Nimotuzumab in GBM

Updates on the current evidences

Innokeys

CIMaHer ™
nimotuzumab 50 mg

CIMaHer Product Profile

Brand Name	**CIMaHer**
Composition	Vial contain: Nimotuzumab 50 mg
Dosage Form	Injection
Manufacturer	Centro De Inmunologia Molecular (CIM), La Habana, Cuba
Mechanism of Action	Anti EGFR

Nimotuzumab (Indonesia)

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Glioblastoma (GBM) is most primary brain tumor which mostly occur in adults (60-70%) GBM has a characteristics : **aggressive, invasive and poor prognosis.**

MGMT Status as a Clinical Biomarker in Glioblastoma

- **O^6-methylguanine-DNA methyl-transferase (MGMT) Gene Status** as a prognostic and promising predictive biomarker in glioblastoma
- *MGMT* promoter **methylation** status has emerged as one of the leading determinants of prognosis and potential predictor of response to TMZ (Temozolomide)
- Based on RTOG0525 study, MGMT status has a prognosis :
  - Patient with MGMT-Methylated shows median survival **21.2 months** vs. **14 months** in unmethylated cases

Need to find out new treatment approach for unmethylated MGMT status to increase survival

Guidelines:

- Maximum extent resection under the premise of ensuring safety, concurrent chemoradiotherapy (CCRT) with temozolomide (TMZ), and adjuvant chemotherapy (AC) with TMZ which only prolongs PFS up to 6,9 months and OS up to 14.6 months.
- **GBM with unmethylated O6-methylguanine-DNA methyltransferase (MGMT) promoter has a worse prognosis, with a PFS of only 5.3 months and an OS of only 12.7 months**

Need new treatment approaches to enhance outcome from patient.

EGFR in many variant of tumor

Tumor type	Tumors with expressed EGFR (%)
Head and Neck	90–95
Breast	82–90
Renal carcinoma	76–89
Cervix/uterus	90
Esophagael	43–89
Pancreatic	30–89
Non-small-cell lung	40–80
Prostate	40–80
Colon	25–77
Ovarian	35–70
Glioma	40–63
Bladder	31–48
Gastric	4–33

- 40 - 63% GBM has EGFR expression
- **Nimotuzumab, humanized Anti EGFR, can block EGFR that can suppress tumor growth.**
- Nimotuzumab can enhance sensitivity of TMZ and RT.

Retrospective Study:

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Radiotherapy Plus Temozolomide With or Without Nimotuzumab Against the Newly Diagnosed EGFR-Positive Glioblastoma: A Retrospective Cohort Study

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Patient Characteristics & Treatment

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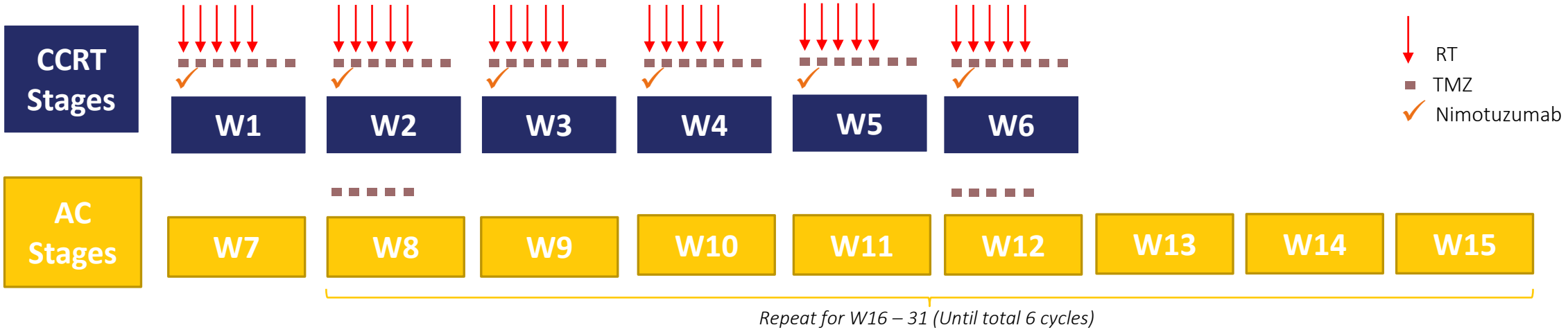
- ✓ Patient: 56 patient with retrospective analysis.
- ✓ Criteria: Naive GBM and EGFR+

