

Supplemental Table 1. List of relevant diagnosis codes

Description	ICD-9-CM Diagnosis Code	Cause of death (defined by ICD-10)
Lip, oral cavity and pharynx	140.0; 140.1; 140.3-140.6; 140.8; 140.9; 141.0-141.6; 141.8; 141.9; 142.0-142.2; 142.8; 142.9; 143.0; 143.1; 143.8; 143.9; 144.0; 144.1; 144.8; 144.9; 145.0-145.6; 145.8; 145.9; 146.0-146.9; 147.0-147.3; 147.8; 147.9; 148.0-148.3; 148.8; 148.9; 149.0; 149.1; 149.8; 149.9	C00 - C14
Digestive organs	150.0-150.5; 150.8; 150.9; 151.0-151.6; 151.8; 151.9; 152.0-152.3; 152.8; 152.9; 153.0-153.9; 154.0-154.3; 154.8; 155.0-155.2; 156.0-156.2; 156.8; 156.9; 157.0-157.4; 157.8; 157.9; 158.0; 158.8; 158.9; 159.0; 159.1; 159.8; 159.9	C15 – C26
Oesophagus, Stomach, and small intestine	150.0-150.5; 150.8; 150.9; 151.0-151.6; 151.8; 151.9; 152.0-152.3; 152.8; 152.9	
Colorectum	153.0-153.9; 154.0-154.3; 154.8	
Colon	153.0-153.9	
Rectum / Anus	154.0-154.3; 154.8	
Liver	155.0-155.2	
Gallbladder and extrahepatic bile duct	156.0-156.2; 156.8; 156.9	
Pancreas	157.0-157.4; 157.8; 157.9	C30 – C39
Respiratory system	160.0-160.5; 160.8; 160.9; 161.0-161.3; 161.8; 161.9; 162.0; 162.2-162.5; 162.8; 162.9; 163.0; 163.1; 163.8; 163.9; 164.0-164.3; 164.8; 164.9; 165.0; 165.8; 165.9	
Bone, skin and soft tissue	170.0-170.9; 171.0; 171.2-171.9; 172.0-172.9; 173.00-173.09; 173.10-173.12; 173.19; 173.20- 173.22; 173.29; 173.30-173.32; 173.39; 173.40-173.42; 173.49; 173.50-173.52; 173.59; 173.60- 173.62; 173.69; 173.70-173.72; 173.80-173.82; 173.89; 173.90-173.92; 173.99; 176.0-176.5; 176.8; 176.9	C40 – C49
Breast and genital organs	174.0-174.6; 174.8; 174.9; 175.0; 175.9; 179; 180.0; 180.1; 180.8; 180.9; 181; 182.0; 182.1; 182.8- 183.5; 183.8; 183.9; 184.0-184.4; 184.8; 184.9; 185; 186.0; 186.9; 187.1-187.9	C50 – C63
Urinary organs	188.0-188.9; 189.0-189.4; 189.8; 189.9	C64 – C68
Eye, brain and central nervous system, endocrine glands	190.0-190.9; 191.0-191.9; 192.0-192.3; 192.8; 192.9; 193; 194.0; 194.1; 194.3-194.6; 194.8; 194.9	C69 – C75
Lymphatic and haematopoietic tissue	200.00-200.08; 200.10-200.18; 200.20-200.28; 200.30-200.38; 200.40-200.48; 200.50-200.58; 200.60-200.68; 200.70-200.78; 200.80-200.88; 201.00-201.08; 201.10-201.18; 201.20-201.28; 201.40-201.48; 201.50-201.58; 201.60-201.68; 201.70-201.78; 201.90-201.98; 202.00-202.08; 202.10-202.18; 202.20-202.28; 202.30-202.38; 202.40-202.48; 202.50-202.58; 202.60-202.68; 202.70-202.78; 202.80-202.88; 202.90-202.98; 203.00-203.02; 203.10-203.12; 203.80-203.82; 204.00-204.02; 204.10-204.12; 204.20-204.22; 204.80-204.82; 204.90-204.92; 205.00-205.02; 205.10-205.12; 205.20-205.22; 205.30-205.32; 205.80-205.82; 205.90-205.92; 206.00-206.12; 206.20-206.22; 206.80-206.82; 206.90-206.92; 207.00-207.02; 207.10-207.12; 207.20-207.22; 207.80-207.82; 208.00-208.02; 208.10-208.12; 208.20-208.22; 208.80-208.82; 208.90-208.92	C76 – C97

