

Ontwikkelingen en behandel mogelijkheden bij onbekende primaire tumor (PTO)

**Nieuwe ontwikkelingen in de Oncologie in
2024" en "Afscheid Jan Ouwerkerk"**

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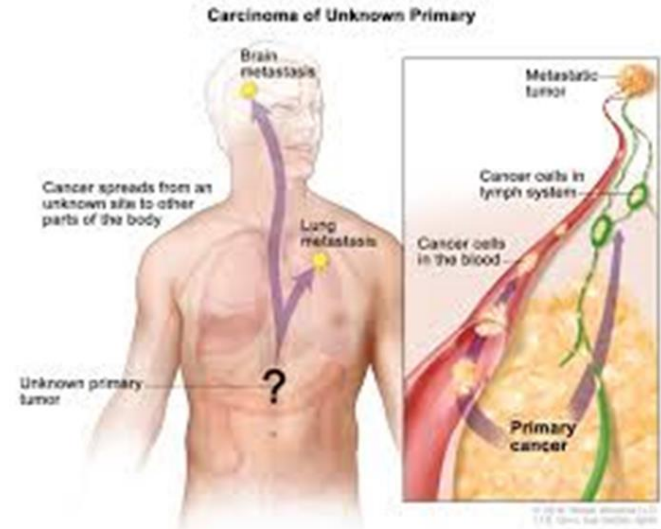
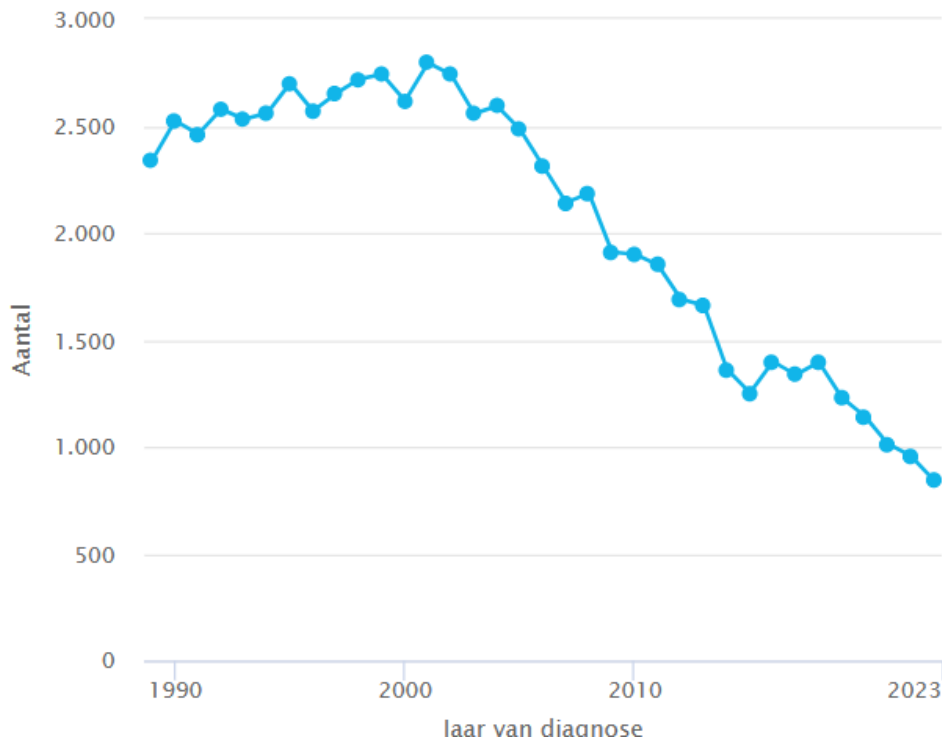


Diagnostisch, medisch en psychologisch dilemma

Incidentie per jaar, Aantal

Kanker met onbekende primaire lokalisatie (PTO)

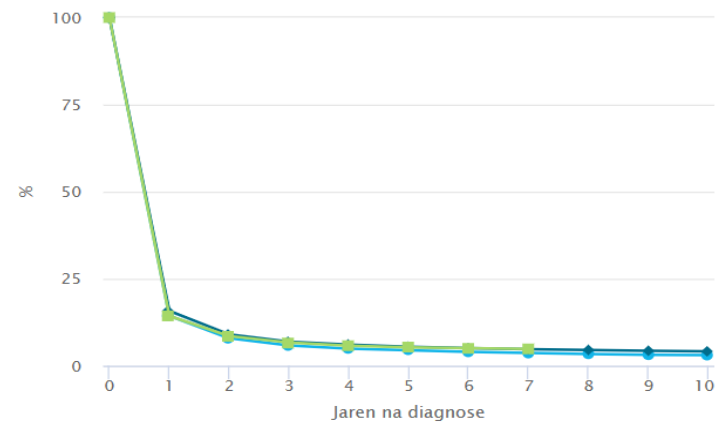
Geslacht: Man en vrouw | **Leeftijdsgroep:** Totaal | **Regio:** Nederland | **Stadium:** Totaal