Treatment Method

- **CCRT Stage : Concurrent RT + Nimotuzumab + TMZ**
  a. Nimotuzumab: 200 mg weekly for 6 cycles
  b. TMZ: 75 mg/m2/day until end of RT
  c. RT: 2.0 Gy/day, 5 days a week (60 Gy for 6 weeks)
- **AC Stage: After 4 weeks of rest after RT, TMZ 150 mg/m2.day for 5 consecutive days with 23 days of course (for 6 cycles)**



Patient Characteristics

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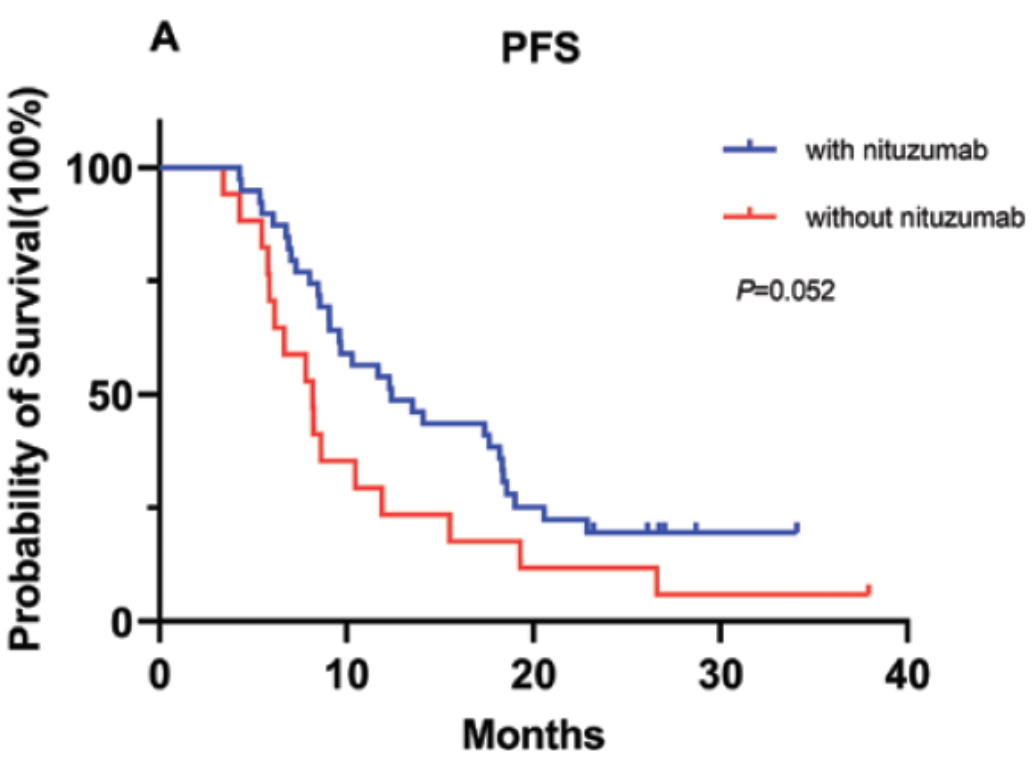