Supplemental Table 2. Baseline characteristics of patient with DPP4i, insulin or TZD as third-line medication after propensity score weighting

	After weighting							
	Total	(A) DPP4i	(B) Insulin	(C) TZD	(A) vs (B) Pairwise ASMD	(B) vs (C) Pairwise ASMD	(A) vs (C) Pairwise ASMD	Maximum pairwise ASMD
Patient characteristics								
General information								
Total number of participants		NA						
Age (year), Mean ± SD	59.53 ± 11.96	59.88 ± 11.63	59.75 ± 12.53	58.98 ± 11.69	0.013	0.040	0.049	0.049
Gender, %					0.083	0.176	0.133	0.176
Female	44.79%	44.15%	44.48%	45.72%				
Male	55.21%	55.85%	55.52%	54.28%				
Clinical parameter								
Laboratory result, Mean ± SD								
HbA1c, %	8.67 ± 1.49	8.64 ± 1.33	8.64 ± 1.63	8.74 ± 1.51	0.008	0.024	0.017	0.024
SBP, mmHg	132.94 ± 16.37	133.27 ± 16.29	132.98 ± 16.93	132.56 ± 15.89	0.009	0.070	0.091	0.091
DBP, mmHg	76.80 ± 9.83	76.82 ± 10.08	76.76 ± 10.11	76.84 ± 9.31	0.005	0.030	0.016	0.030
LDL-C, mmol/L	2.41 ± 0.80	2.38 ± 0.74	2.37 ± 0.76	2.46 ± 0.88	0.003	0.049	0.057	0.057
HDL-C, mmol/L	1.12 ± 0.28	1.13 ± 0.28	1.12 ± 0.29	1.12 ± 0.26	0.023	0.028	0.048	0.048
BMI, kg/m²	28.51 ± 3.99	28.45 ± 3.90	28.46 ± 4.09	28.62 ± 3.96	0.009	0.085	0.107	0.107
Waist, cm	96.68 ± 26.16	96.06 ± 16.06	96.66 ± 18.09	97.32 ± 38.07	0.015	0.064	0.072	0.072
TC, mmol/L	4.36 ± 0.98	4.33 ± 0.89	4.32 ± 0.95	4.44 ± 1.09	0.030	0.073	0.040	0.073
Triglyceride, mmol/L	1.89 ± 1.27	1.86 ± 1.21	1.87 ± 1.32	1.95 ± 1.29	0.018	0.083	0.098	0.098
Creatinine (Serum), umol/L	87.77 ± 40.69	87.43 ± 40.84	89.34 ± 45.44	86.56 ± 35.23	0.050	0.047	0.039	0.050
eGFR, mL/min/1.73m²	83.78 ± 27.94	84.39 ± 28.34	84.53 ± 30.60	82.43 ± 24.56	0.066	0.030	0.130	0.130
Fasting glucose, mmol/L	9.59 ± 2.93	9.50 ± 2.74	9.53 ± 3.09	9.75 ± 2.96	0.126	0.058	0.098	0.126
Duration between first-line medication and third-line medication (year), Mean ± SD	5.47 ± 2.82	5.55 ± 2.66	5.55 ± 2.74	5.30 ± 3.02	0.058	0.107	0.058	0.107

Supplemental Table 2. Baseline characteristics of patient with DPP4i, insulin or TZD as third-line medication after propensity score weighting (Cont.)

	After weighting							
	Total	(A) DPP4i	(B) Insulin	(C) TZD	(A) vs (B) Pairwise ASMD	(B) vs (C) Pairwise ASMD	(A) vs (C) Pairwise ASMD	Maximum pairwise ASMD
Patient characteristics								
Duration of DM (year), Mean ± SD	5.40 ± 2.98	5.39 ± 2.83	5.31 ± 2.93	5.50 ± 3.16	0.057	0.094	0.039	0.094
Duration of DM (year), %					0.010	0.003	0.046	0.046
≤5 years	47.05%	46.75%	46.76%	47.61%				
5-10 years	45.83%	47.67%	47.95%	41.94%				
>10 years	7.12%	5.57%	5.29%	10.45%				
Charlson Comorbidity Index (CCI), %					0.016	0.016	0.045	0.045
1 or 2	13.90%	13.45%	13.64%	14.60%				
3	22.96%	22.81%	22.79%	23.27%				
4	23.77%	24.33%	24.29%	22.71%				
5	16.04%	16.42%	15.90%	15.81%				
6 or above	23.33%	23.00%	23.38%	23.62%				