Overleving

Kanker met onbekende primaire lokalisatie (PTO)

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Jaar van diagnose

● 1995-2004 ◆ 2005-2014 ■ 2015-2021

ESMO richtlijn: klinische workup

Assessment suggested	Target patient population
Thorough medical history and physical examination	All patients
Basic blood and biochemistry analyses	All patients
CT scans of thorax, abdomen and pelvis	All patients
Mammography	Female patients
Work-up for CUP subsets	
Breast MRI	Females with axillary adenocarcinoma
Serum α -fetoprotein and human chorionic gonadotropin	Patients with midline metastatic disease
Serum prostate-specific antigen	Males with adenocarcinomatous bone metastases
Head and neck CT/PET scan (optional)	Cervical squamous cell carcinoma
Endoscopies	Sign/symptom/laboratory-oriented
Octreoscan and plasma chromogranin A	Patients with neuroendocrine tumour CUP
Additional diagnostic pathology	Sign/symptom/laboratory-oriented

ESMO richtlijn 2015: Wat de patholoog kan bijdragen

Table 1. Immunohistochemical work-up in patients with cancers of unknown primary site (CUPs)

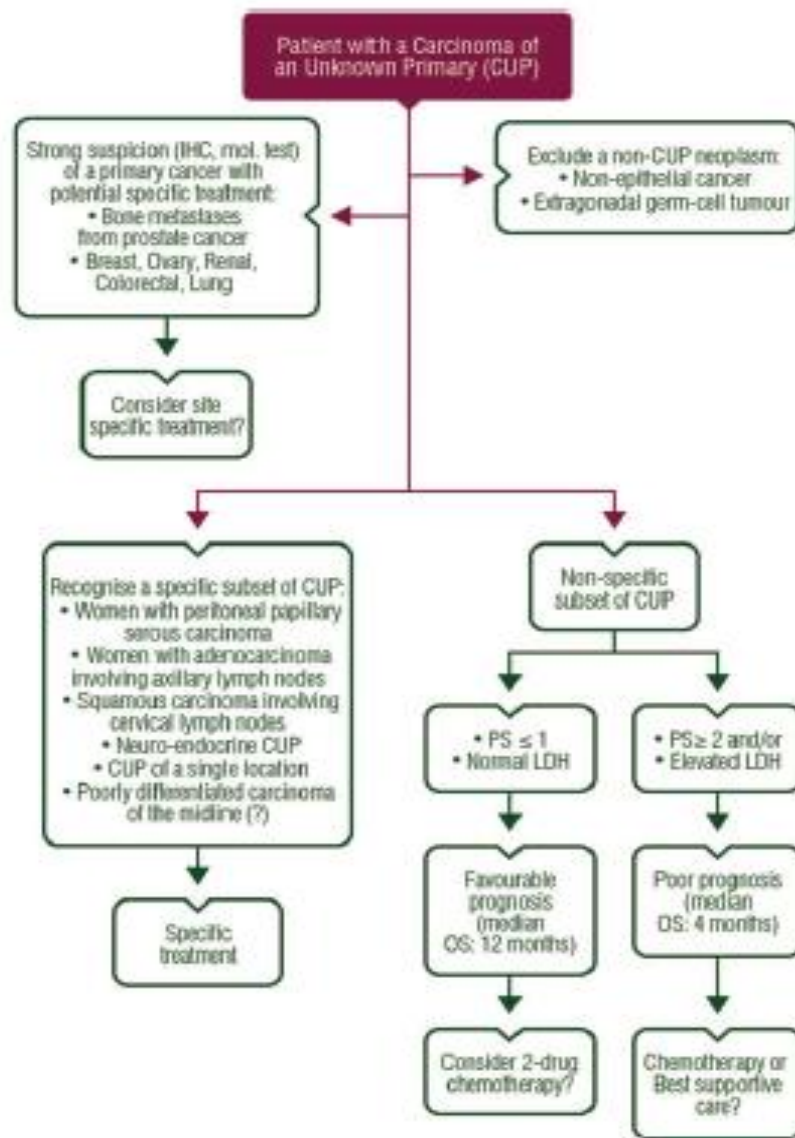
	Cytokeratins	PSA	ER, PgR	CDX2+, CK20+, CK7-	TTF1, NapsinA, CK7+	Thyroglobulin, calcitonin	NSE, chromogranin, synaptophysin	AFP, OCT4, hCG, PLAP	LCA	S100, HMB45	Vimentin, desmin
Undifferentiated carcinoma	+	-	±	-	-	-	-	-	-	-	±
Prostate cancer	+	+	-	-	-	-	-	-	-	-	-
Breast cancer	+	-	±	-	-	-	-	-	-	-	±
Colorectal cancer	+	-	-	+	-	-	-	-	-	-	-
Lung adenocarcinoma	+	-	-	-	+	-	-	-	-	-	-
Thyroid cancer	+	-	-	-	±	+	±	-	-	-	-
Neuroendocrine	+	-	-	-	±	±	+	-	-	-	-
Germ-cell cancer	+	-	-	-	-	-	-	+	-	-	±
Lymphoma	-	-	-	-	-	-	-	-	+	-	-
Melanoma	-	-	-	-	-	-	-	-	-	+	±
Sarcoma	-	-	-	-	-	-	-	-	-	±	+