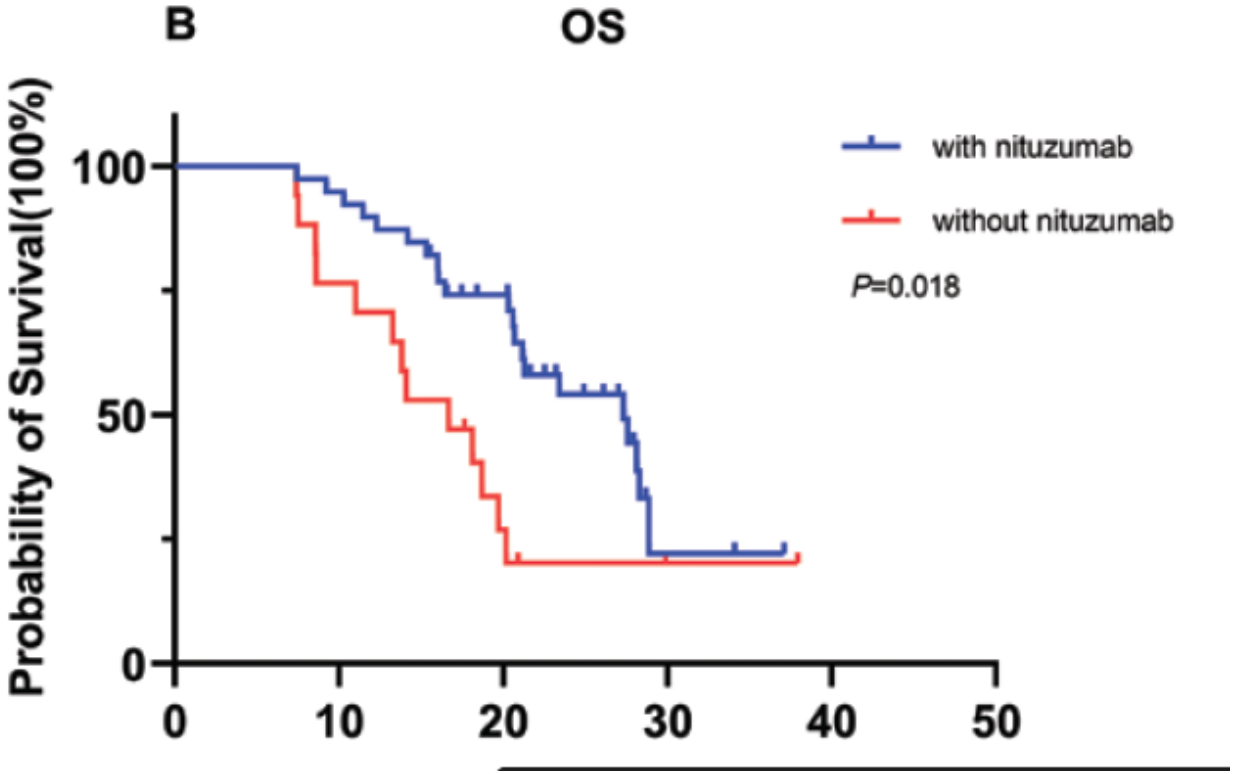
Characteristics	With nituzumab ($n = 39$)	Without nituzumab ($n = 17$)	χ^2	P
Median age (year)				
≤50	15	4	1.178	.278
>50	24	13		
Sex				
Male	28	12	0.000	1.000
Female	11	5		
KPS at initial diagnosis				
>70	16	5	0.681	.409
≤70	23	12		
Extent of surgery				
GTR	34	15	0.000	1.000
STR	5	2		
MGMT methylation status				
Methylated	14	4	0.830	.362
Unmethylated	25	13		
IDH mutation status				
Mutated	1	1		.519
Wild type	38	16		