Note: * Imbalance covariate if pairwise ASMD >= 0.2

Abbreviation: ASMD = absolute standardized mean difference; SD = standard derivation; HbA1c = hemoglobin A1c; SBP = systolic blood pressure; DBP = diastolic blood pressure; LDL-C = low density lipoprotein - cholesterol; HDL-C = high density lipoprotein - cholesterol; BMI = body mass index; TC = total cholesterol; Urine ACR = urine albumin creatinine ratio; eGFR = estimated glomerular filtration rate; DM = diabetes mellitus

Supplemental Table 3. E-values for outcomes

	TZD (vs DPP4i)				Insulin (vs TZD)				Insulin (vs DPP4i)			
	HR	95% CI	E-value	CI	HR	95% CI	E-value	CI	HR	95% CI	E-value	CI
All-cause mortality	1.04	(0.93, 1.16)	1.24	1.00	2.34	(2.14, 2.56)	4.10	3.69	2.43	(2.22, 2.65)	4.29	3.87
Cancer mortality	1.24	(0.95, 1.63)	1.79	1.00	1.34	(1.07, 1.67)	2.01	1.34	1.66	(1.32, 2.09)	2.70	1.97
Cancer	1.49	(1.31, 1.69)	2.34	1.94	0.78	(0.69, 0.87)	1.90	1.55	1.16	(1.02, 1.31)	1.58	1.17

Abbreviation: HR = hazard ratio; CI = Confidence interval

Supplemental Table 4. Adjusted hazard ratios for the associations between the outcomes and observed baseline covariates

Baseline covariates	Adjusted hazard ratio (95% CI)		
	All-cause mortality	Cancer mortality	Cancer
Gender	1.21 (1.10, 1.33)	1.28 (0.98, 1.68)	1.43 (1.23, 1.65)
BMI	0.95 (0.94, 0.96)	0.95 (0.91, 0.98)	0.99 (0.97, 1.01)
HbA1c	0.87 (0.84, 0.90)	1.03 (0.94, 1.12)	1.03 (0.98, 1.09)
SBP	1.01 (1.01, 1.01)	1.00 (1.00, 1.01)	0.99 (0.98, 0.99)
DBP	0.99 (0.98, 0.99)	0.97 (0.96, 0.98)	1.00 (1.00, 1.01)
LDL-C	1.15 (0.88, 1.51)	1.56 (0.72, 3.41)	1.22 (0.79, 1.89)
total cholesterol	0.79 (0.60, 1.03)	0.50 (0.23, 1.08)	0.75 (0.49, 1.16)
HDL-C	1.13 (0.85, 1.52)	1.01 (0.43, 2.37)	0.96 (0.59, 1.55)
serum creatinine	1.00 (1.00, 1.00)	0.99 (0.98, 0.99)	0.99 (0.99, 0.99)
triglyceride	0.97 (0.86, 1.08)	0.79 (0.55, 1.14)	0.98 (0.82, 1.18)
fasting glucose	1.00 (0.99, 1.02)	1.01 (0.97, 1.06)	0.98 (0.96, 1.01)
Duration between first-line medication and third-line medication	1.05 (1.02, 1.08)	1.06 (0.98, 1.15)	0.99 (0.95, 1.03)
Duration of DM	1.03 (1.01, 1.06)	1.01 (0.94, 1.08)	1.07 (1.03, 1.12)
CCI	1.47 (1.44, 1.49)	1.67 (1.59, 1.74)	1.83 (1.78, 1.87)

Abbreviation: CI = confidence interval; BMI = body mass index; HbA1c = hemoglobin A1c; SBP = systolic blood pressure; DBP = diastolic blood pressure; LDL-C = low density lipoprotein - cholesterol; HDL-C = high density lipoprotein - cholesterol; DM = diabetes mellitus; CCI = charlson comorbidity index

