukopenia	7/33 (21)	15/112 (13)
	Neutropenia	4/33 (12)	10/112 (9)
Non-hematologic (Any grade)	Skin pigmentation	26/33 (79)	75/112 (67)
	Hypertriglyceridemia	16/33 (48)	50/112 (45)
	Alanine aminotransferase increased	12/33 (36)	35/112 (31)
	Aspartate aminotransferase increased	14/33 (42)	37/112 (33)
	Proteinuria	13/33 (39)	36/112 (32)
	Glutamyl transferase increased	14/33 (42)	35/112 (31)
	Creatine kinase increased	12/33 (36)	41/112 (37)
	Hypokalemia	9/33 (27)	24/112 (21)
	Hypocalcemia	13/33 (39)	23/112 (21)
	Sexual dysfunction	9/33 (27)	22/112 (20)
	Hyperglycemia	12/33 (36)	31/112 (28)
	Fatigue	1/33 (3)	9/112 (8)
	Hyponatremia	6/33 (18)	13/112 (12)
	Fever	4/33 (12)	8/112 (7)
	Muscle and/or joint pain	3/33 (9)	29/112 (26)
	Alkaline phosphatase increased	6/33 (18)	18/112 (16)
	Rash	2/33 (6)	20/112 (18)
	Hypertension	5/33 (15)	24/112 (21)
	Sinus tachycardia	3/33 (9)	9/112 (8)
	Hypoproteinemia	4/33 (12)	24/112 (21)
	Lipase increased	5/33 (15)	9/112 (8)
	Pneumonia	2/33 (6)	5/112 (4)
	Nausea and/or vomiting	1/33 (3)	4/112 (4)
	Hemorrhage	1/33 (3)	2/112 (2)
	Diarrhea	1/33 (3)	4/112 (4)
	Pericardial effusion	2/33 (6)	2/112 (2)
	Arterial and/or venous obstructive events	2/33 (6)	10/112 (9)
	Atrial fibrillation	1/33 (3)	2/112 (2)
	Sinus bradycardia	1/33 (3)	3/112 (3)
	Heart failure	1/33 (3)	2/112 (2)
	Thyroid dysfunction	0/33 (0)	2/112 (2)
	Pulmonary arterial hypertension	0/33 (0)	3/112 (3)

PSM, propensity score matching; QOD, every other day.

Supplement Table 4. Treatment-related adverse events (Real-world post-marketing cohort).

Treatment-related adverse events (Patients with event / total available patients, %)		30mg QOD (n = 33)	40mg QOD (n = 104)
Hematologic (Grade ≥ 3)	Thrombocytopenia	13/33 (39)	37/99 (37)
	Leukopenia	5/33 (15)	14/99 (14)
	Neutropenia	5/33 (15)	11/99 (11)
Non-hematologic (Any grade)	Skin pigmentation	14/29 (48)	46/88 (52)
	Hypertriglyceridemia	9/30 (30)	23/85 (27)
	Alanine aminotransferase increased	9/30 (30)	24/89 (27)
	Aspartate aminotransferase increased	7/30 (23)	17/89 (19)
	Proteinuria	6/27 (22)	24/88 (27)
	Glutamyl transferase increased	5/30 (17)	10/89 (11)
	Creatine kinase increased	2/29 (7)	9/86 (10)
	Hypokalemia	5/29 (17)	3/88 (3)
	Hypocalcemia	1/29 (3)	10/88 (11)
	Sexual dysfunction	5/29 (17)	7/49 (14)
	Hyperglycemia	2/30 (7)	14/89 (16)
	Fatigue	9/30 (30)	18/84 (21)
	Hyponatremia	4/29 (14)	5/88 (6)
	Fever	4/26 (15)	10/96 (10)
	Muscle and/or joint pain	6/30 (20)	15/82 (18)
	Alkaline phosphatase increased	2/30 (7)	8/89 (9)
	Rash	6/30 (20)	10/82 (12)
	Hypertension	3/29 (10)	13/88 (15)
	Sinus tachycardia	4/33 (12)	5/72 (7)
	Hypoproteinemia	2/30 (7)	8/89 (9)
	Lipase increased	1/27 (4)	6/72 (8)
	Pneumonia	2/27 (7)	3/88 (3)
	Nausea and/or vomiting	3/30 (10)	5/83 (6)
	Hemorrhage	3/33 (9)	3/85 (4)
	Diarrhea	2/30 (7)	3/82 (4)
	Pericardial effusion	0/33 (0)	3/72 (4)
	Arterial and/or venous obstructive events	1/33 (3)	7/101 (7)
	Atrial fibrillation	0/33 (0)	2/72 (3)
	Sinus bradycardia	0/33 (0)	1/72 (1)
	Heart failure	0/33 (0)	2/72 (3)
	Thyroid dysfunction	0/20 (0)	4/48 (8)
	Pulmonary arterial hypertension	1/33 (3)	0/72 (0)

PSM, propensity score matching; QOD, every other day.