Therapie

Table 3. Therapy for patients with favourable-risk cancers of unknown primary site (CUPs)

CUP subtype	Proposed treatment	Potential equivalent tumour
Poorly differentiated neuroendocrine carcinomas of an unknown primary	Platinum + etoposide combination chemotherapy	Poorly differentiated neuroendocrine carcinomas with a known primary
Well-differentiated neuroendocrine tumour of unknown primary	Somatostatin analogues, streptozocin+5-FU, sunitinib, everolimus	Well-differentiated neuroendocrine tumour of a known primary site
Peritoneal adenocarcinomatosis of a serous papillary histological type in females	Optimal surgical debulking followed by platinum-taxane-based chemotherapy	Ovarian cancer
Isolated axillary nodal metastases in females	Axillary nodal dissection, mastectomy or breast irradiation and adjuvant chemohormonotherapy	Breast cancer (found in 50%–70% when breast MRI is performed)
Squamous cell carcinoma involving non-supraclavicular cervical lymph nodes	Neck dissection and/or irradiation of bilateral neck and head-neck axis. For advanced stages induction chemotherapy with platinum-based combination or chemoradiation	Head and neck squamous cell cancer
CUP with a colorectal IHC (CK20+ CDX2+ CK7–) or molecular profile	Systemic treatment used for colorectal cancer	Metastatic colorectal cancer
Single metastatic deposit from unknown primary	Resection and/or RT ± systemic therapy	Single metastasis
Men with blastic bone metastases or IHC/serum PSA expression	Androgen deprivation therapy ± RT	Prostate cancer

5-FU, 5-fluorouracil; MRI, magnetic resonance imaging; IHC, immunohistochemistry; PSA, prostate-specific antigen; RT, radiotherapy; CK, cytokeratin.