Supplemental Table 5. Hazard ratio of cancer, cancer mortality, and all-cause mortality using complete case analysis

Event	TZD (vs DPP4i)			Insulin (vs TZD)			Insulin (vs DPP4i)		
	HR	95% CI	P-value	HR	95% CI	P-value	HR	95% CI	P-value
Cancer	0.92	(0.71, 1.18)	0.507	1.55	(1.20, 2.01)	<0.001*	1.42	(1.26, 1.616)	<0.001*
Lip, oral cavity and pharynx		NA†			NA†		1.35	(0.67, 2.715)	0.400
Digestive organs	1.25	(0.87, 1.80)	0.225	1.32	(0.92, 1.90)	0.130	1.66	(1.36, 2.015)	<0.001*
Oesophagus, Stomach, and small intestine		NA†			NA†		1.25	(0.68, 2.304)	0.472
Colorectum	1.40	(0.85, 2.30)	0.190	0.75	(0.45, 1.27)	0.287	1.05	(0.78, 1.416)	0.740
Colon	1.27	(0.69, 2.34)	0.442	0.91	(0.48, 1.70)	0.758	1.15	(0.82, 1.614)	0.416
Rectum / Anus	2.04	(1.00, 4.15)	0.050	0.35	(0.16, 0.77)	0.009*	0.72	(0.44, 1.179)	0.190
Liver	0.69	(0.23, 2.11)	0.519	3.53	(1.18, 10.62)	0.025*	2.45	(1.57, 3.808)	<0.001*
Gallbladder and extrahepatic bile duct	16.23	(4.83, 54.59)	<0.001*	0.68	(0.31, 1.47)	0.320	10.95	(3.61, 33.173)	<0.001*
Pancreas	0.59	(0.19, 1.85)	0.367	3.65	(1.18, 11.30)	0.025*	2.16	(1.38, 3.384)	<0.001*
Respiratory system	1.87	(0.90, 3.90)	0.093	1.33	(0.65, 2.69)	0.435	2.49	(1.64, 3.769)	<0.001*
Bone, skin and soft tissue	1.71	(0.69, 4.26)	0.247	0.74	(0.29, 1.87)	0.524	1.27	(0.68, 2.372)	0.462
Breast and genital organs (for female only)	0.77	(0.40, 1.49)	0.439	1.63	(0.83, 3.19)	0.155	1.26	(0.92, 1.707)	0.149
Urinary organs	0.73	(0.25, 2.17)	0.574	0.23	(0.06, 0.90)	0.035*	0.17	(0.07, 0.425)	<0.001*
Eye, brain and central nervous system, endocrine glands	1.57	(0.49, 5.06)	0.450	1.00	(0.31, 3.30)	0.995	1.58	(0.75, 3.302)	0.228
Lymphatic and haematopoietic tissue		NA†			NA†		2.18	(1.36, 3.514)	0.001*
Cancer mortality	0.80	(0.45, 1.41)	0.438	2.53	(1.43, 4.46)	0.001*	2.01	(1.59, 2.547)	<0.001*
All-cause mortality	0.58	(0.45, 0.75)	<0.001*	5.60	(4.33, 7.24)	<0.001*	3.24	(2.96, 3.545)	<0.001*

Supplemental Table 6. Baseline characteristics of patients without DPP4i, insulin or TZD

	Overall (N=137,107)
General information	
Age (year), Mean $\pm$ SD	60.21 $\pm$ 11.51
Gender, n (%)	
Female	68,113 (49.68%)
Male	68,994 (50.32%)
Clinical parameter	
Laboratory result, Mean $\pm$ SD	
HbA1c, %	8.21 $\pm$ 1.63
SBP, mmHg	137.36 $\pm$ 15.88
DBP, mmHg	78.65 $\pm$ 9.35
LDL-C, mmol/L	3.11 $\pm$ 0.81
HDL-C, mmol/L	1.21 $\pm$ 0.26
BMI, kg/m ²	28.44 $\pm$ 3.02
Waist, cm	94.69 $\pm$ 16.33
TC, mmol/L	5.19 $\pm$ 0.94
Triglyceride, mmol/L	1.98 $\pm$ 1.21
Creatinine (Serum), μ mol/L	77.35 $\pm$ 23.34
eGFR, mL/min/1.73m ²	87.97 $\pm$ 58.01
Duration of DM (year), Mean $\pm$ SD	0.79 $\pm$ 1.67
Duration of DM (year), n (%)	
$\leq$ 5 years	102,382 (95.95%)
5-10 years	4,107 (3.85%)
>10 years	219 (0.21%)
Charlson Comorbidity Index (CCI), n (%)	
1 or 2	17,861 (13.03%)
3	31,130 (22.70%)
4	32,744 (23.88%)
5	24,799 (18.09%)
6 or above	30,573 (22.30%)