Abbreviations: KPS, Karnofsky performance status; GTR, gross total resection; STR, subtotal resection; MGMT, O6-methylguanine-DNA methyltransferase; IDH, isocitrate dehydrogenase; RT, radiotherapy.

PFS and OS





PFS with Nimotuzumab: 12.4 months

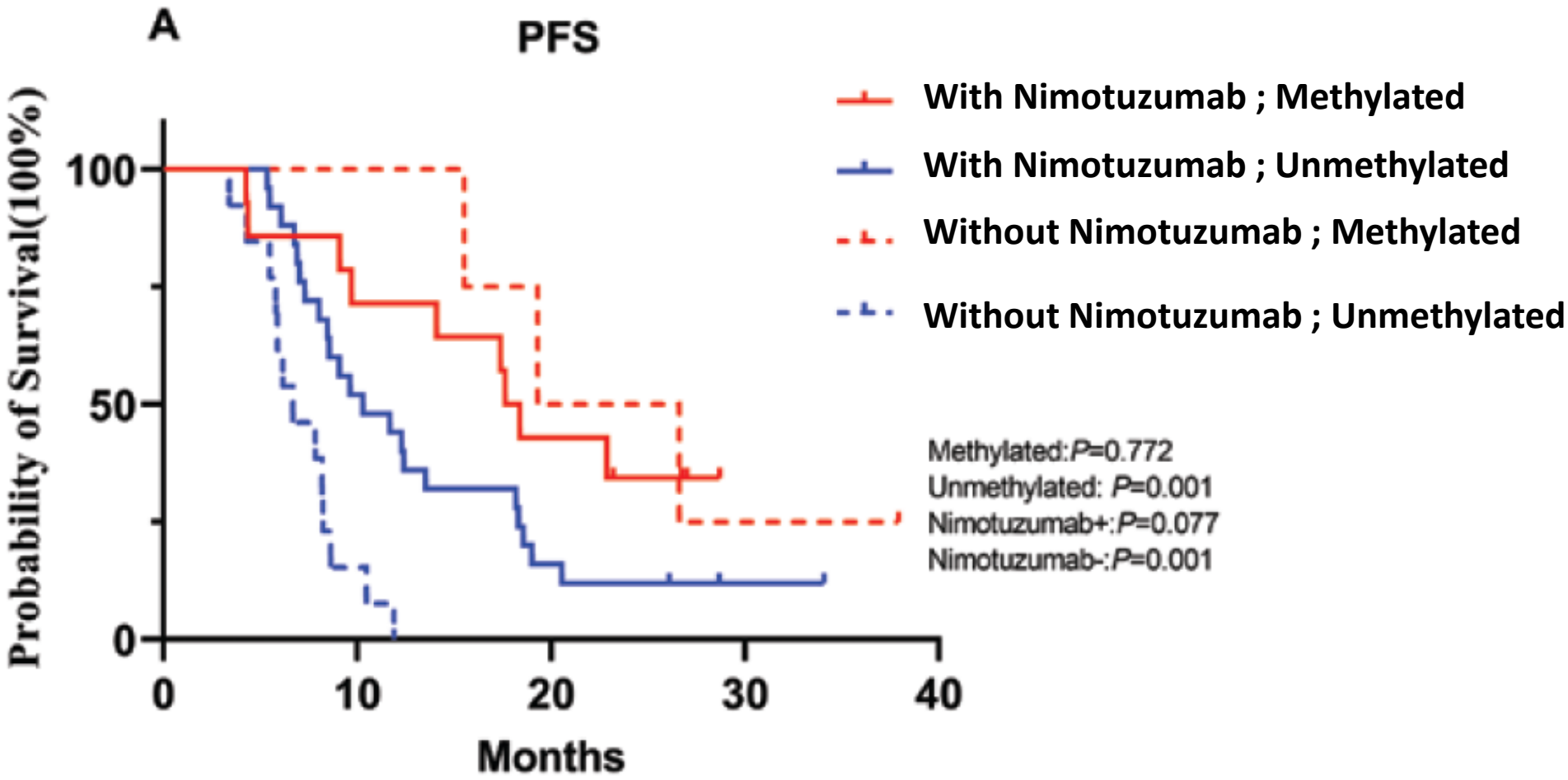
PFS without Nimotuzumab: 8.2 month

OS with Nimotuzumab: 27.3 months

OS without Nimotuzumab: 16.7 months

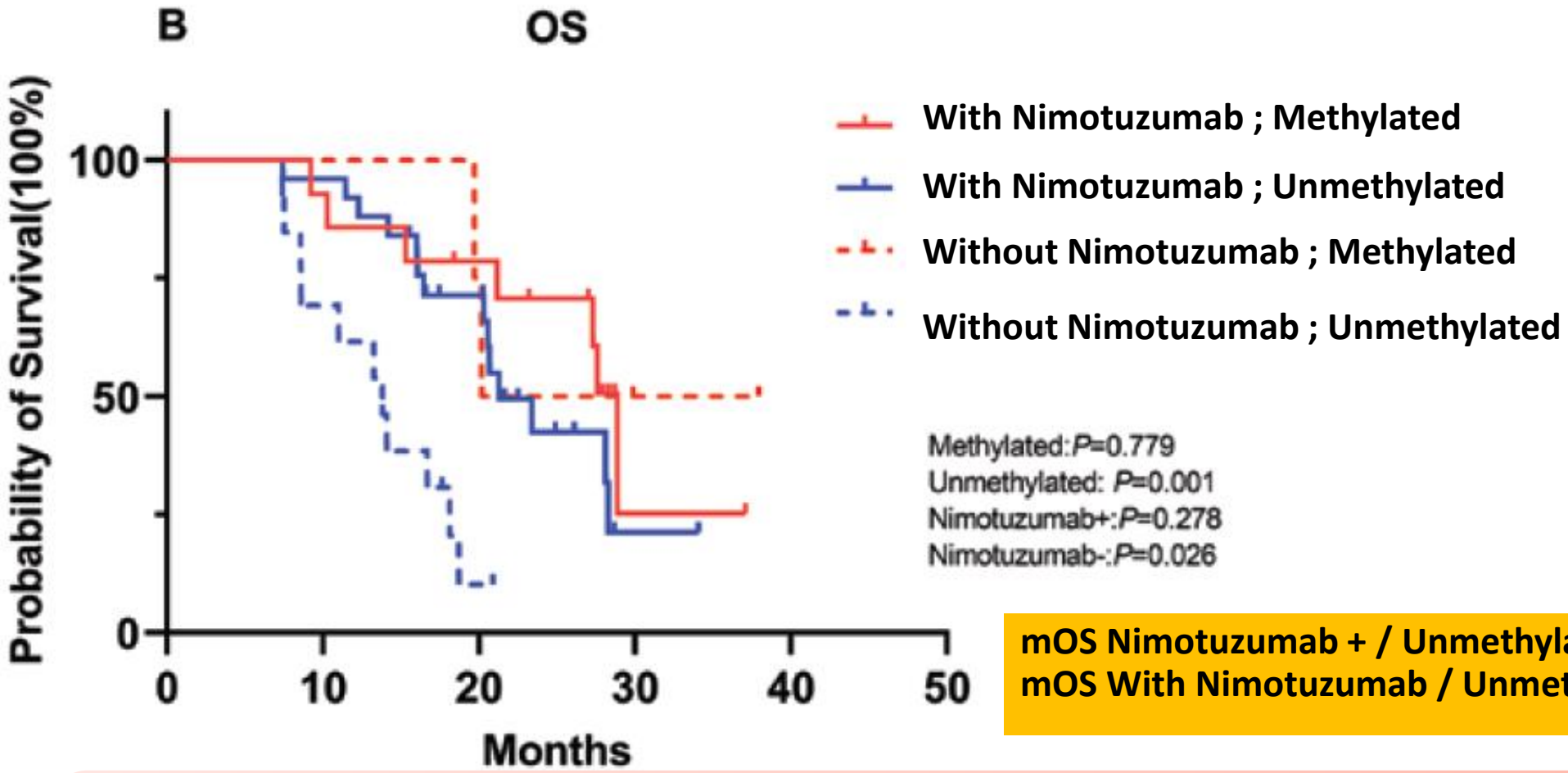
Theres additional PFS up to 4.2 months and OS up to 10.6 months with additional Nimotuzumab VS. without

Sub-group analysis with MGMT status



mPFS Nimotuzumab / Unmethylated: 10.3 months
mPFS without Nimotuzumab / Unmethylated: 6.7 months

Sub-group analysis with MGMT status



mOS Nimotuzumab + / Unmethylated: 21.3 months
mOS With Nimotuzumab / Unmethylated: 13.8 months

In patients with unmethylated MGMT promoter, PFS and OS were significantly better with nimotuzumab than in those without nimotuzumab. **mPFS and OS increase 3.6 months and 7,5 months respectively with additional Nimotuzumab.**

Adverse Event