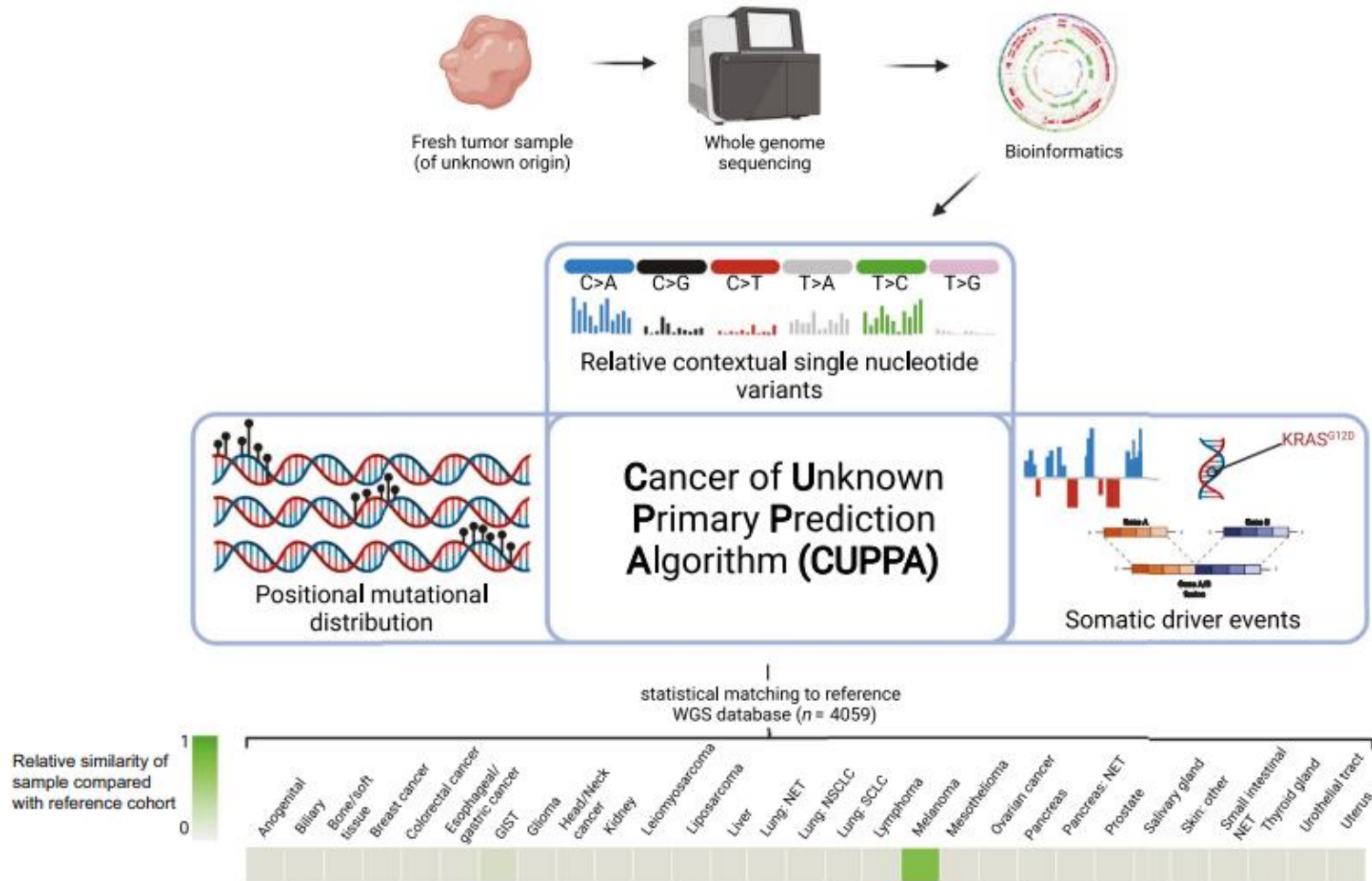


- 1300 (?) ptn per jaar in NL
- Soms lang diagnostisch traject
- Rol moleculaire diagnostiek?
- 30% behandeling
- Kenniscentra en zorgpaden ontbreken
- QvL en goede info ontbreken
- Wetenschappelijk onderzoek niet structureel
- Er is nog veel te winnen

Aanbevelingen IKNL rapport

1. Eenduidige definitie PTO
2. Landelijk beleid noodzakelijk
3. Bundeling in expertpanels regionaal
4. Verbetering diagnostisch traject
5. Beschikbaar stellen moleculaire diagnostiek
6. Optimaliseren afstemming clinicus en patholoog
7. Verbeteren QvL
8. Vastleggen gegevens
9. Patienteninformatie
10. Vergroten maatschappelijk bewustzijn

Mogelijk toegevoegde waarde WGS (Schipper, ESMO open, dec 22)