Supplemental Table 7 Number and incidence rate of cancer, cancer mortality and all-cause mortality of patients with and without third-line medications

	Cumulative incidence		Crude incidence rate (Cases/ 100 person-years)			Median follow-up periods (Months)	Mean follow-up periods (Months)
Event	Cases with event	Rate	Estimate	95% CI*	Person-years		
Patients without third-line medications (N=137,107)							
Cancer	7618	0.056	0.89	(0.87, 0.91)	854560.10	73	75
Lip, oral cavity and pharynx	276	0.002	0.03	(0.03, 0.04)	849224.20	72	74
Digestive organs	2978	0.022	0.35	(0.34, 0.36)	854760.80	73	75
Oesophagus, Stomach, and small intestine	396	0.003	0.05	(0.04, 0.05)	851196.70	73	74
Colorectum	1517	0.011	0.18	(0.17, 0.19)	852613.20	73	75
Colon	1022	0.007	0.12	(0.11, 0.13)	853726.00	73	75
Rectum / Anus	581	0.004	0.07	(0.06, 0.07)	854279.10	73	75
Liver	596	0.004	0.07	(0.06, 0.08)	855163.40	73	75
Gallbladder and extrahepatic bile duct	223	0.002	0.03	(0.02, 0.03)	855236.90	73	75
Pancreas	271	0.002	0.03	(0.03, 0.04)	853972.10	73	75
Respiratory system	1077	0.008	0.13	(0.12, 0.13)	854572.50	73	75
Bone, skin and soft tissue	246	0.002	0.06	(0.05, 0.07)	430816.30	74	76
Breast and genital organs (for female only)	1338	0.020	0.16	(0.15, 0.17)	853880.80	73	75
Urinary organs	459	0.003	0.05	(0.05, 0.06)	854761.40	73	75
Eye, brain and central nervous system, endocrine glands	158	0.001	0.02	(0.02, 0.02)	854515.80	73	75
Lymphatic and haematopoietic tissue	404	0.003	0.00	(0.00, 0.00)	9967045.00	70	71
Cancer mortality	2510	0.018	0.30	(0.29, 0.31)	836033.80	71	73
All-cause mortality	8803	0.064	1.06	(1.04, 1.08)	830587.10	70	73

Supplemental Table 7 Number and incidence rate of cancer, cancer mortality and all-cause mortality of patients with and without third-line medications (Cont.)

	Cumulative incidence		Crude incidence rate (Cases/ 100 person-years)			Median follow-up periods (Months)	Mean follow-up periods (Months)
Event	Cases with event	Rate	Estimate	95% CI*	Person-years		
Patients with third-line medications (N=20,577)							
Cancer	571	0.028	0.97	(0.90, 1.06)	58687.17	28	34
Lip, oral cavity and pharynx	18	0.001	0.03	(0.018, 0.05)	59507.33	28	35
Digestive organs	248	0.012	0.42	(0.37, 0.47)	59240.67	28	35
Oesophagus, Stomach, and small intestine	22	0.001	0.04	(0.02, 0.06)	59514.25	28	35
Colorectum	105	0.005	0.18	(0.15, 0.21)	59382.92	28	35
Colon	75	0.004	0.13	(0.10, 0.16)	59441.92	28	35
Rectum / Anus	43	0.002	0.07	(0.05, 0.10)	59460.92	28	35
Liver	56	0.003	0.09	(0.07, 0.12)	59459.83	28	35
Gallbladder and extrahepatic bile duct	22	0.001	0.04	(0.02, 0.06)	59516.08	28	35
Pancreas	46	0.002	0.08	(0.06, 0.10)	59513.58	28	35
Respiratory system	65	0.003	0.11	(0.08, 0.14)	59471.83	28	35
Bone, skin and soft tissue	22	0.001	0.04	(0.02, 0.06)	59498.33	28	35
Breast and genital organs (for female only)	84	0.009	0.32	(0.26, 0.40)	26283.00	28	35
Urinary organs	36	0.002	0.06	(0.04, 0.08)	59459.83	28	35
Eye, brain and central nervous system, endocrine glands	13	0.001	0.02	(0.01, 0.04)	59512.08	28	35
Lymphatic and haematopoietic tissue	43	0.002	0.07	(0.05, 0.10)	59492.92	28	35
Cancer mortality	179	0.009	0.31	(0.26, 0.35)	58538.83	28	34
All-cause mortality	1,489	0.072	2.54	(2.42, 2.68)	58538.83	28	34