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Table 3. Analysis of adverse events.

Adverse events	With nituzumab (n = 39)	Without nituzumab (n = 17)	χ^2	P
	Grades 1-2 (n, %)	Grades 1-2 (n, %)		
Leukopenia	20(51.3)	8(47.1)	0.084	.771
Neutropenia	13(33.3)	5(29.4)	0.083	.773
Thrombocytopenia	9(23.1)	4(23.5)	0.000	1.000
Fever	1(2.6)	0(0)		1.000
Dizziness	1(2.6)	0(0)		1.000
Vomiting	4(10.3)	5(29.4)	1.957	.162
Rash	4(10.3)	0(0)	0.650	.420
Fatigue	2(5.1)	0(0)	0.044	.834
Constipation	2(5.1)	0(0)	0.044	.834
ALT/AST elevation	1(2.6)	1(5.9)	0.000	1.000

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Nimotuzumab combined with standard TMZ + RT was safe and well-tolerated by patients.

Conclusion:

- ✓ Nimotuzumab combined with CCRT **displayed superior efficacy in patients with newly diagnoses EGFR-positive GBM, parciularly in unmethylated MGMT promoter.**
- ✓ mPFS and OS increase 3.6 months and 7,5 months respectively with **additional Nimotuzumab.**
- ✓ **Combination between Nimotuzumab with CCRT and TMZ is safe and tolerable by patients.**

Thank you