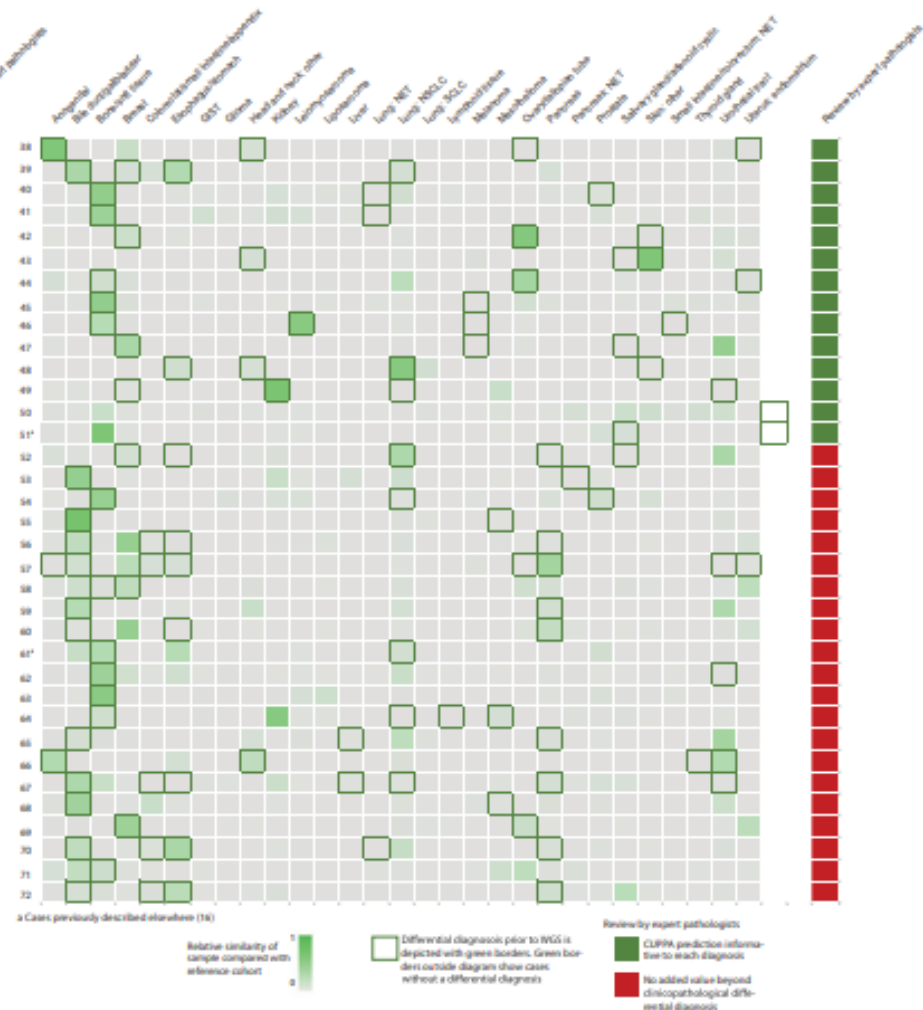


In 68% kon diagnose gesteld worden en in 47% target voor (exp) therapie

A



B



Uitkomsten

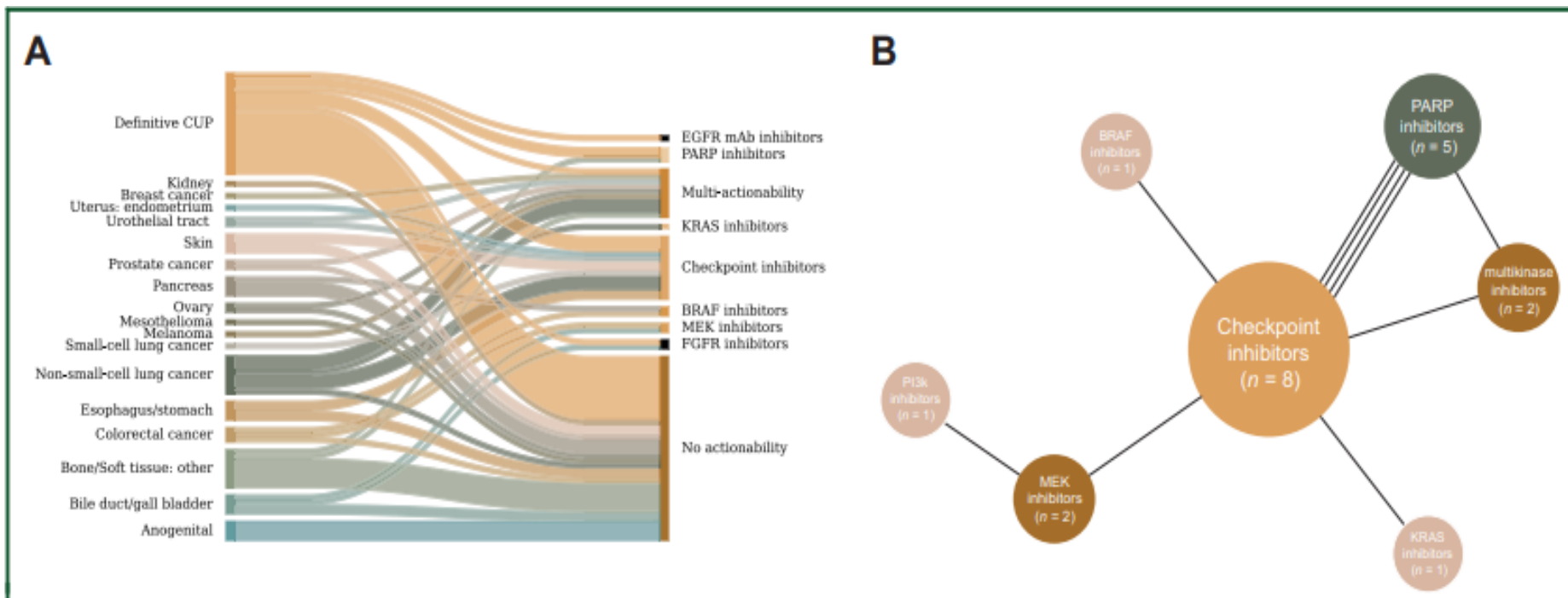
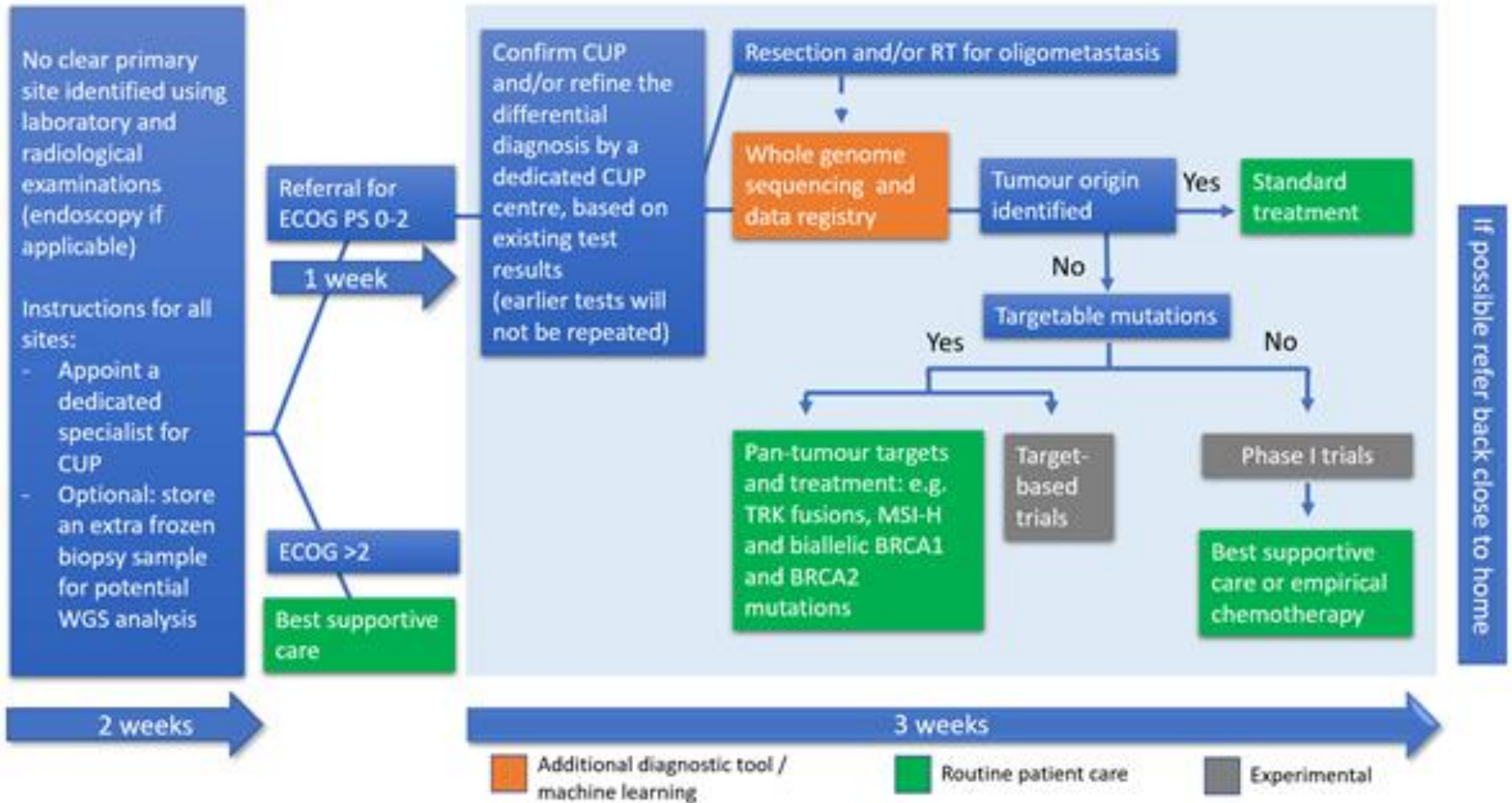