Supplemental Table 8 Hazard ratio of all-cause mortality, cancer mortality, and cancer events

Event	With 3 rd line medications (vs without 3 rd line medications)								
	Overall			Baseline HbA1c < 7%			Baseline HbA1c ≥ 7%		
	HR	95% CI	P-value	HR	95% CI	P-value	HR	95% CI	P-value
Cancer	1.16	(1.06, 1.26)	<0.001*	1.13	(1.03, 1.24)	0.010*	1.56	(1.22, 1.99)	<0.001*
Lip, oral cavity and pharynx	1.03	(0.64, 1.67)	0.897	1.03	(0.63, 1.70)	0.906	0.81	(0.11, 5.98)	0.840
Digestive organs	1.32	(1.16, 1.51)	<0.001*	1.25	(1.08, 1.44)	0.002*	2.11	(1.48, 3.01)	<0.001*
Oesophagus, Stomach, and small intestine	0.97	(0.63, 1.50)	0.883	0.88	(0.54, 1.42)	0.602	1.93	(0.70, 5.34)	0.206
Colorectum	1.10	(0.90, 1.35)	0.348	1.06	(0.86, 1.31)	0.575	1.45	(0.79, 2.66)	0.236
Colon	1.21	(0.95, 1.53)	0.124	1.15	(0.89, 1.48)	0.281	1.76	(0.89, 3.47)	0.101
Rectum / Anus	1.14	(0.84, 1.57)	0.400	1.15	(0.83, 1.59)	0.416	1.02	(0.32, 3.24)	0.977
Liver	1.50	(1.13, 1.98)	0.005*	1.45	(1.07, 1.95)	0.016*	2.11	(0.98, 4.58)	0.058
Gallbladder and extrahepatic bile duct	1.72	(1.10, 2.69)	0.018*	1.58	(0.97, 2.56)	0.064	3.12	(0.94, 10.38)	0.063
Pancreas	2.25	(1.63, 3.09)	<0.001*	2.03	(1.43, 2.90)	<0.001*	4.53	(2.12, 9.67)	<0.001*
Respiratory system	1.02	(0.79, 1.32)	0.859	1.07	(0.82, 1.39)	0.638	0.69	(0.26, 1.87)	0.467
Bone, skin and soft tissue	1.51	(0.97, 2.36)	0.070	1.57	(0.98, 2.52)	0.060	1.30	(0.31, 5.38)	0.720
Breast and genital organs (for female only)	1.06	(0.84, 1.32)	0.636	1.09	(0.86, 1.38)	0.488	0.99	(0.49, 2.01)	0.977
Urinary organs	1.20	(0.85, 1.69)	0.303	1.09	(0.74, 1.60)	0.656	2.37	(1.09, 5.19)	0.030*
Eye, brain and central nervous system, endocrine glands	1.15	(0.65, 2.05)	0.623	1.06	(0.56, 1.97)	0.866	2.19	(0.51, 9.37)	0.289
Lymphatic and haematopoietic tissue	1.80	(1.31, 2.49)	<0.001*	1.72	(1.21, 2.44)	0.002*	2.74	(1.18, 6.37)	0.019*
Cancer mortality	1.44	(1.23, 1.68)	<0.001*	1.33	(1.13, 1.58)	<0.001*	2.55	(1.71, 3.81)	<0.001*
All-cause mortality	3.73	(3.52, 3.95)	<0.001*	3.12	(2.92, 3.33)	<0.001*	9.94	(8.84, 11.17)	<0.001*