Figure 4. Biomarker-based therapy options detected with WGS in CUP patients. In 47% of patients, an actionable event was identified (panel A). In patients with a definitive CUP ($n = 21$), an actionable event was identified in 33% (7 patients). For 10 patients, multiple therapy options were identified. In panel B, each line represents 1 of these 10 patients, showing the multiple therapy options identified in each patient. CUP. cancer of unknown primary; WGS. whole genome sequencing.

Geresulteerd in betaaltitel WGS in PTO

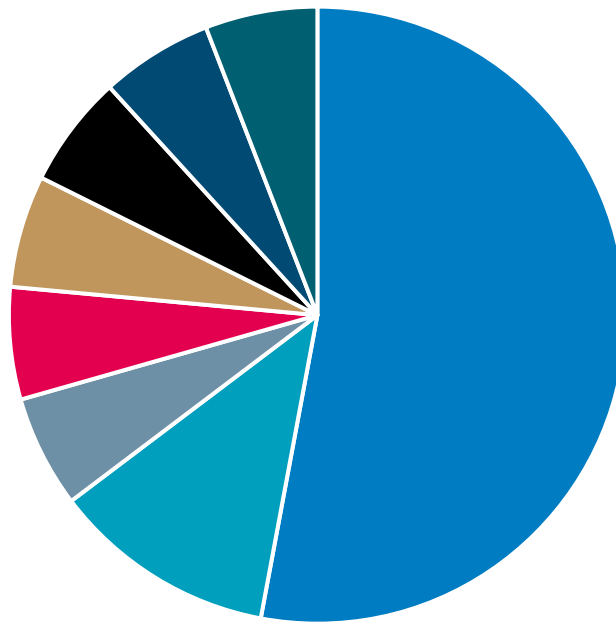


Huidig PTO protocol in NEDerland



LUMC 2022/2023

- Zorgpad sinds januari 2022
- 32 patienten WGS
- 18/32 WGS conclusief (56%)



Man 49 jaar

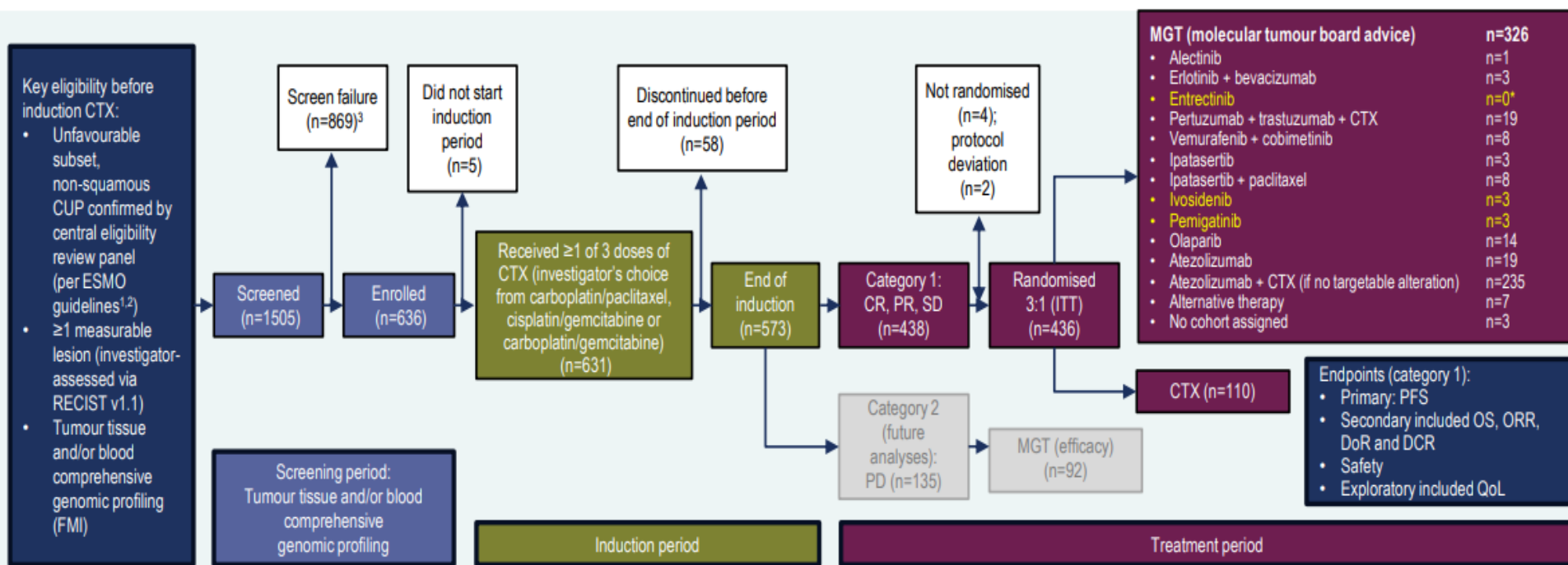
- Al jaar groeiende lesie oksel, huisarts dacht aan hydratenitis
- Maart 2023 resectie polklinisch: plaveiselcelcarcinoom eci
- April PET scan: longmetastasen, geen primaire origine
- Voorts echo abd, MRI hals en MRI mamma gb, CT thorax/abd: groei metastasen
- Juni PA revisie: Her 2 +++/geamplificeerd apocrien carcinoom dd primair cutaan apocrien carcinoom (uitgaande van een apocriene huidadnexstructuur), een metastase van apocrien carcinoom van de mamma, danwel een metastase van een apocrien carcinoom van een speekselklier ('salivary duct adenocarcinoom).
- Sept 23 inclusie DRUP studie trastuzumab/pertuzumab, fraaie en aanhoudende partiele response

Man 65 jaar

- Jan 23 pijn botten: afwijking L1 wv ingreep LUMC
- April 23 Spondylodese L1 metastase adenocarcinoom
- Mei/Juni/Juli radiotherapie, plus 2 andere botmeta's
- Aug 23 CUPPA analyse 97% zeker oesophagus/maagcarcinoom
- Sept 23 ook op PET scan te zien
- Start chemo-immunotherapie
- Januari 24 complete response

CUPISCO studie (ESMO 2023, Mileshkin, LBA 16)

MGT vs standard platinum-based CTX in patients with newly diagnosed, unfavourable CUP



Of the 636 patients enrolled between 10 July 2018 and 9 December 2022, 94 (14.8%) had a tissue biopsy only, 55 (8.6%) had a liquid biopsy only and 483 (75.9%) had both.

*No patients received entrectinib in category 1; only in category 2.

CR, complete response; CTX, chemotherapy; CUP, cancer of unknown primary; DCR, disease control rate; DoR, duration of response; FMI, Foundation Medicine, Inc.;

ITT, intent-to-treat; MGT, molecularly guided therapy; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival;

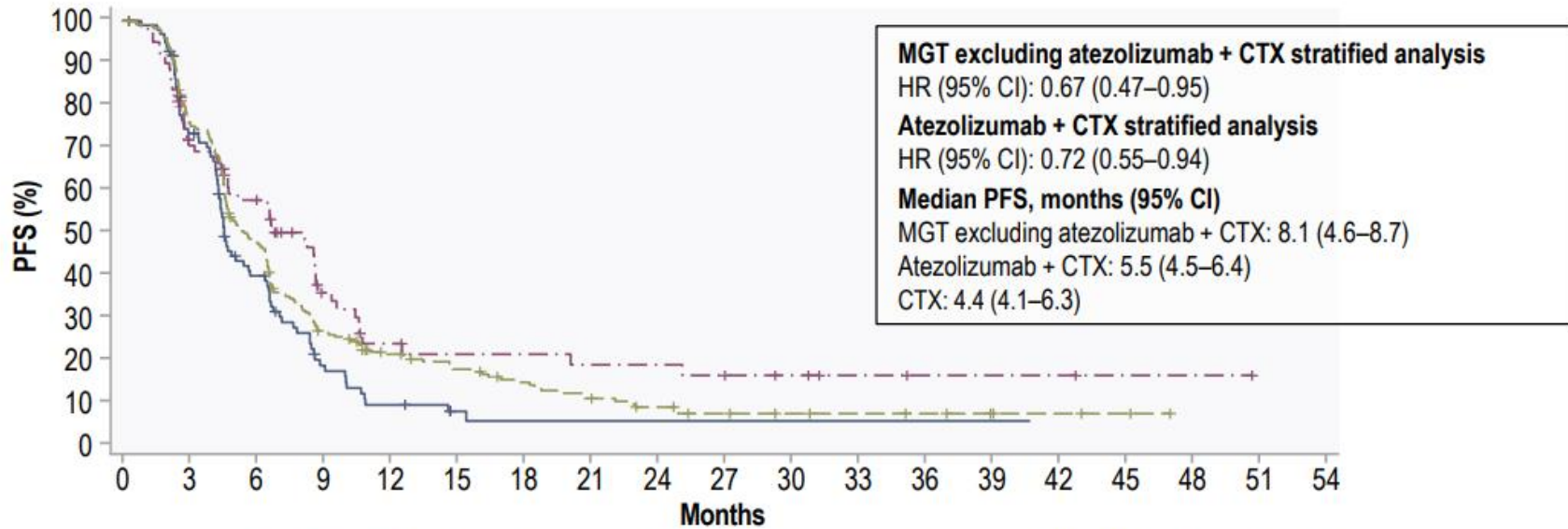
PR, partial response; QoL, quality of life; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

1. Fizazi K, et al. *Ann Oncol* 2015; **26** (Suppl 5):v133–138;

2. Krämer A, et al. *Ann Oncol* 2023; **34**:228–46;

3. Pauli C, et al. *Oncologist* 2021; **26**:e769–79 (earlier cutoff: 30 April 2020).

PFS 8,1 vrs 4,4 mnd



No. at risk	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54
— CTX	101	69	35	15	8	4	3	3	3	2	2	2	2	1	NE	NE	NE	NE	NE
- - - MGT excluding atezolizumab + CTX	83	52	39	19	11	9	9	8	8	7	5	3	2	2	2	1	1	1	NE
- - - Atezolizumab + CTX	229	167	104	57	40	32	25	19	14	10	8	7	6	5	3	2	NE	NE	NE

*All patients who received ≥1 dose of any study drug. CI, confidence interval; CTX, chemotherapy; HR, hazard ratio; MGT, molecularly guided therapy; NE, not evaluable; PFS, progression-free survival.

- Incidentie daalt, diagnostiek verbetert en behandelingsmogelijkheden ook
- Regionale PTO zorgpaden in alle academische centra
- <https://www.lumc.nl/actueel/2023/regionale-samenwerking-binnen-Zorgpad-Primaire-Tumor-Onbekend/>
- www.missietumoronbekend.nl
- Elearning palliatieve zorg:
- <https://www.bsl.nl/shop/palliatieve-zorg-voor-kankerpatienten-met-een-korte-levensverwachting-80732e>

